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Heart failure as a risk factor for acute exacerbations of chronic obstructive pulmonary disease

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Declaration of Originality

I, Eleanor L Axson, hereby certify that the work presented in this thesis is my own and all information presented from other works is properly referenced.

Eleanor L Axson

Copyright Declaration

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Abstract

The purpose of this thesis was to examine the association between comorbid heart failure (HF) and acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in primary care COPD patients to highlight areas in which care can be improved.

The aims of this research were:

i. To describe the burden of HF comorbidity in the COPD population;
ii. To determine the effect of HF comorbidity on exacerbation risk in COPD patients; and
iii. To determine the effect of HF medications on exacerbation risk in COPD patients with HF.

Firstly, a systematic review revealed that HF comorbidity increases COPD-related secondary care utilisation and all-cause mortality of COPD patients; however, the heterogeneity prevented meta-analysis to estimate pooled effects using all available data. Secondly, analysis found that HF incidence was steady from 2006 to 2016 in the COPD population. COPD patients with HF experienced higher short- and long-term mortality rates than those without HF. Thirdly, HF diagnosis was associated with a significantly greater risk for AECOPD compared to patients without evidence of HF. In a population identified as having possible HF, AECOPD risk was also elevated. Only 50% of possible HF patients had documented HF investigation. Finally, incident use of HF medications was associated with increased AECOPD risk compared to non-use of HF medications in COPD patients with diagnosed HF; however, AECOPD risk decreased relative to incident medication use beyond six months of treatment.

These results demonstrate that HF comorbidity has a considerable effect on AECOPD in the primary care COPD population and that management of HF pharmacologically may reduce excess AECOPD risk. Additionally, there appear to be substantial opportunities for earlier recognition of HF in the COPD population in the primary care setting. Proactive targeting of HF in the COPD population by primary care providers may help to improve patient outcomes.

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Abbreviations

95%CI	95% confidence interval
A&E	Accident and emergency
ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AECOPD	Acute exacerbations of chronic obstructive pulmonary disease
AF	Atrial fibrillation
aHR	Adjusted hazard ratio
aMRR	Adjusted mortality rate ratio
APC	Admitted Patient Care
ARB	Angiotensin receptor blocker
ATS	American Thoracic Society
BALR	British Association for Lung Research
BB	Beta-blocker
BLF	British Lung Foundation
BMI	Body mass index
BNF	British National Formulary
BNP	Brain natriuretic peptides
BRC	Biomedical Research Centre
BTS	British Thoracic Society
CAD	Coronary artery disease, also IHD
CAT	Chronic obstructive pulmonary disease Assessment Test
CENTRAL	The Cochrane Central Registrar of Controlled Trials
CCB	Calcium channel blocker
CKD	Chronic kidney disease
CLD	Chronic liver disease
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
DID	Diagnostic Imaging Database
DTR	Danish Twin Registry
EHR	Electronic healthcare records
ERS	European Respiratory Society
ESC	European Society for Cardiology

FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GBD	Global Burden of Disease
GFR	Glomerular filtration rate
GLI	Global Lungs Initiative
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
GP	General practice/practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HTN	Hypertension
HR	Hazard ratio
HRA	Health Research Authority
iHF	Incident heart failure
ICD-10	International Classification of Disease version 10
ICS	Inhaled corticosteroids
IHD	Ischaemic heart disease, also CAD
IMD	Index of Multiple Deprivation
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
LABA	Long-acting beta2 agonists
LAMA	Long-acting muscarinic antagonists
LRTI	Lower respiratory tract infection
LSOA	Lower layer Super Output Area
MeSH	Medical Subject Headings
MHDS	Mental Health Dataset
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
mMRC	modified Medical Research Council
MRA	Mineralocorticoid receptor antagonist
MRR	Mortality rate ratio

NACAP	National Asthma and COPD Audit Programme
NCAP	National Cardiac Audit Programme
NCRAS	National Cancer Registration and Analysis Service
NHFA	National Heart Failure Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPV	Negative predictive value
NT-proBNP	N-terminal pro-B natriuretic peptides
NYHA	New York Heart Association
OCS	Oral corticosteroid
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
OP	Outpatient
OR	Odds ratio
PECOS	Population, Exposure, Comparator, Outcomes, Study characteristics
PHE	Public Health England
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QOF	Quality and Outcomes Framework
SABA	Short-acting beta2 agonists
SAMA	Short-acting muscarinic antagonists
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
TARDIS	Tayside Allergy and Respiratory Disease Information System
THIN	The Health Improvement Network
T_{LCO}	Transfer factor of the lung for carbon monoxide
UK	United Kingdom
VAMP	Value Added Medical Products
WHO	World Health Organisation

Ethics, Support, and Data Disclosure Statement

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Protocols for this research (Chapters IV-VI) were approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol numbers 18_006R2 and 18_074RARA2) and the approved protocol was made available to the journal in which this research is published and to the reviewers during peer review. Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87).

Linked pseudonymised mortality data from the Office for National Statistics (ONS), socioeconomic data from the Index of Multiple Deprivation (IMD), and secondary care data from Hospital Episode Statistics (HES) were provided for these studies by CPRD for patients in England. Data were linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level, with individual patients having the right to opt-out. Use of HES and ONS data are Copyright © (2018), re-used with the permission of The Health & Social Care Information Centre, all rights reserved.

Data are available on request from the CPRD. Their provision requires the purchase of a license, and this license does not permit the authors to make them publicly available to all. This work used data from the January 2018 and the Methods sections for each Chapter have clearly specified the data selection process. To allow identical data to be obtained by others, via the purchase of a license, the code lists have been provided in Appendix III. Licences are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

Chapter I: Background

The chapter provides background information relating to chronic obstructive pulmonary disease (COPD), heart failure (HF), and their comorbidity. This chapter also outlines the rationale, aims, and structure of this thesis.

1.1 Chronic obstructive pulmonary disease (COPD)

COPD is characterised by persistent airflow limitation resulting from exposure to harmful particulates, typically due to tobacco smoking but also occupational and environmental exposures [1]. Airflow limitation in COPD is mostly irreversible and is often accompanied by progressive inflammatory disease of the airways [2].

1.1.1 Epidemiology of COPD

The 2017 Global Burden of Disease (GBD) Study estimated the global prevalence of COPD at just under 300 million cases [3] and an estimated 3.2 million people die from COPD annually [4]. The strongest risk factor for COPD is smoking [1]. The World Health Organisation (WHO) estimates that 73% of COPD mortality is related to smoking [5]. According to one study, the estimated risk for developing COPD among smokers after 25 years of smoking is at least 25% [6], while another study estimated the lifetime risk of smokers developing COPD as around 50% [7]. After smoking, two major sources of particulate exposure are occupation and air pollution; these contribute to the large proportion of COPD cases seen in never smokers [8]. Other risk factors for COPD include ageing, gender, genetics and development, socioeconomic status, and asthma.

In the UK, it is estimated that over 1.2 million people have COPD [9]. Men are still more likely to be diagnosed with COPD than women. COPD is uncommon before age 40 and is prevalent in 9% of those over the age of 71 years [9]. COPD is most common in the North of England and Scotland while London has an abnormally high admissions rate for COPD. COPD is 2.5 times more common in the most deprived areas compared to the least deprived areas [9]. The North and deprived areas have higher smoking rates, but also may be more likely to have occupational or early life exposures, such as prematurity or malnutrition [9].

The UK has one of the highest non-malignant respiratory mortality burdens in the developed world [10, 11]. Mortality of COPD patients in the UK has remained high [12], unlike in other

comparable countries where decreasing mortality has been seen [3]. The greater respiratory mortality experienced by the UK, when compared to other Organisation for Economic Co-operation and Development (OECD) or European countries, is not seen in other disease areas including cardiovascular diseases, cerebrovascular diseases, or cancers [10, 11]. One third of patients with COPD die from COPD, while just over one quarter of deaths are attributed to cardiovascular diseases [12].

1.1.2 Diagnosis of COPD

All patients with suspected COPD in the UK should be assessed according to the National Institute for Health and Care Excellence (NICE) guidelines 2018 [13]. Diagnosis of COPD is considered in patients over 35 years of age, with a risk factor (typically smoking), and who present with one or more symptoms [13]. The most common symptoms of COPD are dyspnoea (breathlessness) on exertion, chronic cough, wheezing, and sputum production.

Diagnosis of COPD is confirmed by measuring the level of airflow obstruction in the lungs. Spirometry measures how much and how quickly air can be passed from the lungs during maximal expiration [14]. A FEV_1/FVC ratio of <0.70 and a FEV_1 <80% predicted are necessary for a diagnosis of airflow obstruction [13]. Spirometry should be performed at the time of diagnosis and at least annually thereafter [13].

1.1.3 Severity of airflow limitation

Severity of airflow limitation is graded according to Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines [1, 15]. Based on post-bronchodilator FEV_1 measurements, airflow limitation is ranks as GOLD stage 1 (mild) to GOLD stage 4 (very severe) in patients with an FEV_1/FVC ratio <0.70 (Table 1.1) [1].

GOLD Stage	FEV_1 Range
1 (mild)	FEV_1 ≥80% predicted
2 (moderate)	50% ≤ FEV_1 < 80% predicted
3 (severe)	30% ≤ FEV_1 < 50% predicted
4 (very severe)	FEV_1 < 30% predicted

Table 1.1. GOLD stage classification of airflow limitation severity. Adapted from GOLD [1].

GOLD staging should be combined with symptom assessment to determine the true burden of COPD on the patient; while the mMRC [16] measures breathlessness, it is now appreciated that symptomatic evaluation should expand beyond breathlessness [1, 17] and there are now many tools available to assess symptoms, including comprehensive [18, 19] and simplified questionnaires [20]. These questionnaires explore breathlessness, along with fatigue, sleep quality, confidence in activities, coughing, mucus production, and chest tightness [1, 20].

1.1.4 COPD in primary care

The Quality and Outcomes Framework (QOF), first introduced in 2004, QOF rewards primary care practices for quality management of indicator conditions, including COPD [21]. Practices are rewarded for quality recording, diagnosis, and ongoing management of these conditions through the use of specified Read codes. The QOF encourages primary care providers to maintain a register of COPD patients including initial diagnosis and ongoing management practices. Initial diagnosis must be confirmed by post-bronchodilator spirometry [21]. Ongoing management includes annual recording of the percentage of patients with a COPD review using the mMRC dyspnoea scale, with a FEV_1 measurement, with oxygen saturation measurement (as appropriate), and/or with an influenza vaccination [21].

1.2 Acute exacerbations of COPD (AECOPD)

Patients with COPD may experience acute episodes of worsening symptoms, termed exacerbations or acute exacerbations (AECOPD), which may require changes in management. Symptoms affected by AECOPD often include breathlessness, cough, increased sputum production, and/or change in sputum colour [13].

1.2.1 Epidemiology of AECOPD

Determining the rate of AECOPD is complicated by the non-specificity of symptoms and by the tendency of patients to under-report events. Misclassification of AECOPD is possible as the primary complaint, dyspnoea, is common in a number of unrelated conditions. Other lung conditions, such as pneumonia, are common causes of acute dyspnoea and other symptoms associated with AECOPD such as cough and sputum. Anxiety is another common cause of acute dyspnoea that may be misclassified as AECOPD in patients with COPD [22]. Finally, cardiovascular conditions, particularly HF, can present with acute dyspnoea and be misclassified as AECOPD in patients with COPD [23]. Under-reporting may be a result of

other clinical coding practices, whereby AECOPD are coded as using non-specific codes (such as COPD, hospitalisation, etc.). Under-reporting of events may also be due to the event being mild enough for a patient to manage at home, patients not recognising an event due to poor understanding of their disease, or due to depression and lack of mobility [24]. Previous studies have shown that patients who report fewer AECOPD also have a poorer quality of life that may be related to AECOPD going unreported and untreated [25].

Despite challenges in identification and reporting, exacerbation rates are increasing in incidence [26] and prevalence [27] in UK primary care and secondary care [24, 27], which may be due, in part, to increased recognition and increased numbers of COPD patients. COPD is responsible for 1.7% of all hospital admissions and bed days in the UK [9]. Elsewhere, the Netherlands has seen decreasing AECOPD in general practice [28], hospitalisations have increased in France [29], and hospitalisations have been steady in Brazil [30]. AECOPD rates in clinical trials vary greatly. In the longitudinal, multinational ECLIPSE study, the AECOPD rate was 1.2 per patient per year in Western patients (North America, Europe, and New Zealand) in secondary and tertiary care [31]. The UK primary care-based Salford Lung Study reported an AECOPD rate of 2.0 per patient per year [32], while the German primary care-based DACCORD Study reported a rate of 0.4 AECOPD per patient per year [33].

There is no specific classification of death due to AECOPD; however, deaths attributed to COPD are likely to occur in patients meeting the definition of AECOPD [24]. Mortality due to COPD is rising, however, it is likely still underestimated as deaths may be attributed to comorbidities [9, 24]. Inpatient mortality from COPD admissions ranges from 4-30% depending on severity, such as presence of respiratory failure or admittance to a specialist or intensive care ward [34]. Long-term survival (15 years) following a severe AECOPD, requiring admission to hospital, is around 7%, with survival decreasing with increasing severity of COPD as measured by GOLD stage [35].

1.2.2 Pathophysiology of AECOPD

AECOPD are characterised by acute worsening of chronic COPD symptoms, including dyspnoea, cough, and sputum production [13]. Patients may be categorised as ‘frequent (≥ 2 events per year)’ or ‘infrequent (< 2 events per year)’ exacerbators [36]. The frequent exacerbator phenotype is relatively stable over time, although frequency increases as the

disease progresses in severity and stability is more common in patients who do not exacerbate [31, 36]. Some patients experience a longer period between the onset of exacerbation symptoms and the peak of those symptoms. One study found that 56% of events had no time (0 days) between onset and peak, while 44% of events had a median of 4 days (IQR: 2-8) between onset and peak [37]. The median duration of an exacerbation event is around 12 days (IQR: 6-26) [37].

The most common cause of AECOPD are bacterial infections, but they are also caused by viruses, environmental exposures, and comorbidities [2, 38]. It is estimated that 60-80% of AECOPD are caused by infections, particularly the bacteria *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* [39]. Viral causes include influenza viruses, rhinoviruses, and coronaviruses [39]. Non-infectious causes account for the remaining 20-40% of AECOPD, including air quality, allergens, and comorbidities including HF, pulmonary embolism, and pneumothorax [39].

Following an insult, an inflammatory cascade leads to exacerbation of COPD symptoms, including emphysema, mucus hypersecretion, airways remodelling, and fibrosis [40]. Most often, AECOPD are associated with a primarily neutrophilic response; however, an important subset are characterised by an eosinophilic response [41].

1.2.3 Severity of AECOPD

The frequency of exacerbations may be assessed in terms of the frequent exacerbator phenotype (Section 1.3.1), the actual number of events (0, 1, 2, etc.), or events per year. Severity of AECOPD is often classified as ‘mild’ if managed at home, as ‘moderate’ if managed by primary care, or as ‘severe’ if managed in hospital. AECOPD that result in death may be included in the ‘severe’ category or classed separately.

In 2011, GOLD introduced a ‘revised combined COPD assessment’ tool that includes assessment of symptoms and exacerbation history, this tool has been revised and the 2017 version will be used in these studies [1]. Patients are diagnosed using spirometry and their airflow limitation severity is assessed. Next, the number and severity of exacerbations in the previous year is assessed along with their mMRC dyspnoea score [16] or their COPD Assessment Test (CAT) score. The information on exacerbation and symptoms is combined

and the patient classified into one of four groups (A-D). The new assessment, including exacerbations and symptoms, was designed to provide insight into future exacerbation risk and inform treatment plans [1]; however, in a national cohort study from Denmark, the GOLD A-D system from 2017 did not perform better than the airflow limitation system in predicting all-cause and respiratory mortality [42]. In the UK, NICE recommends the GOLD stages (1-4) for assessing airflow limitation; however, the current NICE guidance does not include the A-D groups outlined by GOLD [1, 13].

1.2.4 Management of AECOPD

NICE provides guidance for the management of AECOPD at home, in primary care, and in secondary care [13]. Factors for determining location of care include symptom burden (e.g. level of breathlessness, cyanosis, etc.), social situation (living alone, unable to cope, etc.), and comorbidities (cardiovascular disease, diabetes, etc.) [13]. Pharmaceutical interventions, LABA and LAMA, may be provided with nebulisers or inhalers. Systemic corticosteroids should be provided, as long as there are no contraindications, for 5 days [13]. Antibiotic prescribing for AECOPD is outlined in a specialist NICE guideline [43]. First line antibiotics include amoxicillin, doxycycline, and clarithromycin [43].

1.3 Comorbidities in COPD

Patients with COPD often experience comorbidity and the presence of comorbidity contributes to COPD progression, poorer health status, and mortality [44-47]. A detailed discussion of what is known regarding COPD and HF comorbidity follows in **Section 1.5**, after a discussion of HF in **Section 1.4**.

1.3.1 Prevalence of comorbidities in the COPD population

The majority of COPD patients have at least one additional chronic condition, but estimates vary depending on methodology, choice of comorbidities to record, and sample demographics. Presence of comorbidities increases with age but is common across levels of airflow limitation. In the ECLIPSE COPD cohort, prevalence of most comorbidities was independent of severity of airflow limitation [48]. COPD patients in the UK Biobank report largely similar proportions of patients with three or more comorbidities at each level of airflow limitation (ranging 11.5-13.5%) [49]. However, higher estimates have been seen such as in a Dutch study that found

nearly 98% of 213 moderate-to-severe COPD patients attending a tertiary care centre had at least one comorbidity and over half (53%) had four or more documented comorbidities [50].

Common comorbidities in the COPD population including cardiovascular conditions, anxiety, obesity, osteoporosis, diabetes, depression, and CKD; however, most studies show cardiovascular conditions as the most common comorbidities in the COPD population. COPD patients are more likely to report cardiovascular risk factors, including hypertension, diabetes, and smoking, than non-COPD patients [51]. Having COPD is associated with greater risk for a number of cardiovascular diseases, including angina, AF, HF, MI, PAD, PH, and stroke [51-53], especially at younger ages (**Figure 1.1**) [52]. Certain associations between COPD and certain cardiovascular diseases are well documented, including myocardial infarction and stroke [51, 54]; while others less so, notably HF [55].

1.3.2 Effect of comorbidities on management in the COPD population

There is evidence that comorbidities may affect treatment of COPD patients. HF, IHD, and CKD have been associated with decreased odds of receiving corticosteroids and antibiotics for the treatment of AECOPD than patients without these comorbidities [56]. BB, statins, and aspirin are all underutilised after first-time MI in COPD patients compared to non-COPD patients [57]. Delays in diagnosis and management of MI in the COPD population has been shown to increase mortality following these events [58].

1.3.3 Effect of comorbidities on mortality in the COPD population

Several trials have documented cause of death among COPD cohorts, commonly finding high proportions of deaths attributed cardiovascular and malignant causes [59]. In UK primary care, around a third of COPD patients die from non-malignant respiratory diseases, mostly COPD; while, around a quarter of COPD patients die from cardiovascular causes, part of a decreasing cardiovascular mortality trend in the population [12].

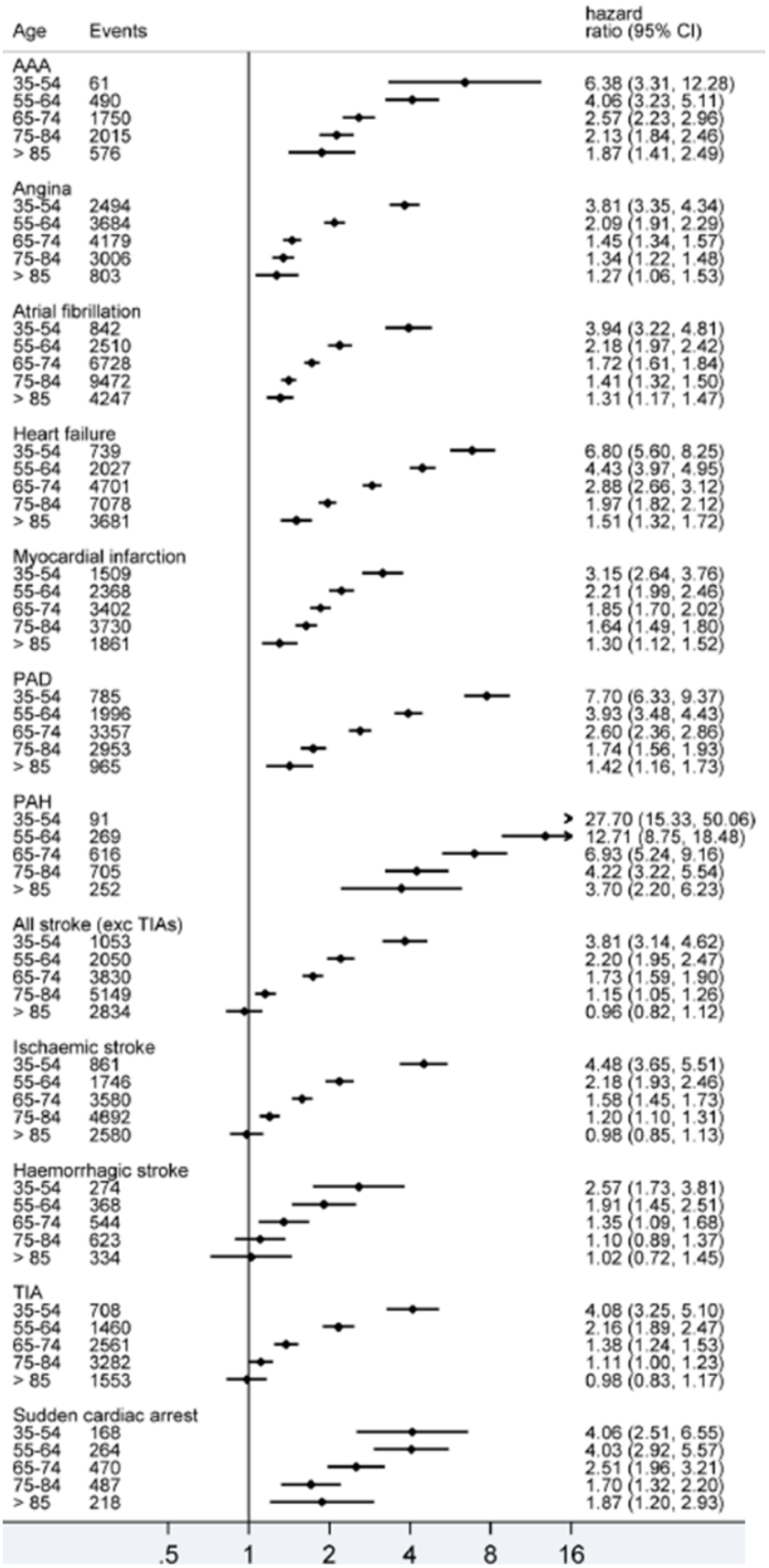

Figure 1.1. Risk of cardiovascular conditions for different age groups in the COPD population. Abdominal aortic aneurysm (AAA). Confidence interval (CI). Transient ischaemic attack (TIA). Reproduced from [52] / © 2018 the authors (permissions in Appendix VII).

1.4 Heart failure (HF)

HF is a syndrome that often serves as the final physiological pathway for other cardiovascular diseases [60].

1.4.1 Epidemiology of HF

The GBD estimates the global prevalence of HF to be around 64 million patients [3]. The crude incidence of HF increased by 2% and the absolute number of patients with HF increased by 12% in the general population of the UK from 2002 to 2014, but the age- and sex-standardised incidence decreased by 7% over the same period [61]. Changes in the crude incidence of HF and in the absolute number of patients with HF in the UK are thought to be driven by changing demography resulting from the increasing proportion of older adults in the population [61].

Cardiac risk factors for HF include IHD, hypertension, cardiomyopathy, and valve disease [60]. Other risk factors include genetics, hypercholesterolaemia, diabetes, obesity, and exposure to cardiotoxic agents (e.g. alcohol, radiation, tobacco smoking, air pollution, etc.) [60]. The primary mechanism by which the aforementioned risk factors lead to HF is cardiac damage.

Mortality of HF patients remains high, with 5-year survival for men estimated at 55.8% and for women at 49.5% [62]. Cardiovascular-related deaths are most common in the years immediately following HF diagnosis, but after 3-5 years deaths due to non-cardiovascular causes dominate [63]. Studies looking at mortality trends over time in the UK are mixed. One study found no improvement from 1998 to 2012 in 1-year, 5-year, or 10-year survival following HF diagnosis [64]. Another study found 1-year, 5-year, and 10-year survival improved by ~7% from 2000-2017 [65]. A third study estimated a 3-4% decrease 1-year and 5-year mortality risk of HF patients from 1998-2017 [63].

1.4.2 Types of HF

Right ventricular failure is often called cor pulmonale, if it is secondary to chronic lung disease. Severe PH (≥35 mmHg) increases strain on the right-side of the heart, which can lead to the clinical syndrome of right-sided HF [66].

Left-sided HF is often classed based on left ventricular ejection fraction. According to the latest guidelines from the European Society for Cardiology (ESC), for HF to be present 1) a patient

must present with symptoms; 2) patients may have either reduced (HFrEF, < 40%), mid-range (HFmrEF, 40-49%), or preserved (HFpEF, ≥50%) left ventricle ejection fraction; and, in certain cases, 3) must have a relevant structural heart disease or diastolic dysfunction [67].

1.4.3 Diagnosis of HF

HF is a syndrome meaning that recognition of HF requires the recognition of signs and symptoms [68]. The main symptoms of HF are breathlessness, swelling (oedema) of the lower extremities, and less oxygenated blood circulating around the body, known as hypoperfusion. Just as important is identification of the underlying cardiac cause, such as IHD, as this can direct treatment [67]. HF can present as chronic or acute. Chronic HF is the result of long-term cardiac dysfunction [68]. Acute HF is the sudden worsening of symptoms stemming from cardiac dysfunction and may present *de novo* or as a result of acute decompensation of chronic HF [68]. Following presentation with *de novo* acute HF, a patient will subsequently be known to have chronic HF.

The NICE guidelines for the diagnosis of chronic HF were most recently updated in 2018 [69]. Patients with suspected chronic HF- based on clinical history, signs, and symptoms- should have their levels of N-terminal pro-B natriuretic peptides (NT-proBNP) measured and anyone with NT-proBNP >400 ng/L referred for an echocardiogram [69]. Blood concentration of brain natriuretic peptides (BNP) or NT-proBNP rises in HF [67]. Raised BNP or NT-proBNP may be seen in other conditions too, such as atrial fibrillation and renal failure, so these measurements alone are not indicative of heart failure and must be considered among other evidence [70].

1.4.4 Management of HF

Treatment of HF is outlined by the NICE guidelines for chronic heart failure management from 2018 [69]. Firstly, all stable HF patients should be referred to cardiac rehabilitation including exercise, education, and psychological support [69]. Secondly, loop diuretics should be prescribed to reduce fluid retention in all HF patients with oedema [13]. Loop diuretics work on the ascending tube of the loop of Henle in the kidneys, inhibiting the carrier of sodium, potassium, and chloride ions into the cell, increasing their concentration in the urine and facilitating the release of water [71]. Additionally, patients with HFrEF should be managed

with angiotensin-converting enzyme inhibitor (ACEi) and a beta-blocker as first line treatments [69]. Patients with fluid retention should be prescribed loop diuretics [69].

ACEi reduce angiotensin II levels by blocking the conversion of angiotensin I by the angiotensin-converting enzyme [72]. Lower angiotensin II levels increases vasodilation, reducing blood pressure, and increases salt levels in the kidneys, increasing water excretion and decreasing blood volume [72]. Angiotensin receptor blockers (ARB) can be used in patients who do not tolerate ACEi [69]. ARB work by blocking the binding of angiotensin II to receptors, similarly reducing blood pressure and decreasing blood volume [73].

Beta-blockers, also known as beta-adrenergic blocking agents, are first line treatment for patients with HF or following MI [69, 74]. Beta-blockers work by preventing the binding of adrenaline and noradrenaline to β_1 and β_2-receptors leading to reduced heart rate and reduced force of heart pumping [75]. β_1-receptors are primarily located in the heart and kidneys; whereas β_2-receptors can be found in many other locations, including the lungs. Non-cardioselective beta-blockers have similar affinity for both β_1 and β_2-receptors; whereas, cardioselective beta-blockers have a higher affinity for β_1-receptors, but will bind β_2-receptors at high enough concentrations [75].

Mineralocorticoid receptor antagonists (MRA) should be added to treatment regimens in patients who still experience symptoms [69] as the effect of ACEi can diminish over time and levels of aldosterone can return to or exceed baseline [76]. Aldosterone production is stimulated when angiotensin II binds with angiotensin II type 1 receptors [76]. Mineralocorticoid receptors are activated by aldosterone and aldosterone can increase the number of mineralocorticoid receptors and the amount of angiotensin converting enzyme [76]. As ACEi and MRA work with different mechanisms to reduce the effects of aldosterone, the use of both in tandem is recommended [69, 76]. Originally, MRA were developed as potassium-sparring diuretics by acting on mineralocorticoid receptors in the renal system and were prescribed alongside other diuretics to reduce water retention and blood pressure [76].

1.4.5 HF in primary care

Per the QOF, primary care providers are encouraged to maintain a register of all patients with HF. This includes initial diagnosis and ongoing management. Initial diagnosis must be

confirmed by echocardiogram or by specialist assessment [21]. Ongoing management is assessed in patients with a diagnosis of HF as the percentage of patients on ACEi-ARB [21]. Ongoing management is further assessed as the percentage of patients additionally treated with a beta-blocker [21]. In addition to QOF, the National Heart Failure Audit (NHFA) was introduced in 2007 to ensure stable quality of coding practices in secondary care by measuring the use of echocardiograms in diagnostics among other measures [77]. Despite these measures, HF is generally undertreated [78].

1.5 Comorbid COPD-HF

In the context of this thesis, COPD will be treated as the index disease, as it is the effect of HF on COPD that is of interest; therefore, HF will be referred to as a comorbidity of COPD. The reality is most probably more complex, with COPD and HF being a part of systemic dysfunction leading to multiple chronic conditions that interact, or multimorbidity.

There are two main schools of thought as to how comorbidity in COPD or multimorbidity with COPD develop. Firstly, the 'spill-over' theory posits that events in the lungs, due to COPD, progress in such a way that they trigger systemic involvement. This theory favours COPD as an index disease and other conditions as comorbidities and treatment focused on the lungs. Secondly, the systemic theory posits that COPD is merely a component of wider systemic disorder and, therefore, is one part of multimorbidity where treatment may be focused on the systemic inflammatory state [79, 80]. In this thesis, the terminology for the spill-over theory will be used; however, the distinction of which theory best describes reality is beyond the scope.

1.5.1 Epidemiology of COPD-HF

The 2017 GBD Study estimated the global prevalence of COPD cases with HF comorbidity at over 14.8 million cases [81], or around 5% of all COPD cases. Patients with COPD experience 2.6 times greater risk for HF than the general population [51]. Studies in HF cohorts have found the prevalence of patients with HFrEF and COPD ranges from 8-52% [82]. An Italian study in primary care found the prevalence of HF in COPD patients to be 22.5% [83]. A Scottish study in primary care found increased prevalence of COPD in the HF population rising from 19.8% in 1999 to 23.8% in 2004 [84]. COPD was more common in older HF patients and increased

with greater socioeconomic deprivation [84]. COPD patients experience higher rates of HFpEF than the general population with HF [85-87].

Smoking is a common risk factor for COPD and HF [88, 89]. Patients with COPD experience an increased risk for a number of cardiovascular conditions, especially at young ages. COPD patients aged 35-54 experience nearly seven times greater risk for HF, over three times greater risk for MI, over 27 times greater risk for pulmonary arterial hypertension, and nearly four times greater risk for AF, angina, and stroke than the general population at these ages [52].

1.5.2 Pathophysiology COPD-HF

The association between COPD and right-sided HF due to lung disease is well established [90], but COPD patients experience additional burden for left-sided HF as well [91]. There are a number of physiological mechanisms linking the heart and lungs and contributing to development of pulmonary and cardiovascular conditions (**Figure 1.2**) [92].

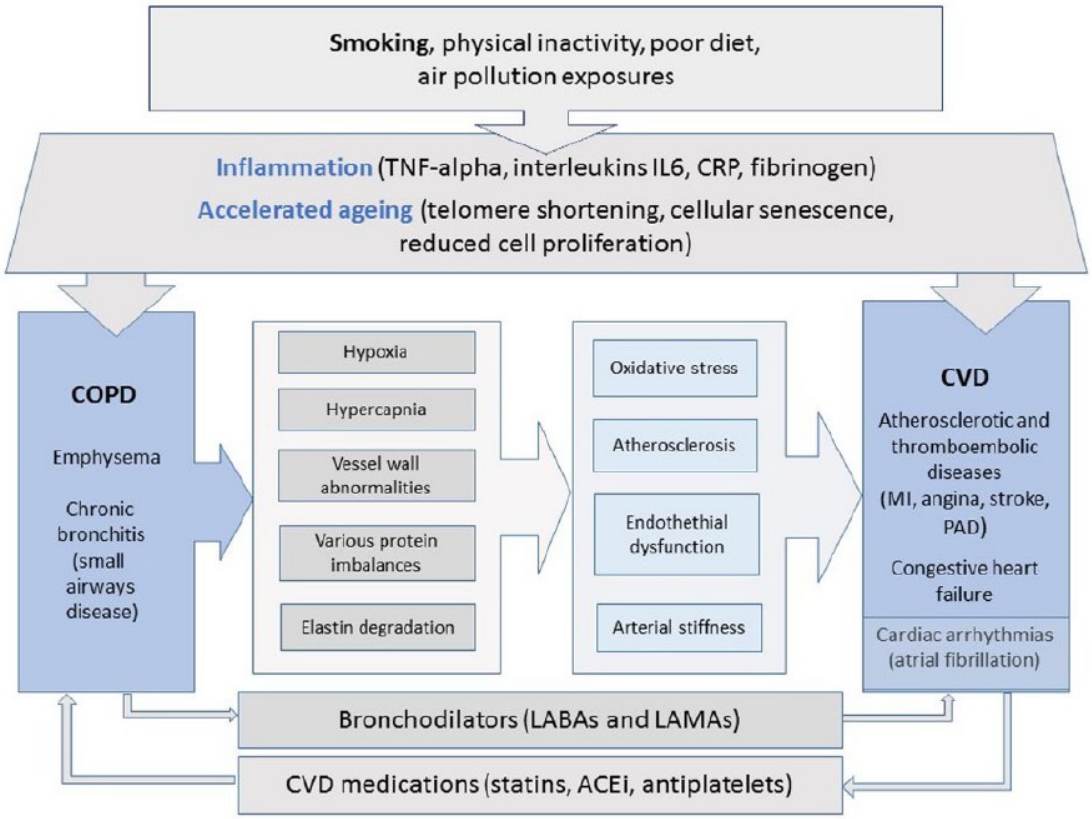

Figure 1.2. Physiological connections between diseases of the heart and lungs. Reproduced from [92] / CC BY-NC.

Accelerated ageing

Chronic cardiovascular and lung diseases are characterised by accelerated ageing and it is thought that this characteristic may be an important physiological link between these conditions [93]. Accelerated ageing manifests in a number of cellular and molecular processes including telomere shortening, cellular and immuno-senescence, defective autophagy, oxidative stress, stem cell exhaustion, microRNAs, and epigenetics [93]. Common physiological mechanisms related to accelerated ageing in a number of chronic conditions, including COPD and HF, are thought to play a role in the development of each condition and in the development of multimorbidity [94].

Hyperinflation, hypoxaemia and hypoxia

Hyperinflation may increase pressure in the cardiopulmonary system, reducing cardiac output [95]. Hypoxaemia due to COPD can trigger pulmonary vasoconstriction resulting in pulmonary hypertension, cor pulmonale, and eventually left-sided HF [95]. Hypoxaemia is also associated with altered cardiac repolarisation and subsequent increased risk for arrhythmias and sudden cardiac death [96].

Hypoxia can be constant in COPD patients with severe disease. The hypoxic state increases heart rate and cardiac index, a measure of cardiac output in relation to body size [97]. Hypoxia also increases cellular adhesion molecules, foam cells, and systemic inflammation [97]. Foam cells, lipid-loaded macrophages, are beacons for atherosclerotic lesion formation [97]. Atherosclerosis progression contributes to IHD and, ultimately, HF [55].

Hypoxia can also aid the development of arterial stiffness [98]. Additionally, management of COPD may affect arterial stiffness. A previous systematic review found conflicting evidence for the effect of pulmonary rehabilitation on arterial stiffness, with evidence that, in some patients, pulmonary rehabilitation may actually increase cardiovascular risk [99].

Pulmonary hypertension

PH can occur secondary to chronic lung disease [100, 101]; however, it is rare and mostly limited to very severe COPD [66, 101, 102]. PH secondary to left-sided HF is increasingly common [101] and may play a part in the development of dyspnoea.

Systemic inflammation

Smoking, a common risk factor for COPD and HF, is associated with systemic inflammation in susceptible individuals [92]. Systemic inflammation can initiation and accelerate coronary atherosclerosis progression aiding the development of HF [55]. Systemic inflammation due to comorbidities, including COPD, is hypothesized to contribute to the development of HFpEF [60, 103].COPD is considered partly a consequence of an abnormally heightened immune response to inhaled particulates [92]. There is evidence that COPD can contribute to chronic systemic inflammation that increases with disease severity and during exacerbations [104-106]. Systemic inflammation due to COPD is hypothesized to contribute to the initiation and acceleration of atherosclerosis and that acute events, including respiratory infections and AECOPD, can induce plaque rupture and subsequent cardiovascular events [92]. COPD patients with cardiovascular disease experience higher levels of systemic inflammatory biomarkers than COPD patients without cardiovascular disease [107].

1.5.3 AECOPD and HF

It is known that acute HF is often misclassified as AECOPD [23]. Similarly, diagnosis of MI and pulmonary embolism are often delayed or missed in COPD patients as they are initially seen as AECOPD [108, 109]. Respiratory infections are the most common cause of AECOPD and they also increase the risk of vascular events [110-112]. Hypoxaemia, tachycardia, and increased systemic inflammation seen during AECOPD can also trigger cardiovascular events [113]. Frequent exacerbators are more likely to have comorbidities, especially cardiovascular disease [114].

Previous work has shown that underlying cardiovascular instability instigating AECOPD due is probably common [115], with one study estimating that up to 20% of AECOPD could be due to acute HF or cardiac arrhythmias [116]. Another cohort found 26% of AECOPD were due to HF, the second most common cause after bacterial infections [117]. Underlying cardiac problems have been seen in around a quarter of AECOPD episodes when echocardiography has been performed [118, 119]. Cardiac biomarkers, such as troponin [120-123], NT-proBNP or BNP [122-124], and copeptin [122, 125], are associated with poor outcomes, including death, in AECOPD.

1.5.4 Diagnosis and management of COPD-HF

The diagnosis of HF in the presence of COPD, or vice versa, is complex due to shared symptomology and risk factors [126]. There are currently no bespoke guidelines available and clinicians are advised to consult the appropriate guidelines for the diagnosis and management of each condition [13, 69]. While HF is often undertreated [78], COPD patients experience an even greater under-treatment burden [127].

Recognition of COPD-HF comorbidity

There are a number of diagnostic challenges for clinicians trying to recognise and diagnose HF in the presence of COPD, and vice versa. COPD and HF share a number of symptoms including dyspnoea, fatigue, and exercise intolerance, which are non-specific. Research has shown that the majority patients presenting to primary care with dyspnoea wait over six months for a diagnosis of asthma, COPD, or IHD and around 1 in 10 patients wait >3 years for a diagnosis [128]. These patients also experienced higher mortality and delayed treatment compared to patients who did not report dyspnoea [128]. In patients with COPD, the median time between symptom presentation and HF diagnosis in primary care was over 3 years, compared to only 2.4 years in patients without COPD [127]. HF treatment was delayed as well, with COPD patients waiting 2.9 years compared to only 1.9 years in patients without COPD [127]. These studies suggest there are missed opportunities in primary care for early diagnosis and management of dyspnoeic conditions, including recognition of HF in patients with COPD.

There are a number of challenges with performing spirometry in cardiovascular patients. Chronic congestion may lead to reduced airflow in some patients, with some studies showing that obstruction can been reversed with proper management of congestion [129, 130]. Cardiovascular patients are typically older and as lung function reduces naturally with ageing, using fixed cut-offs may overdiagnosis COPD in these patients [131]. Ideally, spirometry should be performed in stable cardiovascular patients [132]. Perhaps as a result of these challenges, spirometry is under-used in cardiovascular patients [133]. Dalsgaard et al. performed spirometry on patients attending HF clinics in Denmark, they found obstructive airflow in 39% of patients at attendance, with only 12% previously having been diagnosed with COPD [130]. Within primary care, an Italian study [83] found that only 57.1% of COPD-HF patients had spirometry, whereas 63.9% of COPD only patients and 5.2% of HF only patients had spirometry [83]. Chest X-ray and pulmonary visits, however, were more common in

COPD-HF patients (74.1% and 87.7%, respectively) than in COPD patients (68.8% and 84.5%, respectively) or HF patients (50% and 5.9%, respectively) [83].

Regarding cardiac investigations, COPD can affect quality of cardiac imaging. Air trapping due to pulmonary disease can affect echocardiogram acoustic windows and unsatisfactory imaging quality can range from 10% in stable primary care COPD patients up to 50% in COPD patients with very severe airflow obstruction [132]. The limited availability of other imaging techniques, such as magnetic resonance imaging (MRI), means that the lack of a confirmed diagnosis of HF in patients with COPD, especially severe COPD, is challenging to improve. Echocardiogram was performed for 85.7% of primary care COPD-HF patients and 81.6% of HF patients, but only 38.9% of COPD patients in Italy [83]. In the same primary care study, electrocardiogram was performed for 95.2% of COPD-HF patients and 95.4% of HF patients, but only 84.5% of COPD patients [83]. Cardiology visits were seen for 94.5% of COPD-HF patients and 95.4% of HF patients, but only 73.8% of COPD patients [83].

Bronchodilators and HF

The use of beta-2 agonists in patients with cardiovascular disease is an ongoing debate [132, 134]. Long-term use of beta-2 agonists may stimulate the beta-2 adrenergic receptors of the heart and lead to tachycardia, arrhythmias, ischaemia, and other cardiac disturbances [132, 134]. The level of risk of uncertain and some studies have found no differences in long-term mortality of HF patients on beta-2 agonists compared to those not on beta-2 agonists [135]. Use of long-term bronchodilators, both beta-2 agonists and muscarinic antagonists, was associated with increased incidence of cardiovascular conditions in a number of meta-analyses and observational studies [136-138]. Primary care COPD patients on long-term bronchodilators experience higher risk for HF development [139].

The SUMMIT trial investigated mortality risk and cardiovascular outcomes in COPD patients with heightened cardiovascular risk; however, excluded patients with severe HF [140]. Patients were randomised to LABA/ICS, LABA alone, ICS alone, or placebo [140]. Mortality and cardiovascular outcomes were not affected by treatment with LABA and/or ICS and treatments were well tolerated by patients [141].

Beta-blockers and COPD

There used to be a concern that beta-blockers, particularly β_2-receptor blockers, may increase bronchoconstriction by acting on β_2-receptor in the airways and therefore should be avoided in patients with COPD [132]; however, COPD is not listed as a contraindication for beta-blocker prescription in HF guidelines [67, 142]. There is only one beta-blocker approved for use in HF that has β_2-receptor blocking effects, carvedilol [132]. Other beta-blockers approved for use in HF are cardioselective, meaning they preferentially block β_1-receptors and are associated with lower risk for bronchoconstriction [132]. A nationwide observational study in Denmark found that COPD patients with HF and diabetes using carvedilol experienced increased risk for HF-related hospitalisation compared to users of the cardioselective beta-blocker, metoprolol [143]. However, multiple reviews have demonstrated the safety of beta-blockers, specifically cardioselective beta-blockers, in COPD patients [144, 145].

Despite evidence that cardioselective beta-blockers are safe and beneficial for COPD patients with an indication for beta-blocker use, there is systemic under-prescription of beta-blockers in the COPD population with indications for their use. A diagnosis of COPD has been shown to be one reason why beta-blockers were not prescribed to patients with indications for their use [146]. Previous studies have found that 40-45% of COPD patients with an indication for beta-blockers and no contraindications were not prescribed beta-blockers [147-150]. Within primary care, a Scottish study found that only 18% of HF patients with COPD were prescribed beta-blockers in 2004, compared to 41% of HF patients without COPD [84]. An Italian study found 40% of primary care patients with COPD-HF were prescribed beta-blockers, compared to 68% of HF patients without COPD [83]. Of note, research has shown that COPD patients are at a greater risk for HFpEF [85-87], for which beta-blockers are not currently recommended [67, 142]. Therefore, establishing HF type is important for ensuring correct management.

Previous observational studies have shown that beta-blockers, even in the absence of HF or another cardiovascular indication, may reduce mortality and exacerbations in COPD patients. Beta-blockers have been shown to reduce mortality of COPD patients with co-occurring hypertension [151]. Another study, using data from the TARDIS repository in Scotland, found a 22% reduction in all-cause mortality for COPD patients taking beta-blockers compared to those not taking beta-blockers [152]. A Dutch study also reported improved survival in COPD patients taking beta-blockers and additionally reported those patients experienced a reduced risk for exacerbations [153]. The COPDGene study found that beta-blocker use was

significantly associated with fewer exacerbations, but was not associated with long-term mortality [154].

The BLOCK COPD clinical trial (NCT02587351) aimed to assess whether the cardioselective beta-blocker, metoprolol, reduced exacerbations in COPD patients who did not have an indication for beta-blocker use [155]. The trial was stopped early because patients taking metoprolol experienced increased rates for severe or very severe exacerbations [155]. There is currently another clinical trial, BRONCHIOLE [156], being conducted to further investigate the effect of beta-blockers on COPD in the absence of cardiovascular indications (NCT03566667).

1.6 Rationale

It is only recently that more formal assessments of the relationship between HF comorbidity in the COPD population have been undertaken. A previous meta-analysis found that patients with COPD were at 2.6 times greater risk for HF than the general population [51]. Estimates of the prevalence of HF in the COPD population vary from around 10% in community-based studies to around 30% in more selective studies [92]. Previous research has found that patients with COPD are at greater risk of hospitalisation due to HF than the general population [157-160]; however, not all studies have found an increased risk of morbidity and mortality due to HF or other cardiovascular diseases in COPD patients [161, 162]. There is a need for greater understanding of the burden of comorbid COPD-HF within the COPD population. The first aim of this thesis is to describe the effect of HF on morbidity and mortality of COPD patients and to describe the burden of HF in the COPD population in UK primary care.

COPD patients experience periods of acute worsening of symptoms, termed acute exacerbations of COPD (AECOPD), but the effect of HF comorbidity on AECOPD risk is unknown. Additionally, research suggests that the presence of COPD may hinder or delay subsequent diagnosis of HF [23, 163]. Studies have found anywhere from 10-46% previously unrecognised left-sided HF in various COPD patient populations ranging from suspected COPD to stable COPD to severe COPD [91]. The second aim of this thesis is to determine the effect of diagnosed and unrecognised, possible HF on AECOPD risk.

In 2015, a joint statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) called explicitly for more research into appropriate management of HF in patients with COPD [164]. There is significant underuse of cardiovascular medications, especially beta-blockers, in the management of COPD patients with cardiovascular indications [113, 165, 166]. A number of studies have investigated the role of cardiovascular medications on mortality in COPD patients [167, 168]; however, investigations on the effect of cardiovascular medications on AECOPD are less common. Additionally, a number of studies have been affected by biases, such as immortal and immeasurable time biases [169]. The third aim of this thesis is to investigate whether HF management impacts AECOPD risk.

Understanding the current situation with respect to the diagnosis and management of HF in COPD patients may affect exacerbation risk experienced by patients through highlighting areas in which care can be improved.

1.6.1 Specific Aims and Objectives

Following from the rationale, the following specific aims and objectives were derived to address knowledge gaps (**Figure 1.3**).

Specific Aim #1: To describe the burden of HF comorbidity in the COPD population

Objective 1.1: To review the literature on the effect of HF comorbidity on hospitalisation and mortality of COPD patients.

Objective 1.2: To determine the incidence of HF diagnosis in a UK primary care COPD population and whether this has changed over time.

Objective 1.3: To determine the effect of incident HF diagnosis on short- and long-term mortality in the UK primary care COPD population and whether this has changed over time.

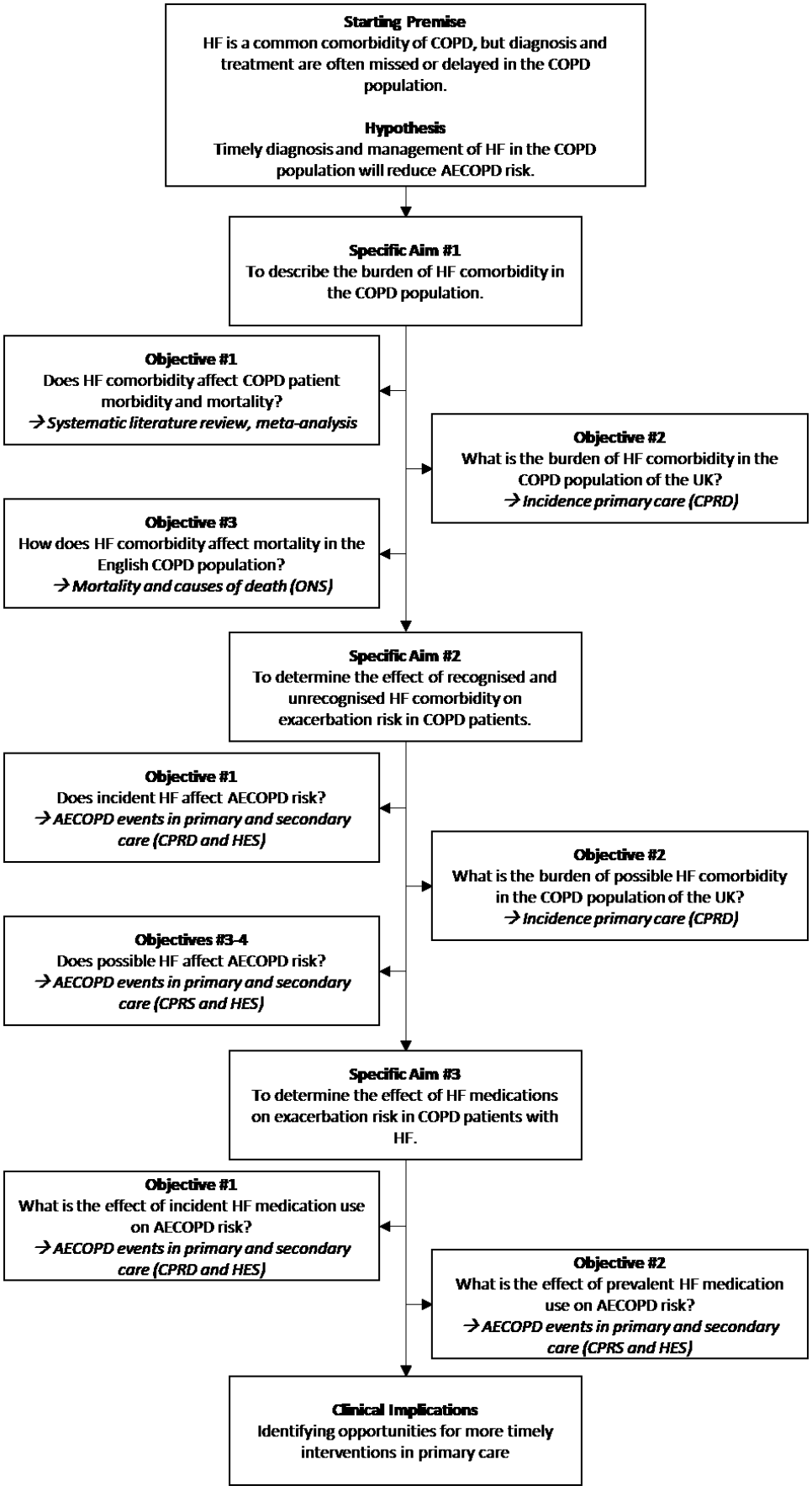

Figure 1.3. Overview of thesis aims, objectives, and clinical implications.

Specific Aim #2: To determine the effect of HF comorbidity on exacerbation risk in COPD patients.

Objective 2.1: To determine the effect of incident HF on AECOPD risk.

Objective 2.2: To identify COPD patients with evidence of possible HF in the absence of a HF diagnosis.

Objective 2.3: To compare the risk of AECOPD in COPD patients with possible HF to COPD patients without evidence of HF.

Objective 2.4: To compare the risk of AECOPD in COPD patients with possible HF to COPD patients with newly diagnosed HF.

Specific Aim #3: To determine the effect of HF medications on exacerbation risk in COPD patients with HF.

Objective 3.1: To determine the effect of incident HF medication use affects AECOPD risk in COPD patients with HF.

Objective 3.2: To determine if prevalent HF medication use affects exacerbation risk in COPD patients with HF.

1.6.2 Structure and organisation of this thesis

Chapter II presents the results of a systematic review and meta-analysis to assess the effect of HF comorbidity on the morbidity and mortality of COPD patients. The protocol and review have both been published and are appended to this thesis (see **Appendices VII and VIII**).

Analyses for this thesis used data from routinely collected electronic healthcare records, from both primary and secondary care in England and the UK. **Chapter III** describes in detail the data sources and basic variable definitions used in the analysis chapters that follow.

The following three chapters contain the analyses conducted for this thesis. Each chapter provides a brief introduction, followed by detailed methodology, results, and discussion of the findings in the context of the literature. Strengths and limitations for each study are considered. **Chapter IV** details the epidemiology of HF comorbidity in the primary care COPD population of England and the UK, including incidence and mortality over time. **Chapter V** explores the effect of HF comorbidity on AECOPD risk. **Chapter VI** explores the effects of cardiovascular medications on AECOPD risk in COPD patients with HF.

The results from Chapters II and IV have been published (see **Appendices VII and VIII**). The results from Chapters V and VI are currently undergoing peer review (see **Appendix VIII**).

The final chapter (**Chapter VII**) provides a broader discussion focusing on the collective findings from this thesis in the context of the literature, as well as potential implications for clinical practice and directions for future research.

1.7 Conclusions

Both COPD and HF are increasingly recognised as systemic diseases affecting physiology beyond the heart and lungs, contributing to disease interaction and the development of multimorbidity. HF and COPD share aetiology, symptoms, and the potential to exacerbate the other condition leading to higher health care utilization costs and mortality in patients with both conditions [170, 171]. Recent international guidelines have recommended increased consideration of comorbid conditions when assessing COPD and HF, demonstrating recognition of the influences of comorbidities on disease progression and prognosis in both populations [13, 171].

The aims of this thesis are to describe the burden of COPD-HF comorbidity in the UK and to describe the association between HF and HF management on AECOPD risk in order to identify areas where clinical primary care can be improved.

Chapter II: Hospitalisation and mortality in people with comorbid COPD and HF - a systematic review and meta-analysis

2.1 Introduction

The first aim of this thesis is to describe the burden of HF comorbidity in the COPD population. The first objective is to review the literature on the effect of HF comorbidity on morbidity and mortality of COPD patients.

As discussed in the previous chapter, COPD and HF share aetiology and symptoms complicating the identification and management of either condition in the presence of the other [170-172]. Mechanisms such as systemic inflammation contribute to the interaction of COPD and HF and may exacerbate both conditions. Additionally, patients with COPD and HF also have higher rate of other chronic comorbidities and increasing frailty [160, 173]. HF is often unrecognised or diagnosed later in the COPD population [91, 127, 174-176]. Furthermore, cardiovascular disease is systemically mismanaged in the COPD population [166]. Understanding the effect of HF comorbidity on the morbidity and mortality of COPD patients is important for informing the development of bespoke guidelines for the diagnosis and management of HF in the presence of COPD.

A previous systematic review investigated the effect of a number of cardiovascular diseases, including HF, on outcomes of COPD patients compared with patients without COPD [53]. There was a greater risk for cardiovascular-related hospitalisations for COPD patients compared with patients without COPD. When broken down to component cardiovascular diseases, results were mixed. COPD status does not significantly impact patient risk for ischaemic heart disease-related hospitalisation, while the effects of COPD status on the risk of arrhythmia-related and stroke-related hospitalisation were mixed. Having COPD significantly increased a patient's risk of HF-related hospitalisations compared with someone without COPD [53].

The primary aim of this systematic review was to determine if COPD patients with comorbid HF experience greater morbidity and mortality than COPD patients without HF. This refines

the previous review in focusing on HF alone, as opposed to a composite cardiovascular disease exposure. This systematic review had two objectives:

- To assess hospitalisation and rehospitalisation of COPD patients with and without comorbid HF.
- To assess mortality of COPD patients with and without comorbid HF.

An outline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines with details of where to find the information is located in **Appendix I**. Additional supplementary information for this chapter is located in **Appendix II**.

The protocol for this review was peer-reviewed and published prior to the review's completion [177] (see **Appendix VIII**). A peer-reviewed publication [178] was produced in association with this chapter (see **Appendix VIII**). Figures and tables in this chapter may have been reproduced from the aforementioned publications with permission of the copyright holder (see **Appendix VII**).

2.2 Methods

This protocol follows the PRISMA protocols guidelines [179] and outlines strategies for study screening, data extraction, and analyses. This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) ([180]; registration number: CRD42018089534).

2.2.1 Eligibility criteria

Study design/characteristics

Eligible studies included randomised controlled trials, although none were found, and observational studies (cohorts and case-control). Studies published post-1980, reported in English, and not conducted on animals were eligible.

Participants

Ideally, included studies would have drawn participants from the general population aged 35+ years old. Studies drawing participants from the general population aged 18+ years old were be included when the number of studies found was small.

Exposure

The primary exposure of interest was HF comorbidity in COPD patients. Ideally, both HF and COPD were confirmed clinically. Clinical diagnosis of COPD includes spirometry confirmation with a post-bronchodilator FEV_1/FVC ratio <0.70 per NICE guidelines [13]. Clinical diagnosis of HF should include measurement of NT-proBNP levels and echocardiogram screening per NICE guidelines [69]. Studies relying on self-reported COPD or HF were included when the number of studies found was small.

Comparators/controls

Studies that compare the outcomes of interest between the exposed group (COPD patients with HF) and a group of unexposed individuals (COPD patients without HF) were eligible for inclusion.

Outcome

The primary outcomes of interest were all-cause mortality at any time and/or emergency (unplanned) all-cause hospitalisation or rehospitalisation. Secondary outcomes of interest were respiratory-related deaths and/or respiratory-related hospitalisation or rehospitalisation.

2.2.2 Information sources

MEDLINE is the online repository for journal citations and abstracts pertaining to biomedical literature made available by the US National Library of Medicine [181]. Embase is an online biomedical database made available by Elsevier [182]. Both MEDLINE and Embase were searched via the Ovid interface via the Imperial College Library [183] for potentially relevant articles using the search strategy outlined below. PROSPERO was searched for ongoing and completed systematic reviews [180] and The Cochrane Central Registrar of Controlled Trials (CENTRAL), from The Cochrane Library, was regularly searched for relevant clinical trials [184]. A manual search of the references of included studies was conducted to check for other relevant articles.

Search strategy

The medical literature was searched using Medical Subject Headings (MeSH) terms and free text using appropriate terms to delimit each of ‘COPD’, ‘HF’, ‘mortality’, ‘hospitalisation’, and ‘rehospitalisation’ (**Table 2.1**).

Concept	Type of Term	MEDLINE Terms	Embase Terms
COPD	MeSH	Pulmonary Disease, Chronic Obstructive/ Emphysema/ Pulmonary Emphysema/ Bronchitis, Chronic/ Lung Diseases, Obstructive/	Chronic obstructive lung disease/ Emphysema/ Lung emphysema/ Chronic bronchitis/ Obstructive airway disease/
	Free Text	Chronic obstructive pulmonary disease; COPD; emphysema; chronic bronchitis; obstructive airway/respiratory/lung/pulmonary disease; chronic airway/respiratory disease; COAD; AECB	
HF	MeSH	Heart Failure/ Ventricular Dysfunction, Left/	Heart failure/ Heart left ventricle failure/
	Free Text	Heart failure; left ventricular failure; cardiac failure; myocardial failure	
Mortality	MeSH	Mortality/	Mortality/
	Free Text	Mortality; death	
Hospitalisation	MeSH	Hospitalization/ Patient Admission/	Hospitalization/ Hospital admission/
	Free Text	Hospitalization; hospital admission; patient admission	
Rehospitalisation	MeSH	Patient Readmission/	Hospital readmission/
	Free Text	Hospital readmission; patient readmission	

Table 2.1. Search terms used for literature searching in MEDLINE and Embase.

In order to ensure maximum capture of appropriate studies, a series of search symbols were used. The search term 'exp/' was used in conjunction with MeSH terms to conduct searching of all terms included within the MeSH term. The search symbol '*' was used to denote possible pluralisation. For example, searching for 'death*' will search for both 'death' and 'deaths'. The search symbol '?' was used to denote 'unknown' letter. For example, searching for 'hospitali?ation' will search for both 'hospitalization' and 'hospitalisation'.

The concepts 'COPD' and 'HF' were combined with the Boolean logic operator 'AND'. The concepts 'mortality', 'hospitalisation', and 'rehospitalisation' were combined with the Boolean logic operator 'OR'. These two statements were then combined using the Boolean logic operator 'AND'. For example, ((chronic obstructive pulmonary disease AND heart failure) AND (mortality OR hospitalisation)).

The exact searches used in MEDLINE and Embase are appended (**Supplementary Figures 1-2**). Searches were conducted on 05 February 2019.

Study records

PRISMA guidelines recommend that at least a proportion of the study selection, data extraction, and risk of bias assessment process be conducted by two reviewers, independently, in order to ensure quality. Therefore, Kishan Ragutheeswaran repeated half of the study

selection, data extraction, and risk of bias assessment process independently from the candidate. Dr Quint adjudicated any discrepancies between findings of the two reviewers.

Data management

Literature search results were uploaded and stored in EndNote (Version X8). Duplicates were removed.

Selection process

Titles and abstracts of found literature were screened against the predefined eligibility criteria. Next, full texts were obtained and screened against the eligibility criteria. Reasons for rejection of a study at the full text stage were recorded.

2.2.3 Data extraction

Information from included studies was extracted into a predefined extraction template (**Supplementary Table 2.1**).

Data items

The data extraction template was designed using the Population, Exposure, Comparator, Outcomes, Study characteristics (PECOS) framework, including:

- Population: age and sex distribution, size of population, inclusion and exclusion criteria
- Exposure: definition and identification of exposure
- Comparators: definition and identification of unexposed individuals
- Outcomes: definition of deaths, hospitalisation, rehospitalisation
- Study characteristics: setting, design, follow-up, aims

Where appropriate, the maximally adjusted estimates were recorded along with the covariates used in adjustment.

Outcomes and prioritisation

Studies must have reported risk ratios, rate ratios, or hazard ratios for all-cause mortality, hospitalisation, or rehospitalisation. Outcomes for respiratory-related mortality, hospitalisation, or rehospitalisation were recorded if detail permitted.

2.2.4 Risk of bias assessment in individual studies

Risk of bias was assessed using methodology derived from the Newcastle-Ottawa scale [185, 186]. The tool assesses bias in eight domains: 1) adequacy of follow-up, 2) follow-up long enough for outcomes to occur, 3) assessment of outcome, 4) comparability of groups based on design or analysis, 5) outcome of interest not present at start of study, 6) ascertainment of exposure, 7) selection of non-exposed, and 8) representativeness of exposed. Each domain was assessed for each included study and rated as 'low risk of bias', 'unclear risk of bias', or 'moderate to high risk of bias'.

2.2.5 Data synthesis

The I^2 statistic was used to assess the level of heterogeneity and appropriateness for meta-analysis. Pooled effect estimates were calculated for hospitalisation, rehospitalisation, and mortality, if appropriate. Funnel plots and Egger's test for asymmetry were used to assess publication bias in meta-analysis. For outcomes with considerable heterogeneity (>70%), a narrative synthesis was conducted.

2.3 Results

After searching and screening, 28 observational studies were included in this systematic review (**Figure 2.1**). The majority of rejected studies were due to the reporting of an inappropriate outcome measure, i.e. no reported rate ratio, risk ratio, OR, or HR (**Figure 2.1; Supplementary Table 2.2**). The majority of studies were published between 2011 and 2018 using European and North American databases and following-up patients for over two years (**Table 2.2; Supplementary Table 2.3**). Overall, there was a low risk of bias in the included studies; however, there was a lot of under-reporting with regards to comparability of exposed and unexposed groups and with regards to the selection of non-exposed groups (**Figure 2.2**).

2.3.1 Description of the study populations

Summary statistics for the included studies are reported in **Table 2.3**.

All studies were of patients aged ≥18 years of age. Two studies required patients to be at least 35 years old [187, 188]. Seven studies required patients to be at least 40 years old [189-195]. Bertens et al. studied a cohort of 45 year olds [196]. Yeatts et al. required patients to be at least 45 years old [197]. Two studies required patients to be at least 65 years old [198, 199]. An

additional three studies required patients to be at least 40 years old and included upper age limits of either 64 years old [200], 75 years old [201], or 89 years old [202].

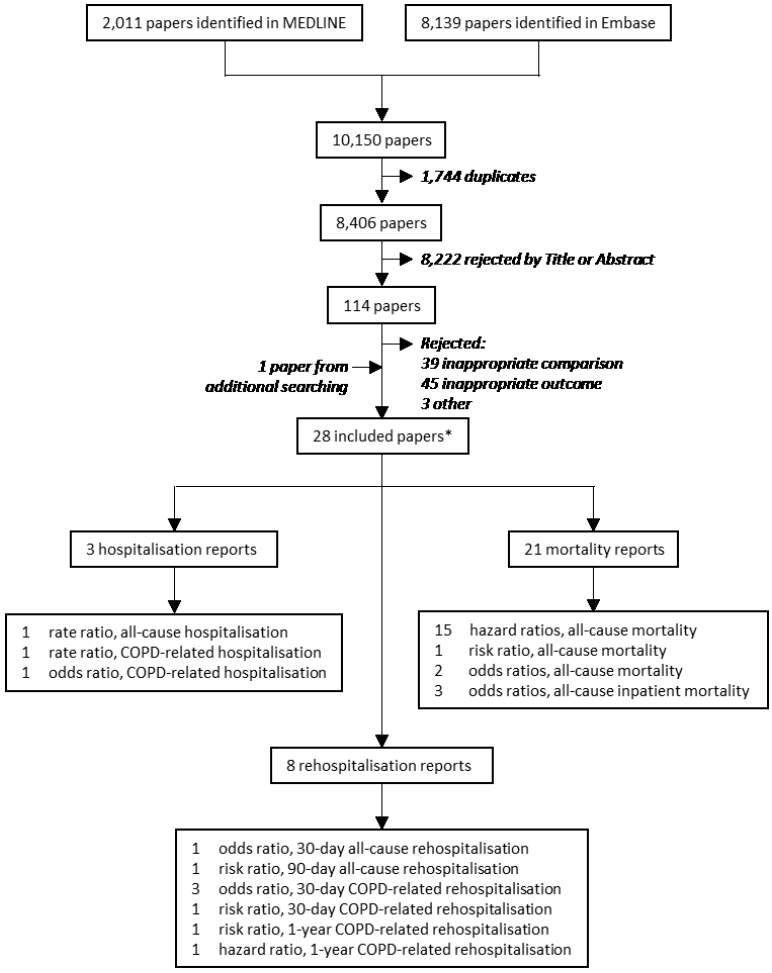

Figure 2.1. PRISMA flowchart for the study selection process.

The average age at start of follow-up was reported by 22 studies [187-190, 192, 194, 196, 198, 200-212], with age stratified by readmission status reported Chen et al. [191]. Median age at start of follow-up was reported by one study [199]. Age groups were reported by Yeatts et al. [197] and Simmering et al. [195], who stratified by readmission status. Lau et al. reported the proportion of patients aged >65 years old in both their derivation and validation cohorts [193]. Two studies did not report the age distributions of their cohorts [213, 214].

Sex distribution was reported by all but one, Bertens et al. [196], study. Lau et al. reported the ratios of males-to-females in their derivation and validation cohorts [193].

Only three studies required patients to have a history of smoking [189, 201, 206], with Abukhalaf et al. requiring at least 20 pack-years of smoking history and Divo et al. requiring at least 10 pack-years of smoking history in order to be included in their studies [189, 206]. The proportion of current smokers was reported by four studies [189, 190, 201, 203], of former smokers was reported by three studies [189, 190, 203], and of never smokers by one study [188]. Four studies reported the average smoking history of their cohorts [189, 190, 201, 203] and one study reported the median smoking history for patients with and without HF [198].

Study Characteristics N = 28	
Year of Publication	
1980-1990	0
1991-2000	0
2001-2010	6
2011-2018	22
Geographic Region	
Africa	0
Asia	2
Australia/New Zealand	0
Europe	12
Multi-continent	2
North America	12
South America	0
Not Reported	0
Setting	
Single Centre	6
Multicentre (one country)	1
Multicentre (multi-country)	2
Database	19
Duration of Follow-Up	
< 1 year	5
≥ 1 and < 2 years	5
≥ 2 and < 3 years	3
≥ 3 years	9
Not Reported	6

Table 2.2. Overview of included study characteristics.

Baseline FEV_1 % predicted was reported by 11 studies [189, 190, 198, 201, 203, 204, 206, 207, 210-212], with Boudestein et al. reporting stratified by HF status [198]. Baseline FEV_1 (L) was reported by four studies [190, 207, 210, 212]. The proportion of patients with airflow limitation classified as GOLD3-4 (severe-to-very-severe) was reported by 8 studies [188-190, 198, 204, 206, 209, 210, 212]. Additionally, 40% of the cohort studied by Boudestein et al. had GP-diagnosed COPD, but did not meet GOLD criteria for COPD diagnosis [198].

2.3.2 Identification of COPD

In the UK, diagnosis of COPD should be considered in adults aged 35 years or older with a history of smoking and airflow limitation defined as a FEV_1/FVC ratio of <0.70 [13]. The studies included in this review defined COPD in a variety of different ways. In relation to the UK guidelines, 16 studies required patients to be at least 35 years old at start of follow-up, but not necessarily at time of COPD diagnosis [187-202]. Only three studies explicitly required any history of smoking [189, 201, 206] and only eight studies explicitly reported that a COPD diagnosis required a FEV_1/FVC ratio of <0.70 [188-190, 198, 201, 203, 206, 212].

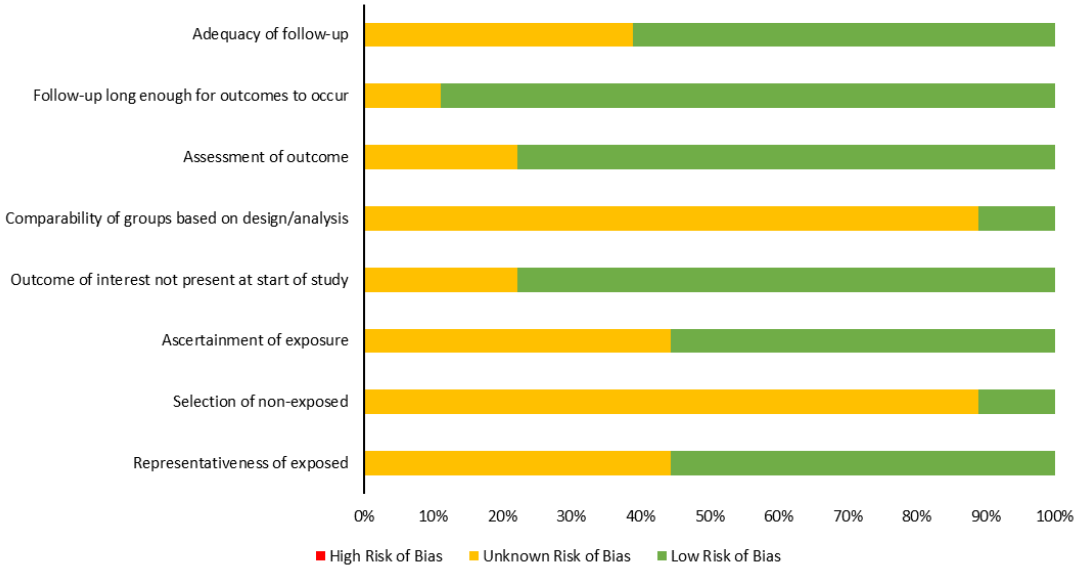

Figure 2.2. Risk of bias in individual studies.

The majority of studies relied exclusively on electronic diagnostic coding for the identification of COPD or COPD-related hospital visits [187, 191-197, 199, 200, 202, 204, 205, 208, 213, 214]. Five studies used clinical diagnosis to identify COPD [189, 198, 201, 207, 212] and two studies used diagnostic coding and clinical diagnosis [209, 211].

In studies identifying patients via COPD-related emergency visit or admission, five required COPD exacerbation coded as the primary diagnosis for the visit or admission [200, 208, 211, 212, 214]. Genao et al. required COPD as primary diagnosis, Yeatts et al. required COPD as primary or secondary diagnosis, and Chen et al. required COPD in the top five diagnostic positions [191, 197, 199]. Perera et al. required COPD coded alongside pneumonia or

mechanical ventilation [194]. Hasegawa et al. allowed COPD to be recorded in any diagnostic position [192].

Two studies identified COPD patients differently. Hoiseth et al. identified patients admitted through emergency with a primary complaint of dyspnoea and used an endpoint committee to reach a consensus on diagnosis [207]. Carter et al. identified COPD patients from the admitted patient population, regardless of cause of admission [205].

2.3.3 Identification of HF

The majority of studies relied on electronic diagnostic coding [187-189, 191-197, 199, 200, 202, 204, 205, 208, 209, 211-214] and/or clinical diagnosis [188, 198, 206, 207, 209-211] for the identification of HF. Ejection fraction measures were explicitly used to identify HF patients in two studies [198, 203] and an additional two studies used medications as an indicator of HF diagnosis [206, 210]. Two studies used questionnaires to identify HF [190, 201], while Divo et al. used a combination of questionnaires, clinical diagnosis, and medication [206].

2.3.4 Hospitalisation

Hospitalisation was defined as emergency visit and/or admission to inpatient care. All-cause, COPD-related, and COPD- and cardiovascular-related hospitalisations were assessed (**Figure 2.3**). All studies compared rate or risk of hospitalisation for COPD patients with HF with those without HF.

There were not enough studies reporting on comparable measures of hospitalisation to conduct a meta-analysis (**Figure 2.3**). Schwab et al. reported adjusted rate ratios for all-cause and COPD-related hospitalisation [202]. Santibáñez et al. reported crude and adjusted ORs for COPD-related hospitalisation [188]. Boudestein et al. reported crude and adjusted HRs for COPD- or cardiovascular-related hospitalisation in their entire cohort and in a subcohort of COPD patients who met the GOLD criteria for COPD diagnosis [198].

2.3.5 Rehospitalisation

Rehospitalisation was defined as emergency visit and/or admission to inpatient care following an index emergency visit or admission. All-cause and COPD-related rehospitalisation following and index hospitalisation for COPD were assessed (**Figure 2.4**). All studies

compared rate or risk of rehospitalisation of COPD patients with HF with those without HF, following an index hospitalisation for COPD.

Characteristic	Studies Reporting	Values	
Age (mean, SD)	[187-190, 192, 194, 196, 198, 200-212]	**Minimum** 56.6 ± 5.73 [200]	**Maximum** 73.0 ± 5.3 [198]
	[191]	**Without readmission** 71.6 ± 11.4	**With readmission** 73.5 ± 9.8
Age (median, IQR)	[199]	77 (71, 83)	
Age (groups)		65-69 (most populous)	
	[195]	**Without readmission** 70-79 (most populous)	**With readmission** 70-79 (most populous)
Age (proportion ≥65 years)	[193]	**Derivation cohort** 70.2%	**Validation cohort** 67.6%
Sex (% male)	[187-192, 194, 195, 197-214]	**Minimum** 41%	**Maximum** 89%
Sex (male : female)	[193]	1.25 : 1	1.24 : 1
Proportion of:			
Current Smokers	[189, 190, 201, 203]	**Minimum** 36% [201]	**Maximum** 45.8% [203]
Former Smokers	[189, 190, 203]	**Minimum** 41.4% [203]	**Maximum** 94.2% [190]
Never Smokers	[188]	15.7%	
History of smoking (pack-years)			
Mean, SD	[189, 190, 201, 203]	**Minimum** 43.1 ± 23.7 [189]	**Maximum** 55.5 ± 28 [190]
Median, IQR	[198]	**COPD with HF** 25.0 (1.6, 41.8)	**COPD without HF** 15.0 (0.0, 38.1)
Severity of airflow limitation			
FEV_1 % pred (mean, SD)	[189, 190, 198, 201, 203, 204, 206, 207, 210-212]	**Minimum** 39 ± 17% [207]	**Maximum** 67 ± 28% [198]
	[198]	**COPD with HF** 81.7 ± 24.2%	**COPD without HF** 83.7 ± 25.9%
FEV_1 (mean, SD)	[190, 207, 210, 212]	**Minimum** 0.96 ± 0.43 L [207]	**Maximum** 1.19 ± 0.54 L [190]
GOLD3-4 (%)	[188-190, 198, 204, 206, 209, 210, 212]	**Minimum** 11.2% [198]	**Maximum** 72.3% [210]

Table 2.3. Description of the study populations.

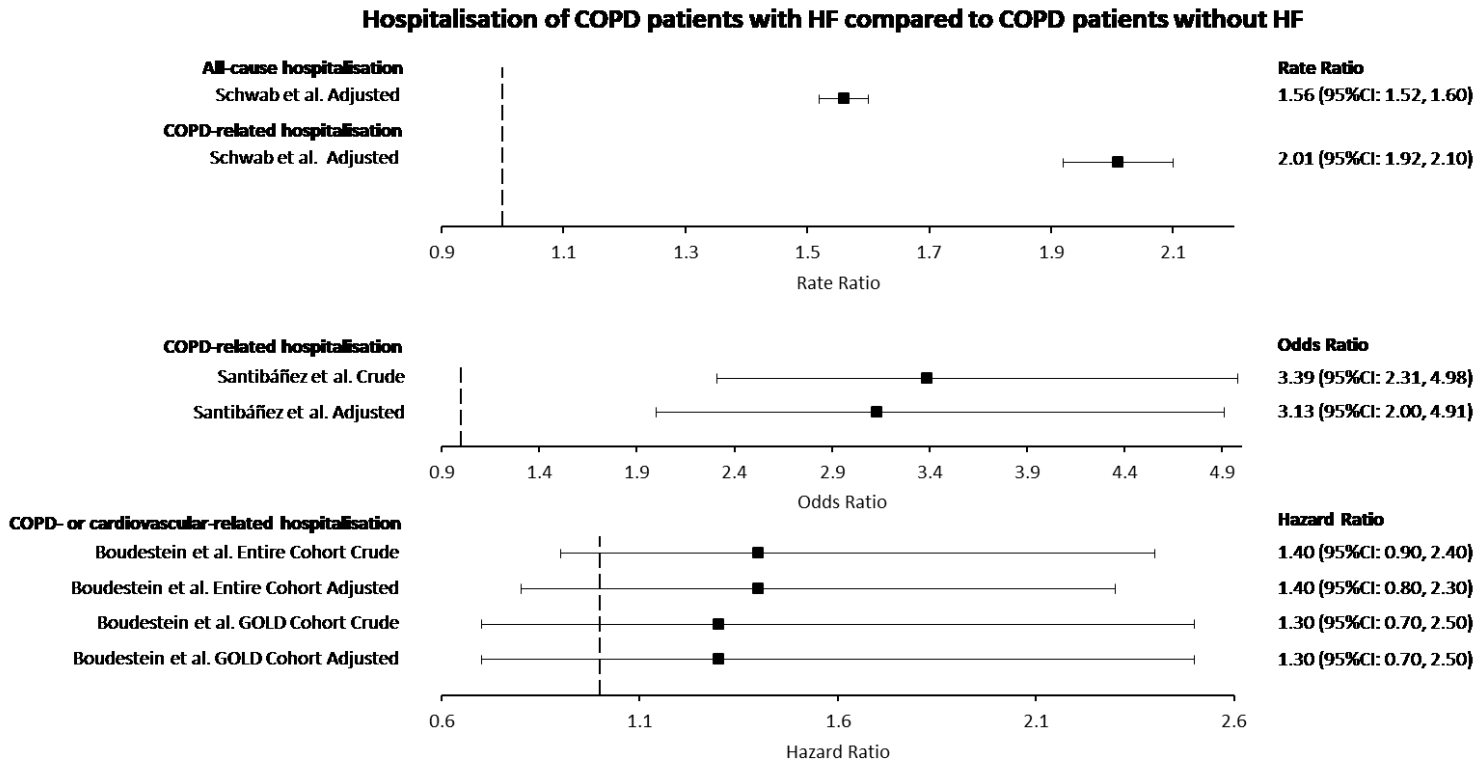

Figure 2.3. Summary of effect estimates for the effect of HF comorbidity on hospitalisation of COPD patients.

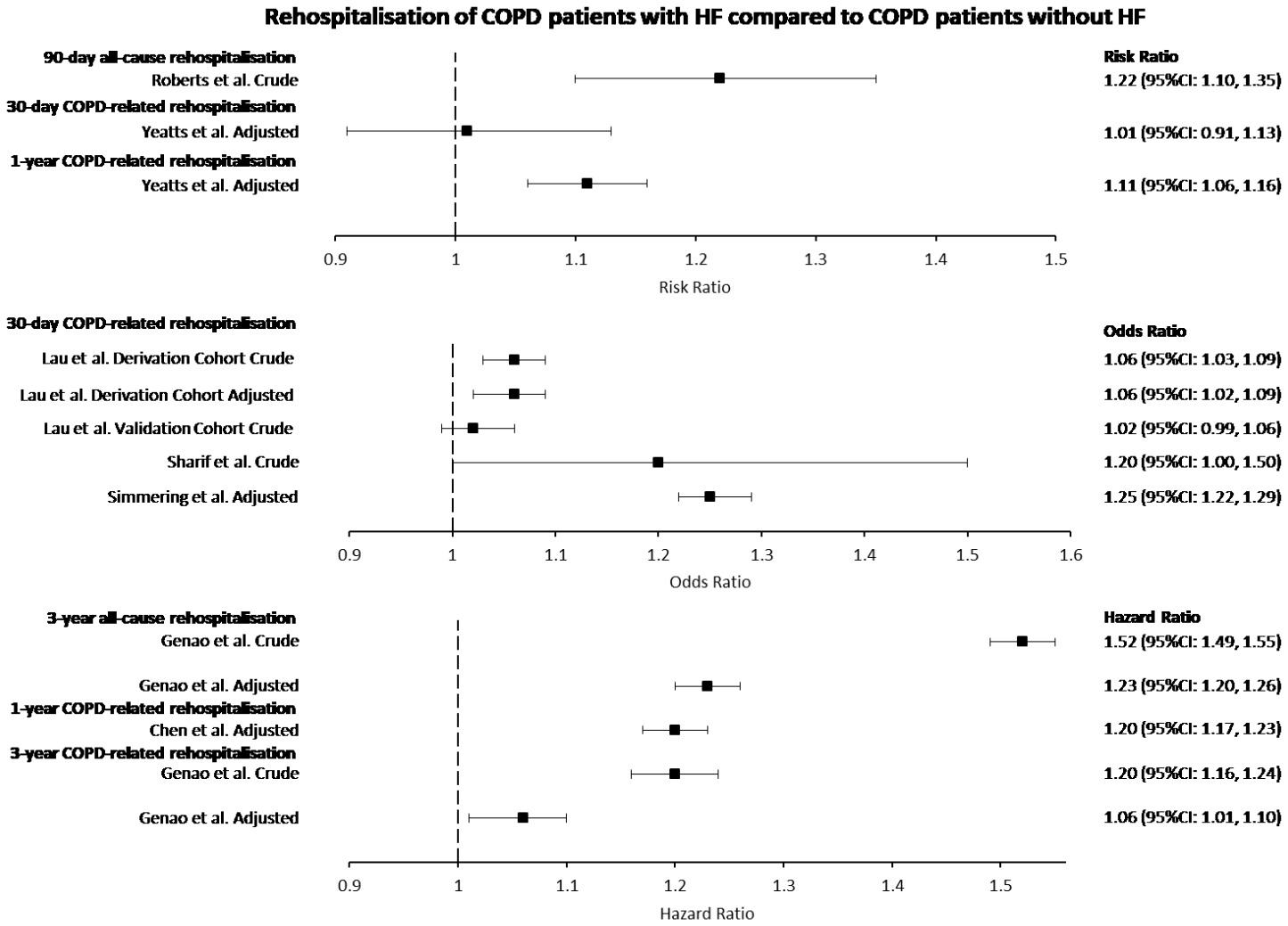

Figure 2.4. Summary of effect estimates for the effect of HF comorbidity on rehospitalisation of COPD patients.

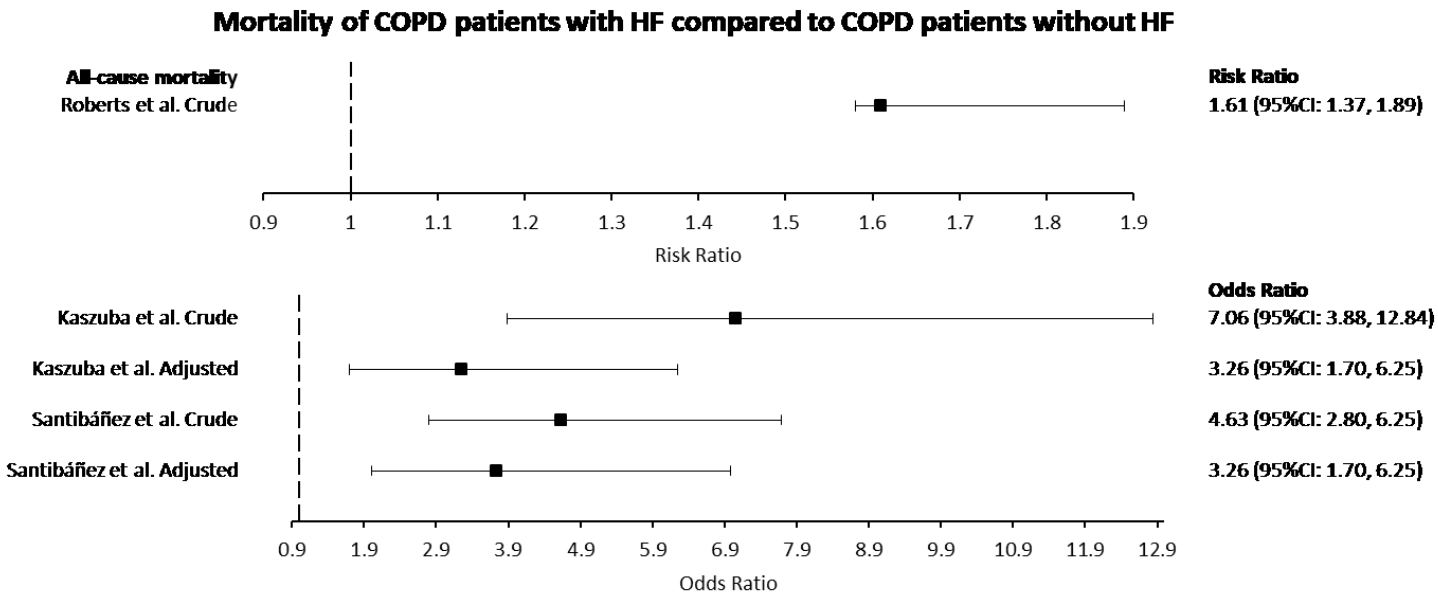

Figure 2.5. Summary of effect estimates for risk and odds for the effect of HF comorbidity on all-cause mortality of COPD patients.

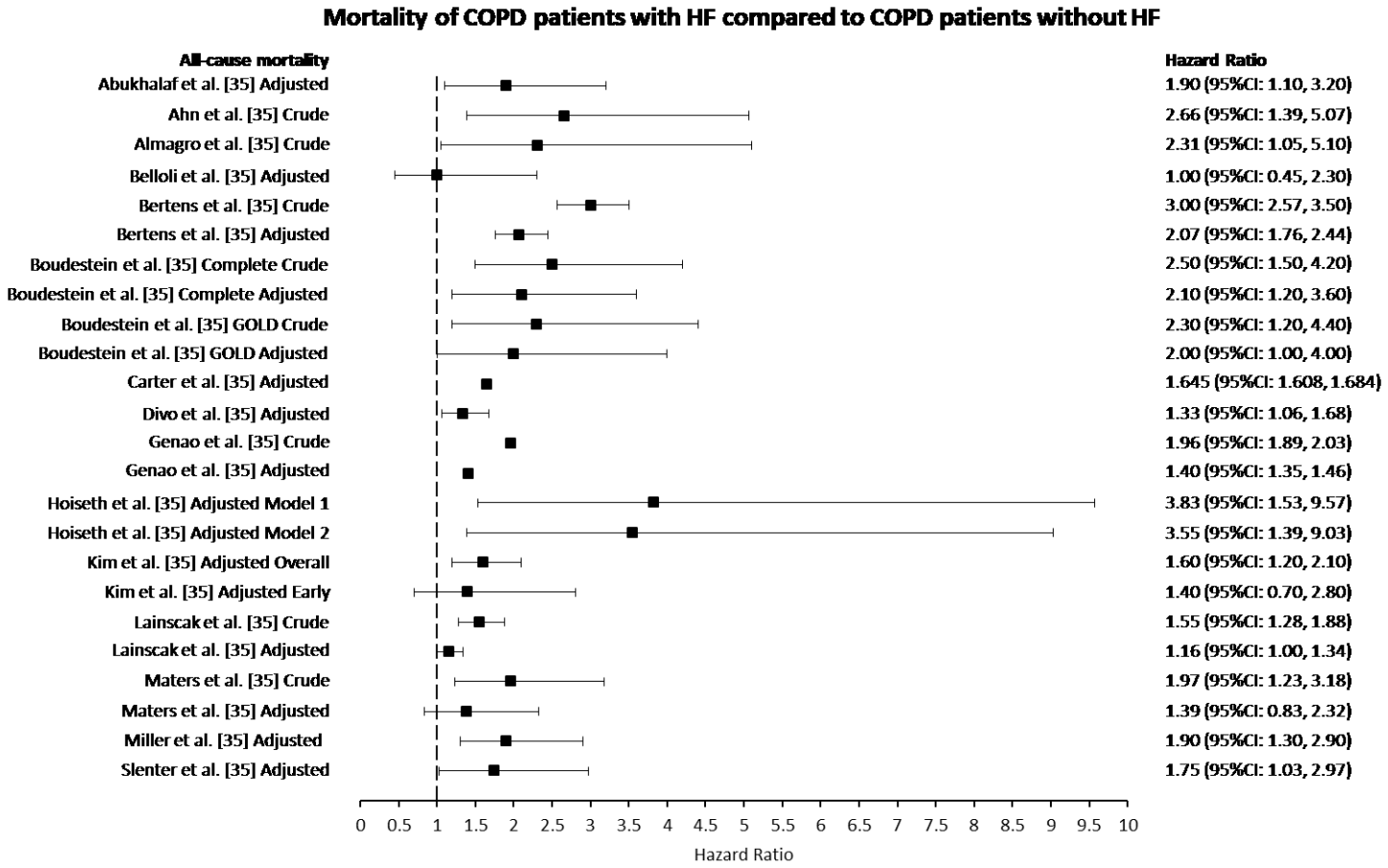

Figure 2.6. Summary of effect estimates for hazard ratios for the effect of HF comorbidity on all-cause mortality of COPD patients.

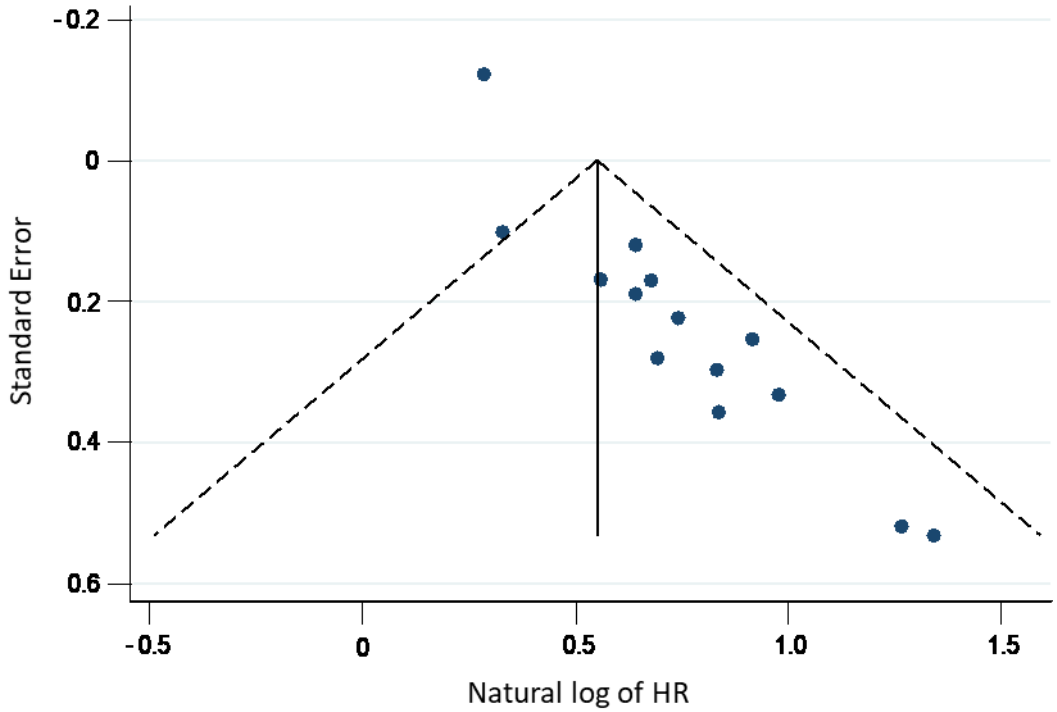

Figure 2.7. Funnel plot assessing publication bias in the meta-analysis of studies reporting HR for the effect of HF comorbidity on all-cause mortality of COPD, diagnosed with spirometry, with pseudo-95% confidence limits (dashed lines). Begg's test for asymmetry (p = 0.002).

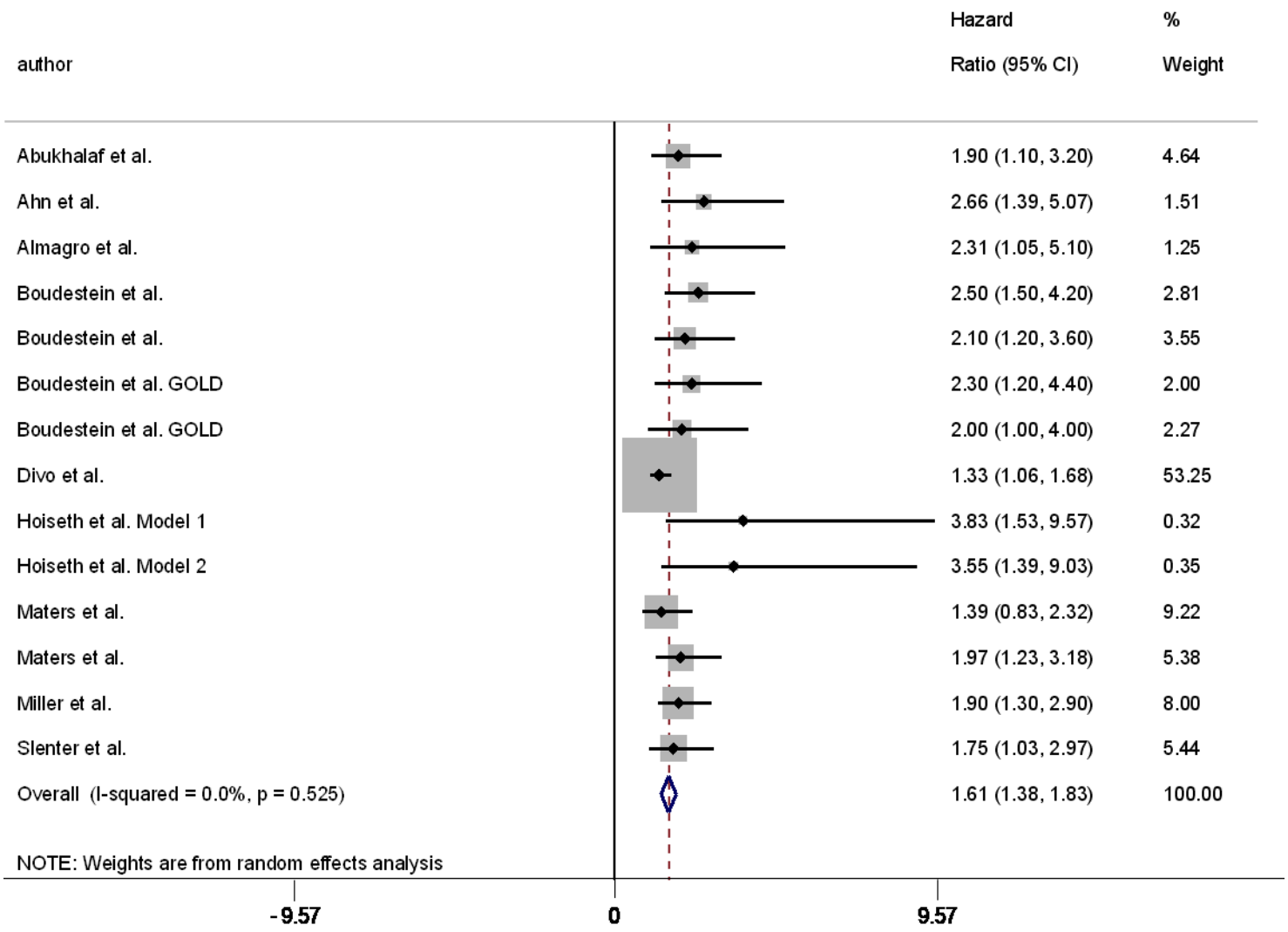

Figure 2.8. Pooled estimate for the effect of HF comorbidity on all-cause mortality of COPD patients diagnosed with spirometry.

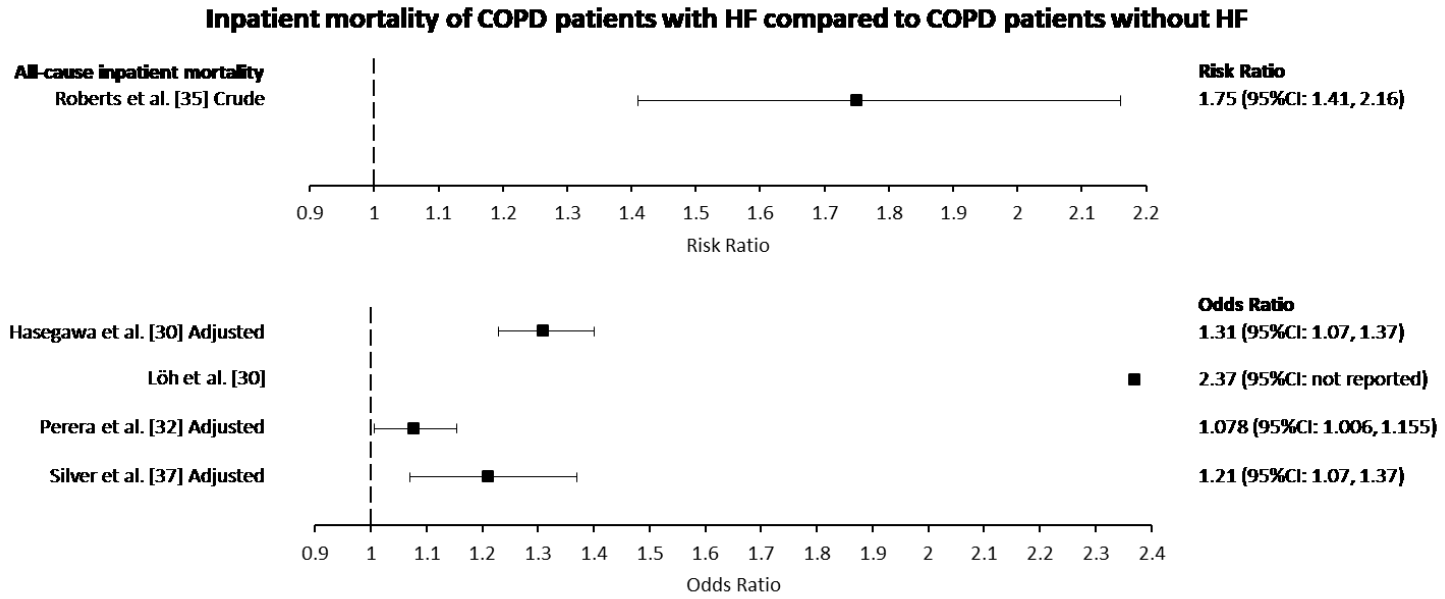

Figure 2.9. Summary of effect estimates for the effect of HF comorbidity on all-cause inpatient mortality of COPD patients.

There were not enough studies reporting on comparable measures of rehospitalisation to conduct a meta-analysis (**Figure 2.4**). Roberts et al. reported a crude risk ratio for 90-day all-cause rehospitalisation [211]. Yeatts et al. reported adjusted risk ratios for 30-day and 1-year COPD-related rehospitalisation [197]. Lau et al. reported crude and adjusted ORs for 30-day COPD-related rehospitalisation in their derivation cohort and the crude OR for their validation cohort [193]. Sharif et al. reported a crude OR for 30-day COPD-related rehospitalisation [200]. Simmering et al. reported an adjusted OR for 30-day COPD-related rehospitalisation [195]. Genao et al. reported crude and adjusted HRs for 3-year all-cause and COPD-related rehospitalisation [199]. Chen et al. reported an adjusted HR for 1-year COPD-related rehospitalisation [191].

2.3.6 All-cause mortality

Rate or risk of all-cause mortality comparing COPD patients with HF with those without HF was assessed. There were not enough measures for risk ratios and ORs to conduct meta-analyses (**Figure 2.5**). Roberts et al. reported a crude risk ratio for all-cause mortality [211]. Kaszuba et al. and Santibáñez et al. reported crude and adjusted ORs for all-cause mortality [188].

There were enough estimates of crude and adjusted HRs for all-cause mortality to attempt meta-analysis (**Figure 2.6**) [189, 190, 196, 198, 199, 201, 203-210, 212]; however, meta-analysis proved inappropriate due to high heterogeneity. When considering all HR estimates, heterogeneity (I^2) was 90.3%. When considering crude HR only, heterogeneity was 74.9%. When considering adjusted HR only, heterogeneity was 83.3%. Meta-analysis was also attempted stratifying by average length of follow-up (long-term >1 year and short-term ≤1 year). Heterogeneity remained high for long-term studies (n = 21) at 91.5%. There were only three studies with short-term follow-up [190, 208, 212] and meta-analysis was not conducted. Stratification by location of patient identification, primary care (I^2 = 90.1%) or secondary care (I^2 = 90.9%) did not reduce heterogeneity. When limiting the analysis to those studies that explicitly required spirometry for the diagnosis of COPD [189, 190, 198, 201, 203, 206, 207, 210, 212], heterogeneity disappeared (I^2 = 0.0%); however, there was evidence of publication bias (Begg's test: p = 0.002; **Figure 2.7**). The pooled HR estimate for the effect of HF on all-cause mortality was 1.61 (95%CI: 1.38, 1.83) (**Figure 2.8**).

Inpatient mortality

Five studies explicitly reported estimates for the rate or risk of all-cause inpatient mortality comparing COPD patients with HF with those without HF. There were not enough estimates to conduct a meta-analysis (**Figure 2.9**). Roberts et al. reported a crude risk ratio for inpatient mortality [211]. Hasegawa et al., Perera et al., and Silver et al. reported adjusted ORs for all-cause inpatient mortality [192, 194, 214]. Löh et al. reported an OR for all-cause inpatient mortality but did not state whether it was crude or adjusted [213].

2.4 Discussion

This systematic review investigated the effect of HF comorbidity on morbidity and mortality of COPD patients. Hospitalisation and mortality were more common in COPD patients with HF than in COPD patients without HF. In COPD patients diagnosed with spirometry, those with HF experienced 1.61 (95%CI: 1.38, 1.83) times greater risk of all-cause mortality than those without HF.

2.4.1 Hospitalisation and rehospitalisation

COPD patients with HF experienced greater rates and risk of all-cause and COPD-related hospitalisation than COPD patients without HF. Hospitalisation was defined as emergency visits and/or admission into inpatient care. Schwab et al. reported higher rates of all-cause and COPD-related hospitalisation in COPD patients with HF than in those without HF [202]. Both the crude and adjusted estimates for COPD-related hospitalisation reported by Santibáñez et al. found statistically significantly higher odds of COPD-related hospitalisation for COPD patients with HF compared to those without HF, despite large amounts of variance [188]. Boudestein et al. found increased risk of COPD- or cardiovascular-related hospitalisations for COPD patients with HF compared to those without HF; however, there was large variance in the hazard ratio estimates [198]. Heterogeneity in the COPD populations studied created large amounts of variance in the estimates; however, it is likely that COPD patients with HF do experience a greater burden of hospitalisations than COPD patients without HF.

COPD patients with HF experienced greater rates and risk of all-cause and COPD-related rehospitalisation than COPD patients without HF. Rehospitalisation was defined as re-attendance at emergency and/or re-admission into inpatient care following an initial hospitalisation for COPD. There were four different time periods assessed for rehospitalisation:

30 day, 90 day, 1 year, and 3 year. All-cause rehospitalisation was assessed by two studies at 90 days and 3 years. Roberts et al. found significantly increased all-cause crude risk of 90 day rehospitalisation in COPD patients with HF compared with those without HF [211]. Genao et al. found significantly increased risk of 3-year all-cause rehospitalisation of COPD patients with HF compared with those without HF; the risk attenuated when adjusted, but remained significant [199]. COPD-related rehospitalisation was assessed by six studies at 30 days, 1 year, and 3 years. Yeatts et al. found no increased risk for COPD-related rehospitalisation at 30 days, but there was a significant increase in risk for COPD-related rehospitalisation at 1 year [197]. Lau et al. found significantly increased crude and adjusted odds of COPD-related rehospitalisation at 30 days between COPD patients with HF compared with those without HF in their derivation cohort, but found no difference in risk for COPD-related rehospitalisation at 1 year in their validation cohort [193]. Sharif et al. found no difference in odds of COPD-related rehospitalisation at 30 days for COPD patients with HF compared with those without HF [200]. Simmering et al. found significantly increased 30 day COPD-related rehospitalisation for COPD patients with HF compared with those without HF [195]. Chen et al. found significantly increased risk for 1 year COPD-related rehospitalisation in COPD patients with HF compared with those without HF [191]. Finally, Genao et al. found significantly increased risk of 3 year COPD-related rehospitalisation in COPD patients with HF compared with those without that attenuated, but remained significant, following adjustments [199].

The evidence with the most support was for significantly increased COPD-related hospitalisation and rehospitalisation in COPD patients with HF compared with those without HF. The evidence suggests that HF increases severe exacerbations of COPD, those that require hospitalisation. Previous work has demonstrated this relationship. Criner et al. found that COPD patients with HF experience, on average, 1.5 times more exacerbations per person-year of follow-up than COPD patients without HF [215]. Additionally, Cerezo Lajas et al. reported that the odds of frequent rehospitalisation, defined as ≥2 rehospitalisation events within 30 days of the index hospitalisation, were over 5 times higher for COPD patients with destabilised HF compared with those without [216]. Of note, many previous studies have reported the effect of a compound variable representing ‘cardiovascular comorbidities’ on exacerbation incidence and severity; however, these studies have found conflicting evidence, but this may be explained by the heterogeneity of conditions included within such as compound variable [114, 161, 217].

Based on the evidence compiled by this review [188, 191, 193, 195, 197, 199, 200, 202], and evidence from elsewhere [215, 216], there is evidence that HF comorbidity increases COPD-related secondary care utilisation; however, the magnitude of this effect is difficult to assess. There was a large variety of measures (rate ratio, risk ratio, OR, HR) and follow-up periods (30 day, 90 day, 1 year, 3 year) reported by studies, and none of these reached enough instances for meta-analysis. Future studies should look at distinguishing the short-term and long-term effects of HF comorbidity on COPD-related secondary care utilization and to investigate whether the effects are different for different COPD phenotypes, HF types, or HF severity.

2.4.2 Mortality

COPD patients with HF experience greater all-cause mortality than COPD patients without HF. Robert et al. found COPD patients with HF to have significantly higher risk of all-cause mortality than COPD patients without HF [211]. Kaszuba et al. and Santibáñez et al. both found significantly higher odds of all-cause mortality, which attenuated but remained significant following adjustments, in COPD patients with HF compared with those without HF [187, 188]. There were 24 estimates of hazard ratios for all-cause mortality; however, there was considerable heterogeneity that prevented meta-analysis. Only five adjusted hazard estimates for all-cause mortality failed to reach statistical significance [198, 204, 208-210] and all estimates trended towards higher mortality in COPD patients with HF compared with those without HF. There was considerable heterogeneity in the estimates of the effect of HF comorbidity on all-cause mortality of COPD patients, preventing estimation of a pooled effect estimate based on all available data. Heterogeneity remained high when meta-analysis was attempted stratified by length of follow-up, crude or adjusted estimates, sample size, or by location of patient identification (primary or secondary care). Meta-regression was not considered as there was highly inconsistent reporting of covariates among the studies. Only when considering just the studies that explicitly called for a spirometric diagnosis of COPD was heterogeneity low enough to pool estimates ($I^2 = 0.0\%$); however, there was evidence of publication bias. In COPD patients diagnosed with spirometry, those with HF experienced 1.61 times greater risk of all-cause mortality than those without HF (pooled HR; 95%CI: 1.38, 1.83). Studies that used electronic diagnostic coding to identify COPD patients had high heterogeneity ($I^2 = 96.0\%$).

Five studies found significantly increased all-cause inpatient mortality for COPD patients with HF compared with those without HF. Roberts et al. estimated that COPD patients with HF experienced 1.75 times the risk for all-cause inpatient mortality compared with those without HF [211]. The conference abstract by Löh et al. did not provide a confidence interval for their estimate that COPD patients with HF experience 2.37 times greater odds of all-cause mortality than COPD patients without HF, nor did they specify whether the estimate was crude or adjusted [213]. Three additional studies also reported significantly higher adjusted odds, ranging from 7% to 31%, of all-cause inpatient mortality for COPD patients with HF compared with those without HF [192, 194, 214].

There was considerable heterogeneity in the smoking histories and severity of airflow limitation in the COPD population studied. For example, Ahn et al. included patients with no history of smoking through to patients with over 50 pack-years of smoking history. In terms of airflow limitation severity, the study by Almagro et al. included patients with mild (21.6%), moderate (44.8%), severe (44%), and very severe (11%) airflow limitation. It may be that the effect of HF comorbidity on the rate or risk of all-cause mortality is greater in certain COPD phenotypes than in others, which is a potential topic for future research. As with hospitalisations, HF type and severity may also impact its effect on mortality and may be a topic for future research.

2.4.3 COPD comorbidity in HF patients

There has been a number of works investigating the opposite relationship, that is, the effect of comorbid COPD on the morbidity and mortality of HF patients. Previous work has found that HF patients with COPD experience increased all-cause hospitalisation compared with those without COPD [218, 219]. Following an initial hospitalisation for HF, Gulea et al. found that patients with comorbid COPD were at greater risk for all-cause, respiratory-related, and cardiovascular-related rehospitalisation in the 30 days following initial discharge [220]. COPD comorbidity significantly increased all-cause mortality (pooled HR: 1.39, 95%CI: 1.2-1.6; I^2 = 37.7%) of HF patients in a meta-analysis by Rushton et al. [221]. These results support ours and further highlight the difficultly of identifying and managing COPD or HF in the presence of the other.

2.4.4 Potential mechanisms for increased secondary care utilisation and mortality of COPD patients with HF comorbidity

There are a number of potential drivers for the increased morbidity and mortality of COPD patients with HF comorbidity. HF often goes unrecognised in COPD patients [91, 174-176]. Dyspnoea is a primary complaint for both HF and COPD and determining the underlying cause for dyspnoea is difficult [222]. Diagnosing HF in the presence of COPD is complicated by difficulty in echocardiogram interpretation and limitation of natriuretic peptides accuracy in COPD patients [223-225]. Therefore, HF diagnosis is often delayed in COPD patients. Delayed diagnosis means HF is not recognised until it is more severe and that survival-modifying medications are delayed [127]. Even when recognised, cardiovascular disease is systemically mismanaged in the COPD population [166]. This mismanaged may hasten the development of HF or the progression of HF once established. Finally, COPD patients with HF comorbidity have been shown to have a higher additionally comorbidity burden, beyond COPD and HF, which may also contribute to increased morbidity and mortality [160, 173]. All of these mechanisms work together to increase secondary care utilisation and mortality of COPD patients with HF compared with those without HF. In order to improve patient quality of life and outcomes, specific guidelines detailing proper diagnosis and management of HF in the presence of COPD are required.

2.4.5 Strengths and limitations of included studies

There was a large amount of incomplete reporting of study methodology and participant selection in the studies included in this review leading to unknown risk of bias. The majority of studies relied on clinical diagnosis or electronic recording of diagnosis for COPD and/or HF. In many studies, HF was a covariate, not a specified exposure; as a result, most studies do not specify exactly how HF status was determined. Ultimately, the validity of COPD and HF status in studies relying on clinical diagnosis or electronic coding is unknowable and reliant on the acumen of the clinical practitioners recording diagnosis or on patient self-report. The unknown validity of patient identification using electronic coding contributed to the high heterogeneity seen in attempted meta-analyses. Only analysis limited to those studies that explicitly required spirometry for the diagnosis of COPD had a heterogeneity estimate compatible with meta-analysis; however, for these studies there was evidence of publication bias.

2.4.6 Strengths and limitations of this review

This study utilised a comprehensive search strategy designed to capture all potentially pertinent information. The wide search criteria allowed for the inclusion of a variety of studies that investigated diverse COPD populations and thus are widely representative of the entire COPD community. COPD is a highly heterogeneous disease [48, 226], which is reflected in the studies and populations included in this review.

The effect of HF on all-cause mortality as estimated by HR was the only effect for which meta-analysis could be considered; however, heterogeneity was high when including all available data. Limiting the analysis to those studies that explicitly required spirometry for a diagnosis of COPD reduced heterogeneity to an acceptable amount for meta-analysis. Meta-analysis was not possible for the outcomes hospitalisation, rehospitalisation, and inpatient mortality due to insufficient data. A number of studies were found during searching that reported only adjusted OR for the outcomes of interest in this review; however, adjusted OR are not compatible with meta-analysis as their magnitudes cannot be compared between statistical models [227].

2.5 Conclusions

There is evidence that HF comorbidity increases COPD-related secondary care utilisation and all-cause mortality of COPD patients; however, the heterogeneity of the COPD population prevented meta-analysis to estimate pooled effects using all available data. For COPD patients diagnosed using spirometry, those with HF experienced 1.61 times greater risk of all-cause mortality than those without HF. Future research in this area should utilise validated definitions of COPD and HF, where available, or conduct adjudication of diagnoses. Additionally, future research should consider reporting effect estimates stratified by patient characteristics, such as smoking status or severity of airflow limitation. Additionally, HF type and severity may influence its effect on morbidity and mortality and should be investigated. There are a number of potential mechanisms contributing to the effect of HF comorbidity on the morbidity and mortality of COPD patients. Ultimately, these mechanisms must be addressed by the development of specialised guidelines, pathways, and education for the diagnosis and management of HF in the presence of COPD to improve patient quality of life and outcomes.

Chapter III: Data Sources and Variable Definition

This chapter describes the data types and sources used for the following chapters, including the ethical approval statement for the use of these sources. This chapter also outlines the basic definitions of variables from these data sources, such as HF status, that are used in the following chapters.

3.1 Electronic Healthcare Records

EHR are digital repositories of patient data primarily serving clinicians in providing continuing and efficient care for patients [228]. EHR contain longitudinal information that can secondarily be securely shared, stored, and used by researchers [228]. They are increasingly recognised in research for their high statistical power and generalisability. EHR allow researchers to track healthcare patterns in real-life, as opposed to RCTs and other bespoke studies that select participants based on strict inclusion and exclusion criteria. EHR allow for a variety of different research applications including observational studies, safety surveillance, clinical research, and regulation [229]. They are used in a variety of healthcare settings, including primary care, outpatient clinics, emergency rooms, hospital inpatients, and even home care. These records can be used individually or together to create a comprehensive picture of patient care [229].

There are important limitations to EHR that must be considered when using them for research purposes. Firstly, the majority were not designed specifically for research, meaning that important data may not be available or may not be recorded with the necessary accuracy [229]. Linking records from a variety of EHR sources is one way to gain information missing from one source; however, linkage requires that patients are able to be matched accurately, meaning that study size is often diminished as a result [230]. Secondly, validity of case definition within EHR may require complex algorithms [231, 232] and may be limited by clinician acumen. Validation studies should be undertaken to assess the ability of algorithms and code lists to identify cases [231]. Case definition and validation will be discussed more thoroughly later in this chapter. Balancing internal validity, generalisability, and power is essential when using EHR in research.

In the UK, there are a number of sources of routine primary care data: The Health Improvement Network (THIN) [233], QResearch [234], Secure Anonymised Information Linkage (SAIL) Databank [235], and the CPRD [236]. These databases contain information on patient demographics, diagnosis, tests, and treatments. Primary care data may be linked with secondary data sources to create a more complete picture of patient care. In the UK, other sources of data may include clinical audits, such as the National Cardiac Audit Programme (NCAP) [237] or the National Asthma and COPD Audit Programme (NACAP) [78], or national data, such as those from HES [238] or the ONS [239].

Data in these databases is de-identified for research purposes. In the case of CPRD, data is de-identified at the practice level, meaning identifiable information is never uploaded to the research data server (**Figure 3.1**). If linkages are made, identifiable data is sent directly from the practice to NHS Digital, the third party responsible for linkages, and connected with other data before being de-identified and sent to the CPRD research server [240].

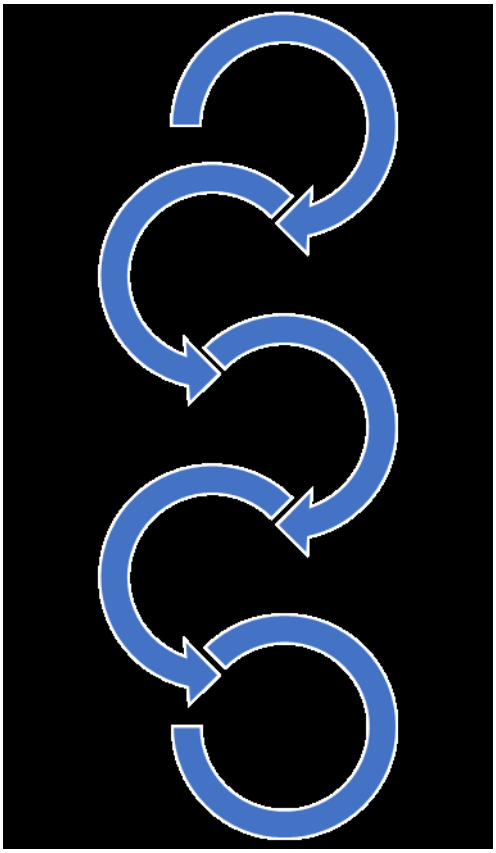

Figure 3.1. Process of data acquisition in CPRD.

This thesis will use data from CPRD with linkages to HES, ONS, and socioeconomic data as appropriate. These data sources are described in more detail below.

3.1.1 Clinical Practice Research Datalink (CPRD)

CPRD is a primary care database of anonymised electronic health records from general practitioners representing 6.9% of the UK population [236, 241]. CPRD was established in 1987 as the Value Added Medical Products (VAMP) dataset, growing into the General Practice Research Database (GPRD) in 1992, and finally expanding into CPRD in 2012 [236]. The database is one of the largest collections of longitudinal primary care medical records in the world [236] and has been shown to be representative of the UK with respect to age, sex, BMI, and ethnicity [241, 242].

Data is collected monthly from general practices that have opted in at a practice level, and all patients from participating practices are included unless the patient individually opts out [236]. Additionally, 75% of practices from England have consented to their data being linked to secondary care data, mortality data, deprivation data, and a variety of disease registries [236]. Linkage is done by a third party, NHS Digital, where patient-level data from practices is linked and anonymised [236, 243]. Data from the GP and the secondary data source is collected by NHS Digital, and patients in both datasets are identified using a progressive algorithm matching NHS number, sex, date of birth, and postcode, where accuracy of the match is determined by the number of concordant identifiers [243]. Correctly matched data is then de-identified and made available to researchers.

Linkage sets contain information on the patients who are eligible for linkage with various external datasets and are provided by CPRD on a regular basis. External datasets regularly linked with CPRD include: 1) mortality from the ONS; 2) the IMD for England; 3) HES including Admitted Patient Care (HES APC), outpatient (HES OP), accident and emergency visits (HES A&E), and diagnostic imaging (HES DID); 4) National Cancer Registration and Analysis Service (NCRAS) data from Public Health England (PHE); and 5) Mental Health Dataset (MHDS) [230]. Linkages with other external data sources can be negotiated but take time to approve and set up.

Accessing CPRD data

Observational studies using CPRD data must be approved by the ISAC. Studies incorporating methods beyond observation may require additional ethical approval from appropriate bodies. Standardised statements regarding ethics approval are required by CPRD to be present in papers published using data and linkages that they provide.

Access to CPRD data is provided upon purchase, one-time or through license, and upon ISAC approval. Data provided by CPRD are sourced from two widely used electronic records systems: VISION and EMIS®. The CPRD system responsible for VISION data is known as CPRD GOLD and the system responsible for EMIS® data is known as CPRD AURUM. The studies conducted for this thesis will use data collected from VISION and provided by CPRD GOLD. Henceforth, 'CPRD' will refer exclusively to CPRD GOLD.

Upon all appropriate approvals, data may be downloaded from CPRD in a two-step process. Firstly, the 'define' feature is used to generate a list of patients that meet the specified inclusion/exclusion criteria. These criteria are usually based on a medical event (such as 'diagnosis with COPD') as defined by Read codes. Read codes are terms entered by physicians at the time of the event and can represent diagnoses, procedures, symptoms, test results, screening, and history [242]. In CPRD, each condition also has a specified 'medcode' that corresponds to a Read code and researchers may use either to define their cohort. Researchers may also define based on product use using BNF codes. Again, CPRD has its own 'prodcode' that corresponds to BNF codes and may be used to define a cohort. Researchers can use the 'Code Browser' provided to search for Read codes/medcodes and BNF codes/prodcodes appropriate for their study. It is also possible to specify the study period, age or sex restrictions, or registration status in the define process. Next, the 'extract' feature pulls data for the patients identified through the define procedure. Once extracted, the data may be downloaded for use.

Organisation of CPRD data

CPRD data is organised into a series of files containing data for each patient meeting the requirements specified during 'define' and 'extract' (**Figure 3.2**).

The patient file contains demographic information. The practice file identifies the practice from which a patient came and where it is located regionally. The staff file contains information on the member(s) of staff the patient interacted with on each visit. Each visit is identified in the consultation file. The clinical file details diagnoses and symptoms, while the additional file provides records of specific details, including blood pressure, height, and weight measures. The therapy file details prescriptions given and the referral file details if a referral to a specialist was made and for what. The test file indications any tests performed and the results of those

tests. The immunisation file details the immunisation history of the patient. Free text, additional information entered by the physician, is no longer regularly provided by CPRD.

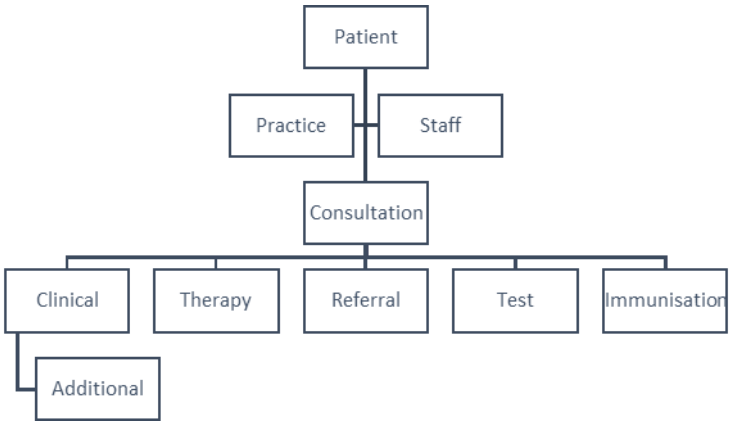

Figure 3.2. Organisation of CPRD datasets. Adapted from Herrett et al. 2015 [57].

3.1.2 Office of National Statistics (ONS)

In order to ensure accurate information relating to time and cause of death, CPRD data can be linked with mortality data from the ONS. The ONS provides mortality rates and population size estimates for England and Wales. Registration of deaths for England and Wales is nearly 100% complete with a large proportion of registered deaths certified by a medical practitioner [239]. Cause of death was recorded using ICD-10 codes [244, 245]. In 1893, the International Statistical Institute generated the first International List of Causes of Death [246]. In 1948, the WHO took over the creation of the international classification of disease (ICD) [246]. The ICD-10 [247] was endorsed by the World Health Assembly in 1990 [246].

Since 1993, automated coding has been in place for cause of death with application of WHO rules allowing for international comparisons [248]; however, there are issues surrounding the accuracy of the underlying cause of death provided by ONS, which is a derived variable [249]. The underlying cause of death is defined as ‘the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury’ by WHO [250]. In a review undertaken by ONS, the proposed and confirmed underlying cause of death matched at ICD chapter level in 88% of cases and there was exact agreement (to 4 digits) in 78% of cases, rising to 80% when records matching to 3 digits were included [251]. Additionally, a previous study established that the underlying cause of death derived by the ONS algorithm was an acceptable means of categorising cause of death

[252]. Upon registry of the death, data is stored with ONS. Data from ONS linkage with CPRD lists the date of death, the derived underlying cause of death, and up to 15 additional direct and contributing causes of death.

While date of death is reported in primary care records, the accuracy of this recording has come into question [253, 254]. Gallagher et al. found that 98.2% of deaths recorded in ONS were recorded in CPRD from 1998 to 2013; however, exact date of death was in agreement 78.0% of the time in 2013 [254]. Harshfield et al. looked at accuracy of recording from 2010 to 2015 and found, similarly, that exact date of death matched in 76.8% of cases [253]. Harshfield et al. also found there was notable variation between practices and that the greatest discrepancies were seen in unexplained deaths and younger patients [253]. Both reports recommend that in studies were exact date of death is important, ONS data should be used over CPRD data. Additionally, cause of death is not recorded in CPRD, therefore studies requiring this information must use ONS.

3.1.3 Hospital Episode Statistics (HES)

HES data are gathered by NHS Digital from all NHS trusts in England [238]. HES details secondary care events, including hospital admissions, A&E visits, outpatient visits, and diagnostic imaging. Admitted patient data has been collected since 1989, while outpatient visits have been collected since 2003 and A&E visits since 2007 [255]. Data is collected at time of patient visit and submitted so that hospitals may be compensated for the care provided [238]. Upon linkage with HES, CPRD provides a number of datasets detailing patient secondary care utilisation. The suite of datasets regarding inpatient stays, A&E visits, and outpatient appointments includes information on the patient's practice, ethnicity, admission date, discharge date, diagnoses, and procedures [255]. HES linkage is available for around 60% of the CPRD population, as it is only available in England [236]. During my study period, HES used the ICD-10 codes to record diagnoses [245].

3.1.4 Index of Multiple Deprivation (IMD)

The IMD is a composite measure of relative deprivation at the neighbourhood, termed the LSOA, level (average population of 1500 people) in England [256]. There are 32,482 LSOAs in England, representing homogenous communities [256]. Relative deprivation does not equate to affluence [256], but rather provides a measure of a patient's socioeconomic status in relation

to their postcode modelled using income, employment, health and disability, education-skills-training, barriers to housing and services, living environment, and crime data from their LSOA [256]. These studies will use the IMD 2010, as it is the closest IMD to the mid-point of the study period. IMD was broken into quintiles from 'most deprived' to 'least deprived'.

3.2 Ethical Approval

In clinical research, the requirement for approval of studies by research ethics committees is laid out in the Helsinki Declaration, most recently updated in 2000 [257]. Ethics approval is designed to ensure that best practices are used to ensure promotion of life, health, privacy, and dignity of human subjects [257]. Ethics approvals for the studies in this thesis were sought from the appropriate governing body. The ethics approval and data sharing statement for the use of CPRD with linked ONS, HES, and IMD data is laid out at the beginning of this thesis.

3.3 Variable Definition

This section briefly outlines the identification of variables clinically and for research using CPRD. Identification of patients with COPD, HF, and other diagnoses within this thesis was undertaken in CPRD; if another source was used in addition to CPRD to identify conditions, it will be specified within the specific algorithms outlined below.

3.3.1 Overview of variable definition within CPRD

Researchers identify conditions and other information from within EHR using code lists. Sometimes, multiple code lists and/or algorithms are needed including codes for clinical diagnoses as well as medication use. Code lists require careful thought during their construction as they are used to identify patients with the exposure, outcome, and covariates. Code lists are a key component of cohort definition using electronic health records; however, they are not often published alongside the papers for which they were used [232]. Movement towards transparency in code lists has led to the creation of online code repositories [232, 245]. Within CPRD, code lists are created using appropriately chosen Read codes.

Read codes are a hierarchical classification of conditions that were used by the NHS until 2020 [258, 259]. Read codes are alphanumeric (A-Z, 0-9) consisting of levels, building in specificity (**Table 3.1**) [259]. Read codes correspond to CPRD-specific 'medcodes', which may also be used to identify conditions. Read codes have been retired by the NHS and SNOMED CT codes

have replaced them [258]; however, for the years studied in this thesis, Read codes were still in use and are therefore used as the basis of variable definition.

First Level	G…	Circulatory system diseases
Second Level	G7..	Cerebrovascular disease
Third Level	G71.	Cerebral haemorrhage
Fourth Level	G711 G712 G713 G714	Subarachnoid haemorrhage Intracerebral haemorrhage Extradural haemorrhage Subdural haemorrhage

Table 3.1. Example of Read code levels building specificity.

Additionally, drug substance, route of administration, strength, formulation, and BNF codes may be available. CPRD provides common dosages for 95% of all therapy data [260]. Each product is provided with a dosage identifier, which can be merged with the common dosages information to identify daily dose.

To create a code list in CPRD, I generated a list of all terms/synonyms used to describe a specific medical event, search the 'Code Browser' for these terms, crosscheck the codes found with published code lists, and consult at least one speciality physician to select the most appropriate codes.

Code lists may be validated, meaning that their sensitivity, specificity, PPV, and/or NPV are determined using a reference standard derived from clinical review of patient files and questionnaires [261]. In terms of code list validity, sensitivity is a measure comparing the number of persons with a diagnosis with the number of persons with a specific Read code for that diagnosis [262]. Specificity is a measure comparing the number of persons without a diagnosis with the number of persons without a specific Read code for that diagnosis [262]. Often more useful are measures of predictive value. The PPV of a Read code is the proportion of persons with that Read code who actually have the condition, while the NPV is the proportion of persons who do not have that Read code who do not have the condition [262].

If a validated code list or algorithm exists for the condition of interest, this served as a basis for the code lists used in this thesis; however, not all conditions have been validated within CPRD. The development of code lists for conditions that have not been validated, or the updating of validated code lists, requires judgement as to what the code means and how it is used in clinical

practice. When crosschecking code lists, I consulted codes listed from the QOF [21], the Cambridge Code List Index , published code lists/algorithms, and/or validated code lists/algorithms. Additional codes were added through searching the CPRD Code Browser at the time of cohort definition in 2018. Persons with clinical knowledge determined the final code lists and/or algorithms.

Code lists are useful for identifying certain conditions within CPRD; however, some items of clinical information are entered as measurements. For example, information such as height and weight are stored directly in the additional file, while test results such as lung function measurements are located in the test file. When utilising these types of information, methods for identifying reasonable measures are required. For example, a height of 500cm is unreasonable and should not be utilised in analysis.

3.3.2 Identification of COPD

A diagnosis of COPD in the UK requires a patient to be over 35 years old with a history of smoking and one or more symptoms [13]. Diagnosis should be confirmed by post-bronchodilator spirometry [13].

Identification of COPD within CPRD

The coding of COPD within CPRD was validated in 2014 [261]. The algorithm required the use of a code list and inclusion of patients over the age of 35 with a history of smoking [261]. Using these criteria, COPD patients were identified with a PPV of 86.5% (95%CI: 77.5-92.3%) [261].

Since four years had passed since the creation of the validated COPD code list at the time of cohort definition, a new search of the CPRD Code Browser was undertaken to identify if any new useful Read codes for COPD had been defined since 2014 (**Figure 3.3**). There were ten codes identified, accounting for 5% of all COPD codes and including five QOF 2017-18 codes [21]. These ten codes were used in addition to the validated code list to identify COPD in CPRD.

The final algorithm for the identification of COPD patients within CPRD was:

1. Presence of COPD code from the final code list (**Appendix III**) in the medical record
   and
2. Age 35 years or older at time of diagnosis
   and
3. History of smoking (current or former smoker)

Identification of AECOPD in CPRD and HES

Algorithms for the identification of AECOPD in CPRD and HES have been validated previously [263, 264]. A number of different algorithms were tested as part of the validation studies. Exacerbations occurring within 14 days of a pervious exacerbation were taken as a continuing event.

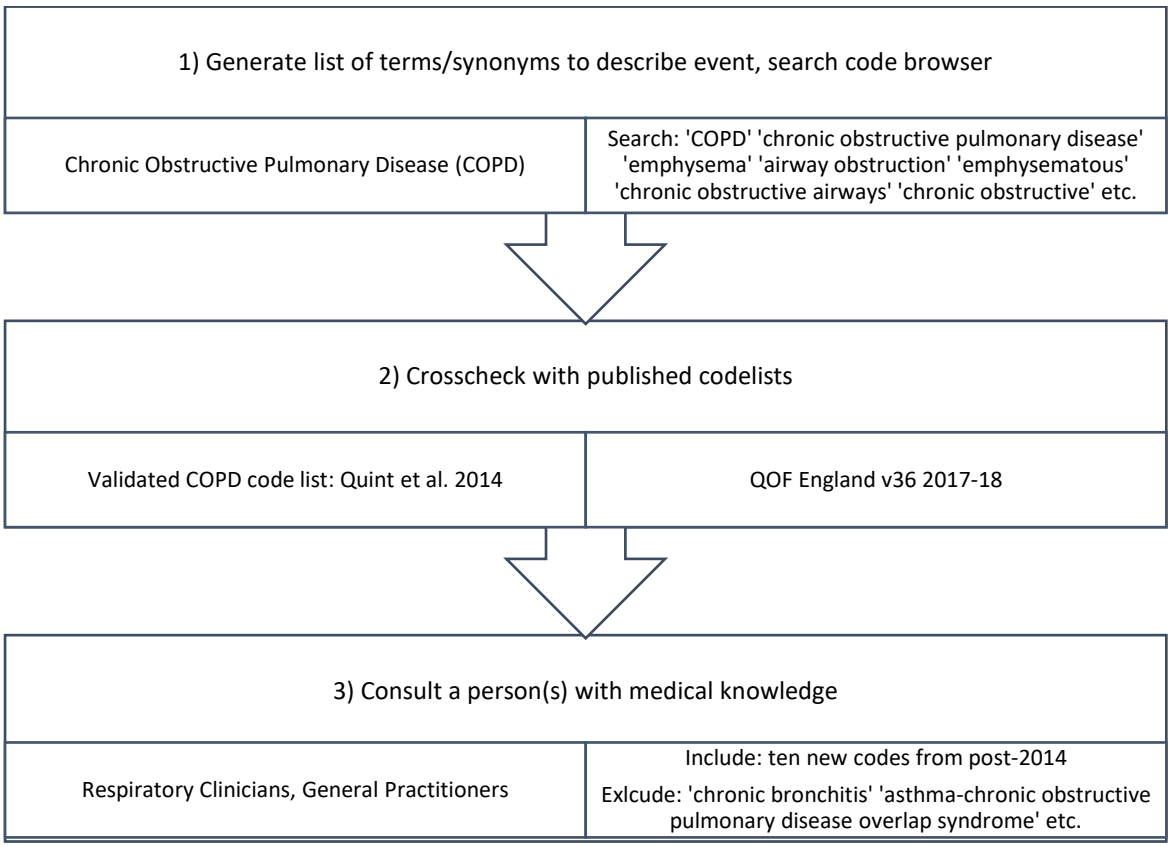

Figure 3.3. COPD code list creation in CPRD. Quint et al. 2014 [261]. Quality and Outcomes Framework (QOF) England version 36 2017-18 [21].

The recommended algorithm for the identification of AECOPD in CPRD had a PPV of 85.5% (95%CI: 82.7-88.3) and a sensitivity of 62.9% (95%CI: 55.4-70.4) [263]. The algorithm calls for:

- Medical diagnosis of LRTI or AECOPD

  or
- Symptom definition with OCS or COPD-specific antibiotic prescription on the same date

  …where symptom definition indicates increase in two or more symptoms including breathlessness, cough, sputum volume, sputum purulence

  or
- Prescription of COPD-specific antibiotics in combination with OCS for 5-14 days.

Code lists for the identification of AECOPD, LRTI, OCS, COPD-specific antibiotics, breathlessness, cough, and sputum in CPRD are available in **Appendix III**.

The recommended algorithm for the identification of AECOPD hospitalisation in HES had a sensitivity of 87.5% (95%CI: 72.4-94.9) [264]. The algorithm calls for:

- Specific AECOPD code in any diagnostic position

  or
- Specific LRTI code in any diagnostic position

  or
- COPD code in the first diagnostic position.

ICD-10 codes for the identification of AECOPD, LRTI, and COPD in HES are available in **Appendix III**.

Assessing COPD severity in CPRD

Spirometry data is available in the CPRD test files as percent predicted FEV_1, predicted FEV_1, or measured FEV_1. Patient height data is available in the CPRD additional files. The most recent recording of spirometry and height measures were used. The percent predicted FEV_1 was calculated, when not recorded, based on predicted and measured FEV_1 using the following equation:

$$percentFEV_1 = \left(\frac{measuredFEV_1}{predFEV_1}\right) * 100$$

When predicted FEV_1 was not recorded, it was calculated using the GLI-ERS Task Force 2012 equations [265]. According to their percent predicted FEV_1, airflow limitation severity was categorised for patients as GOLD 1-4 per NICE guidelines [1, 13].

3.3.3 Identification of HF

In the UK, HF should be diagnosed according to NICE guidelines [69]. It is recommended that levels of NT-proBNP be measured followed by referral for echocardiogram and specialist assessment [69]. Extensive tests are recommended to exclude other diagnoses, such as chest X-ray, additional blood tests, urinalysis, and spirometry [69]. Following diagnosis, assessment should focus on the severity, aetiology, precipitating factors, and type of HF [69]. Availability of these tests, referral times, and use of these tests by GPs may vary from practice to practice [266].

Identification of HF within CPRD and HES

Johansson et al. validated the coding of incident HF within CPRD finding an 81.8% PPV for cases in 1996 [267]; however, since the introduction of the QOF in 2004, HF coding has not been formally validated within CPRD. The QOF and the NHFA report that approximately 90% of recorded HF diagnoses in England are referred for echocardiography, specialist assessment, or BNP measurement [77, 268].

In order to identify patients with HF, the CPRD Code Browser was searched using synonyms for 'heart failure' (**Figure 3.4**). Next, the results of this search were crosschecked against the QOF codes for HF [21] and the codes utilised by Conrad et al. [61]. Finally, persons with clinical knowledge, including a cardiologist, assessed the Read codes. The final codes used to identify HF are listed in **Appendix III**.

Conrad et al. [61] performed two sensitivity analyses when assessing the validity of their HF definition. Firstly, Conrad et al. restricted the diagnostic codes used to those included the QOF and the NHFA. Conrad et al. found that 97% of patients in their cohort had a diagnostic code used in the QOF or the NHFA [61]. Secondly, Conrad et al. restricted case identification to those cases diagnosed in secondary care or referred for specialist assessment or

echocardiogram. Conrad et al. found that 92% of patients included in their cohort fit this definition [61].

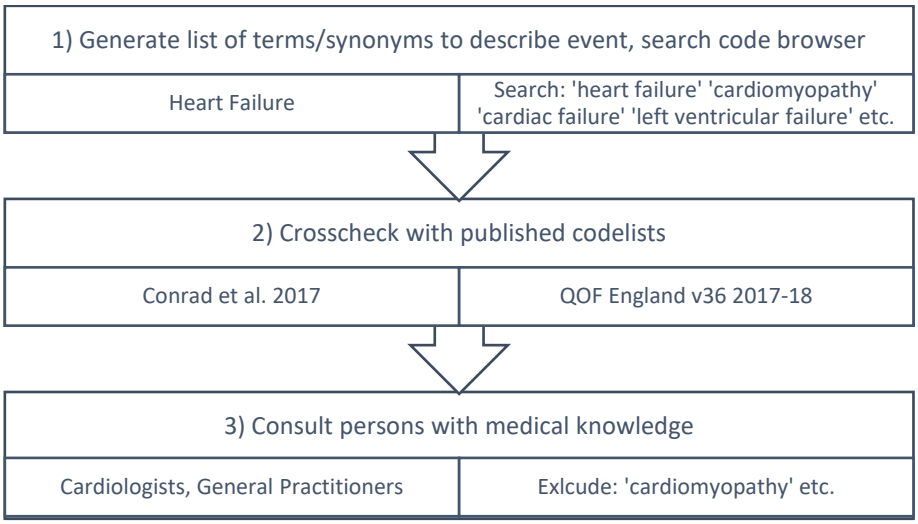

Figure 3.4. Creation of heart failure code list. Conrad et al. 2017 [61]. Quality and Outcomes Framework (QOF) England version 36 2017-18 [21].

Patients with HF diagnosed under the age of 18 years old were excluded from these analyses. Paediatric HF is more commonly caused by congenital abnormalities or cardiomyopathies than adult heart failure and appropriate management is based primarily on the application of knowledge from studies with adults due to the scarcity of studies with children [269].

The final algorithm for the identification of HF patients using CPRD was:

1. Presence of a HF code from the final code list (**Appendix III**) in the medical record *and*
2. Age 18 years or older at HF diagnosis.

History of HF hospitalisation were identified as those with a HF diagnostic code as the primary or secondary condition related to a hospitalisation [270]. HF hospitalisation was identified in HES A&E data using the ICD-10 codes I11.0, I13.0, I13.2, I50, I50.0, I50.1, or I50.9. Cardiology outpatient visits were identified in HES Outpatient data using the main or treatment specialty code '320 – Cardiology'.

3.3.4 Identification of COPD-HF comorbidity

COPD and HF are non-reversible, life-long conditions; therefore, any patient with an eligible code for COPD and an eligible code for HF was considered to have both diseases from the date

of the diagnosis of the second condition. In some analyses, only incident HF in the presence of prevalent COPD was assessed.

3.3.5 Identification of patient characteristics in CPRD and HES

This section outlines the definitions of age, ethnicity, BMI, sex, and smoking status, BNP tests, and echocardiography in CPRD and HES, as appropriate.

Age in CPRD

Exact date of birth is not available in CPRD in the interest of patient privacy. Year of birth is provided. Month and day of birth were set to mid-year, 01 July, for purposes of calculating age. Age groups, where used, were 35-64 years, 65-74 years, 75-84 years, and 85+ years.

Classification of ethnicity in HES

Recording of ethnicity in HES is available in inpatients, outpatients and A&E records. Ethnicity was used for the purposes of calculating GFR (see below).

Identification or calculation of BMI in CPRD

BMI, height, and weight are recorded in CPRD additional files. For patients without a BMI record, the most recent height and weight records were used to calculate BMI in kg/m^2 using the following formula:

$$BMI = \frac{weight}{(height)^2}$$

Classification of sex in CPRD

Sex is recorded as male, female, indeterminate, or not known/recorded. Only patients with a recorded sex as male or female were included in these analyses.

Identification of smoking status in CPRD

Smoking status is recorded using medcodes in CPRD clinical files (**Appendix III**). A history of smoking is required for a diagnosis of COPD in the UK [13]. Patients were classified as 'current smoker' or 'former smoker' based on the smoking code closest to the start of follow-up. Patients without a recorded history of smoking were excluded from these analyses.

Unfortunately, extent of smoking history (i.e. cigarettes per day, pack-years, etc.) is not reliably recording within CPRD. There is an entity type where clinicians can enter the number of 'cigarettes per day'; however, it is not used regularly. This information may be placed within additional text, which is no longer provided by CPRD.

Identification of BNP tests in CPRD

Tests for BNP levels, which rise in HF [19], were identified using Read codes: 44AN.00, 44AR.00, 44AP.00, 44AF.00, or 44AF.00.

Identification of echocardiography in CPRD

History of echocardiography was identified in CPRD using the echocardiography Read codes from the QOF [21].

3.3.6 Identification of medications in CPRD

This section outlines the identification of medication prescription in CPRD.

COPD medications

Code lists for the prescription of LABA, LAMA, and ICS can be found in **Appendix III**. Code lists for the prescription of COPD-specific OCS and antibiotics used in the identification of AECOPD are also available in **Appendix III**.

CVD medications

Code lists for the prescription of ACEi, ARB, CCB, LD, MRA, statins, and vasodilators are in **Appendix III**.

BB were identified using the code list in **Appendix III**. Depending on their affinity for receptors, BB are classified as either cardioselective or non-cardioselective. Cardioselective BB were identified as acebutolol, atenolol, bisoprolol, metoprolol, and nebivolol [271].

3.3.7 Identification of other clinical conditions in CPRD

Code lists for the identification of AF, CLD, diabetes, IHD (including myocardial infarction, angina, and acute coronary syndrome), PAD, and stroke are in **Appendix III**.

Identification of hypertension

The algorithm for the identification of HTN was as follows:

1) Presence of a HTN code (**Appendix III**) in the medical record

or

2) Patients without a diagnosis of HF or AF, on antihypertensive medications (one class)

   or

   Patients on two classes of antihypertensive medications

   Where classes of antihypertensive drugs were defined as (at least two scripts for):

   - CCB
   - BB
   - Diuretics
   - Vasodilators
   - ACEi-ARB

Codes to identify the prescription of each drug class are available in **Appendix III**.

Identification of chronic kidney disease

The algorithm for the identification of CKD was as follows:

1) Presence of a CKD code (**Appendix III**) in the medical record

or

2) Estimated GFR <60 mL/min/1.73m^2 estimated from the most recent measure of serum creatinine levels within five years of the start of follow-up [272]

   Where GFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas [273] from serum creatinine levels as recorded in the test files from CPRD per NICE guidelines [274];

   and

   Where ethnicity ('black' or 'non-black') is determined from the ethnicity variable in HES A&E or Outpatient data;

   and

   Where ethnicity is assumed to be 'non-black' for all those patients with 'unknown' or unrecorded ethnicity [272, 275].

CLD and CKD status was determined for analyses in **Chapter V**, where loop diuretic use was used as a proxy for unrecognised HF. As CLD and CKD are other indications for loop diuretic use, these patients were excluded from those analyses.

Chapter IV: Temporal trends in the incidence of heart failure and its impact on mortality among COPD patients in UK primary care

4.1 Introduction

This chapter continues the exploration of Specific Aim #1, to assess the burden of HF comorbidity on the COPD population. The previous objective established that HF comorbidity significantly affects morbidity and mortality of COPD patients (**Chapter II**). The next two objectives describe the burden of incident HF on the COPD population over time.

The incidence of COPD in the UK has remained steady since 2008 [9]. Meanwhile, the incidence of HF in the UK increased by 2% from 2002 to 2014 [61]. Many studies have estimated the prevalence of HF in the COPD population, but the prevalence of HF in COPD patients varies depending on population characteristics. In a review by Rutten et al., included studies have found anywhere from 10-46% previously unrecognised left-sided HF in various COPD populations [91]. In studies that did not explicitly exclude patients with ischaemic heart disease, left ventricular dysfunction <50% was found in up to 46% of COPD patients [91]. Estimates of HF prevalence in community-based cohorts are around 10% [92].

Previous research has shown that HF comorbidity often goes unrecognised in COPD patients due to their shared symptomology [91, 174-176], but it is not known whether HF case finding in the COPD population has improved over time. Additionally, HF patients have seen increased survival in recent years [63, 65], but it is not known whether COPD patients with HF have also seen increased survival.

The primary purpose of these analyses was to assess the incidence of HF and the impact of incident HF on mortality among patients with prevalent COPD. Additionally, causes of death in this population were assessed over time and by severity of airflow limitation.

Supplementary information for this chapter is located in **Appendix IV**. A peer-reviewed publication [276] was produced in association with this chapter (see **Appendix VIII**). Figures and tables in this chapter may have been reproduced from the aforementioned publication with permission of the copyright holder (see **Appendix VII**).

4.2 Methods

4.2.1 Data sources

Data were obtained from the CPRD and ONS, which are described in Chapter III.

4.2.2 Case ascertainment and exposure

COPD patients were identified from 2006 to 2016. COPD and HF were identified as described in Chapter III. For these analyses, all patients with a diagnosis of HF (prevalent HF) prior to the start of follow up were excluded. The start of follow-up was defined as the latest date of the following: 1) practice up-to-standard date per CPRD, 2) the current registration date for the patient, 3) the patient's 35th birthdate, 4) the start of the study on 01 January 2006, or 5) the date of COPD diagnosis.

4.2.3 Covariates

Sex, age groups, smoking status, BMI, and severity of airflow limitation per GOLD [1] were defined as described in Chapter III. History of cardiovascular disease included prior diagnosis of IHD, PAD, AF, HTN, and/or stroke, which were identified as described in Chapter III.

4.2.4 Statistical analyses

I calculated sex, age, smoking and GOLD status specific, HF incidence rates per 100 person years for each year (2006-2016) in patients with COPD.

For the analysis of the impact of incident HF on mortality among patients with COPD and changes in rates over time, crude mortality rates for COPD patients with incident HF (COPD-iHF) were calculated across three different time periods: 2006 (1-year, 5-year, and 10-year mortality rates), 2011 (1-year and 5-year mortality rates) and 2015 (1-year mortality rates). Censoring was defined as transfer from practice, last date for which practice data were available, last date for which linked ONS data was available, or the end of the study. COPD patients without incident HF (COPD-no HF) for the same time periods (2006, 2011, or 2015) were used as comparators for this mortality analyses. In addition to the aforementioned censoring events, the comparator patients were also censored upon date of subsequent HF diagnosis (**Figure 4.1**). Crude mortality rate ratios (MRR) were calculated comparing the 1-year, 5-year, and 10-year mortality rates of COPD-iHF patients with COPD-no HF patients in 2006, 2011, and 2015. Mortality rate ratios adjusted for adjusted for age, sex, BMI, GOLD,

smoking status, history of cardiovascular disease, and diabetes (aMRR) were estimated using Poisson regression. Robust variance estimates were used to account for possible clustering on GP. A Kaplan-Meier survivor curve was produced comparing COPD patients with and without incident HF diagnosis in 2006 over 10 years of follow-up.

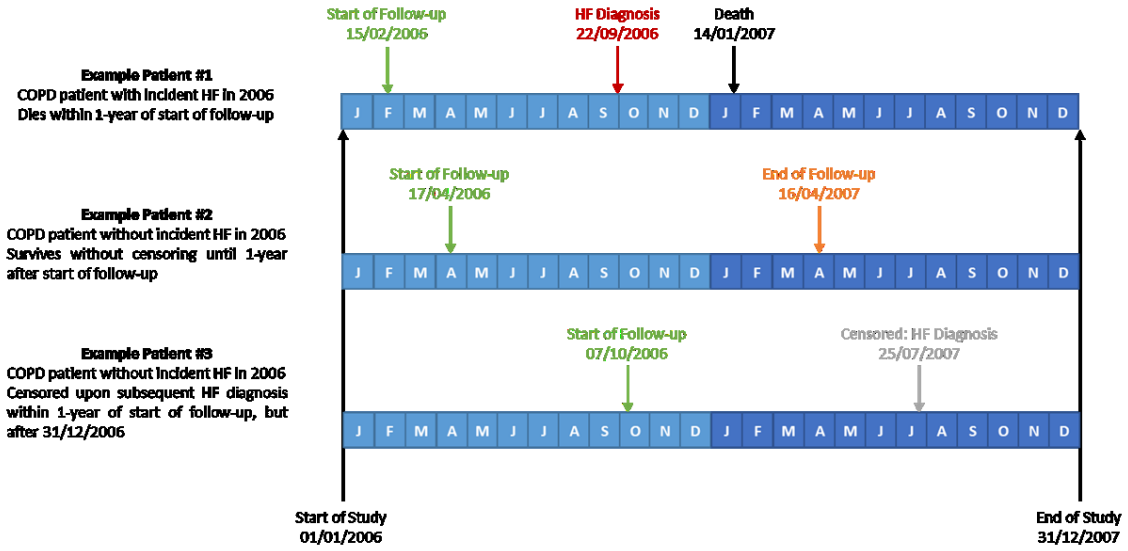

Figure 4.1. Example follow-up for three patients from start of follow-up until death or censoring for the calculation of 1-year mortality in 2006. Patients were followed for up to 1-year from their start of follow-up. The start of follow-up was defined as the latest date of the following: 1) practice up-to-standard date per CPRD, 2) the current registration date for the patient, 3) the patient's 35th birthdate, 4) the start of the study on 01 January 2006, or 5) the date of COPD diagnosis. The end of follow-up was defined as the earliest date of the following: 1) transfer from practice, 2) last date for which practice data was available, 3) last date for which linked ONS data was available, or 4) the end of the study. For patients who did not develop HF during the year of interest (in this case 2006), censoring could also occur at the date of subsequent HF diagnosis (as in Example Patient #3).

Crude MRR were calculated comparing 1-year mortality rates of COPD-iHF patients in 2011 and 2015 with COPD-iHF patients in 2006 as the reference. Additionally, changes in long-term mortality were evaluated by comparing 5-year mortality rates (crude and adjusted) of COPD-iHF patients in 2011 with the 5-year mortality rate of COPD-iHF patients in 2006. This analysis was performed to evaluate the changes in the management of incident HF over a decade among patients with COPD.

Finally, 1-year, 5-year, and 10-year mortality rates ratios of COPD-iHF patients diagnosed in 2006 compared with COPD-no HF patients were calculated, stratified by severity of airflow limitation.

4.2.5 Cause of death

ONS mortality data was analysed to assess the trends in the cause of death for COPD-iHF and COPD-no HF over a decade (2006-2010 and 2011-2016). Additionally, cause of death by severity of airflow limitation (GOLD1-2 vs GOLD3-4) was assessed from 2006-2016 for COPD-iHF in 2006.

4.3 Results

4.3.1 Baseline Characteristics

181,705 COPD patients without a HF diagnosis were identified at the start of follow-up (**Figure 4.2**). COPD-iHF patients were more likely to be older, male, obese, former smokers and have moderate to severe airflow limitation (**Table 4.1**) compared with people with COPD-no HF. Additionally, they were more likely to have traditional risk factors for HF including atrial fibrillation, diabetes, hypertension, and vascular disease (ischaemic heart disease and peripheral artery disease) at the start of follow-up. Descriptive information stratified by type of HF and by year of incident HF are available in **Appendix IV**. The average length of follow-up for COPD-iHF and COPD-no HF in 2006, 2011, and 2015 can be found in **Table 4.2**.

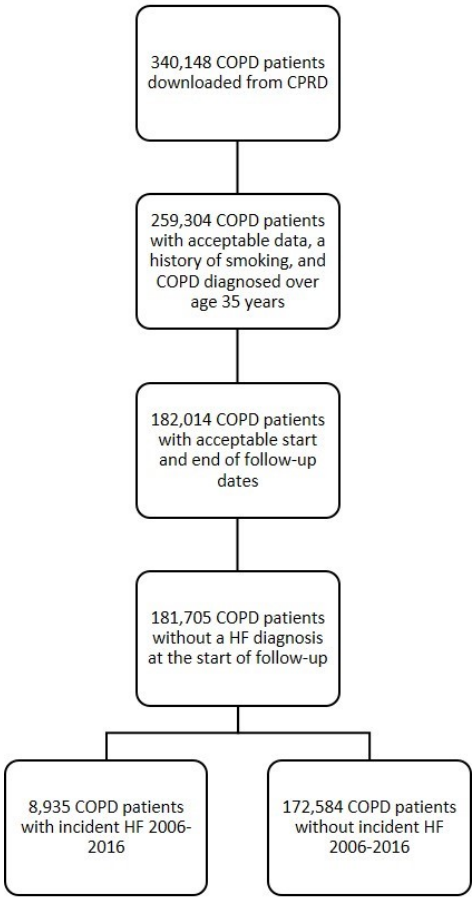

Figure 4.2. Defining the study population.

	Incident HF n (%)	No Incident HF n (%)
Number of Patients (N)	8,935	172,584
% of COPD patients	4.9	95.1
Female	3,480 (39.0)	81,542 (47.3)
Age at COPD Diagnosis, years Median (interquartile range)	69.4 (61.5, 76.4)	64.4 (56.4, 72.6)
Age at HF Diagnosis, years Median (interquartile range)	76.1 (69.0, 82.2)	~
Smoking Status		
Current Smoker	3,007 (33.7)	77,630 (45.0)
Former Smoker	5,928 (66.4)	94,954 (55.0)
Body Mass Index		
Underweight (< 18.5)	290 (3.3)	8,923 (5.2)
Healthy Weight (18.5-24.9)	2,403 (26.9)	58,312 (33.8)
Overweight (25.0-29.9)	2,869 (32.1)	53,702 (31.1)
Obese (>= 30)	3,131 (35.0)	45,491 (26.4)
Missing Data	242 (2.71)	6,156 (3.57)
GOLD Stage		
1: Mild	3,172 (35.5)	64,795 (37.5)
2: Moderate	1,819 (21.0)	36,241 (21.0)
3: Severe	1,231 (13.8)	18,108 (10.5)
4: Very Severe	285 (3.2)	4,015 (2.3)
Missing	2,428 (27.2)	49,425 (28.6)
HF Risk Factors‡		
Atrial Fibrillation	1,218 (13.6)	8,648 (5.0)
Diabetes	1,653 (18.5)	19,767 (11.5)
Hypertension	4,461 (49.9)	83,038 (48.1)
Ischaemic Heart Disease	27,241 (15.8)	2,936 (32.9)
Peripheral Artery Disease	909 (10.2)	10,263 (6.0)
Stroke	805 (9.01)	11,249 (6.52)

Table 4.1. Descriptive statistics. Presented for the COPD with incident HF during the study period and those without incident HF during the study period. GOLD staging of COPD severity [1]. ‡Recorded at start of follow-up; patients could have multiple risk factors.

Cohort	Average follow-up in years					
	1-year Mortality		5-year Mortality		10-year Mortality	
	Incident HF	No Incident HF	Incident HF	No Incident HF	Incident HF	No Incident HF
2006	0.83	0.95	2.69	3.82	5.51	3.51
2011	0.83	0.93	2.34	3.19	~	~
2015	0.70	0.81	~	~	~	~

Table 4.2. Average length of follow-up in years for 1-year, 5-year, and 10-year mortality analyses. Presented for the 2006, 2011, and 2015 cohorts by whether or not incident HF was experienced.

4.3.2 Incidence of HF among patients with COPD

The crude incidence of all HF types in the COPD population was steady from 2006 to 2016 (**Figure 4.3**), averaging 1.15 per 100 person-years (95%CI: 1.08, 1.24). Most commonly, type of HF was unspecified, the crude incidence of unspecified HF was relatively stable, averaging 0.57 per 100 person-years (95%CI: 0.51, 0.63). Left-sided only HF was the second most commonly recorded, averaging 0.47 per 100 person-years (95%CI: 0.42, 0.52). Right-sided only HF was the third most commonly recorded, averaging 0.11 per 100 person-years (95%CI: 0.09, 0.14). Lastly, biventricular failure averaged 0.02 per 100 person-years (95%CI: 0.01, 0.03).

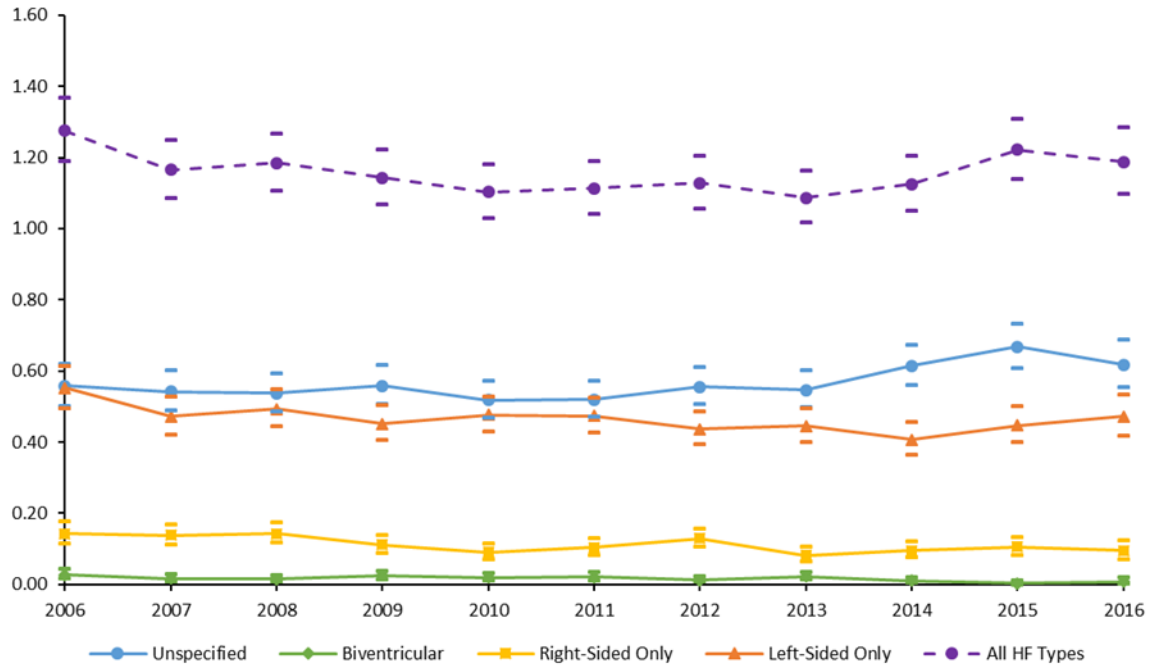

Figure 4.3. Crude incidence of HF types in the COPD population, 2006-2016. Incidence per 100 person-years. 95% confidence intervals shown.

4.3.3 Mortality

Comparison of mortality rates COPD-iHF vs COPD-no HF and the changes over time

In 2006, COPD-iHF patients experienced three times greater 1-year mortality (aHR 3.77, 95%CI: 2.81, 5.05) than COPD-no HF patients (**Figure 4.4a**). The trends were similar in 2011 (aHR 3.86, 95%CI: 3.04, 4.91) and 2015 (aHR 3.57, 95%CI: 2.64, 4.82) (**Figure 4.4a**). For 5-year mortality, COPD-iHF in 2006 experienced over two times greater 5-year mortality (aHR 2.52, 95%CI: 2.13, 2.99) than COPD-no HF patients in the same year, with similar trends

observed in 2011 (aHR 2.28, 95%CI: 1.99, 2.61) (**Figure 4.4b**). There was two-times greater 10-year mortality (aHR 2.00, 95%CI: 1.74, 2.30) experienced by COPD-iHF in 2006 when compared with COPD-no HF in 2006 (**Figure 4.4c**). The difference in mortality rates between COPD patients with incident HF diagnosed in 2006 compared with COPD patients without incident HF in 2006 was consistent over 10 years of follow-up (**Figure 4.5**).

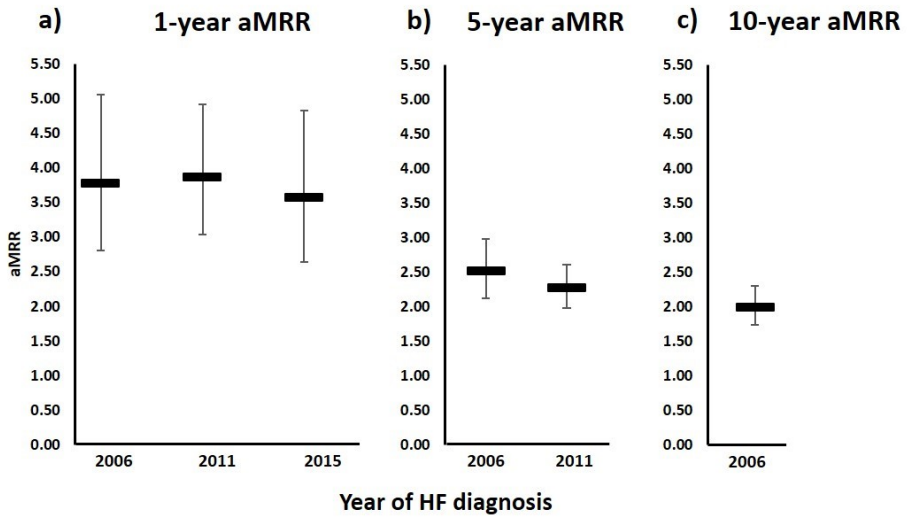

Figure 4.4. aMRR comparing the a) 1-year, b) 5-year, and c) 10-year mortality of COPD patients with incident HF in 2006, 2011, and 2015 with the 1-year, 5-year, and 10-year mortality of COPD patients without incident HF in 2006, 2011, and 2015, respectively.

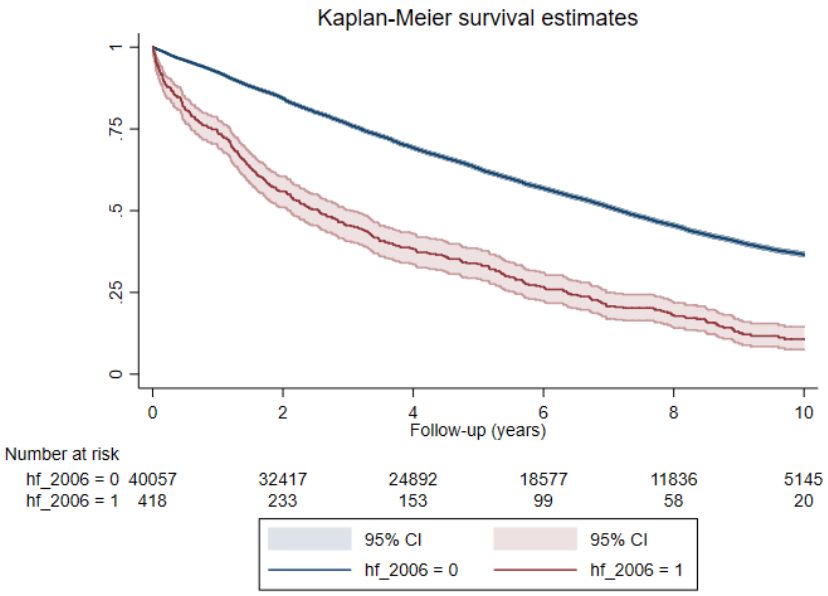

Figure 4.5. Kaplan-Meier survivor curve comparing COPD patients with and without incident HF in 2006 over 10 years of follow-up.

Comparison of mortality rates COPD-iHF by severity of airflow limitation

There was a higher 1-year mortality in COPD-iHF patients with more severe airflow limitation (GOLD1-2: aMRR 2.92, 95%CI: 1.99, 4.29; GOLD3-4: aMRR 4.05, 95%CI: 2.78, 5.89); however, this was not statistically significant (**Figure 4.6a**). There was no difference in the effect of incident HF on the 5-year (GOLD1-2: aMRR 2.15, 95%CI: 1.76, 2.62; GOLD3-4: aMRR 2.54, 95%CI: 2.01, 3.20) or 10-year (GOLD1-2: aMRR 1.82, 95%CI: 1.55, 2.14; GOLD3-4: aMRR: 1.95, 95%CI: 1.59, 2.40) mortality of COPD patients with GOLD3-4 versus GOLD1-2 (**Figure 4.6bc**). Patients without recent spirometry experienced mortality similar to GOLD1-2 patients (1-year: aMRR 2.93, 95%CI: 2.14, 4.02; 5-year: aMRR 2.33, 95%CI: 1.88, 2.88; 10-year: aMRR 2.01, 95%CI: 1.66, 2.44) (**Figure 4.7**).

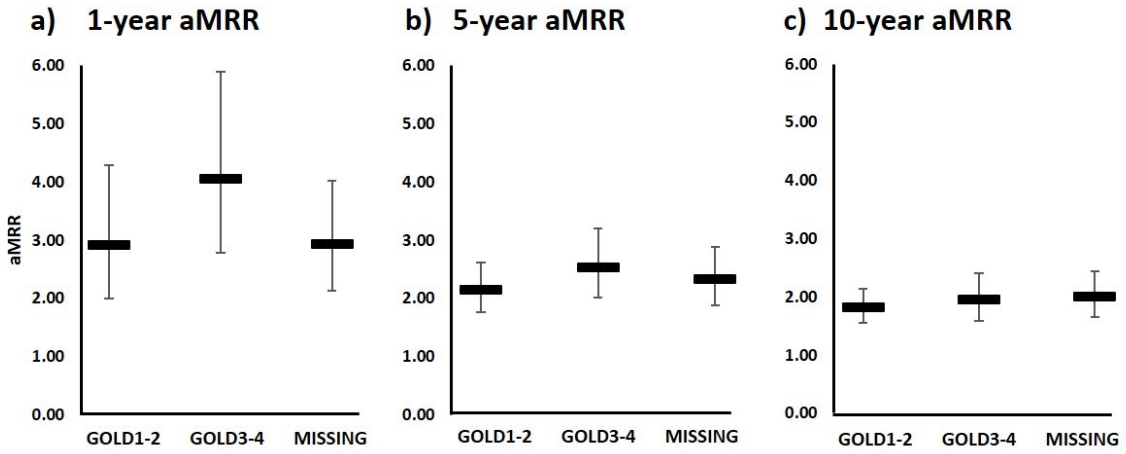

Figure 4.6. aMRR comparing the 1-year, 5-year, and 10-year mortality of COPD patients with incident HF in 2006 with the mortality of COPD patients without incident HF in 2006 stratified by severity of airflow limitation.

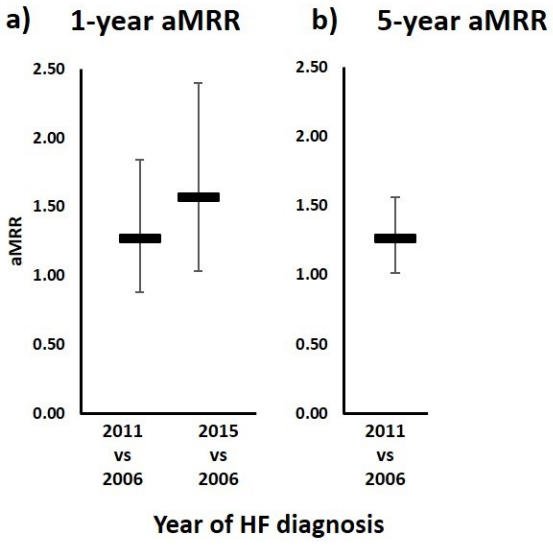

Figure 4.7. aMRR comparing the 1-year and 5-year mortality of COPD patients with incident HF in 2011 and 2015 with the mortality of COPD patients with incident HF in 2006.

Changes in the mortality rates among COPD-iHF patients from 2006 to 2016

COPD-iHF patients in 2011 (aHR 1.27, 95%CI: 0.88, 1.84) experienced 1-year mortality rates that were no different from those who developed incident HF in 2006 (**Figure 4.7a**). COPD-iHF patients in 2015 experienced was higher than in 2006 (aHR 1.57, 95%CI: 1.03, 2.40) (**Figure 4.7a**). The 5-year mortality rate among COPD-iHF patients in 2011 was similar (aHR 1.26, 95%CI: 1.01, 1.56) to COPD-iHF patients in 2006 (**Figure 4.7b**).

4.3.4 Causes of death

Overall, reported underlying causes of death by ICD-10 chapter within 5-years of HF diagnosis did not change for COPD-iHF patients diagnosed in 2011 as compared with patients diagnosed in 2006 (**Figure 4.8**). Approximately one third of all deaths were attributed to COPD, regardless of whether a patient experienced incident HF and regardless of whether incident HF occurred in 2006 or 2011 (**Table 4.3**). There increased in cardiovascular mortality over time among COPD-iHF patients, with a slightly higher proportion of deaths attributed to cardiovascular causes in 2011-2016 vs 2006-2010 (37% vs 31%) (**Figure 4.8**).

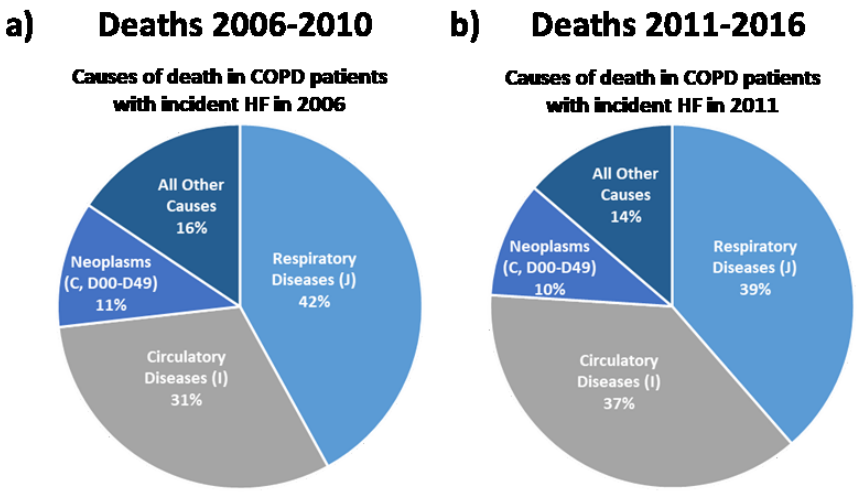

Figure 4.8. The proportion of deaths attributed to respiratory (J), circulatory (I), neoplasm (C, D00-D49), and all other causes for COPD patients with incident HF in 2006 and 2011 over five years of follow-up.

Underlying causes of death by severity of airflow limitation

For COPD-iHF in 2006, the proportion of deaths, over 10 years of follow-up, attributed to respiratory diseases increased with more severe airflow limitation (35% GOLD1-2 vs 40% GOLD3-4; **Figure 4.9**). The proportion of deaths attributed to cardiovascular diseases did not differ by airflow limitation (34% GOLD1-2 vs 33% GOLD3-4; **Figure 4.9**).

Deaths 2006-2010				
	COPD-iHF in 2006		COPD-no HF in 2006	
1	35.2%	COPD, bronchitis, emphysema (J40-J44)	31.0%	COPD, bronchitis, emphysema (J40-J44)
2	18.2%	Ischaemic heart disease/myocardial infarction (I21-23, I25)	13.1%	Lung/bronchus cancer (C34)
3	3.64%	Lung/bronchus cancer (C34)	11.0%	Ischaemic heart disease/myocardial infarction (I21-23, I25)
	2.83%	*Heart failure (I11.0, I13.0, I13.2, I50)*	*1.01%*	*Heart failure (I11.0, I13.0, I13.2, I50)*
Deaths 2011-2016				
	COPD-iHF in 2011		**COPD-no HF in 2011**	
1	31.5%	COPD, bronchitis, emphysema (J40-J44)	30.3%	COPD, bronchitis, emphysema (J40-J44)
2	21.2%	Ischaemic heart disease/myocardial infarction (I21-23, I25)	13.4%	Lung/bronchus cancer (C34)
3	5.00%	Cerebrovascular diseases (I60-I69)	9.72%	Ischaemic heart disease/myocardial infarction (I21-23, I25)
	3.08%	*Heart failure (I11.0, I13.0, I13.2, I50)*	*0.71%*	*Heart failure (I11.0, I13.0, I13.2, I50)*

Table 4.3. Proportion of deaths attributed to the top-3 underlying causes of death for all deaths of COPD patients with and without incident HF diagnosed in 2006 or 2011 over 5 years of follow-up. Including proportion of all deaths attributed to HF.

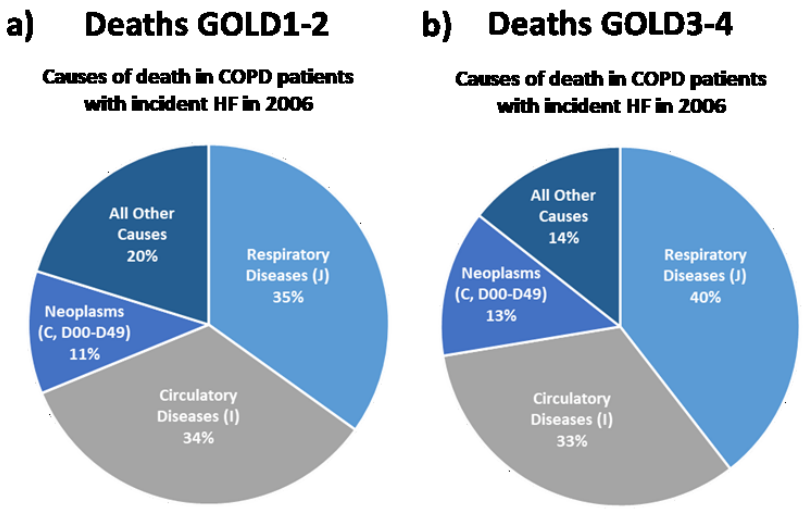

Figure 4.9. The proportion of deaths attributed to respiratory (J), circulatory (I), neoplasm (C, D00-D49), and all other causes for COPD patients with incident HF in 2006 over ten years of follow-up stratified by severity of airflow limitation. Severity of airways limitation was grouped as GOLD1-2 (mild-to-moderate) and GOLD3-4 (severe-very severe) [18].

4.4 Discussion

This study investigated the incidence of HF within a primary care COPD population and the impact of incident HF on mortality in these patients. The crude incidence of HF in the COPD population was steady over time and HF increased COPD patient mortality two-to-three times

that of COPD patients without HF. The effect of incident HF on the short- and long-term mortality of COPD patients did not change over time, nor was it different in relation to severity of airflow limitation.

The crude incidence of HF in the COPD population averaged to 1.15 per 100 person-years (95%CI: 1.08, 1.24). These results are in line with a previous, community-based, study that also found the incidence of HF in patients with severe airflow limitation to be 1.15 per 100 person-years [85]. The crude incidence of HF in the COPD population was steady over time; meanwhile, the crude incidence of HF in the general UK population is increasing [61]. It has previously been demonstrated that HF is often underdiagnosed in the COPD population [91, 174-176] and that COPD patients are at greater risk for developing HF and HF precursors, such as angina and myocardial infarction, than people without COPD [52]. COPD patients are also more likely to develop HFpEF than the general population, which is more difficult to diagnose than HFrEF [85-87]. Furthermore, COPD patients are systemically under-prescribed cardiovascular medications compared with people without COPD [166], which may hasten development of HF or increase HF severity. Taken together, these results suggest that recognition of HF in the COPD population is no better today than it was a decade ago, which would have significant implications for patient morbidity and mortality. HF is managed with survival-modifying medications, and COPD patients without a recognised diagnosis of HF may be missing out on therapies that could extend their life [69].

COPD-iHF patients experienced between three times greater 1-year and two times greater 5- and 10-year age- and sex-adjusted mortality over the study period compared with COPD-no HF patients. HF carries a worse prognosis than COPD [134], which could account for the increased mortality; however, this may not be the only driver. Previous research has shown that COPD patients with concomitant HF experience greater numbers of additional concomitant conditions (beyond COPD and HF) compared with COPD patients without concomitant HF [160] and that increased levels of comorbidity in COPD patients results in greater mortality [173]. Therefore, COPD patients with concomitant HF are also sicker more generally compared with COPD patients without HF, and this, in addition to the poorer prognosis for HF, may contribute to the higher mortality seen in COPD-iHF compared with COPD-no HF.

COPD-iHF patients experienced greater short- and long-term mortality than COPD-no HF patients, regardless of severity of airflow limitation; however, the effect of HF on COPD

patient mortality, short- or long-term, did not differ by severity of airflow limitation. There was slightly greater effect of HF comorbidity on the 1-year mortality of COPD patients with more severe airflow limitation (GOLD3-4) compared with COPD patients with milder airflow limitation (GOLD1-2); however, there was considerable variance in the estimates due to short follow-up time and few deaths within 1-year of HF diagnosis. As time went on, the variance of the estimates decreased and the difference in the effect of HF comorbidity on 5-year and 10-year mortality of COPD patients with more severe airflow limitation was no different than for COPD patients with milder airflow limitation. This may reflect a survival bias, whereby those patients who survive incident HF are eventually managed with cardiovascular medications, and this management is not dependent on severity of airflow limitation. This is supported by previous work by Dransfield et al., who found no difference in lung function between COPD patients on beta-blockers and those not on beta-blockers [277]. It is important to note that despite no difference in the effect of HF on long-term mortality of COPD patients based on airflow limitation, these patients still experience higher mortality than COPD-no HF patients with similar airflow limitation. This may be attributed to the higher mortality of HF than COPD [134], the higher comorbidity burden of COPD patients with HF [160, 173], and/or the systemic under-treatment of cardiovascular conditions in COPD patients [166].

Previously, Lawson et al. found the effect of COPD on mortality of incident HF patients increased with increasing airflow limitation compared with incident HF patients without COPD with a median follow-up of 2.6 years [278]. When looking only at incident HF patients with COPD, Lawson et al. found significantly greater adjusted odds of mortality for patients with more severe airflow limitation (GOLD3-4) compared with those with milder airflow limitation (GOLD1-2) [278]. The main difference between these analyses and that of Lawson et al. is that mortality rate was evaluated here, while Lawson et al. evaluated odds of mortality. Here, a trend towards increased effect of HF on the mortality rate of COPD patients with more severe airflow limitation in the short-term (1-year) was seen, but the difference was not significant and attenuated when looking at longer-term mortality rates. The cohort from Lawson et al. had a higher proportion of patients with severe-to-very-severe airflow limitation than this cohort, which may also contribute to the differences.

Previously, Mannino et al. found that increased respiratory impairment was associated with a greater effect of cardiovascular comorbidity on 5-year risk of death from baseline [279]. This present analysis is different from that of Mannino et al. in a number of ways. Firstly, the effect

of incident HF on COPD patient mortality was evaluated here, whereas Mannino et al. looked at a combined cardiovascular variable for those patients with history of myocardial infarction, stroke, heart failure, angina, or transient ischaemic attack at baseline. Secondly, mortality in both the short- and long-term from date of incident HF diagnosis was assessed here, whereas Mannino et al. evaluated 5-year mortality from baseline without information on cardiovascular disease duration. Finally, mortality rate ratios comparing COPD patients with incident HF with those without incident HF were calculated here, whereas Mannino et al. evaluated mortality risk for COPD patients with cardiovascular comorbidity and for COPD patients without cardiovascular comorbidity. A composite 'cardiovascular comorbidity' exposure may not reflect the heterogeneity of conditions that could be considered to fit within such a variable (e.g. angina vs heart failure), nor is what conditions to include in a 'cardiovascular comorbidity' variable standardised (e.g. some include cerebrovascular disease and/or diabetes).

The 1-year and 5-year mortality of COPD-iHF patients did not change over time, whereas survival following incident HF has improved in the general population [65]. HF is diagnosed later in COPD patients compared with the general population [127], which may mean HF is diagnosed when it is more severe and more likely to contribute to mortality. Delays in HF diagnosis in the COPD population correspond with delayed cardiovascular treatment initiation [127]. Additionally, there is systemic under treatment of HF in the COPD population compared with the general population [166]. The delay or absence of survival-modifying HF therapies in COPD patients with HF could account for why COPD patients with HF have not experienced the same survival gains as seen in the general population with HF.

Causes of death at the ICD-10 chapter level did not significantly change over the study period in COPD-iHF patients; however, the proportion of deaths attributed to cardiovascular causes in the COPD-iHF population rose minimally from 31% to 37% over the study period. This contrasts with the trend seen in the wider COPD population towards decreasing cardiovascular deaths [12]. Increasing mortality attributed to cardiovascular causes in the COPD-iHF population suggests greater recognition of the role of cardiovascular disease in the morbidity and mortality of COPD patients with diagnosed cardiovascular disease.

Taylor et al. looked at causes of death in HF patients from the general UK primary care population from 2000-2017, but did not look at changes over time [65]. Taylor et al. found that 55.7% of HF patient deaths were attributed to cardiovascular causes [65], which is much more

than the 37% of deaths attributed to cardiovascular causes in the COPD-iHF population from 2011-2016 seen here. The difference does appear to be made up by a greater proportion of deaths attributed to respiratory causes in the COPD-iHF population than in the wider HF population (COPD-iHF vs wider HF population [65]: 40% vs 16%) as proportions of death attributed to all other causes were similar in the two populations. Increasing airflow limitation brought an increase in deaths attributed to COPD but no change in deaths attributed to cardiovascular causes in COPD-iHF patients. These trends are similar to those seen in the wider COPD population, where deaths due to respiratory causes increase and deaths due to cardiovascular causes decrease with increasing airflow limitation [280]. This may represent a survival bias, whereby patients with more severe COPD have survived long enough for COPD to progress by avoiding earlier severe cardiovascular morbidity or mortality.

4.4.1 Strengths and Limitations

A major strength of this study is the use of one of the largest longitudinal, nationally representative databases in the world, CPRD [236], linked with mortality data from ONS that is nearly 100% complete [281]. There is a potential for misclassification of cause of death; however, in a review undertaken by ONS, the proposed and confirmed underlying cause of death matched at ICD chapter level in 88% of cases and there was exact agreement (to 4 digits) in 78% of cases, rising to 80% when records matching to 3 digits were included [282]. A potential limitation is the validity of case definitions within electronic health care records. A validated case definition for COPD was used [261]; however, no validation of a case definition for HF has been undertaken in CPRD. Read codes reviewed by two cardiologists and two respiratory physicians were used to identify HF. Another limitation is that measurements of ejection fraction and biomarkers used to determine the severity of HF are not available in CPRD data. Recording of HF type was rare with most codes referring to unspecified HF.

4.5 Conclusions

Steady incidence of HF in the COPD population suggests that a substantial proportion of HF cases are still going undiagnosed. COPD patients with concomitant HF experience higher short- and long-term mortality rates than those without HF. COPD patients with incident HF have not seen the same increases in survival previously seen in the general population with incident HF. Bespoke clinical guidelines for the diagnosis and management of HF in the presence of COPD are needed in order to improve survival.

Chapter V: Effect of unrecognised and confirmed heart failure on AECOPD risk

5.1 Introduction

The previous aim established that HF comorbidity is associated with increased morbidity and mortality in the COPD population (**Chapter II**). Additionally, Specific Aim #1 showed that the recognition of HF comorbidity in the COPD population has not improved over time and that the COPD population with HF has not seen survival gains over the past decade, contrary to the general population with HF (**Chapter IV**). This chapter explores Specific Aim #2, to determine the effect of HF comorbidity on exacerbation risk in COPD patients.

There have been a number of studies investigating the effect of cardiovascular disease on AECOPD; however, results from previous studies are conflicting, possibly as a result of these varied exposure definitions. Some studies have found that cardiovascular comorbidity is associated with greater AECOPD risk or rate. Cardiovascular comorbidity, defined as diagnosis, procedure, or cardiovascular medication within +/- 1 year of COPD diagnosis, was associated with significantly increased risk for AECOPD hospitalisation or A&E visit in the following year [158]. In another study, having one or more cardiovascular condition, defined using the *Medical Dictionary for Regulatory Activities* [283], significantly increased AECOPD risk [217]. McGarvey et al. found that frequent exacerbators with ≥2 exacerbations in the previous year, experienced a higher rate of cardiovascular comorbidity than infrequent exacerbators [114].

Contrastingly, other studies have found no difference in AECOPD risk or rate based on cardiovascular comorbidity. IHD was not associated with increased rate of AECOPD in a study by Patel et al., although IHD was associated with increased length of AECOPD symptom duration [284]. Similarly, cardiovascular comorbidity, defined as IHD, PAD, stroke, MI, or diabetes with target organ disease, did not increase AECOPD rate in the ACCESS study (NCT01516528) [161].

Composite 'cardiovascular comorbidity' variables are useful in many ways, but are not standardised as to what should be included; for example, some studies include cerebrovascular

diseases or diabetes in the composite [161], while others do not include these conditions [114]. Nor do composite 'cardiovascular comorbidity' variables detail how individual cardiovascular conditions effect the outcome; for example, angina may have a very different effect on AECOPD than HF. The use of unstandardized, composite cardiovascular disease variables as exposures and the subsequent conflicting results have thus far failed to assess the impact of these common comorbidities on AECOPD risk in the COPD population.

The primary purpose of these analyses is to determine the effect of HF comorbidity on AECOPD risk. Additionally, since diagnosis of HF is often delayed or absent in the COPD population [127, 176], patients with 'possible HF' were identified and their risk for AECOPD was assessed.

Supplementary information for this chapter is located in **Appendix V**. A publication produced in association with this chapter is currently undergoing peer-review (see **Appendix VIII**).

5.2 Methods

5.2.1 Data sources

Data were obtained from CPRD, HES, and ONS, which are described in **Chapter III**. The study period was 01/01/2006 to 31/12/2016.

5.2.2 Inclusion criteria

COPD and HF patients were identified as described in **Chapter III**. HF was identified through diagnosis in primary care and HF diagnosis must have followed COPD diagnosis. Patients with chronic kidney disease stages 3-5, nephrotic syndrome, and chronic liver disease were excluded, as these are non-cardiac indications for loop diuretic use. Possible HF was defined as continuous loop diuretic use, in the absence of other indications and in the absence of a HF diagnosis in primary care. Continuous use was defined as three consecutive prescriptions within 100 days, as the indication for loop diuretic use is less certain GPs may be more likely to prescribe shorter trial periods than with other medications. Possible HF, identified through loop diuretic use, has been investigated previously [285].

5.2.3 Outcome

Moderate and severe AECOPD were identified as described in **Chapter III**.

5.2.4 Follow-up

Start of follow-up was defined as the latest of: 1) date data was deemed acceptable for research by CPRD, 2) date from which the patient has continuous data, 3) date of COPD diagnosis or date of exposure, if exposed, or 4) the start of the study on 01/01/2006. Patients were censored upon 1) transferring from the practice, 2) last data collection from the practice, 3) last date for which linked data was available, 4) death, or 5) the end of the study on 31/12/2016.

5.2.5 Covariates

Sex, age groups, smoking status, BMI, severity of airflow limitation per GOLD [1], COPD inhaler use, and cardiovascular medication use were defined at baseline as described in **Chapter III**. COPD inhalers included SABA, SAMA, LABA, LAMA, ICS, or combination. Cardiovascular medications included ACEi, ARB, beta-blockers, CCB, MRA, statins, and vasodilators. History of cardiovascular disease included prior diagnosis of IHD, PAD, AF, HTN, and/or stroke, which were identified as described in **Chapter III**.

5.2.6 HF hospitalisation and investigation

HF hospitalisation, cardiology outpatient visits, and referral for BNP test or echocardiography were identified in CPRD and HES as described in **Chapter III**.

5.2.7 Cohort matching

COPD patients with possible or diagnosed HF were matched 1:2 on sex and age (+/- 1.0 year) to COPD patients without evidence of HF. The matched cohort design limited the sex and age differences between cohorts.

5.2.8 Statistical analyses

Risk of moderate-severe AECOPD were assessed using Stratified Cox regression. Beyond matching, age and sex were further controlled for using the Stratified Cox regression model. Stratified Cox regression allowed the baseline hazards to vary between each matched set, and thus sex and age [286, 287]. Robust variance estimates were used to account for possible clustering by GP, allowing for some control over differences in diagnostic and prescribing procedures between GPs. Regression was adjusted for the covariates listed above. Adjusted hazard ratios (aHR) compared AECOPD risk in patients with possible or diagnosed HF to

AECOPD risk in COPD patients without evidence of HF. The proportionality assumption for Cox regression was assessed for each model using Schoenfeld residuals [288]. The proportional hazards assumption for Cox regression requires that the hazard ratio is constant over time [286].

5.2.9 Sensitivity analyses

Firstly, risk for AECOPD was compared in COPD patients with a diagnosis of HF (with or without chronic kidney or liver disease) to COPD patients without a diagnosis of HF (with or without chronic kidney or liver disease). This was to assess whether excluding patients with chronic kidney or liver disease changed AECOPD risk in the populations.

Secondly, risk for AECOPD was compared in possible HF patients with evidence of HF investigation at any time in their history to possible HF patients without evidence of HF investigation. HF investigation was defined as any cardiology outpatient visit, echocardiography code, or BNP code in a patient's history. This was to assess whether there was a difference in AECOPD risk between possible HF patients who may have been investigated and HF diagnosis may have been ruled out and those who did not appear to be investigated for HF.

Thirdly, risk for AECOPD was compared between possible HF patients who had a cardiology outpatient visit with those who only had an echocardiography or BNP test. This was to assess whether investigation of HF in secondary care affect AECOPD risk compared to those investigated within primary care.

Lastly, patients with a history of HF hospitalisation without a primary care diagnosis were reclassified as having newly diagnosed HF, as opposed to possible HF. Classifying COPD patients with a HF hospitalisation during follow-up, but no HF diagnosis recorded in primary, as having a HF diagnosis made 449 possible HF patients become prevalent HF patients prior to the start of follow-up and made 532 possible HF patients become newly diagnosed HF patients during follow-up. Patients were then matched according to their new status and regression performed per the methods.

5.3 Results

There were 86,795 COPD patients without prevalent HF and without chronic kidney or liver disease at the start of follow-up. Of these, 60,047 patients had no evidence of HF, 8,476 patients had possible HF, and 2,066 patients had HF diagnosed during follow-up (**Figure 5.1**). COPD patients with possible or diagnosed HF were older, former smokers, obese, with GOLD3-4, greater exacerbation history, increased triple inhaler therapy (LABA+LAMA+ICS), and had a greater history of cardiovascular disease compared to COPD patients without evidence of HF (**Table 5.1**). Patients with newly diagnosed HF had a median 6 month (IQR: 0.11, 2.12) loop diuretic use prior to their HF diagnosis (**Table 5.2**). Patients with possible HF had a median of 1.85 years (IQR: 0.90, 3.81) of loop diuretics use before the end of follow-up (**Table 5.2**).

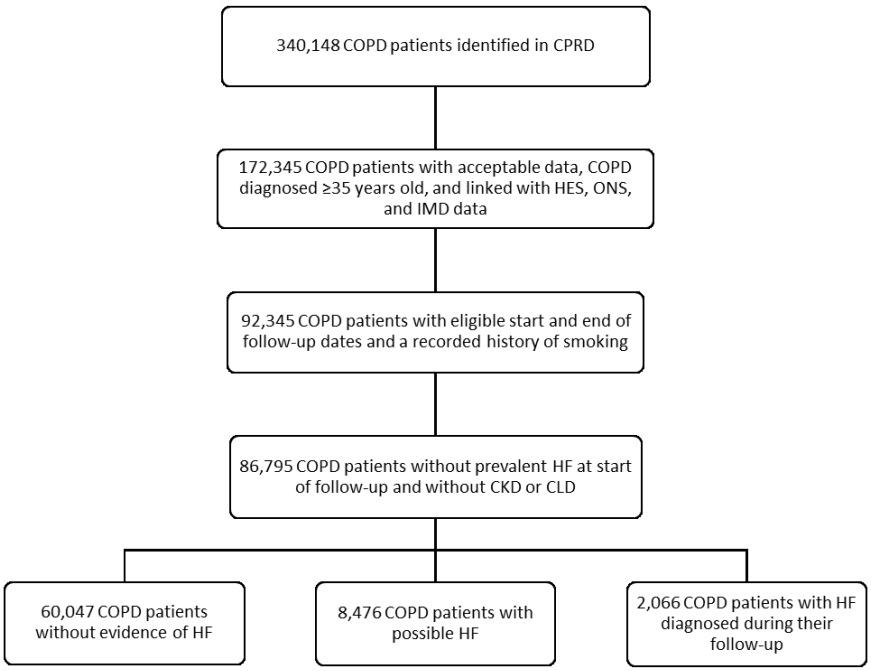

Figure 5.1. Derivation of the study population for analyses of the influences of HF on exacerbation.

	COPD patients without evidence of HF	COPD patients with possible HF	COPD patients with diagnosed HF
Number of Patients (N)	60,047	8,476	2,066
Female	27,155 (45.2)	4,247 (50.1)	743 (36.0)
Age, years (IQR)	66 (59, 74)	73 (66, 80)	74 (67, 81)
Smoking Status			
Current Smoker	26,291 (43.8)	2,566 (30.3)	497 (24.1)
Former Smoker	33,756 (56.2)	5,910 (69.7)	1,569 (75.9)
Body Mass Index			
Underweight (< 18.5)	3,295 (5.49)	356 (4.20)	113 (5.47)
Healthy Weight (18.5-24.9)	21,463 (35.7)	2,253 (26.6)	640 (31.0)
Overweight (25.0-29.9)	18,982 (31.6)	2,339 (27.6)	595 (28.8)
Obese (>= 30)	14,581 (24.3)	3,183 (37.6)	667 (32.3)
Missing Data	1,726 (2.9)	345 (4.1)	51 (2.5)
Index of Multiple Deprivation			
1 – Most deprived	8,581 (14.3)	1,144 (13.5)	268 (13.0)
2	11,540 (19.2)	1,718 (20.3)	403 (19.5)
3	11,698 (19.5)	1,613 (19.0)	406 (19.7)
4	13,978 (23.3)	1,972 (23.3)	473 (22.9)
5 – Least deprived	14,250 (23.7)	2,029 (23.9)	516 (25.0)
GOLD Stage			
1: Mild	23,860 (39.7)	2,998 (35.4)	703 (34.0)
2: Moderate	15,336 (25.5)	1,762 (20.8)	486 (23.5)
3: Severe	7,767 (12.9)	1,449 (17.1)	426 (20.6)
4: Very Severe	1,776 (3.0)	401 (4.7)	166 (8.0)
Missing	11,308 (18.8)	1,866 (22.0)	285 (13.8)

	COPD patients without evidence of HF	COPD patients with possible HF	COPD patients with diagnosed HF
Exacerbation History*	1.52 (0-15)	2.17 (0-13)	2.70 (0-14)
COPD medications†			
SABA/SAMA	37,990 (63.3)	6,222 (73.4)	1,489 (72.1)
LABA alone	1,453 (2.4)	250 (3.0)	31 (1.5)
LAMA alone	4,744 (7.9)	537 (6.3)	163 (7.9)
ICS alone	5,969 (9.9)	947 (11.2)	92 (4.5)
LABA+LAMA	631 (1.1)	81 (1.0)	29 (1.4)
LABA+ICS	14,685 (24.5)	2,435 (28.7)	476 (23.0)
LAMA+ICS	1,121 (1.9)	206 (2.4)	27 (1.3)
Triple	10,239 (17.1)	1,925 (22.7)	823 (39.8)
No long-acting inhaler	21,205 (35.3)	2,095 (24.7)	425 (20.6)
History of Cardiovascular Disease‡	29,504 (49.1)	6,527 (77.0)	1,687 (81.7)
Atrial fibrillation	2,120 (3.5)	999 (11.8)	671 (32.5)
Hypertension	24,759 (41.2)	5,474 (64.6)	1,033 (50.0)
Ischaemic heart disease	7,343 (12.2)	2,231 (26.3)	838 (40.6)
Peripheral artery disease	3,023 (5.0)	654 (7.7)	222 (10.8)
Stroke	3,195 (5.3)	788 (9.3)	231 (11.2)
Diabetes mellitus	5,794 (9.7)	1,358 (16.0)	459 (22.2)
CVD medications†			
ACEi	9,789 (16.3)	2,446 (28.7)	1,230 (59.5)
ARB	3,538 (5.9)	900 (10.6)	332 (16.1)
Beta-blockers	4,491 (7.5)	1,007 (11.9)	737 (35.7)
Calcium channel blockers	5,054 (8.4)	1,464 (17.3)	329 (15.9)
MRA	248 (0.4)	276 (3.3)	479 (23.2)
Statins	17,000 (28.3)	3,499 (41.3)	1,152 (55.8)
Vasodilators	3,504 (5.8)	1,257 (14.8)	320 (15.5)

Table 5.1. Descriptive statistics for COPD patients without evidence of HF, possible HF, and newly diagnosed HF. Severity of airflow limitation using the GOLD guidelines [1]. *Average number of exacerbations per patient (range) in the year prior to the start of follow-up. †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

5.3.1 HF hospitalisation and investigation

A history of HF hospitalisation, prior to HF diagnosis in primary care, was seen in 33.5% of newly diagnosed HF patients with a median of 1 year (IQR: 0.72, 1.04) between the most recent HF hospitalisation and diagnosis (**Table 5.2**). A history of HF hospitalisation, prior to end of follow-up, was seen in 11.6% of possible HF patients with a median of 1.68 years (IQR: 0.42, 4.13) between the most recent HF hospitalisation and the end of follow-up (**Table 5.2**).

	Possible HF N = 8,476	**Newly Diagnosed HF N = 2,066**
Median length of time on loop diuretics before end of follow-up or HF diagnosis	1.85 years (IQR: 0.90, 3.81)	0.50 years (IQR: 0.11, 2.12)
History of HF hospitalisation (n, %) HF as primary or secondary diagnostic code	981 (11.6)	692 (33.5)
Median time between most recent HF hospitalisation and end of follow-up or HF diagnosis	1.68 years (IQR: 0.42, 4.13)	1.00 year (IQR: 0.72, 1.04)
History of echocardiography (n, %)	3,569 (42.1)	1,854 (89.7)
Median time between most recent echocardiography and end of follow-up or HF diagnosis	2.76 years (IQR: 1.18, 5.28)	1.00 year (IQR: 0.83, 1.15)
History of BNP test (n, %)	1,480 (17.5)	425 (20.6)
Median time between most recent BNP test and end of follow-up or HF diagnosis	1.78 (IQR: 0.81, 3.18)	1.08 years (IQR: 1.00, 1.31)
History of an outpatient cardiology visit (n, %)	1,249 (14.7)	435 (21.1)
Median time between most recent outpatient cardiology visit and end of follow-up or HF diagnosis	1.93 years (IQR: 0.67, 4.63)	2.98 years (IQR: 1.54, 4.99)
History of HF investigation: echocardiography, BNP test, and/or outpatient cardiology visit	4,545 (53.6)	1,898 (91.9)

Table 5.2. Proportion of COPD patients with possible HF and newly diagnosed HF with a history of hospitalisation due to HF, a history of echocardiography, a history of BNP measures, and/or a history of an outpatient cardiology visit and the median (IQR) time between the most recent of these and the end of follow-up or HF diagnosis.

A history of echocardiography, prior to HF diagnosis in primary care, was seen in 89.7% of newly diagnosed HF patients with a median of 1 year (IQR: 0.83, 1.15) between the most recent echocardiography and diagnosis (**Table 5.2**). A history of echocardiography, prior to end of follow-up, was seen in 42.1% of possible HF patients with a median of 2.76 years (IQR: 1.18, 5.28) between the most recent echocardiography and the end of follow-up (**Table 5.2**).

A history of BNP test, prior to HF diagnosis in primary care, was seen in 20.6% of newly diagnosed HF patients with a median of 1.08 years (IQR: 1.00, 1.31) between the most recent BNP test and HF diagnosis (**Table 5.2**). A history of BNP test, prior to end of follow-up, was

seen in 14.7% of possible HF patients with a median of 1.78 years (IQR: 0.81, 3.18) between the most recent BNP test and the end of follow-up (**Table 5.2**).

A history of cardiology outpatient visit, prior to HF diagnosis in primary care, was seen in 21.1% of newly diagnosed HF patients with a median of 2.98 years (IQR: 1.54, 4.99) between the most recent of these and HF diagnosis (**Table 5.2**). A history of cardiology outpatient visit, prior to end of follow-up, was seen in 14.7% of possible HF patients with a median 1.93 years (IQR: 0.67, 4.63) between the most recent of these and the end of follow-up (**Table 5.2**).

In all, 91.9% of newly diagnosed HF patients had evidence of HF investigation at any time prior to their HF diagnosis in primary care, while 53.6% of possible HF patients had evidence of HF investigation at any time prior to the end of follow-up (**Table 5.2**).

5.3.2 Effect of newly diagnosed HF on AECOPD risk

There were 2,066 patients with newly diagnosed HF, of whom 100% were matched to 4,132 patients without evidence of HF (**Supplementary Table 5.1**). COPD patients with newly diagnosed HF experienced 1.45 times greater risk for moderate-to-severe AECOPD than COPD patients without evidence of HF (**Figure 5.2**; 95%CI: 1.30, 1.62), following adjustments. The crude estimate was 1.62 (95%CI: 1.53, 1.72).

5.3.3 Effect of possible HF on AECOPD risk

There were 8,423 patients with possible HF, of whom 99.4% were matched to 16,792 patients without evidence of HF (**Supplementary Table 5.2**). COPD patients with possible HF experienced 1.65 times greater risk for moderate-to-severe AECOPD than COPD patients without evidence of HF (**Figure 5.2**; 95%CI: 1.58, 1.72), following adjustments. The crude estimate was 1.69 (95%CI: 1.64, 1.75), but did not meet the proportionality requirement for Cox regression ($p = 0.0000$).

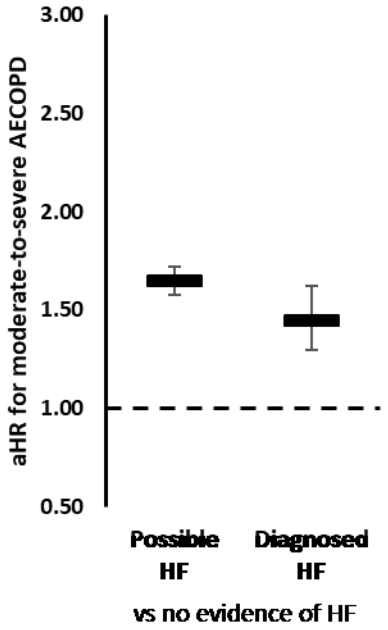

Figure 5.2. aHR comparing risk for moderate-to-severe exacerbations of in COPD patients with possible HF and diagnosed HF compared to COPD patients without evidence of HF. Estimates from Stratified Cox regression stratified by matched set (sex and age) and adjusted for smoking status, body mass index, index of multiple deprivation, exacerbation history, severity of airflow limitation, inhaler use, history of cardiovascular disease, and cardiovascular medication use.

5.3.4 Sensitivity analyses

Including patients with chronic kidney or liver disease

COPD patients with a diagnosis of HF, with or without chronic kidney or liver disease, experienced 1.47 times greater risk for moderate-to-severe AECOPD (95%CI: 1.32, 1.63) and 2.08 times greater risk for severe AECOPD (95%CI: 1.66, 2.60), following adjustments, than COPD patients without a diagnosis of HF, with or without chronic kidney or liver disease. The crude estimates were 1.43 (95%CI: 1.36, 1.51) for moderate-to-severe AECOPD and 2.01 (95%CI: 1.84, 2.21) for severe AECOPD. The crude model for severe AECOPD did not meet the proportionality requirement for Cox regression ($p = 0.0326$).

Investigated vs not investigated for HF in possible HF patients

COPD patients with possible HF without evidence of ever being investigated for HF experienced 1.27 times greater risk for moderate-to-severe AECOPD (95%CI: 1.18, 1.38), following adjustments, than COPD patients with possible HF with evidence of ever being investigated for HF. There was no difference in risk for severe AECOPD between these groups (HR = 1.15, 95%CI: 0.98, 1.34). The crude estimates were 1.34 (95%CI: 1.27, 1.42) for moderate-to-severe AECOPD and 1.33 (95%CI: 1.21, 1.46) for severe AECOPD.

COPD patients with possible HF with evidence of ever being investigated for HF experienced 1.54 times greater risk for moderate-to-severe AECOPD (95%CI: 1.43, 1.65) and 2.34 times greater risk for severe AECOPD (95%CI: 2.01, 2.74), following adjustments, than COPD patients with no evidence of HF. The crude estimates were 1.48 (95%CI: 1.42, 1.55) for moderate-to-severe AECOPD and 2.16 (95%CI: 1.99, 2.34) for severe AECOPD, but both these models did not meet the proportionality assumption (p = 0.0093 and p = 0.0285, respectively).

Cardiology visit vs echocardiography/BNP only in possible HF patients

There was no difference in moderate-to-severe AECOPD risk (aHR = 0.96, 95%CI: 0.84, 1.10) or severe AECOPD risk (aHR = 0.79, 95%CI: 0.59, 1.05), following adjustments, in COPD patients with possible HF with a cardiology outpatient visit ever compared to those with an echocardiography or BNP test ever. The crude estimates were 1.04 (95%CI: 0.95, 1.14) for moderate-to-severe AECOPD and 1.02 (95%CI: 0.87, 1.20) for severe AECOPD.

History of HF hospitalisation in the absence of a primary care diagnosis treated as having HF

Compared to COPD patients without evidence of HF, COPD patients with newly diagnosed HF (including patients with HF hospitalisation during follow-up, but no primary care HF diagnosis) experienced greater risk for moderate-to-severe AECOPD (aHR = 1.63, 95%CI: 1.49, 1.79).

Compared to COPD patients without evidence of HF, COPD patients with possible HF (excluding patients with history of HF hospitalisation or HF hospitalisation during follow-up, but no primary care diagnosis) experienced a greater risk for moderate-to-severe AECOPD (aHR = 1.69, 95%CI: 1.61, 1.76).

5.4 Discussion

COPD patients with possible and newly diagnosed HF experienced significantly greater risk for moderate and severe AECOPD compared to COPD patients without evidence of HF. COPD patients with possible HF experienced higher risk for moderate and severe AECOPD compared to COPD patients with newly diagnosed HF, but this was not statistically significant. Notably, COPD patients with possible HF were more similar to COPD patients with newly diagnosed

HF in demographic and baseline characteristics than COPD patients without evidence of HF. COPD patients with possible HF without a history of HF investigation experienced higher risk for moderate and severe AECOPD compared to those who had a history of HF investigation; however, those with a history of HF investigation still experienced higher risk for moderate and severe AECOPD than COPD patients without evidence of HF.

Previous research has shown under recognition of HF in a variety of COPD populations [91], which logically suggests the existence of a group of COPD patients with possible HF. In patients with COPD, the median time between symptom presentation and HF diagnosis in UK primary care has been showed to be over 3 years, compared to only 2.4 years in patients without COPD [127]. HF treatment is delayed as well, with COPD patients waiting 2.9 years compared to only 1.9 years in patients without COPD [127]. Under recognition and delayed diagnosis of HF occur in the COPD population despite evidence that COPD patients are at increased risk for HF compared to patients without COPD and that this risk is especially noticeable at younger ages [52]. Possible HF patients were more likely to be female and/or obese compared to patients with newly diagnosed HF, which may indicate a proclivity towards HFpEF [85-87]. HFpEF is difficult to diagnosis, as it requires the systematic elimination of other possible causes, including COPD [85-87]. Clinicians may be less inclined to suspect or diagnosis HF in these patient populations, as they are in the COPD population as a whole.

The NICE guidelines for the diagnosis of chronic HF in the UK recommend that patients with suspected HF undergo BNP measurement, echocardiography, and/or referral to a cardiologist [69]; however, this recommended pathway is rarely followed in primary care [270, 289] and any investigation is often delayed in the COPD population [127]. Air trapping due to pulmonary disease can affect echocardiogram acoustic windows leading to unsatisfactory imaging quality and making diagnosis even more difficult [132]. Severity of COPD may be overestimated in patients with comorbid HF as part of the reduction may be caused by HF [290]. Previous cohort studies have found the up to 26% of exacerbations may be triggered by HF or other cardiovascular conditions, such as arrhythmia [115-117]. Underlying cardiac problems have been seen in around a quarter of exacerbation episodes when echocardiography has been performed [118, 119].

There was no record of HF investigation at any time for nearly half of COPD patients with possible HF. Of those who were investigated, half of the investigations were nearly two years

old. In contrast, over 90% of COPD patients with newly diagnosed HF were investigated, most within one year of their diagnosis in primary care. Only 15% of COPD patients with possible HF patients and 20% of COPD patients with newly diagnosed HF patients were referred to a cardiologist, less than the 38% of general population patients diagnosed with HF in a previous study [270]. HF-related hospitalisation prior to diagnosis in primary care was rare, with only one third of COPD patients with newly diagnosed HF and only 12% of COPD patients with possible HF having this in their history. This is contrary to evidence suggesting that the majority of HF cases in the general population are first identified in secondary care [270]. This evidence suggests that there is the opportunity for earlier recognition of HF in COPD patients in the primary care setting.

Possible and newly diagnosed HF were both associated with an increased risk for moderate and severe AECOPD in the COPD population. There are a number of possible mechanisms for the effect of HF on AECOPD risk. Firstly, delayed or sub-optimal management of HFrEF may hasten the progression of HFrEF and/or patient decline, leading to increased AECOPD risk. The prescription of beta-blockers is particularly substandard [166] and research has shown delays in procuring HF treatment in the COPD population [127]. Similarly, the absence of evidence-based management for HFpEF [103, 291] may also contribute to increased AECOPD risk. Secondly, COPD patients with HF are also more likely to have additional comorbidity burden compared to COPD patients without HF [160, 292]. Increased comorbidity burden is associated with increased risk for death [173] and increased systemic inflammation [92, 292], which may translate to increased AECOPD risk. For patients with HFpEF the role of systemic inflammation in increasing AECOPD risk may be particularly profound, as systemic inflammation due to comorbidities is thought to contribute significantly to the aetiology of HFpEF [103, 293]. Finally, it is possible that HF-related events are misclassified as AECOPD [40, 113]. Previous research has shown that many HF patients are initially treated for AECOPD or other respiratory conditions [60]. The shared signs, symptoms, and risk factors of COPD and HF make the recognition of one in the presence of the other very difficult for clinicians [23, 163]. Additionally, the most common cause of AECOPD, respiratory infections, also increases the risk of vascular events [110].

5.4.1 Strengths and limitations

Recording of HF type and severity are not currently adequate in CPRD to be described. A code for BNP or echocardiography indicates that a test was considered, but does not indicate whether the test was performed or the outcomes of the test. Testing for BNP does not exclusively suggest HF investigation, as BNP levels rise in other cardiac conditions, such as AF [70].

Crude estimates of the effect of possible HF on AECOPD risk, of HF diagnosis on severe AECOPD risk in the population including patients with chronic kidney and liver disease, and the crude model comparing investigated and not investigated possible HF patients did not meet the requirement for proportionality in Cox regression; however, all other crude and adjusted models met this requirement.

One strength of this study is the exclusive focus on the effect of HF on AECOPD risk. Previous research has focused on the effect of composite 'cardiovascular comorbidity' exposures on AECOPD, with conflicting findings [114, 158, 161, 217, 294]. For these purposes, a composite variable for 'cardiovascular history' was used for adjustments; however, it was not used to generate risk estimates. The purpose of the composite variable in this study was to indicate whether a person had a recognised history of conditions that may have influenced the procurement of a subsequent diagnosis of HF.

The main limitation of this study is the definition of possible HF, which at best only identifies possible HF patients with fluid congestion, which may not be experienced in all cases of HF. Patients with chronic kidney and liver disease were excluded, as these are other indications for loop diuretic use; however, these conditions are more common in the HF population. In a sensitivity analysis, COPD patients with a HF diagnosis were compared to COPD patients without a HF diagnosis, retaining patients with chronic kidney or liver disease. There was a similarly increased risk for AECOPD in those with a HF diagnosis compared to those without a HF diagnosis as was seen in the more selected population that excluded patients with chronic kidney and liver disease.

The similarity of demographic and baseline characteristics in COPD patients with possible HF and COPD patients with newly diagnosed HF was encouraging, suggesting internal validity. Similar techniques have been used in previous research to identify possible HF [285].

Nonetheless, COPD patients with long-term loop diuretic use in the absence of non-cardiac indications experienced increased risk for moderate and severe AECOPD compared to patients without this characteristic. These patients therefore represent a high-risk group for whom special concern should be taken with regards to diagnosis and management of potential HF.

In a sensitivity analysis, we redefined what was required to be classified as newly diagnosed HF, including patients who had a history of HF hospitalisation but lacked a primary care HF diagnosis. Compared to COPD patients without evidence of HF, COPD patients with newly diagnosed HF experienced greater risk for moderate-to-severe AECOPD. This estimate was larger than that seen in the main analysis; however, the new definition by its nature shifted more symptomatic and sicker individuals into the newly diagnosed HF category and that would increase AECOPD risk. Compared to COPD patients without evidence of HF, COPD patients with possible HF experienced a greater risk for moderate-to-severe AECOPD. The risk for moderate-to-severe AECOPD was not affected by the new categories compared to the main analysis.

5.5 Conclusions

HF diagnosis was associated with a significantly greater risk for moderate and severe AECOPD compared to patients without evidence of HF. There was a large population of COPD patients with possible HF, which was over four times larger than the COPD population with newly diagnosed HF. Possible HF was also associated with a significantly increased risk for moderate and severe AECOPD compared to patients without evidence of HF and the increase was comparable to that seen in patients with newly diagnosed HF. There was no history of HF investigation for nearly half of COPD patients with possible HF; however, those who were investigated still experienced increased AECOPD risk compared to COPD patients without evidence of HF. There appears to be a substantial opportunity for earlier recognition of HF in the COPD population in the primary care setting. Increased support of primary care through improved access to specialists, nurses, and tests could improve diagnostic and management capabilities.

Chapter VI – Effect of HF medications on risk for AECOPD in primary care patients with COPD-HF comorbidity

6.1 Introduction

The previous aim showed that HF comorbidity is associated with an increased risk for AECOPD (**Chapter V**). This chapter explores Specific Aim #3, to determine the effect of HF medication use on AECOPD risk in COPD patients with HF comorbidity.

Previous studies of the effect of HF medications on COPD patients have focused primarily on their effects on mortality, particularly following MI or another indication besides HF. ACEi-ARB as a combined exposure showed no change in mortality in one study [167], while another study looking at each individually found increased mortality in ACEi users and reduced mortality in ARB users [295]. One study found reduced mortality in users of MRA compared to non-users [295]. Results for the effect of BB on mortality of COPD patients are mixed, with some studies finding increased mortality [167] and other reduced [295-297].

Studies examining the effect of HF medications on AECOPD risk are scarcer. An observational study of COPD patients using ACEi or ARBs found that ARBs were associated with fewer severe AECOPD than ACEi [298]. A systematic review of 15 publications found that BB use most probably resulted in no change or reduced risk for AECOPD in COPD patients with cardiovascular disease or risk factors for cardiovascular disease [299]. The effect of BB use on AECOPD has also been of interest in clinical trials of COPD patients without cardiovascular indications for BB use; however, the recent BLOCK COPD trial ended early as BB were associated with higher hospitalisation [277]. At normal doses, loop diuretic (LD) use is not associated with changes in pulmonary function; however, intravenous LD may be beneficial during AECOPD by reducing cardiac stress [300]. There has been little research on the effect of MRA on AECOPD risk; however, as MRA have some angiotensin-II blocking effects they may slightly improve lung diffusion [301].

A number of studies examining the effect of cardiovascular medications on outcomes, such as mortality and AECOPD, have been found to have immortal time bias [169, 302]. Immortal time bias refers to a period of time during which death cannot occur and can arise when periods

of follow-up are either excluded or have been assigned an inappropriate exposure status [302]. Immortal time bias has been shown to significantly affect the results of observational studies [169, 303].

The purpose of these analyses was to assess the effect of incident and prevalent HF medication use on AECOPD risk in COPD patients with diagnosed HF. A person-time definition of exposure was used to avoid the problem of immortal time bias. The HF medications of interest were ACEi, ARB, BB, LD, and MRA.

Supplementary information for this chapter is located in **Appendix VI**. A publication produced in association with this chapter is currently undergoing peer-review (see **Appendix VIII**).

6.2 Methods

This was a retrospective cohort study.

6.2.1 Data sources

This study used primary care data from CPRD, secondary care data from HES, mortality data from ONS, and socioeconomic data from IMD. These data sources are described in detail in **Chapter III**.

6.2.2 Inclusion criteria

Patients with comorbid COPD and HF were identified as described in **Chapter III**. In these analyses, order of diagnosis did not matter, and patients were eligible from diagnosis of the second condition. Patients with only right-sided HF codes (n = 659) or a HFpEF-specific code at any time (n = 31) were excluded, as the management under investigation is that for HFrEF.

6.2.3 Follow-up

Start of follow-up was defined as the latest of 1) start of study (01/01/2006), 2) current registration date for the patient, 3) date practice was declared up-to research standards by CPRD, and 4) date of COPD-HF comorbidity.

End of follow-up was defined as the earliest of 1) end of study (31/12/2016), 2) date of last data collection from CPRD, 3) date of last linked data collection, 4) date patient transferred from practice, and 5) date of death per ONS.

6.2.4 Exposure

There were three possible exposure statuses: 1) unexposed to the drug of interest, 2) incident continuous exposure to the drug of interest, and 3) prevalent continuous exposure to the drug of interest. Continuous exposure was defined as having at least two prescriptions for the drug of interest and having no more than 90 days between each subsequent prescription. Patients were censored 90 days after their last continuous prescription for the drug of interest as longer gaps between prescriptions make determining continuous exposure less accurate. Incident continuous exposure was defined as the time from first continuous prescription of the drug of interest through six months of continuous exposure or end of continuous exposure. Prevalent continuous exposure was defined as the time from six months of continuous exposure until end of follow-up or end of continuous exposure. Exposure was assessed at the start of follow-up and throughout follow-up until end of continuous exposure or end of follow-up.

Exposure was defined using person-time, as opposed to a patient-based exposure definition. This was to avoid the problem of immortal time bias, which has been shown to affect a number of previous studies in this area [169, 302]. Using a person-time definition of exposure meant that patients could have multiple exposure-statuses throughout follow-up (**Figure 6.1**).

6.2.5 Outcome

Moderate and severe AECOPD were identified as described in **Chapter III**.

6.2.6 Covariates

Sex, age groups, smoking status, BMI, severity of airflow limitation per GOLD [1], COPD inhaler use, and cardiovascular medication use were defined at baseline as described in **Chapter III**. COPD inhalers included SABA, SAMA, LABA, LAMA, ICS, or combination. Concurrent use of other HF medications was defined as having at least two prescriptions in the year prior to start of follow-up. History of cardiovascular disease included prior diagnosis of IHD, PAD, AF, HTN, and/or stroke, which were identified as described in **Chapter III**.

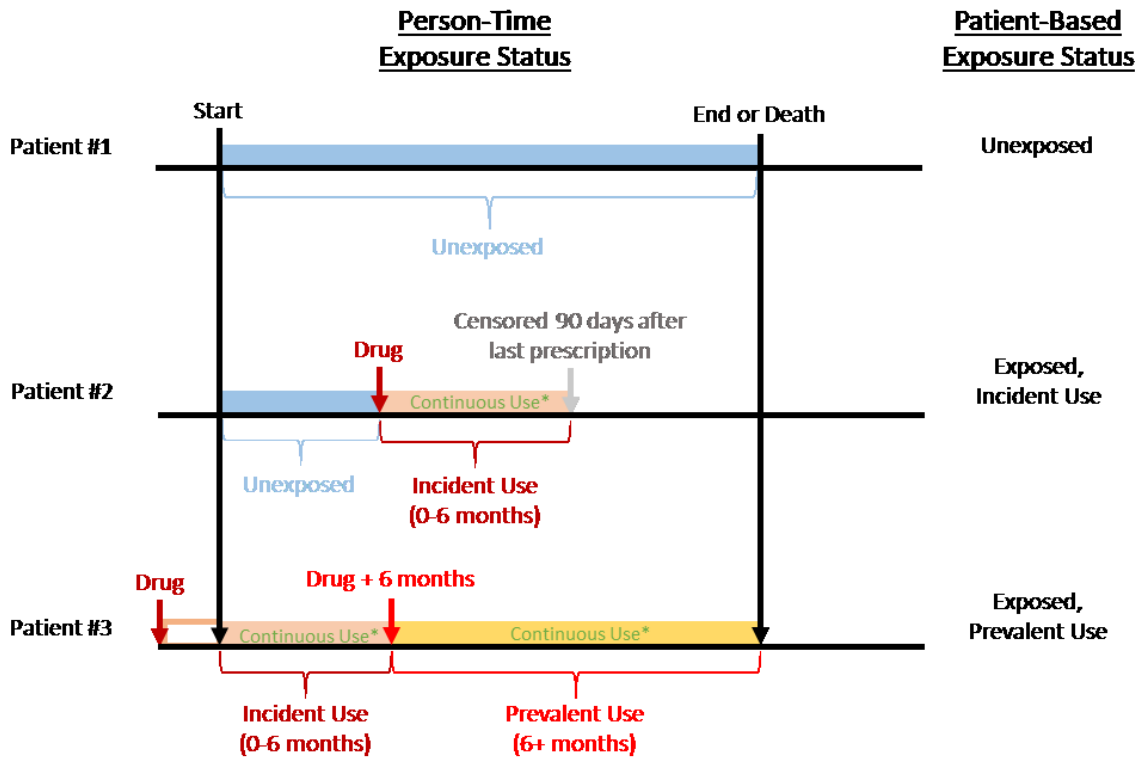

Figure 6.1. Example of person-time based follow-up.

Patient #1 enters the study at their start of follow-up unexposed, they remain unexposed until their end of follow-up. In a patient-based exposure definition, this patient would be unexposed. **Patient #2** enters the study at their start of follow-up unexposed. They become exposed to incident drug use upon first prescription of the drug of interest and remain exposed throughout continuous use of the drug. They are censored 90 days after their last prescription within continuous use, which occurs within 6 months of their first prescription. In a patient-based exposure definition, this patient would be exposed to incident drug use. **Patient #3** enters the study at their start of follow-up exposed to incident continuous drug use, whereby their first prescription of the drug of interest was within 6 months of their start of follow-up. They remain exposed to incident continuous drug use until 6 months after their first prescription, thereafter they are exposed to prevalent continuous drug use until their end of follow-up. In a patient-based exposure definition, this patient would be exposed to prevalent drug use. *Continuous drug use was defined as at least two prescriptions of the drug of interest and gaps between prescriptions were no more than 90 days. Patients were censored 90 days after their last prescription in a continuous run.

6.2.7 Statistical analyses

Continuous descriptors were reported using median and interquartile range (IQR). Categorical descriptors were reported using count (n) and percentage (%). Cox proportional hazards regression was used to compare incident drug users to non-users and prevalent users. Robust variance estimates were used to account for possible clustering by GP, allowing for some control over differences in diagnostic and prescribing procedures between GPs. Regression was adjusted for the covariates listed above.

6.3 Results

We identified 8,901 COPD patients with diagnosed HF who met the inclusion criteria (**Figure 6.2**). For all HF medications, most patients were non-users or prevalent users at the start of follow-up (**Figure 6.3**). Changing exposure status, in the direction of not exposed to exposed, was uncommon, with most non-users remaining as non-users for all medication types (**Figure 6.3**).

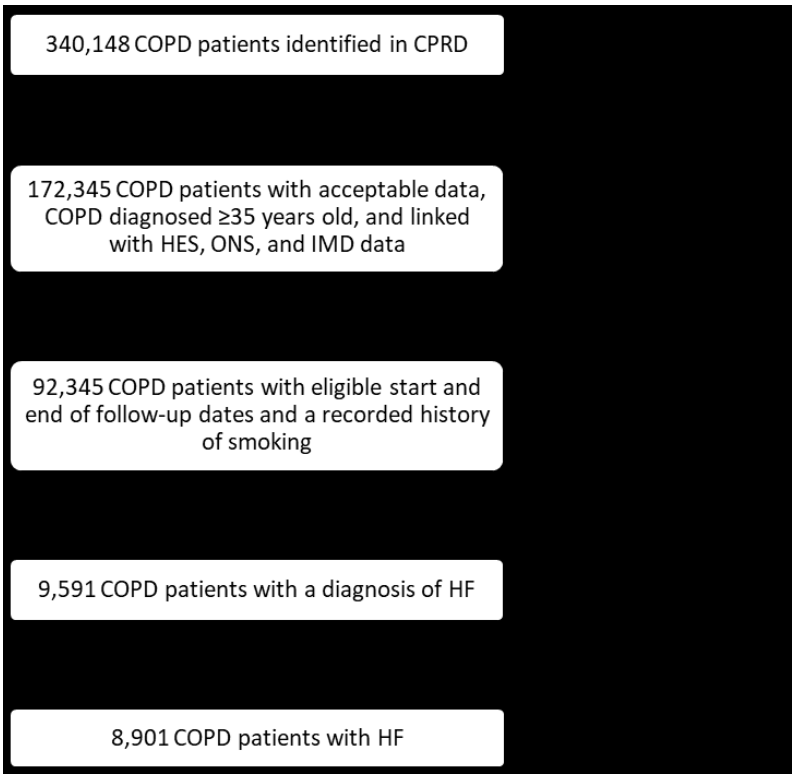

Figure 6.2. Derivation of the study populations for analyses of the influence of HF medications on exacerbation risk.

Patients were mostly male, former smokers with a median age of 77.5 years at baseline (**Table 6.1**). Patients were mostly overweight or obese from higher socioeconomic status with mild airflow obstruction and a median of two exacerbations in the year prior to baseline (**Table 6.1**). All patients were prescribed some form of short-term inhaler and the majority of patients were prescribed LABA+ICS or triple long-term inhaler therapy in the year prior to baseline (**Table 6.1**). The majority of patients had recognised cardiovascular comorbidity at baseline, mostly hypertension and/or IHD (**Table 6.1**). Demographics stratified by exposure status to each medication are available in **Appendix VI**.

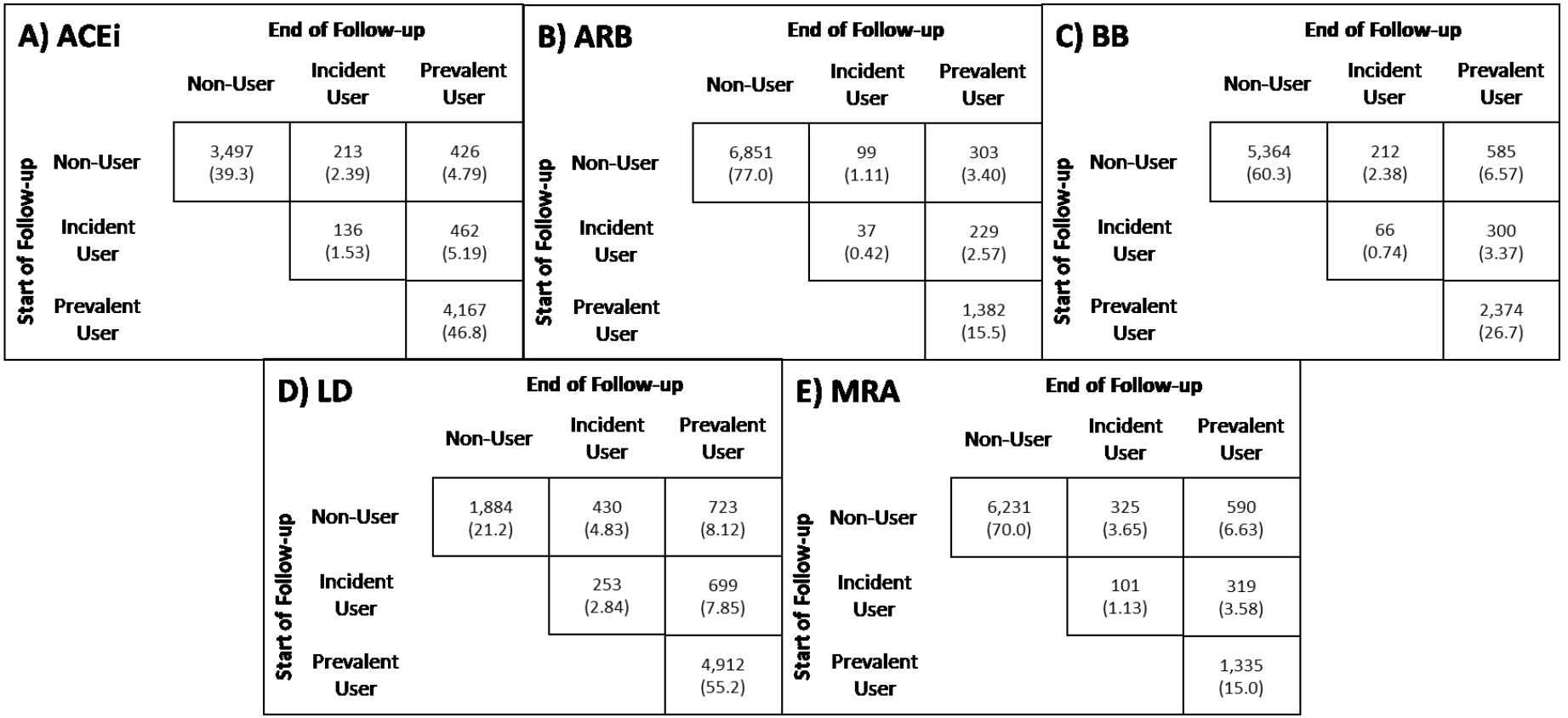

Figure 6.3. HF medication exposure status for COPD patients with HF at start and end of follow-up for A) ACEi, (B) ARB, (C) BB, (D) loop diuretics (LD), and (E) MRA. Population size: N = 8,901. Count (%).

	COPD-HF Patients		COPD-HF Patients
Number of Patients (N)	8,901	**Exacerbation History (IQR)**	2 (0, 3)
Female	3,278 (36.8)	**COPD medications**†	
Age, years (IQR)	77.5 (70.5, 83.3)	SABA/SAMA	8,901 (100)
Smoking Status		LABA alone	194 (2.18)
Current Smoker	1,848 (20.8)	LAMA alone	703 (7.90)
Former Smoker	7,053 (79.2)	ICS alone	775 (8.71)
Body Mass Index		LABA+LAMA	109 (1.22)
Underweight (< 18.5)	303 (3.40)	LABA+ICS	2,203 (24.8)
Healthy Weight (18.5-24.9)	2,470 (27.8)	LAMA+ICS	150 (1.69)
Overweight (25.0-29.9)	2,769 (31.1)	Triple	2,174 (24.4)
Obese (>= 30)	3,014 (33.9)	No long-acting inhaler	0
Missing Data	345 (3.88)	**History of Cardiovascular Disease**‡	7,926 (89.1)
Index of Multiple Deprivation		Atrial fibrillation	3,142 (35.3)
1 – Most deprived	1,236 (13.9)	Hypertension	5,037 (56.6)
2	1,770 (19.9)	Ischaemic heart disease	4,878 (54.8)
3	1,760 (19.8)	Peripheral artery disease	1,202 (13.5)
4	2,041 (22.9)	Stroke	1,271 (14.3)
5 – Least deprived	2,094 (23.5)		
GOLD Stage			
1: Mild	3,220 (36.2)		
2: Moderate	1,923 (21.6)		
3: Severe	1,345 (15.1)		
4: Very Severe	353 (3.97)		
Missing	2,060 (23.1)		

Table 6.1. Descriptive statistics of COPD patients with HF comorbidity at baseline. Presented as n (%), unless otherwise stated. GOLD staging of COPD severity [1]. ‡Recorded at baseline; patients could have multiple risk factors.

Incident use of ACEi, ARB, BB, loop diuretics, and MRA were associated with increased risk for moderate-to-severe AECOPD compared to non-use (**Figure 6.4a; Supplementary Table 6.6**). Prevalent use of ACEi, ARB, BB, loop diuretics, and MRA were also associated with increased risk for moderate-to-severe AECOPD compared to non-use (**Figure 6.4b; Supplementary Table 6.6**). Prevalent use of ACEi, ARB, BB, loop diuretics, and MRA was associated with decreased risk for moderate-to-severe AECOPD compared to incident use (**Figure 6.4c; Supplementary Table 6.6**).

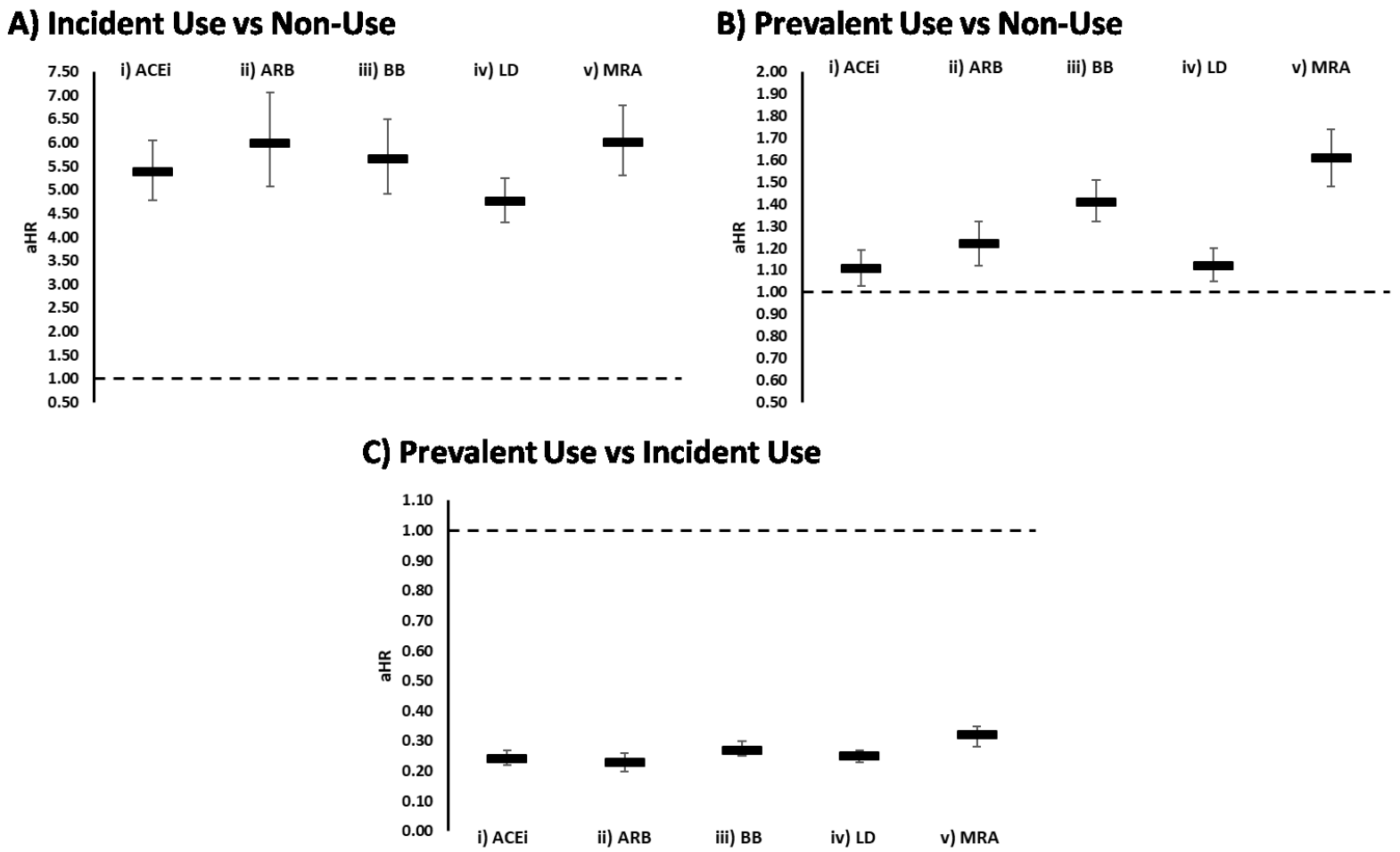

Figure 6.4. aHR for the risk of moderate-to-severe AECOPD comparing incident medication use (< 6 months) to non-use; (B) prevalent medication use (≥ 6 months) to non-use; and (C) prevalent medication use to incident medication use for i) ACEi, (ii) ARB, (iii) BB, (iv) loop diuretics (LD), and (v) MRA. Estimates with 95% confidence intervals from Cox regression adjusted for age, sex, smoking status, body mass index, index of multiple deprivation, exacerbation history, severity of airflow limitation, inhaler use, history of cardiovascular disease, and cardiovascular medication use.

6.4 Discussion

In these analyses, the effect of HF medication use – ACEi, ARB, BB, loop diuretics, and MRA – on AECOPD risk was assessed in a primary care COPD population with diagnosed HF. Both incident (< 6 months) and prevalent (≥ 6 months) use of all HF medications were associated with an increased risk of AECOPD compared to non-use. Interestingly, prevalent use was associated with decreased risk for AECOPD compared to incident use for all medication types, suggesting that well managed HF is associated with a reduction in AECOPD risk.

Compared to non-use of HF medications, incident medication use was associated with a higher risk for AECOPD. The increased risk associated with incident use was similar for all drug types, despite each type having a unique mechanism of action. This suggests that it is not the effect of the individual medication on AECOPD risk that is being seen, but rather the effect of symptomatic HF, indicative of the need for medication, on AECOPD risk that is being seen. This is known as confounding by indication, whereby the clinical indication for the use of a medication also affects the outcome [304]. COPD patients with diagnosed HF who were prescribed HF medications were likely more symptomatic than COPD patients with diagnosed HF who were not prescribed HF medications.

Prevalent use of HF medications was also associated with higher AECOPD risk compared to non-use. Prevalent use of BB and MRA were associated with slightly greater risk for AECOPD compared to non-use than seen in the other drug types. Again, this may be an effect of confounding by indication. BB are a first-line medication for HF management in the UK [69]; however, previous research has shown that BB are underutilised in the COPD population [83, 84, 166]. BB prescription and continued use may be indicative of more severe symptom burden than seen in COPD patients not given BB. MRA is not a first-line HF medication, but rather should be given to patients who remain symptomatic despite treatment with the first-line medications [69]. Therefore, it is unlikely that BB and MRA individually increase risk for AECOPD, but rather that prescription and long-term use of BB and MRA in the COPD population with HF is indicative of patients with more severe HF, greater symptom burden, and therefore higher risk of AECOPD compared to non-users of these medications.

Interestingly, prevalent use of all HF medications was associated with decreased AECOPD risk compared to incident use. Again, the effect was similar for all drug types, suggesting that it is

not the individual medication impacting AECOPD risk but rather adequate HF management. A previous study from Greece suggested a similar conclusion, though it investigated a very different COPD population [305]. Matamis et al. examined 107 consecutive AECOPD patients admitted to intensive care for the presence of unrecognised HF. They found 41% had unrecognised left ventricular dysfunction and that these patients experienced shorter time on mechanical ventilation, shorter intensive care stays, improved quality of life, and decreased mortality compared to patients with normal heart function. The authors hypothesized that the targeting of unrecognised HF and subsequent management of that HF were the underlying mechanisms leading to these non-intuitive results, meaning HF treatment was responsible for better outcomes following AECOPD [305]. Though the COPD populations studied here and by Matamis et al. are different (primary care vs intensive care) and they present at different severity (stable vs acute COPD), the effect of HF management on reducing AECOPD risk and severity is evident. These results suggest that early diagnosis and management of HF in the COPD population may ultimately reduce symptom burden and improve quality of life.

Failure to optimally manage HF may enable and/or hasten the progression of HF or general patient decline, both of which may increase exacerbation risk. Pathophysiologically, there are a number of mechanisms by which underlying HF, particularly uncontrolled HF, may increase exacerbation risk. Chronic congestion may lead to reduced airflow in some patients and studies show that this airflow obstruction can been reversed with proper management of congestion [129, 130]. Pulmonary oedema, reduced QT, and impaired oxygen transport due to HF may intensify dyspnoea and reduced exercise capacity already present due to lung hyperinflation in COPD [95]. Cardiomegaly may contribute to worsening alveolar gas diffusion, resulting in a restrictive lung pattern and reduced alveolar volume [306]. Obesity and diabetes, risk factors for HF and more common in our COPD patients with HF, are associated with reduced pulmonary function and airway hyperactivity [307].

6.4.1 Strengths and limitations

As discussed in the previous chapter, the definitions of COPD and AECOPD have been validated in CPRD; however, the definition of HF has not been validated. Also discussed previously, the recording of HF type in CPRD is not detailed enough for stratified analysis. While these analyses excluded patients with only right-sided HF codes or with HFpEF codes, the use of these specific codes was rare, and it is very likely that a number of included patients

have a clinical diagnosis of HFpEF or right-sided HF. Particularly, the inclusion of HFpEF patients may have influenced the effect estimates reported here. The inclusion of these patients likely attenuated the effect of HFrEF drugs on AECOPD risk when comparing incident and prevalent use to non-use. As there are currently no guidelines for the management of HFpEF, these patients are likely to be symptomatic. Alternatively, patients with HFpEF may have other indications for the use of HF medications, such as history of MI for BB use, which may reduce their symptom burden with prevalent use and would increase the estimates seen here when compared to incident use.

The number of tablets prescribed is not always recorded in CPRD and therefore duration of prescription cannot be adequately estimated. Importantly, the information is only for prescriptions and does not indicate whether the prescription was used by the patient. To minimize these limitations, all patients were required to have at least two prescriptions for a given drug type and a gap in prescriptions of more than 90 days triggered censoring. As a result, time-varying medication exposure was allowed in one direction (non to incident to prevalent use), but not in other direction (incident/prevalent to non-use). Censoring of this type was relatively common with 43.5% of prevalent ACEi users experiencing a gap of more than 90 days between prescriptions, similarly 45.0% of prevalent ARB users, 30.1% of prevalent BB users, 41.5% of loop diuretic users, and 46.0% of prevalent MRA users were censored in this way. Transitioning from incident use to non-use was less common with 19.0% of incident ACEi users experiencing a gap of more than 90 days between prescriptions, similarly 12.4% of incident ARB users, 12.0% of incident BB users, 22.1% of incident loop diuretics users, and 18.0% of incident MRA users were censored in this way. Examination of the effects of transitioning from incident or prevalent medication use to non-use is an important area for future research.

6.5 Conclusions

Use of all HF medications investigated – ACEi, ARB, BB, loop diuretics, and MRA – was associated with higher AECOPD risk compared to non-use in the COPD population; however, prevalent medication use (≥ 6 months) was associated with reduced AECOPD risk compared to incident use (< 6 months) for all medications. Active screening for HF in the COPD population followed by appropriate management has the potential to improve COPD patients' lives through reduction in AECOPD risk and severity.

Chapter VII: Discussion

This final chapter summarises the findings of each aim in the context of current understanding and potential implications for clinical practice. Finally, areas for future research to address some unanswered questions are discussed.

7.1 Summary of Findings and Clinical Implications

Previous research has established that HF is a common comorbidity in the COPD population; however, its diagnosis and management are often missed or delayed [127, 176]. The overarching aim of this thesis was to explore the relationship between COPD and HF in the primary care setting and the effect of HF comorbidity on AECOPD to identify areas where primary care clinical intervention may be improved. It was hypothesized that timely HF intervention in the COPD population would reduce AECOPD risk.

At the beginning of this thesis, I declared that COPD would be considered the index disease and HF the comorbidity for the purposes of these analyses; while the terminology of the spill-over theory simplifies discussion, researchers are recognising the systemic nature of chronic diseases and clinicians are facing growing numbers of patients experiencing multimorbidity. In practice, clinical care of patients with COPD and HF is still very much separate. The organ system-specific organisation of healthcare means that coordination of care between specialties is not adequately supported and often results in fragmented, delayed, and complicated care strategies for patients, caregivers, and medical professionals.

7.1.1 Specific Aim #1: To describe the burden of HF comorbidity in the COPD population

Re: Chapter II (systematic review)

A review of the literature was conducted to examine the effect of HF comorbidity on hospitalisation and mortality in the COPD population. Previous research focused on the broader effect of cardiovascular comorbidity [53] or on the reverse relationship, examining COPD comorbidity in the HF population [218-220]. In my review, both hospitalisation and mortality were higher in COPD patients with HF compared with those without HF. There were two points worth highlighting from the systematic review. Firstly, there was strong evidence that HF comorbidity increased COPD-related secondary care utilisation, in addition to all-cause mortality. Increased secondary care utilisation suggests that COPD patients with HF experience

more and/or more severe AECOPD than those without HF, laying the groundwork for the analyses in **Chapter V**.

Secondly, heterogeneity in the COPD population and in reporting of findings makes it difficult to appropriately synthesize the available evidence. The COPD populations investigated in the studies reviewed varied greatly in a number of characteristics including method of COPD/HF diagnosis, smoking history, severity of airflow limitation, length of follow-up, etc. Reporting of patient characteristics was also varied amongst the studies. Attempts to pool estimates using all available data was hindered by this heterogeneity and variation in characteristic reporting. Additionally, a number of methods were used to estimate risk (HR, OR, risk ratio) and rate (rate ratio), but often this variety resulted in not enough studies reporting a given outcome for meta-analysis to be appropriate.

Re: Chapter IV (data analysis)

This study found the crude incidence of HF in the COPD population was steady from 2006 to 2016. This is contrary to rising HF incidence in the general population [61]. As expected, COPD-iHF patients experienced greater short- and long-term mortality than COPD patients without HF, regardless of severity of airflow limitation. The 1-year and 5-year mortality of COPD-iHF patients did not change over time. There was a slight increase in the number of deaths attribute to cardiovascular causes in the COPD-iHF population over the study period, contrasting decreasing cardiovascular mortality in the wider COPD population [12].

The most probable explanation for steady HF incidence is that recognition of HF comorbidity in the COPD population has not improved over time. In light of the results from the systematic review, this continued under recognition of HF may have significant effects on patient morbidity and mortality. Additionally, these results suggest that the survival gains seen in the general population with HF have not been seen in the COPD population. Delays in HF diagnosis and management in the COPD population may be responsible for this discrepancy in survival.

Proactive screening for cardiovascular health in the COPD population, in combination with bespoke guidance on how and when to screen, could significantly improve the lives of COPD patients with appropriate management. The lack of bespoke guidance for cardiovascular management in the COPD population is surprising. Patients with arthritis, CKD, and diabetes

all benefit from tailored guidance and recommendations for screening and management of cardiovascular comorbidities [308]. While there have been increasing calls to improve research and clinical practice [164], the prevailing recommendation to diagnose and treat cardiovascular comorbidity in the COPD population as if they did not have COPD is distressingly inadequate and impractical [1].

7.1.2 Specific Aim #2: To determine the effect of HF comorbidity on AECOPD risk

Re: Chapter V (data analysis)

These analyses were designed to identify the effect of HF on AECOPD risk. COPD patients with newly diagnosed HF experienced higher risk of moderate and severe AECOPD compared with COPD patients without evidence of HF. COPD patients with possible HF experienced significantly higher risk of AECOPD that was comparable to that seen in patients with newly diagnosed HF. There was no record of HF investigation at any time for nearly half of COPD patients with possible HF, suggesting there is room for earlier identification of HF in primary care. This study provides the theoretical basis for clinical trials of cardiovascular screening programmes in the COPD population and is further supported by the findings in the following chapter regarding the effect of HF management on AECOPD risk.

The first hurdle for clinicians managing COPD patients with HF comorbidity is diagnosis. Cardiac comorbidities present a particular challenge in the COPD population, as signs and symptoms associated with early disease are non-specific and can be mistaken for worsening COPD. In the case of HF, which is an end-stage cardiac syndrome, identification and management of its risk factors and precursors is perhaps more important. An audit of cardiovascular risk and management recording in COPD patients in the respiratory outpatient services of two Irish hospitals paints a troubling picture [309]. The researchers found that cardiovascular history was documented, such as hypertension or hyperlipidaemia, but that detailed risk factor level recording was very poor. Less than half of patients had blood pressure and heart rate measures, while recording of risk factors such as waist circumference and lipid levels was essentially non-existent [309].

There are a number of clinical time points where cardiovascular screening could be introduced into COPD patient care. Firstly, at the time of COPD diagnosis may be a good point to assess baseline cardiovascular risk and address any underlying issues. Secondly, COPD patients should undergo an annual COPD review, where disease progression and management are

assessed. These annual appointments may be ideal places to introduce basic cardiac screening and risk assessment in the primary care or outpatient setting. Thirdly, COPD patients often switch medications in attempts to manage their symptoms; at these times patients may be particularly vulnerable to cardiac events [310]. Medication switching often involves multiple contacts with healthcare and may provide opportunities for cardiac screening.

Another opportunity for introducing cardiovascular screening into routine COPD patient care is at the time of AECOPD, whether managed in primary or secondary care. AECOPD increase cardiovascular risk and may expose previously unrecognised cardiac dysfunction [113]. AECOPD can affect quality of cardiac imaging; however, prognostic biomarkers, such as BNP and troponin, are associated with increased mortality and may provide an indication that further cardiac investigations should be undertaken sooner rather than later [121, 311]. Cardiac assessment at time of AECOPD and following discharge is complicated and would benefit greatly from tailored guidance.

7.1.3 Specific Aim #3: To determine the effect of HF medications on AECOPD risk

Re: Chapter VI (data analysis)

These analyses investigated the effect of common HF medications on AECOPD risk in COPD patients with diagnosed HF. Compared with non-use, both incident and prevalent medication use was associated with greater AECOPD risk. Interestingly, prevalent use was associated with decreased AECOPD risk compared with incident use. These results suggest that managing HF successfully does improve COPD patient symptoms and, potentially, quality of life.

This study was unique in that it measured medication exposure using person-time and stratified exposure by length of medication use. Exposure to a given mediation was determined using a person-time approach, to avoid the issues around immortal time bias that has been seen in previous studies of this type. Exposure was also stratified by incident use (< 6 months) and prevalent use (≥ 6 months). While all medication use was associated with higher AECOPD risk than non-use, AECOPD risk appeared to decrease with prevalent compared to incident use. Physiologically, pulmonary congestion resulting from unmanged HF may contribute to the initially increased risk seen with incident use, which is then reduced over time.

Previously, there had been concerns regarding beta-agonist and beta-blocker use in COPD patients with cardiovascular comorbidity. Evidence from observational studies and a limited

number of trials has largely removed these concerns, particularly regarding the use of cardioselective beta-blockers, though the debate still rages [140, 141, 144, 145]. Clinical practice has been slow to adapt and beta-blockers are still under prescribed in the COPD population with indications for their use [57].

COPD patients with HF comorbidity are more likely to have other chronic comorbidities than COPD patients without HF [160, 292]. This multimorbidity increases the risk of overly complex management strategies and polypharmacy [312, 313]. Data from the UK Biobank has shown that COPD patients are significantly more likely to be prescribed over five medications compared with non-COPD patients and that those with cardiovascular comorbidities experienced increased adverse drug reactions [49]. The complexity of these patients means that they require careful consideration and would benefit greatly from tailored guidance.

Unfortunately for patients with COPD, the benefits of an organ-system approach to healthcare are limited. Currently, there are no medications or management strategies for COPD that improve survival or slow progression of the disease [314]. Focusing intently on optimising COPD management without explicitly addressing comorbidities can therefore only minimally improve quality of life. Management of HF, at least HFrEF, involves survival-modifying medications, as does the management of many HF risk factors and precursors, such as MI or hypertension. There is increasing recognition of the multimorbid patient by healthcare authorities [312, 313], but the translation of this into clinical practice has been slow. These results highlight the need for more collaborative management of patients with chronic heart and lung conditions, increased awareness and screening for conditions beyond the first one to be recognized, and the development of bespoke guidelines for diagnosis and management of patients with COPD and HF. Increasing patient-centered care over specialty-focused care could reduce symptom burden in patients with COPD and HF.

7.2 Areas for Future Research

There are two main areas that could aid in the development of bespoke guidance for diagnosis and management of patients with COPD-HF comorbidity.

7.2.1 Effect of HF type and severity on morbidity and mortality of COPD patients

A major limitation of this thesis was the inability to accurately classify HF type and severity using CPRD and HES data. As discussed previously, HF type impacts management options and HFpEF has no evidence-based survival-modifying medications. COPD patients experience higher rates of HFpEF than the general population with HF [85-87]. Risk factors, comorbidities, and cardiac ageing play an important role in the development of HFpEF [103, 293]. Differences in pathophysiology and management options between HF types, and severity, may impact COPD patient outcomes very differently.

7.2.2 Effect of proactive cardiovascular screening and management on morbidity and mortality in the COPD population

Prospective studies assessing the effect of cardiovascular screening and management on outcomes in the COPD population are the most needed and least common. Oddly, trial focus has been placed on the effect of BB on AECOPD risk in patients without cardiac indications for their use [155, 156]. This interest was based on observational evidence that BB reduced AECOPD; however, the patients in the observational studies were taking BB for a cardiac indication [277]. A trial investigating the effect of BB and other cardiovascular medications on outcomes in COPD patients with cardiac indications for their use would be beneficial to the development of bespoke management guidelines. Outcomes of interest may include the effect of prevalent medication use on AECOPD risk and the effect of HF management on quality of life. Though ethics would prevent a trial from withholding proven cardiovascular medications from patients with indications for their use, it may be possible to generate a virtual control arm [315].

7.3 Conclusions

Prior to this work, it was known that HF was an under-recognised and under-managed comorbidity in the COPD population. The aim of this thesis was to describe the effect of HF comorbidity in the COPD population and its effect on AECOPD risk. In **Chapter II**, a review of the literature found that HF comorbidity increased COPD-related secondary care utilisation and all-cause mortality in the COPD population. In **Chapter IV**, analysis showed steady incidence of HF diagnosis in the UK COPD population over the past decade with no evidence of improved survival. **Chapter V** found that both diagnosed and possible HF were associated with increased AECOPD risk. **Chapter VI** found that both incident and prevalent use of HF

medications were associated with increased AECOPD risk; however, the risk associated with prevalent medication use was significantly less than that associated with incident use. Overall, the analyses in this thesis suggest that there are missed opportunities to diagnose and manage HF in the primary care COPD population and that optimising these processes may reduce AECOPD risk.

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Appendix I: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data	

		synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix II: Additional supplementary material to Chapter II

Data extraction items

Study information

- Author
- Year of publication
- Type of study
- Inclusion criteria
- Exclusion criteria
- Number of patients
- Length of follow-up
- Outcomes reported
- Setting

Baseline characteristics

- Number of females
- Age
- Current smokers
- Pack-years
- BMI
- Exacerbation history
- GOLD stages
- mMRC dyspnoea score
- FEV_1 (L)
- FEV_1 % predicted
- Ejection fraction
- Number of patients with
  - HF
  - AF
  - Arrhythmias
  - Diabetes
  - HTN
  - IHD
  - Stroke

Mortality (Outcome)

- All-cause mortality
  - Number of deaths
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL
- Respiratory mortality
  - Number of deaths
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL
- CVD mortality
  - Number of deaths
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL

Hospitalisation (Outcome)

- All-cause hospitalisation
  - Number of hospitalisations
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL
- Respiratory hospitalisation
  - Number of hospitalisations
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL
- CVD hospitalisations
  - Number of hospitalisations
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL

Re-hospitalisation (Outcome)

- All-cause re-hospitalisation
  - Number of re-hospitalisations
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL
- Respiratory re-hospitalisation
  - Number of re-hospitalisations
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL
- CVD re-hospitalisations
  - Number of re-hospitalisations
  - Hazard ratio, LCL, UCL
  - Risk ratio, LCL, UCL
  - Rate ratio, LCL, UCL

Additional notes of interest

Supplementary Table 2.1. Data extraction items.

Study	Inappropriate Comparison	Inappropriate Outcome	Other	Specifics
Abdulfattah et al. 2018	1			Cor pulmonale
Abroug et al. 2006		1		Biomarkers
Abusaid et al. 2009		1		Diastolic dysfunction
Acanfora et al. 2018	1			Stratified on lymphocyte count
Afonso et al. 2011	1			Stratified on B-Blocker use
Almagro et al. 2006	1			Cor pulmonale
Almagro et al. 2015		1		Same data as included Almagro et al. 2012
Almagro et al. 2010	1			HR compares cohorts to each other
Amusa et al. 2017	1			CVD
Amusa et al. 2018	1			CVD
Andrijevic et al. 2017	1			Ejection fraction <50%
Annangi et al. 2014		1		Do not report HR or RR
Ashraf and Ashraf 2017		1		Do not report HR or RR
Baillargeon et al. 2012	1			Does not contain cohort of patients with HF
Barnett et al. 2013	1			Compare to COPD readmission
Blasi et al. 2010		1		Frequency of exacerbations
Calder et al. 2014	1			COPD or HF
Cerezo Lajas et al. 2018	1			Low vs high frequency resadmission
Consentino et al. 2019		1		Do not report HR or RR
Curkendall et al. 2006	1			Compare to non-COPD
Curkendall et al. 2006b	1			Compare to non-COPD
Cuthbert et al. 2018	1			Compare to non-COPD/HF
El-Shabrawy and Eldamanhory 2016		1		Do not report HR or RR
Gale et al. 2011	1			Ejection fraction, NT-BNP
Garcia-Sanz et al. 2017		1		No HF
Germini et al. 2018		1		Do not report HR or RR
Go et al. 2017		1		Do not report HR or RR
Goto et al. 2018	1			Not compared to group with HF
Hijjawi et al. 2015		1		Do not report HR or RR
Ho et al. 2014	1			Not compared to group with HF
Hoiseth et al. 2012	1			Not compared to group with HF
Holguin et al. 2005		1		Do not report HR or RR
Huiart et al. 2005	1			Not compared to group with HF
Hutchinson et al. 2010		1		Do not report HR or RR

Supplementary Table 2.2. Reasons for study rejection.

Study	Inappropriate Comparison	Inappropriate Outcome	Other	Specifics
Inabnit et al. 2018		1		Length of stay
Iribarren et al. 2012	1			General population controls
Jeong et al. 2016		1		Do not report HR or RR
Jia et al. 2018		1		Do not report HR or RR
Kang et al. 2016		1		ICU admissions
Kang et al. 2018	1			Don't compare to COPD without HF
Koul et al. 2017		1		Do not report HR or RR
Kumar et al. 2012		1		Do not report HR or RR
Kumbhare et al. 2015	1			No HF
Kurmi et al. 2015	1			Not compared to group with HF
Liao et al. 2017	1			Beta-blocker use
Lim et al. 2015		1		Do not report HR or RR
Lin et al. 2013		1		Cor pulmonale
Lundback et al. 2009		1		HF combined with MI
Mapel et al. 2009		1		Prevalence ratio
Macrun et al. 2012	1			Biomarkers
Marti et al. 2006	1			no HF
Matamis et al. 2014	1			Have respiratory failure
Matera et al. 2017	1			Beta-blocker use
Matkovic et al. 2012		1		Adverse outcome; no HF group
Miller et al. 2010	1			CVD overall
Miniati et al. 2014	1			Compare to those without COPD
Pienaar et al. 2015		1		Do not report HR or RR
Piquet et al. 2013		1		Do not report HR or RR
Plachi et al. 2018	1			Don't compare to COPD without HF
Reechaipichitkul 2014		1		Do not report HR or RR
Rossi et al. 2017		1		Compare statins
Sadigov et al. 2017		1		Do not report HR or RR
Sessa et al. 2018	1			Beta-blocker use
Shah et al. 2014		1		Do not report HR or RR
Sharif et al. 2014			1	Abstract for Sharif et al. 2014b
Shin et al. 2018	1			Community acquired pneumonia
Sibila et al. 2014	1			CVD
Sidney et al. 2005	1			non-COPD comparators

Supplementary Table 2.2. Reasons for study rejection. (Continued)

Study	Inappropriate Comparison	Inappropriate Outcome	Other	Specifics
Sloots et al. 2017		1		OR; IHD or HF
Spece et al. 2018		1		OR; treatment provision
Sprooten et al. 2012			1	Abstract for Slenter et al. 2013
Stallberg et al. 2014		1		Do not report HR or RR
Stallberg et al. 2018		1		Rate ratios only for number of severe exacerbations
Stallberg et al. 2011		1		Combined IHD and HF
Steer et al. 2010			1	Literature review
Stefan et al. 2012	1			Beta-blocker use
Terzano et al. 2010		1		Do not report HR or RR
Tsapenko et al. 2013		1		Do not report HR or RR
Udrescu et al. 2017		1		Do not report HR or RR
Urff et al. 2014		1		CCQ score
Vallabhajosyula et al. 2018	1			Don't compare to COPD without HF
Wang et al. 2014		1		OR; length of stay
Westney et al. 2017		1		Do not report HR or RR
Wheaton et al. 2015		1		Do not report HR or RR
Yilmaz et al. 2017		1		Do not report HR or RR
Yu et al. 2015	1			Combined HF and heart disease
Zhang et al. 2016		1		Do not report HR or RR
Totals	**39**	**45**	**3**	

Supplementary Table 2.2. Reasons for study rejection. (Continued)

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Abukhalaf et al. 2018 [189]	Retrospective Cohort	Pre- or post-bronchodilator $FEV_1/FVC < 0.70$; ≥40 years; >20 pack-years smoking; clinical diagnosis of COPD	Diagnosis of bronchiolitis, granulomatosis with polyangitis, or asthma Post-bronchodilator $FEV_1/FVC > 0.70$	512	Median (IQR): 3 years (1.4-5.2)	Hazard ratio for mortality adjusted for lung function, BMI, smoking, comorbidities, exacerbation history	University of New Mexico Health Sciences Center (USA)
Ahn et al. 2015 [203]	Retrospective Cohort	Post-bronchodilator $FEV_1/FVC < 0.70$ Left heart failure was defined as ≤40% ejection fraction	Abnormal chest x-ray; no spirometry	229	Average (SD): 6.48 years (4.09)	Univariate hazard ratio for mortality	Ajou University Hospital (Republic of Korea)
Almagro et al. 2012 [190] EPOC en Servicios de Medicina Interna (ESMI) study	Longitudinal cohort	Post-bronchodilator $FEV_1/FVC < 0.70$; post-bronchodilator FEV_1 < 80% predicted; ≥40 years; admission for COPD exacerbation	Asthma; bronchiectasis; pulmonary oedema; pneumonia; no spirometry; admission for reason other than COPD exacerbation	606	0.23 years (12 weeks)	Univariate hazard ratio for mortality	70 A&E and internal medicine services (Spain)
Belloli et al. 2011 [204] Abstract	Retrospective Cohort	COPD coded in registry	ND	1132	Median (IQR): 1.55 years (0.74-2.5)	Hazard ratio for mortality adjusted for age, sex, lung function, comorbidities, NT-proBNP	University of Pittsburgh COPD Patient Registry and Molecular and Cellular Determinants of Disease Heterogeneity in COPD Registry (USA)
Bertens et al. 2010 [196] Abstract	Retrospective Cohort	COPD coded in general practice medical records; aged 45	ND	2230	ND	Hazard ratio for mortality adjusted for age, sex, comorbidities, medications	23 general practices (Netherlands)

Supplementary Table 2.3. Overview of included studies.

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Boudestein et al. 2009 [198]	Prospective Cohort	Clinical diagnosis of COPD by general practitioner; ≥65 years old; post-bronchodilator $FEV_1/FVC < 0.70$ HF identified by expert panel including two cardiologist using European Society of Cardiology (ESC) guidelines classification as systolic, diastolic, or right-sided; systolic ≤45% left ventricular ejection fraction	Previous cardiologist-confirmed diagnosis of HF	404	Average (SD): 4.2 years (1.4)	Hazard ratio for mortality adjusted for age, sex, smoking, comorbidities, medications	Recruited from 51 general practices; study took place at University Medical Center Utrecht (Netherlands)
Carter et al. 2019 [205]	Prospective Cohort	Age ≥18 years old; COPD admission coded using the International Classification of Disease 10th edition (ICD-10) and Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4)	ND	31,646	Average (SD): 5.2 years (3.6)	Hazard ratio for mortality adjusted for age, sex, comorbidities, ethnicity	7 NHS hospitals in North West of England (UK)
Chen et al. 2009 [191]	Retrospective Cohort	≥40 years old; hospitalised for COPD where COPD was coded using International Classification of Diseases, Version 9 (ICD-9) as one of the first five diagnoses for the admission	Death prior to discharge from initial hospitalisation	108,726	Maximum of 1 year	Hazard ratio for COPD readmission adjusted for sex, age, Canadian province, length of stay at baseline	Health Person-Oriented Information (HPOI) Database (Canada)

Supplementary Table 2.3. Overview of included studies. (Continued)

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Divo et al. 2012 [206] BODE cohort [316]	Prospective Cohort	Post-bronchodilator $FEV_1/FVC < 0.70$; history of smoking >10 or >20 pack-years, there is a discrepancy between the number reported in Divo et al. and the number reported in the description of the BODE cohort [316] cited by Divo et al.	Asthma; no spirometry; no six-minute walk test; myocardial infraction in previous 4 months; unstable angina; congestive HF (New York Heart Association class III or IV)	1,659	Median (IQR): 4.25 years (2.3-6.5)	Hazard ratio for mortality adjusted for age, sex, race, BMI, lung function, dyspnoea, exercise capacity	Pulmonary clinics (USA and Spain)
Genao et al. 2015 [199]	Retrospective Cohort	≥ 65 years old; AECOPD admission coded in the primary position of inpatient claim or emergency visit using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); continuously enrolled in Medicare fee-for-service for at least 12 months prior to and after (barring death) initial hospitalisation	Death prior to discharge from initial hospitalisation	52,741	Maximum of 3 years	Hazard ratios for mortality, for all-cause readmission, and for COPD-related readmission adjusted for age, sex, comorbidities, Medicare and Medicaid eligibility, malnutrition, race	Medicare fee-for-service claims data from U.S. Centers for Medicare and Medicaid Services (USA)

Supplementary Table 2.3. Overview of included studies. (Continued)

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Hasegawa et al. 2014 [192]	Retrospective Cohort	> 40 years old; COPD in any diagnostic position following emergency hospital admission	ND	172,707	ND	Odds ratio for all-cause inpatient mortality	Diagnosis Procedure Combination (DPC) database (Japan)
Hoiseth et al. 2016 [207]	Prospective Cohort	Admission for dyspnoea as primary complaint; adjudication of AECOPD based on GOLD guidelines; Adjudication of HF according to ESC guidelines	Disseminated malignant disease; inability to cooperate	75	Median (IQR): 1.27 years (0.83-1.9)	Hazard ratio for long-term mortality adjusted for age, BMI, systolic blood pressure, pulmonary attenuation, pH, troponin levels, insulin use, aldosterone antagonist use	Akershus Cardiac Examination (ACE) 2 Study (Norway)
Kaszuba et al. 2018 [187]	Prospective Cohort	≥ 35 years old; COPD coded using ICD-10 codes in at least one primary or secondary care consultation HF coded as ICD-10 code I50	Left Blekinge County during observation period	984	7 years	Odds ratio for all-cause mortality	Blekinge County council health care register (Sweden)
Kim et al. 2009 [208]	Retrospective Cohort	COPD admission coded in the first position of inpatient or emergency room visit using ICD-9 codes	ND	482	Median (IQR): 3.09 years (1.2-4.3)	Hazard ratio for mortality adjusted for age, sex, marital status, comorbidities, exacerbation history	Research Patient Data Repository at Partners HealthCare (USA)

Supplementary Table 2.3. Overview of included studies. (Continued)

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Lainscak et al. 2009 [209] Abstract	Retrospective Cohort	COPD and HF coded in registry by ICD-10; diagnosis ascertained by review of medical records	ND	960	2.8 years	Hazard ratio for mortality adjusted (variables for adjustment not reported)	Central Population Registry (Slovenia)
Lau et al. 2017 [193]	Retrospective Cohorts Derivation and validation cohorts	> 40 years old; index admission for COPD coded by ICD-10	ND	339,389 + 258,113	30 days	Odds ratio for 30-day COPD-related readmission; Odds ratio for inpatient all-cause mortality	State Inpatient Database (USA)
Löh et al. 2014 [213] Abstract	Retrospective Cohort	Primary diagnosis of COPD using ICD-10 codes; Primary diagnosis of respiratory failure with secondary diagnosis of COPD using ICD-10 codes	ND	995,044	ND	Odds ratio for inpatient all-cause mortality	German-diagnosis-related-groups (G-DRG) database from German Federal Statistical Office (Germany)
Maters et al. 2014 [210]	Prospective Cohort	COPD diagnosed according to GOLD guidelines; stable COPD for at least 6 weeks; available medical history	Inability to fill out questionnaires, perform cycle ergometry, and/or perform spirometry	224	4.2 years	Univariate hazard ratio for mortality	Center for Rehabilitation of the University Medical Center Groningen (UMCG) (Netherlands)
Miller et al. 2013 [201] ECLIPSE study [317] NCT00292552	Prospective Cohort	COPD patients aged 40-75 years; post-bronchodilator $FEV_1/FVC < 0.70$; post-bronchodilator $FEV_1 < 80\%$ predicted; smoking history ≥10 pack-years	Ability to comply with protocol; availability for study visits over three years; presence of a respiratory disorder other than COPD; active rheumatoid arthritis or inflammatory bowel disease; exacerbation within 4 weeks of enrolment	2,164	3 years	Univariate hazard ratio for mortality	Multinational

Supplementary Table 2.3. Overview of included studies. (Continued)

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Perera et al. 2012 [194]	Retrospective Cohort	≥ 40 years old; ICD-9 code for COPD with concurrent diagnosis for pneumonia or mechanical ventilation	ND	1,254,703	ND	Odds ratio for all-cause inpatient mortality	Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample for 2006 (USA)
Roberts et al. 2011 [211] UK National COPD Audit 2008 [318]	Prospective Cohort	COPD admission identified through the audit	ND	9169	90 days	Unadjusted risk ratio for all-cause 90 day mortality; unadjusted risk ratio for all-cause 90 readmission	UK National COPD Audit 2008
Santibáñez et al. 2016 [188]	Retrospective Cohort	≥ 35 years old; COPD coded using International Classification of Primary Care; post-bronchodilator $FEV_1/FVC < 0.70$	post-bronchodilator $FEV_1/FVC > 0.70$ or not recorded	900	1 year	Odds ratio for COPD-related hospitalisation; Odds ratio for inpatient mortality	Electronic clinical databases in province of Cantabria (Spain)
Schwab et al. 2017 [202]	Retrospective Cohort	≥2 medical claims with a COPD diagnosis recorded using ICD-9 in primary or secondary position; 40-89 years old at diagnosis; continuously enrolled in Medicare Advantage plans with Prescription Drug benefits for 12 months prior to index date and 24 months after index date	Enrolment in Administrative Services Only or commercial plan with data sharing restrictions; ≥1 medical claim with cystic fibrosis, pulmonary tuberculosis, or malignant neoplasms coded using ICD-9 at any position during study period	52,643	2 years	Rate ratios for all-cause and COPD-related hospitalisations adjusted for age, sex, geographic location, influenza vaccination status, comorbidities, exacerbation history, pre-index all-cause hospitalisation/ emergency visits/ outpatient visits	US national health plan (Humana Inc., Louisville, KY, USA)

Supplementary Table 2.3. Overview of included studies. (Continued)

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Sharif et al. 2014 [200]	Retrospective Cohort	40-64 years old; hospitalised with primary discharge diagnosis of COPD using ICD-9 codes	Incomplete data for 12 months prior to index hospitalisation; transferred to long-term facility; nonspecific bronchitis and asthma discharge codes	8,236	30 days	Odds ratio for 30-day all-cause readmission	The Clinformatics Data Mart, managed by OPTUMInsight of Minneapolis, MN (USA)
Silver et al. 2010 [214]	Cross-sectional	Hospitalised for COPD exacerbation in primary diagnostic position	NS	69,841	ND	Odds ratio for all-cause inpatient mortality	Premier's Perspective Comparative Database (USA)
Simmering et al. 2016 [195]	Retrospective cohort	≥ 40 years old; COPD in first diagnostic position for index hospitalisation; discharged alive; complete covariate information	Inpatient death at index hospitalisation	286,313	30 days	Odds ratio for all-cause 30-day rehospitalisation	Healthcare Cost and Utilization Project (HCUP) State Inpatient Database for California (USA)
Slenter et al. 2013 [212]	Retrospective Cohort	COPD admission coded using ICD-9; $FEV_1/FVC < 0.70$ and FEV_1 reversibility <11% *or* clinical diagnosis; treatment with systemic glucocorticoids during admission	Patients transferred into hospital following initial admission at another hospital	260	1 year	Hazard ratio of 1 year mortality adjusted for age, sex, prior COPD-related hospitalisation in last two years, $PaCO_2$ at admission, urea level at admission	Pulmonary wards of Maastricht University Hospital (Netherlands)

Supplementary Table 2.3. Overview of included studies. (Continued)

Study	Design	Inclusion Criteria	Exclusion Criteria	Patients	Length of Follow-Up	Outcome(s)*	Setting
Yeatts et al. 2013 [197]	Retrospective Cohort	≥45 years old; ≥1 COPD-related emergency visit coded in the first or second discharge position using ICD-9	Bronchitis	33,799	30 days or 1 year	Unadjusted risk ratios for COPD-related readmission within 30 days or 1 year	North Carolina Public Health Data Group and the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) surveillance system (USA)

Supplementary Table 2.3. Overview of included studies. (Continued) *Details which outcome(s) were used in these analyses and therefore may not reflect the full scope of the individual study. *Abbreviations:* Accident and emergency (A&E). Body mass index (BMI). Chronic obstructive pulmonary disease (COPD). Forced expiratory volume in one second (FEV1). Forced vital capacity (FVC). Interquartile range (IQR). National Health Service (NHS). Not described (ND). N-terminal pro brain natriuretic peptide (NT-proBNP). Partial pressure of carbon dioxide in the arterial blood (PaCO2). Standard deviation (SD). United Kingdom (UK). United States of America (USA).

# ▲	Searches	Results	Type	Actions	Annotations
1	chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/	70878	Advanced	Display Results | More	
2	COPD.mp.	41168	Advanced	Display Results | More	
3	emphysema.mp. or *Emphysema/ or exp Pulmonary Emphysema/	33051	Advanced	Display Results | More	
4	chronic bronchitis.mp. or exp Bronchitis, Chronic/	10001	Advanced	Display Results | More	
5	obstructive lung disease*.mp. or *Lung Diseases, Obstructive/	18050	Advanced	Display Results | More	
6	obstructive pulmonary disease*.mp.	44177	Advanced	Display Results | More	
7	chronic airway disease*.mp.	536	Advanced	Display Results | More	
8	chronic respiratory disease*.mp.	3044	Advanced	Display Results | More	
9	COAD.mp.	293	Advanced	Display Results | More	
10	AECB.mp.	224	Advanced	Display Results | More	
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	109126	Advanced	Display Results | More	
12	heart failure.mp. or exp Heart Failure/	188527	Advanced	Display Results | More	
13	left ventricular failure.mp. or exp Ventricular Dysfunction, Left/	30410	Advanced	Display Results | More	
14	cardiac failure.mp.	11549	Advanced	Display Results | More	
15	myocardial failure.mp.	752	Advanced	Display Results | More	
16	12 or 13 or 14 or 15	215449	Advanced	Display Results | More	
17	11 and 16	4686	Advanced	Display Results | More	
18	exp Mortality/ or mortality.mp.	1148531	Advanced	Display Results | More	
19	death*.mp.	828603	Advanced	Display Results | More	
20	18 or 19	1712931	Advanced	Display Results | More	
21	exp Hospitalization/ or hospitalization*.mp.	298981	Advanced	Display Results | More	
22	hospital admission*.mp.	34412	Advanced	Display Results | More	
23	hospital readmission*.mp.	5202	Advanced	Display Results | More	
24	*Patient Admission/ or patient admission*.mp.	23891	Advanced	Display Results | More	
25	*Patient Readmission/ or patient readmission*.mp.	14377	Advanced	Display Results | More	
26	hospitalisation*.mp.	15923	Advanced	Display Results | More	
27	21 or 22 or 23 or 24 or 25 or 26	329142	Advanced	Display Results | More	
28	20 or 27	1942242	Advanced	Display Results | More	
29	17 and 28	2224	Advanced	Display Results | More	
30	limit 29 to (english language and yr="1980 -Current")	2011	Advanced	Display Results | More	

Supplementary Figure 2.1. Search of MEDLINE. Screen shot of the exact search strategy used for the literature search of Medline on 05 February 2019 [181].

# ▲	Searches	Results	Type	Actions	Annotations
1	chronic obstructive pulmonary disease.mp. or exp chronic obstructive lung disease/	125305	Advanced	Display Results | More	
2	COPD.mp.	77454	Advanced	Display Results | More	
3	emphysema.mp. or exp lung emphysema/ or *emphysema/	58044	Advanced	Display Results | More	
4	chronic bronchitis.mp. or exp chronic bronchitis/	20929	Advanced	Display Results | More	
5	obstructive lung disease*.mp.	119685	Advanced	Display Results | More	
6	obstructive pulmonary disease*.mp.	65320	Advanced	Display Results | More	
7	*obstructive airway disease/ or obstructive airway disease*.mp.	3431	Advanced	Display Results | More	
8	obstructive respiratory disease*.mp.	465	Advanced	Display Results | More	
9	COAD.mp.	405	Advanced	Display Results | More	
10	AECB.mp.	285	Advanced	Display Results | More	
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	204818	Advanced	Display Results | More	
12	heart failure.mp. or exp heart failure/	521504	Advanced	Display Results | More	
13	left ventricular dysfunction.mp. or exp heart left ventricle failure/	37451	Advanced	Display Results | More	
14	cardiac failure.mp.	19425	Advanced	Display Results | More	
15	myocardial failure.mp.	1192	Advanced	Display Results | More	
16	12 or 13 or 14 or 15	530313	Advanced	Display Results | More	
17	11 and 16	18341	Advanced	Display Results | More	
18	mortality.mp. or exp mortality/	1377559	Advanced	Display Results | More	
19	death*.mp.	1288591	Advanced	Display Results | More	
20	18 or 19	2322318	Advanced	Display Results | More	
21	exp hospitalization/ or hospitalization*.mp.	413711	Advanced	Display Results | More	
22	*hospital admission/	16951	Advanced	Display Results | More	
23	*hospital readmission/	10556	Advanced	Display Results | More	
24	patient admission*.mp.	2664	Advanced	Display Results | More	
25	patient readmission*.mp.	725	Advanced	Display Results | More	
26	hospitalisation*.mp.	28582	Advanced	Display Results | More	
27	hospital admission*.mp.	193636	Advanced	Display Results | More	
28	hospital readmission*.mp.	51986	Advanced	Display Results | More	
29	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	619652	Advanced	Display Results | More	
30	20 or 29	2749054	Advanced	Display Results | More	
31	17 and 30	8697	Advanced	Display Results | More	
32	limit 31 to (english language and yr="1980 -Current")	8139	Advanced	Display Results | More	

Supplementary Figure 2.2. Search of Embase. Screen shot of the exact search strategy used for the literature search of Embase on 05 February 2019 [182].

Appendix III: Supplementary material to Chapter III

ISAC Protocol 18_006R2

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form**' found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title[§] (*Please state the study title below)*
Causes of mortality in patients with comorbid COPD and heart failure in the United Kingdom, 2005-2017

[§]*Please note: This information will be published on the CPRD's website as part of its transparency policy.*

2. Has any part of this research proposal or a related proposal been previously submitted to ISAC?
Yes * ☒ No ☐

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

17_086R approved the analyses pertaining to causes of death for COPD patients for 2005-2015; however, it excluded patients with comorbid COPD-HF from the COPD group and did not include data up to 2017. In these analyses, three patients groups will be investigated from 2005-2017: patients with COPD and no HF, patients with HF and no COPD, and patients with both COPD and HF. Therefore, the rates and causes found for COPD patients in this analysis may differ from those found in ISAC 17_086R due to the removal of COPD patients with HF from the COPD analysis and the increase in the study period to 12 years.

3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)
Yes* ☐ No ☒

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☐	Other*	☐

**If Other, please specify the type of study here and in the lay summary below:*

5. Health Outcomes to be Measured[§]

[§]Please note: This information will be published on CPRD's website as part of its transparency policy.

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Causes of Mortality for Heart Failure and COPD Patients
- Causes of Death for Patients with Comorbid COPD and Heart Failure
- Excess Risk of Death for Patients with Comorbid COPD and Heart Failure

[Please add more bullet points as necessary]

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☒	Regulatory purposes	☐
Other*	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator[§]

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Dr Jennifer Quint, Senior Clinical Lecturer in Respiratory Epidemiology, Imperial College London
j.quint@imperial.ac.uk

[§]Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy

CV has been previously submitted to ISAC	☒ **CV number:**	042_15CEPSL
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

8. Affiliation of Chief Investigator (full address)

Respiratory Epidemiology, Occupational Medicine and Public Health
G48, Emmanuel Kaye Building,
Manresa Road
National Heart and Lung Institute
Imperial College
London, SW3 6LR
Tel +44 (0) 207 594 8824

9. Corresponding Applicant[§]

Please state the full name, affiliation(s) and e-mail address below:

Eleanor L Axson, Research Assistant in Statistics and Epidemiology and PhD Student, Imperial College London, e.axson@imperial.ac.uk

[§]Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy

Same as chief investigator ☐
CV has been previously submitted to ISAC ☒ **CV number:** 276_17
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

10. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Eleanor L Axson, Research Assistant in Statistics and Epidemiology and PhD Student, Imperial College London, e.axson@imperial.ac.uk
CV has been previously submitted to ISAC ☒ **CV number:** 276_17
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Chloe Bloom, Postdoctoral Research Associate, Imperial Collage London, chloe.bloom.06@imperial.ac.uk
CV has been previously submitted to ISAC ☒ **CV number:** 312_16
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Alicia Gayle, PhD Student, Imperial College London, alicia.gayle14@imperial.ac.uk
CV has been previously submitted to ISAC ☒ **CV number:** 292_16
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator:
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary]

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work
There are no conflicts of interest associated with this work.
**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	**Yes**	**No**

Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Axson, Bloom, Gayle	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Axson, Bloom, Gayle	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint	☒	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London, UK
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London, UK
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐
The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☒
A data set will be provided by the CPRD[¥€] ☐
CPRD has been commissioned to extract the data and perform the analyses[€] ☐
Other: ☐
If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*
***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*
[¥]*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.*
[€]*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher	Reference number (where available)	Date of contact

17. Primary care data

Please specify which primary care data set(s) are required)
Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.
Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:
Name of CPRD Researcher Reference number (where available) Date of contact

18. Site Location of Data

a) Processing location(s): National Heart and Lung Institute, Imperial College London, London, UK

Location area - UK / EEA / Worldwide: UK

Organisation address: Emmanuel Kaye Building, Manresa Road, National Heart and Lung Institute, Imperial College, London, SW3 6LR

Note: Please enter the location details of where the data for this study will be used (processed).

b) Storage Location(s): National Heart and Lung Institute, Imperial College London, London, UK

Location area - UK / EEA / Worldwide: UK

Organisation address: Emmanuel Kaye Building, Manresa Road, National Heart and Lung Institute, Imperial College, London, SW3 6LR

Note: Please enter the location details of where the data for this study will be stored.

c) Territory of analysis - UK / EEA / Worldwide: UK

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

19. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset, PROMS data, the Pregnancy Register, Cancer Registration, SACT and CPES data and the Mental Health Services Data Set **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Reference number (where available) Date of contact

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

20. Please select the source(s) of linked data being requested[§]

[§]Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data
☐ HES Admitted Patient Care
☐ HES Outpatient
☐ HES Accident and Emergency
☐ HES Diagnostic Imaging Dataset
☐ HES PROMS (Patient Reported Outcomes Measure)**
☐ CPRD Mother Baby Link
☐ Pregnancy Register
☐ NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data *
☐ NCRAS Cancer Patient Experience Survey (CPES) data*
☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*
☐ Mental Health Services Data Set (MHDS)

☐ Practice Level Index of Multiple Deprivation (Standard)
☐ Practice Level Index of Multiple Deprivation (Bespoke)
☒ Patient Level Index of Multiple Deprivation***
☐ Patient Level Townsend Score ***

**Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*
***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only available for non-commercial purposes, such as academic research, or in connection with delivering services to the NHS.*
**** 'Patient level IMD and Townsend scores will not be supplied for the same study*
*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher Reference number (where available) Date of contact

21. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count)* 2

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

22. Is linkage to a <u>local[¥]</u> dataset with <1 million patients being requested?

Yes * ☐ No ☒

**If yes, please provide further details:*
[¥] Data from defined geographical areas i.e. non-national datasets.

23. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

24. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

25. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

26. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐
Is the questionnaire a validated instrument? Yes ☐ No ☐
If yes, has permission been obtained to use the instrument? Yes ☐ No ☐
Please provide further information:

Other (please describe)

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

27. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

28. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

29. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Dr Jennifer K Quint Date: 06/12/17 e-Signature (type name): JKQuint

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]
[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Causes of mortality in patients with comorbid COPD and heart failure in the United Kingdom, 2005-2017

B. Lay Summary (Max. 200 words)[§]
[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Many patients have both chronic obstructive pulmonary disease (COPD) and heart failure (HF), but it is not well understood how having both of these conditions affects their risk of death. In this study, we aim to compare the causes of death for those patients with both COPD and HF to those for patients with only one of these conditions. Additionally, we will investigate whether patients with both COPD and HF have a greater risk of death than those with only COPD or HF.

C. Technical Summary (Max. 200 words)[§]
[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

There have been many studies investigating whether having both chronic obstructive pulmonary disease (COPD) and heart failure (HF) results in an increased risk of mortality compared to patients with only one of these conditions; however, as of yet there is no consensus. We will use linked Clinical Practice Research Datalink and Office of National Statistics data to investigate changes in causes of death. We will undertake descriptive analyses to investigate changes in causes of death over time. We will analyse rates of death associated with COPD, HF, and comorbid COPD-HF stratified by age and sex. We will determine the cumulative incidence function to allow adjustment for competing risks and calculate the cumulative probability of dying from a specific cause at each time point having survived to that time without a death from any other cause. This will be derived from baseline functions and estimates of hazards from cause specific Cox regression models. We will calculate crude and age-adjusted, all-cause and cause-specific mortality rates, cumulative incidence function, and excess risk of death. Controls will be matched 2:1 with cases and each patient with comorbid COPD-HF will be matched to 2 patients with just COPD and with 2 patients with just HF.

D. Objectives, Specific Aims and Rationale
Objectives: To investigate causes of mortality and excess risk of death in patients with comorbid COPD-HF.

Specific Aims

1. To determine all-cause and cause-specific mortality by age, sex, smoking status, and BMI (assuming numbers allow) in patients with 1) COPD without HF, 2) HF without COPD, and 3) comorbid COPD-HF. Risk of death in patients with comorbid COPD-HF as compared to patients with either COPD or HF only, annually from 2005 to 2017.
2. To investigate excess risk of death for patients with comorbid COPD-HF as compared to patients with COPD without HF and HF without COPD for all-cause and disease-specific causes of death.

Rationale
There is currently no consensus as to whether having comorbid COPD-HF results in an increased risk of mortality due to CVD. By conducting these analyses we hope to use the large CPRD database to generate a robust estimate of this risk, while expanding beyond past analyses to investigate causes of mortality in this population.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

E. Study Background

It is estimated that 3 million individuals in the United Kingdom (UK) have chronic obstructive pulmonary disease (COPD), but that only one-third are currently diagnosed (1). According to the British Heart Foundation, an estimated 900,000 individuals are living with heart failure in the UK, estimated to be increasing at a rate of over 25,000 new cases per year (2, 3).

Heart failure and COPD often coexist in patients. In older community patients with COPD, 20% have comorbid heart failure; and COPD was diagnosed prospectively in 30% of stable community heart failure patients (4, 5). Heart failure and COPD share aetiology, symptoms, and the potential to exacerbate the other condition leading to higher health care utilization costs and mortality in patients with both conditions (6, 7). Recent international guidelines have recommended increased consideration of comorbid conditions when assessing COPD and heart failure, demonstrating recognition of the influences of comorbidities on disease progression and prognosis (6, 8).

A number of studies have investigated whether having comorbid COPD-HF results in an excess risk of death compared to patients with COPD or HF alone; however, many investigated only one type of HF (such as HF with preserved ejection fraction) and none were completed at the national scale (9-13). These studies also found varying results, some finding patients with the comorbid disease at a greater risk of death (9, 11), while others found no increase in risk of death (10, 12, 13). Additionally, recent study investigated modes of death in patients with heart failure with preserved ejection fraction through systematic review of the literature (14); however, to our knowledge, there are no published data regarding mode of death for patients with comorbid COPD-HF.

Our study aims to investigate causes of death for patients with COPD, HF comorbid COPD-HF at the national level and determine whether there is an excess risk of death for these patients, both all-cause and cause-specific, as compared to patients with COPD or HF alone over a 12-year period.

F. Study Type

This study is descriptive and analytic. We will assess excess risk of death using hazard ratios and do hypothesis testing in Specific Aim #2.

G. Study Design

This is a cohort study.

H. Feasibility counts

The number of patients in CPRD between 1st January 2004 and 31st December 2017 with linked ONS data diagnosed with COPD exceeds 100,000 and the same for HF. We expect around 30% of HF patients to have COPD, or about 30,000 patients.

I. Sample size considerations

As CPRD covers approximately 8% of the UK population and at least 30,000 people die per year in the UK of COPD we expect 2500 deaths in patients with COPD in CPRD per year and conservatively estimate 500 deaths/yr in those with linked ONS data. We will use 10 years of data (2004-2015) and hence estimate 5000 potential deaths in patients with COPD. With 5000 deaths being examined, we will have more than enough numbers to detect a difference in the proportion of deaths from CVD of 5% (e.g. 35% vs. 30%), with a power of 95%, and alpha of 0.05. We expect similar numbers for HF.

From previous studies we know there are approximately 100,000 prevalent HF patients in CPRD. We expect around 30% of these to have COPD (5) – 30,000 patients, of whom approximately 15,000 will be eligible for linkage. The most recent trial found a mortality rate of 7-8% per year for HF patients (21). Conservatively estimating that 7% of patients with comorbid COPD-HF will die annually, we expect 1,050 deaths per year of patients with comorbid COPD-HF. Comparing controls (just HF

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

or COPD) 2:1 cases, we have enough power to detect a 5% difference in the proportion of deaths from CVD with a power of 0.80 and alpha 0.05.

We will not include any cells with counts less than five due to anonymity concerns.

All estimates will be provided with 95% confidence intervals as is standard.

J. Data Linkage Required (if applicable):[§]

[§]*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

ONS data to determine cause of death
IMD data to control for socioeconomic status (SES)

K. Study population

There are three patient groups: 1) COPD without HF, 2) HF without COPD, and 3) comorbid COPD-HF. In all groups, patients with data recording inconsistencies between the databases or inconsistent timing of variables will be excluded, e.g. multiple dates of death.

Patients with comorbid COPD-HF (have both COPD and HF) over 35 years old at COPD diagnosis, identified in CPRD between 1st January 2004 and 31st December 2017 with at least one year of "research standard" CPRD registration before their disease diagnosis and at least one pre-disease (pre-COPD or HF, whichever came first) consultation in their CPRD history will be included. We will consider diagnosis with both conditions at any time to establish comorbidity, as neither condition is fully reversible.

For our analysis of HF deaths, patients with HF, diagnosed at any age, aged 35+ years without comorbid COPD, identified in CPRD between 1st January 2004 and 31st December 2017 with at least one year of "research standard" CPRD registration before their disease diagnosis and at least one pre-disease consultation in their CPRD history will be included.

For our analysis of COPD deaths, patients with COPD aged 35+ years at COPD diagnosis without comorbid HF, identified in CPRD between 1st January 2004 and 31st December 2017 with at least one year of "research standard" CPRD registration before their disease diagnosis and at least one pre-disease consultation in their CPRD history will be included.

This is different from the analyses carried out for ISAC 17_086R as that study measured mortality rates in all COPD patients; unlike this cohort, which is more selective and measuring mortality rates for COPD patients that do not have comorbid HF (as well as patients with HF and COPD-HF).

L. Selection of comparison group(s) or controls

For Specific Aim #2, controls will be matched 2:1 to cases by age, sex, smoking status, BMI (if numbers allow), and GP practice. Each patient with comorbid COPD-HF will be matched to 2 patients with just COPD and with 2 patients with just HF.

M. Exposures, Health Outcomes[§] and Covariates

[§]*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

Exposures: COPD, HF, and comorbid COPD-HF. The COPD code list is published (15). The HF code list is attached as an Appendix.

Outcome: Mortality in ONS – using the derived variable as well as information from all causes mentioned on the death certificate (proposed causes). We have previously used Office of National Statistics mortality data (ONS) and are aware of the limitations. Mortality data for England and Wales are nearly 100% complete, a large proportion of registered deaths are certified by a medical practitioner and accuracy of recording has improved over time (16). Since 1993 automated coding has been in place for cause of death with application of WHO rules allowing international comparisons.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Covariates: Age, sex, SES, smoking status, body mass index (BMI). Covariates will be measured as close to baseline as possible, up to three years prior to/after baseline. Smoking status will be defined as never/not recorded, current, or former (22).

N. Data/ Statistical Analysis

As in ISAC 17_086R, we will determine the commonest causes of death within each cohort (reporting n and %) using information derived by ONS to determine the terminal event, as well as the underlying cause of death code from ONS data which has been derived using standardized guidelines from information available on death certificates (17). Additionally we will use information from all causes mentioned on the death certificate (proposed causes) as we are aware of issues surrounding the accuracy of the underlying cause which is a derived variable (16,18). In a review undertaken by ONS, the proposed and confirmed underlying cause of death matched at ICD chapter level in 88% of cases and there was exact agreement (to 4 digits) in 78% of cases, rising to 80% when records matching to 3 digits were included (23). We will also investigate the recording of each chronic respiratory disease on the death certificates (detailed in part 2) having identified the diagnosis of each chronic respiratory disease cohort using CPRD data.

Specific Aim #1: To determine all-cause and cause-specific mortality by age, sex, smoking status, and BMI (assuming numbers allow) in patients with COPD, HF, and comorbid COPD-HF as compared to patients with either COPD or HF annually from 2005 to 2017.

We will analyse mortality trends from 2005-2017 among people with COPD, HF, and comorbid COPD-HF. We will compare the mortality of patients with comorbid COPD-HF to the morality of patients with COPD or HF alone. We will calculated crude mortality rates by sex and 10 year age groups for COPD, HF, and comorbid COPD-HF patients by calculating the number of deaths in patients within each of our three disease groups and dividing by the midpoint disease group population for that year. We will use direct standardisation to calculate comparative mortality figures separately for males and females.

Crude, age adjusted and age & (smoking) adjusted mortality rates in males and females will be calculated. Cause specific mortality rates will be determined by dividing the number of deaths due to each cause by the total person years of follow up. We will determine the cumulative incidence function to allow adjustment for competing risks and calculate the cumulative probability of dying from a specific cause at each time point having survived to that time without a death from any other cause. This will be derived from baseline functions and estimates of hazards from cause specific Cox regression models. We will use bootstrapping to determine 95% CIs and plot the incidence of death and excess risk of death graphically (19). In addition to stratifying by age, sex, and smoking status, we will consider (if numbers in subgroups permit) of stratifying by BMI and SES.

Specific Aim #2: To investigate excess risk of death for patients with comorbid COPD-HF as compared to patients with either COPD or HF for all-cause and disease-specific causes of death.

Controls will be selected from the COPD or HF populations (patients with either COPD or HF, but not both). Controls will be frequency matched to each case by age at diagnosis within 5-year age bands (20). We will calculated crude and adjusted mortality rates (per Specific Aim #1). The excess risk of death will be calculated as the difference between the cumulative incidence of death for people with comorbid COPD-HF and the cumulative incidence of death for those with COPD alone and those with HF alone. The excess risk of death will be calculated for cases and then hypothesis testing will be used to see if there is a significant difference in excess risk of death for patients with comorbid COPD-HF as compared to those with only COPD or HF. We will plot the cumulative incidence of death and excess risk for each most common cause of death using stacked graphs by each of our three disease groups.

O. Plan for addressing confounding

We will match on age, sex and GP practice and, if counts permit, include SES and BMI in the regression analysis. Depending upon the output form this analysis we will investigate other factors of interest and potential confounders in future work.

P. Plans for addressing missing data

Missing data can be handled by making assumptions about the missing data and seeing how the results are affected by those assumptions i.e. sensitivity testing. Part of this can involve multiple imputation in which several variables are adjusted

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

simultaneously.Where appropriate, and where data are missing at random, we will undertake both a complete case analysis and we will consider using multiple imputation. Where data are not missing at random, for example with spirometry data, but where we expect the data to be 80% complete (based on previous studies), we will use a complete case analysis but will discuss biases that may occur as a result of adopting that approach. Where multiple imputaiton is not appropriate and there are large quantities of data missing, we will consider using those covariates only as part of a secondary analysis and will discuss any biases and limitations that occur as a result of that.

Data on BMI and smoking status are less likely to be missing the the COPD and HF populations than in the general population. Based on previous (unpublished) work, we expect no more than 15% missing data for BMI. With our expected numbers high, we will conduct complete case analysis. For smoking status, one category of classification is 'never/not recorded', thus all patients will be included in analyses by default.

Q. Patient or user group involvement (if applicable)

We have not involved patients in the design or analysis of this study.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals, and will be presented both at appropriate conferences and at other meetings; the latter will include scientific meetings externally, for example for the American and European Respiratory Society Meetings and within academic institutions in London.

S. Limitations of the study design, data sources, and analytic methods

Misclassification of exposures

Specific Read codes have been chosen to maximize the sensitivity of diagnosing each COPD and HF. We are aware there may be misdiagnosis and misclassification of COPD and HF. Ultimately, however, we are limited by the acumen of the reviewing clinician recording the diagnosis.

Misclassification of outcomes

We have previously used Office of National Statistics mortality data (ONS) and are aware of the limitations. Mortality data for England and Wales are nearly 100% complete, a large proportion of registered deaths are certified by a medical practitioner and accuracy of recording has improved over time (16). Since 1993 automated coding has been in place for cause of death with application of WHO rules allowing international comparisons.

We will not include any cells with counts less than five due to anonymity concerns.

All estimates will be provided with 95% confidence intervals as is standard.

T. References

1. Shahab L, Jarvis M J, Britton J, West R. 2006. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax.* 1043-1047.
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Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

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List of Appendices *(Submit all appendices as separate documents to this application)*

Heart Failure Code List

First Minor Amendment to ISAC Protocol 18_006R2

12 February 2019

Dear ISAC Chair,

This letter is regarding the proposed minor amendment to approved ISAC protocol 18_006R2. The proposed minor amendment allows for stratification of mortality and causes of death by severity of chronic obstructive pulmonary disease (COPD). Severity of COPD will be determined per guidelines (1, 2) using spirometry data. This additional stratification will allow for greater description of the mortality burden of patients with COPD, heart failure (HF), and comorbid COPD-HF. The current approved protocol allows for the analysis of rates of death associated with COPD, HF, and comorbid COPD-HF stratified by age, sex, and smoking status, BMI, and SES. The current protocol also allows for the determination of the commonest causes of death within each cohort.

Thank you for your consideration.

Sincerely,

Dr Jennifer K Quint, MSc PhD FHEA FRCP
Reader in Respiratory Epidemiology
Respiratory Epidemiology, Occupational Medicine and Public Health
G48, Emmanuel Kaye Building
Manresa Road
National Heart and Lung Institute
Imperial College
London, SW3 6LR
Tel: +44 (0) 207 594 8821

JKQ/ela

References

1. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. (2010). Retrieved from https://www.nice.org.uk/guidance/cg101
2. GOLD. (2017). Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Retrieved from http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

Second Minor Amendment to ISAC Protocol 18_006R2

15 May 2019

Dear ISAC Chair,

This letter is regarding a second minor amendment to approved ISAC protocol 18_006R2. The new minor amendment regards the investigation of mortality in 1-year, 5-years, and 10-years in addition to the analysis of mortality over the entire study period.

Previously, a different minor amendment (letter dated 12 February 2019) providing for the analysis of mortality by severity of airflow limitation was approved for this ISAC.

Thank you for your consideration.

Sincerely,

Dr Jennifer K Quint, MSc PhD FHEA FRCP
Reader in Respiratory Epidemiology
Respiratory Epidemiology, Occupational Medicine and Public Health
G48, Emmanuel Kaye Building
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ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form**' found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

30. Study Title[§] (*Please state the study title below)*
Heart failure as a risk factor for acute exacerbations of COPD (AECOPD)

[§]*Please note: This information will be published on the CPRD's website as part of its transparency policy.*

31. Has any part of this research proposal or a related proposal been previously submitted to ISAC?
Yes [*] ☐ No ☒

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

32. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)
Yes[*] ☐ No ☒

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*

33. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☒	Methodological Research	☐
Health/Public Health Services Research	☐	Other[*]	☐

[*]*If Other, please specify the type of study here and in the lay summary below:*

34. Health Outcomes to be Measured[§]
[§]*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Incidence of comorbid COPD and HF
- Prevalence of comorbid COPD and HF
- Rates of AECOPD in relation to comorbid COPD-HF

[Please add more bullet points as necessary]

35. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☒	Regulatory purposes	☐
Other*	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

36. Chief Investigator§

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Dr Jennifer Quint, Senior Clinical Lecturer in Respiratory Epidemiology, Imperial College London
j.quint@imperial.ac.uk

§Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy

CV has been previously submitted to ISAC	☒	**CV number:** 042_15CEPSL
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

37. Affiliation of Chief Investigator (full address)

Respiratory Epidemiology, Occupational Medicine and Public Health
G48, Emmanuel Kaye Building
Manresa Road
National Heart and Lung Institute
Imperial College
London, SW3 6LR
Tel: +44 (0)207 594 8824

38. Corresponding Applicant§

Please state the full name, affiliation(s) and e-mail address below:

Eleanor L. Axson, Research Assistant in Statistics and Epidemiology, Imperial College London
e.axson@imperial.ac.uk

Respiratory Epidemiology, Occupational Medicine and Public Health
G05, Emmanuel Kaye Building
Manresa Road
National Heart and Lung Institute
Imperial College

London, SW3 6LR
Tel: +44 (0)207 594 7987

§*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator ☐
CV has been previously submitted to ISAC ☒ **CV number:** 276_17
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

39. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Chloe Bloom, postdoc researcher, Imperial College London, chloe.bloom06@imperial.ac.uk
CV has been previously submitted to ISAC ☒ **CV number:** 312_16
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Eleanor Axson, Research Assistant, Imperial College London,e.axson@imperial.ac.uk
CV has been previously submitted to ISAC ☒ **CV number:** 276_17
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Alex Bottle, Reader in Medical Statistics, Imperial College London, robert.bottle@imperial.ac.uk
CV has been previously submitted to ISAC ☐ **CV number:** 491_15CES
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Martin Cowie, Chair in Cardiology, Imperial College London, m.cowie@imperial.ac.uk
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Varun Sundaram, Research Assistant, Imperial College London, v.sundaram@imperial.ac.uk
CV has been previously submitted to ISAC ☐ **CV number:** 206_17
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary]

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

40. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

Dr Quint's research group has received funding from MRC, Wellcome, BLF, GSK, BI, Insmed, Bayer and AZ for other projects, none of which relate to this work.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

41. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	Yes	No
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Bloom, Quint, Axson, Sundaram, Bottle	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Bloom, Quint, Axson, Sundaram, Cowie, Bottle	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint	☒	☐

42. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

1. Boudestein LC, Rutten FH, Cramer MJ, et al. 2009. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Fail*. 11:1182-1188.

2. Rusinaru D, Saaidi I, Godard S et al. 2008. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *Am J Cardiol*. Feb 1; 101(3):353-8.

3. Quint JK, Herrett E, Bhaskaran K, Timmis A, Hemingway H, Wedzicha JA, et al. 2013. Effect of beta blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ.* 347:f6650.

SECTION C: ACCESS TO THE DATA

43. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London, UK
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

44. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Please specify name and country:* Imperial College London, UK
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

45. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☒

A data set will be provided by the CPRD[¥€] ☐
CPRD has been commissioned to extract the data and perform the analyses[€] ☐
Other: ☐
If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*
***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*
[¥]*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.*
[€]*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher Reference number (where available) Date of contact

46. Primary care data

Please specify which primary care data set(s) are required)
Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐
EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.
Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:
Name of CPRD Researcher Reference number (where available) Date of contact

47. Site Location of Data

d) Processing location(s): National Heart and Lung Institute, Imperial College London, London, UK

Location area - UK / EEA / Worldwide: UK

Organisation address: Emmanuel Kaye Building, Manresa Road, National Heart and Lung Institute, Imperial College, London, SW3 6LR

Note: Please enter the location details of where the data for this study will be used (processed).

e) Storage Location(s): National Heart and Lung Institute, Imperial College London, London, UK

Location area - UK / EEA / Worldwide: UK

Organisation address: Emmanuel Kaye Building, Manresa Road, National Heart and Lung Institute, Imperial College, London, SW3 6LR

Note: Please enter the location details of where the data for this study will be stored.

f) Territory of analysis - UK / EEA / Worldwide: UK

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

48. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset, PROMS data, the Pregnancy Register, Cancer Registration, SACT and CPES data and the Mental Health Services Data Set **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

We have not discussed linkage as we are only asking to access data that we have previous experience of using.

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Reference number (where available) Date of contact

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

49. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data
☒ HES Admitted Patient Care
☒ HES Outpatient
☐ HES Accident and Emergency
☐ HES Diagnostic Imaging Dataset ☐ HES PROMS (Patient Reported Outcomes Measure)**
☐ CPRD Mother Baby Link
☐ Pregnancy Register

☐ NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data *
☐ NCRAS Cancer Patient Experience Survey (CPES) data*
☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*
☐ Mental Health Services Data Set (MHDS)

☐ Practice Level Index of Multiple Deprivation (Standard)
☐ Practice Level Index of Multiple Deprivation (Bespoke)
☒ Patient Level Index of Multiple Deprivation***
☐ Patient Level Townsend Score ***

**Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*
***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only available for non-commercial purposes, such as academic research, or in connection with delivering services to the NHS.*
**** 'Patient level IMD and Townsend scores will not be supplied for the same study*
*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher Reference number (where available) Date of contact

50. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **not** be included in this count)* 4

A risk assessment has been carried out given that we have asked for 4 datasets.

Data access: Users of this dataset do not have access to other datasets which could be used to de-identify patients. Access to data is restricted to the investigators for this study only. All those with access are legally liable through substantive contracts with Imperial College London.

Publication: Data will be published with small numbers supressed in line with NHS Digital small number suppression guidance. Additional care will be taken, including cross-checking with multiple researchers to ensure anonymity according to multiple reviewers.

Re-identification protocol: On actual or suspected re-identification of any patients CPRD will be notified immediately and all publications will be halted using this data until an investigation has been completed.

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

51. Is linkage to a local[¥] dataset with <1 million patients being requested?

Yes * ☐ No ☒

**If yes, please provide further details:*
[¥] Data from defined geographical areas i.e. non-national datasets.

52. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

53. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

54. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

55. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Is the questionnaire a validated instrument? Yes ☐ No ☐
If yes, has permission been obtained to use the instrument? Yes ☐ No ☐
Please provide further information:

Other (please describe)

[Ψ] *Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.*

56. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

57. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

58. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Jennifer K Quint Date: 02/03/2018 e-Signature (type name): JKQuint

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
D. Study Title[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* Heart failure as a risk factor for acute exacerbations of COPD (AECOPD)
E. Lay Summary (Max. 200 words)[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* Heart failure and chronic obstructive pulmonary disease (COPD) often coexist in patients. COPD is often caused by smoking and is characterised by shortness of breath. Patients with COPD often experience acute (sudden) worsening of symptoms, usually due to infections with viruses or bacteria, and these are termed exacerbations. How exacerbations and their triggers affect comorbidities (diseases that coexist in a patient), such as heart failure, is likely to differ not only with different triggers, but also with the severity of the underlying COPD. Understanding the current situation with respect to the diagnosis and management of heart failure in COPD patients may impact the number and severity of exacerbations experienced by patients by highlighting areas in which care can be improved.
F. Technical Summary (Max. 200 words)[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* Heart failure and chronic obstructive pulmonary disease (COPD) share aetiology, symptoms, and the potential to exacerbate the other condition leading to higher health care utilization costs and mortality in patients with both conditions. Recent international guidelines have recommended increased consideration of comorbid conditions when assessing COPD and heart failure, demonstrating recognition of the influences of comorbidities on disease progression and prognosis. In this study, we will investigate the incidence of comorbid COPD and heart failure, the effect of comorbid heart failure on acute exacerbations of COPD (AECOPD), and the impact of suboptimal treatment and under-diagnosis of heart failure on AECOPD. This is a cohort study and will calculate incidence and prevalence. Survival analysis (Cox regression) will be used to investigate delayed HF diagnosis and matched cohort analysis (Cox) will be used to compare AECOPD across patient groups.
T. Objectives, Specific Aims and Rationale The objective of this study is to determine if diagnosing heart failure will reduce exacerbation risk and severity in people with COPD. **Specific Aims:** 1. To determine the incidence and prevalence of comorbid COPD-HF in England and the proportion of COPD patients with potentially undiagnosed HF. 2. To determine if having comorbid HF impacts exacerbation risk and severity in COPD patients and whether this differs by quality of HF management or type of HF. 3. To determine if undiagnosed HF impacts exacerbation risk and severity. **Rationale:** Improve patient quality of life associated with exacerbations of COPD by better recognising co-occurring heart failure.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

U. Study Background

It is estimated that 3 million individuals in the United Kingdom (UK) have chronic obstructive pulmonary disease (COPD), but that only one-third are currently diagnosed (1). According to the British Heart Foundation, an estimated 900,000 individuals are living with heart failure in the UK, estimated to be increasing at a rate of over 65,000 new cases per year (2, 3). Patients with COPD contribute a significant financial burden to the National Health Service (NHS) as health care costs secondary to COPD equate to £805 million per year (4). Similarly burdensome, heart failure costs the NHS 2% of its total expenditure (3).

Heart failure and COPD often coexist in patients. In older community patients with COPD, 20% have comorbid heart failure; and COPD was diagnosed prospectively in 30% of stable community heart failure patients (5, 6). Heart failure and COPD share aetiology, symptoms, and the potential to exacerbate the other condition leading to higher health care utilization costs and mortality in patients with both conditions (7, 8). Recent international guidelines have recommended increased consideration of comorbid conditions when assessing COPD and heart failure, demonstrating recognition of the influences of comorbidities on disease progression and prognosis (7, 9).

Patients with COPD often experience acute exacerbations (AECOPD), which are most commonly triggered by infection. Exacerbations have an enormous impact on a patient - worsening quality of life and accelerating the trajectory of disease decline - and on the NHS - patients require more resources and thus increased cost. Several common comorbidities may also worsen at the time of exacerbation, including osteoporosis, muscle strength, anxiety, depression, diabetes, and heart failure (10). How exacerbations and their triggers affect comorbidities is likely to differ not only with different triggers, but also with the spectrum of the underlying COPD.

For example, COPD patients, and COPD patients with heart failure, were less likely to receive a beta blocker at the time of myocardial infarction - due to fears of bronchoconstriction - increasing their mortality in comparison with patients without COPD (11, 12, 13). However, there is evidence to suggest that beta blockers may help to reduce exacerbations in people with COPD (14). Similarly, understanding the current situation with respect to the diagnosis and management of heart failure in COPD patients may impact the number and severity of AECOPD experienced by patients.

V. Study Type

This is a descriptive study with hypothesis testing.

Aim 1: To determine the incidence and prevalence of comorbid COPD-HF in England and the proportion of COPD patients with potentially undiagnosed HF.
This aim is purely descriptive.

Aim 2: To determine if having comorbid HF impacts exacerbation risk and severity in COPD patients and whether this differs by quality of HF management or type of HF.
This aim will include hypothesis testing using matched cohorts.
Null hypotheses:

- There is no difference in exacerbation risk and severity in COPD patients with and without comorbid HF.
- There is no difference in exacerbation risk and severity in COPD patients with HF with preserved ejection fraction (HFpEF) and COPD patients with HF with reduced ejection fraction (HFrEF).
- There is no difference in exacerbation risk and severity in COPD patients with suboptimally managed HF and optimally managed HF.

Details on the definitions and identification of HFpEF, HFrEF, suboptimal HF management, and optimal HF management can be found in Section M. Details on cohort matching can be found in Section L.

Aim 3: To determine if undiagnosed HF impacts exacerbation risk and severity.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

This aim will include hypothesis testing using matched cohorts.
Null hypotheses:

- There is no difference in exacerbation risk and severity in COPD patients with comorbid HF and COPD patients without HF who are not taking diuretics.
- There is no difference in exacerbation risk and severity in COPD patients taking diuretics who receive a HF diagnosis during the study period and COPD patients without HF who are not taking diuretics.
- There is no difference in exacerbation risk and severity in COPD patients taking diuretics who do not receive a HF diagnosis during the study period and COPD patients without HF who are not taking diuretics.

Prescription of diuretics, in the absence of other indications, will be used as a proxy for undiagnosed HF in COPD patients. This is described in more detail in Section M. Details on cohort matching can be found in Section L.

W. Study Design

This is a cohort study. Incidence, prevalence, and survival analysis in Aim #1. Matched cohorts in Aims #2-3.

X. Feasibility counts

Based on previous work, we know that there are 190,790 with COPD or HF in CPRD who are eligible for linkage with HES, ONS, and IMD between 2004 and 2017. Of these, 126,508 have only COPD, 78,892 have only HF, and 14,611 have both. The numbers should allow us to detect a change of 0.1 in proportions (0.40 to 0.41) with at least 80% power and alpha = 0.05.

Aim 2: To determine if having comorbid HF impacts exacerbation risk and severity in COPD patients and whether this differs by quality of HF management or type of HF.
Around of 55% of HF patients have reduced ejection fraction and 45% have preserved ejection fraction. Therefore we expect around 8,000 patients with comorbid COPD-HF to have reduced ejection fraction and around 6,500 patients to have preserved ejection fraction. In our comparison group of patients with only COPD, we expect 126,508 patients. These numbers should allow us to detect a change of 0.2 in proportions (0.40 to 0.42) with at least 80% power and alpha = 0.05.

Based on trial data, around 45% of COPD patients with HF are suboptimally managed, defined as only taking 2 out of the 3 recommended HF treatments (22). See section M for details on the definitions of the types of HF and quality of HF management. Therefore we expect around 6,500 patients to be suboptimally managed. In our comparison group of patients with only COPD, we expect 126,508 patients. These numbers should allow us to detect a change of 0.2 in proportions (0.40 to 0.42) with at least 80% power and alpha = 0.05.

Stratification by type of HF is dependent on information from a validation study in The Health Care Improvement Network data (THIN) which is currently being conducted. We are aware that this stratification may not be possible depending on the results of this ongoing study.

Aim 3: To determine if undiagnosed HF impacts exacerbation risk and severity.
Our preliminary analysis (from 2010-2016) revealed that 30% of HF patients were on diuretics prior to the diagnosis of HF, excluding other indications for diuretics use, such as chronic kidney disease (detailed further in Section M). Thus, we expect approximately 4,300 patients (0.30*14,611) with comorbid COPD-HF to have diuretic prescription prior to their HF diagnosis. Very generously assuming that 30% of COPD patients without diagnosed HF have diuretic prescription, in the absence of other indications, the comparison group size would be around 75,900 (0.60*126,508). These numbers should allow us to detect a change of 0.3 in proportions (0.40 to 0.43) with at least 80% power and alpha = 0.05.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Y. Sample size considerations

The feasibility counts above (Section H) suggest ample power for these analyses.

We will not include any cells with counts less than five due to anonymity concerns.

All estimates will be provided with 95% confidence intervals as is standard.

Z. Data Linkage Required (if applicable):[§]

[§]*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

ONS data for date of death
IMD data to adjust/stratify for socioeconomic status
HES Inpatient data to identify exacerbation episodes that required hospitalisation (a measure of severity)
HES Outpatient data to identify respiratory and cardiology visits

AA. Study population

There are two main patient groups: 1) COPD without HF and 2) comorbid COPD-HF.

Patients with comorbid COPD-HF (have both COPD and HF): at least 18 years old at HF diagnosis, at least 35 years old at COPD diagnosis, identified in CPRD between 1st January 2004 and 31st December 2017 with at least one year of "research standard" CPRD registration before their disease diagnosis. Order of diagnoses, COPD then HF or HF then COPD will be assessed, but both orders will be acceptable for inclusion in this group provided the patient has

Patients with only HF: diagnosed >18 years old, aged 35+ years without comorbid COPD, identified in CPRD between 1st January 2004 and 31st December 2017 with at least one year of "research standard" CPRD registration before their disease diagnosis. This group will be used as a comparison group, as will the group of COPD only patients described next.

Patients with only COPD: aged 35+ years at COPD diagnosis without comorbid HF, identified in CPRD between 1st January 2004 and 31st December 2017 with at least one year of "research standard" CPRD registration before their disease diagnosis.

In Aims #1 and #3, prescription of diuretics, in the absence of other indications, will be used as a proxy for undiagnosed HF in COPD patients. This is described in more detail in Section M.

Within each aim, cohorts will be stratified on different characteristics as described below.

Aim 1: To determine the incidence and prevalence of comorbid COPD-HF in England and the proportion of COPD patients with potentially undiagnosed HF.
A cohort of patients with comorbid COPD-HF, defined as described above, will be used to determine the incidence and prevalence of comorbid COPD-HF in UK primary care.

A cohort of COPD patients on diuretics who receive a HF diagnosis within the study period will be used to determine the time-to-HF diagnosis. The use of diuretics as a proxy for undiagnosed HF, in the absence of other indications, is detailed in Section M.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Aim 2: To determine if having comorbid HF impacts exacerbation risk and severity in COPD patients and whether this differs by quality of HF management or type of HF.
Patients with comorbid COPD-HF, as defined above, will be stratified in two ways: by quality of HF treatment (optimal, suboptimal) and by type of HF (preserved ejection fraction, reduced ejection fraction). These groups will be used to investigate the impact of HF management and type on exacerbation risk and severity. Details on the definitions for these strata can be found in Section M. Stratification by type of HF is dependent on information from a validation study in The Health Care Improvement Network data (THIN) which is currently being conducted. We are aware that this stratification may not be possible depending on the results of this ongoing study.

Aim 3: To determine if undiagnosed HF impacts exacerbation risk and severity.
There will be four cohorts: 1) comorbid COPD-HF (as defined above), 2) COPD patients on diuretics who get a HF diagnosis within the study period, 3) COPD patients on diuretics who do not get a HF diagnosis within the study period, and 4) COPD patients without diuretics or HF diagnosis. The first three cohorts will be individually compared with the fourth (comparator) cohort with regards to exacerbation risk and severity. The use of diuretics as a proxy for undiagnosed HF, in the absence of other indications, is detailed in Section M.

Further details on statistical analyses for all Aims can be found in Section N.

BB.Selection of comparison group(s) or controls
Aim 1: To determine the incidence and prevalence of comorbid COPD-HF in England and the proportion of COPD patients with potentially undiagnosed HF.
There are no comparison groups.

Aim 2: To determine if having comorbid HF impacts exacerbation risk and severity in COPD patients and whether this differs by quality of HF management or type of HF.
Comparison group: patients with COPD who do not have a diagnosis of HF
Patients with comorbid COPD-HF stratified by HF type will be compared with a group of COPD patients without HF. Patients with comorbid COPD-HF stratified by HF management will be compared with a group of COPD patients without HF.

Aim 3: To determine if undiagnosed HF impacts exacerbation risk and severity.
Comparison group: patients with COPD who are not taking diuretics and do not have a diagnosis of HF
Patients with comorbid COPD-HF will be compared with a group of COPD patients not taking diuretics and who do not have a diagnosis of HF. Patients with COPD who are taking diuretics who receive a HF diagnosis during the study period will be compared with a group of COPD patients not taking diuretics and who do not have a diagnosis of HF. Patients with COPD who are taking diuretics who do not receive a HF diagnosis during the study period will be compared with a group of COPD patients not taking diuretics and who do not have a diagnosis of HF.

In Aims #2-3, cohorts will be matched on age, sex, smoking status, and GP practice.

CC. Exposures, Health Outcomes[§] and Covariates
[§]Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy

Exposure
Comorbid COPD and HF. The COPD code list is published (15). The heart failure code list has been attached as an Appendix. We will consider diagnosis with both conditions at any time in the patient's history to establish comorbidity, as neither condition is fully reversible.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

In Aims #1 and #3, prescription of diuretics, in the absence of other indications (patients with chronic kidney disease stage 4 and 5, chronic liver disease, nephrotic syndrome, rheumatic heart disease, and constrictive pericarditis will be excluded) will be used as a proxy for undiagnosed HF in COPD patients. Our preliminary analysis (from 2010-2016) revealed that 30% of HF patients were on diuretics prior to the diagnosis of HF, excluding other indications for diuretics use. This indicates that these patients most likely had undiagnosed HF and earlier identification/management could potentially alter the prognosis of these patients. The code list for diuretics is attached as an Appendix.

In Aim #2, patients with comorbid COPD-HF will be stratified in two ways:

- By type of HF
    - HF with preserved ejection fraction (HFpEF)
    - HF with reduced ejection fraction (HFrEF)
    - We are currently in the process of validating multiple algorithms for identification of HFpEF and HFrEF using primary care electronic health records (using THIN). It is an ongoing study and we hope to have the final results in 4 months. We are aware that this stratification may not be possible depending on the results of this ongoing study.

- By quality of HFrEF management
    - We will only look into the management of patients with HFrEF as there is not yet an understanding of what optimal management of HFpEF is.
    - Optimal management will be defined as guideline-directed medical therapy (GDMT) (20). We will define GDMT as the proportion of patients on Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker, beta-blockers, Angiotensin Receptor Neprilysn Inhibitor, and mineralocorticoid receptor antagonist. Code lists for these are attached as an Appendix.
    - Suboptimal management will be any management that does not meet guidelines, namely patients taking any less than all three recommended treatment types (though we are aware that some patients may be taking less for medically appropriate reasons)

Covariates

Demographic covariates will include age, sex, socioeconomic status, and ethnicity.

Smoking status will be defined as 1) Never/Not Recorded, 2) Former Smoker, and 3) Current Smoker (16).

Body mass index (BMI) in kg/m^2 will be defined as 1) underweight (<18.5), 2) healthy weight (18.5-24.9), 3) overweight (25-29.9), and 4) obese (>30.0). Should BMI information be missing >15% we will also report results for a 'not recorded' group.

Framingham risk score based on age, sex, total cholesterol, high density lipoprotein (HDL) cholesterol, smoking status, diabetes status, systolic blood pressure, and presence of treatment for high blood pressure. Each of these components will also be examined in their own right. Measurements of each of these components are available in CPRD's 'additional' dataset with information on the measurements provided in the 'Look-up files'.

Severity of COPD will be determined per guidelines (19, 21) using spirometry data.

Additional risk factors to be examined include: hypertension, dyslipidaemia, personal or family history of ischaemic heart disease (IHD), vascular disease, angina/unstable angina, acute coronary syndrome (ACS), atherosclerosis, peripheral arterial disease (PAD), and Medical Research Council (MRC) dyspnoea score.

Medication covariates will include COPD medications and the prescription of drugs to manage vascular risk factors - those in Chapter 2 of the British National Formulary (BNF) - and medications included in the risk scoring systems.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

Covariates will be measured as close to baseline as possible, up to three years prior to/after baseline.

Outcomes

1. Risk factors in patients with comorbid COPD-HF versus patients with just COPD or HF
2. Incidence and prevalence of comorbid COPD-HF
3. Rate of AECOPD in COPD patients with and without heart failure.
    a. Rate stratified by AECOPD severity
    b. HF stratified by quality of management and by type of HF
4. Rate of AECOPD in COPD patients with suspected undiagnosed HF (proxy diuretics)

AECOPD is the acute worsening of symptoms that goes beyond day-to-day variation and may require a change in a patient's treatment (18). AECOPD will be identified using a previously-published, validated algorithm (17-18), which includes oral corticosteroid/antibiotic prescription, exacerbation symptoms, lower respiratory tract infection, and AECOPD codes as defined previously and identified within CPRD-provided data files (17). AECOPD severity will be determined through whether the patient was managed by the GP only, was hospitalised, or died.

DD. Data/ Statistical Analysis

Data will be analysed in STATA 15.

Aim 1: To determine the incidence and prevalence of comorbid COPD-HF in England and the proportion of COPD patients with potentially undiagnosed HF.
This aim is to determine the scale of the public health problem of comorbid COPD-HF in England and to see if it is changing over time.

Information will be collected on patients with COPD, HF, and comorbid COPD-HF. Similarities and differences between these patient groups will be analysed using Chi-squared with respect to demographics and risk factors/comorbidities (as listed in Section M).

A period prevalence of comorbid COPD-HF will be calculated for the time period between 1 January 2006 and 31 December 2016. This will further be broken down to annual prevalence. Should numbers allow, prevalence by age bands (10-year), sex, smoking status, and BMI will be evaluated. As such, all people who already have comorbid COPD-HF at the start of the study and all those who acquire comorbid COPD-HF during the study will be considered in the calculations for the entire study period and for each year as appropriate.

Incidence will be calculated as the number of new cases of comorbid COPD-HF (as indicated by the diagnosis of the second condition) during the time period between 1 January 2006 and 31 December 2016. This will be further broken down to annual incidence of new comorbid COPD-HF. Should numbers allow, incidence by age bands (10-year), sex, smoking status, and BMI will be evaluated. Patients with existing comorbid COPD-HF at the start of the study will not be included in incidence calculations.

The proportion of COPD patients on diuretics (as a proxy for undiagnosed HF, as described in Section M) will be determined. Survival analysis, with cause-specific hazards to handle the competing risk of death, will be used to analyse time-to-HF-diagnosis in these patients. Cumulative incidence function plots will also be used.

Aim 2: To determine if having comorbid HF impacts exacerbation risk and severity in COPD patients and whether this differs by quality of HF management or type of HF.
This aim is to examine how HF, its management and types, impacts exacerbations in COPD patients.

The absolute incidence rate of exacerbations in people with comorbid COPD-HF will be determined by calendar year, age, sex, and smoking status. Their exacerbation rate and severity will be compared with a

cohort of COPD patients without HF using a matched cohort design and Cox regression. Cohorts will be matched on age, sex, smoking status, and GP practice. We will control for the severity of COPD.

Sub-Analysis #1: Using the same method described above, patients with comorbid COPD-HF will be stratified by type of HF (HFpEF or HFrEF) and their exacerbation rate and severity compared with a matched cohort of COPD patients without HF. Patients with HFpEF and HFrEF will be identified using the method currently undergoing validation and described in Section M. Stratification by type of HF is dependent on information from a validation study in The Health Care Improvement Network data (THIN) which is currently being conducted. We are aware that this stratification may not be possible depending on the results of this ongoing study.

Sub-Analysis #2: Using the same method described above, the exacerbation rate and severity in patients with comorbid COPD-HFrEF will be compared with a matched cohort of COPD patients without HF. Patients with comorbid COPD-HFrEF will be stratified by the quality of their HF management (optimal vs. suboptimal) as described in Section M.

Null hypotheses:

- There is no difference in exacerbation risk and severity in COPD patients with and without comorbid HF.
- There is no difference in exacerbation risk and severity in COPD patients with HF with preserved ejection fraction (HFpEF) and COPD patients with HF with reduced ejection fraction (HFrEF).
- There is no difference in exacerbation risk and severity in COPD patients with suboptimally managed HF and optimally managed HF.

Aim 3: To determine if undiagnosed HF impacts exacerbation risk and severity.
This aim is to determine whether delayed diagnosis of comorbid HF in COPD patients impacts exacerbation risk and severity.

Three separate cohorts will individually have their exacerbation rate and severity compared with a matched cohort of COPD patients without diuretic use and without a HF diagnosis. Cause-specific hazard regression and cumulative incidence function plots will be used. Cohorts will be matched on age, sex, smoking status, and GP practice. We will control for the severity of COPD. These three cohorts are:

- Patients with comorbid COPD-HF
- Patients with COPD, on diuretics, who receive a HF diagnosis during the study period (these patients will be censored at the time of their HF diagnosis)
- Patients with COPD, on diuretics, who do not receive a HF diagnosis during the study period

Null hypotheses:

- There is no difference in exacerbation risk and severity in COPD patients with comorbid HF and COPD patients without HF who are not taking diuretics.
- There is no difference in exacerbation risk and severity in COPD patients taking diuretics who receive a HF diagnosis during the study period and COPD patients without HF who are not taking diuretics.
- There is no difference in exacerbation risk and severity in COPD patients taking diuretics who do not receive a HF diagnosis during the study period and COPD patients without HF who are not taking diuretics.

EE. Plan for addressing confounding

We are using matched cohorts in Aims #2-3 to limit confounding. We will control for COPD severity, determined by GOLD staging (21).

Unmeasured confounders, including HF severity and other indications for diuretic use (not controlled for as described in Section M), may potentially bias our results. Measurements of ejection fraction and biomarkers

used to determine the severity of HF are not available in CPRD or HES data. We have tried to eliminate as many other indications for the prescription of diuretics as described in Section M; however, there may be some indications unrelated to undiagnosed heart failure that we missed.

FF. Plans for addressing missing data

Where appropriate, and where data are missing at random, we will undertake both a complete case analysis and we will consider using multiple imputation. Where data are not missing at random, for example with spirometry data, but where 80% of the data is expected to be complete, based on previous studies, we will use a complete case analysis. A discussion of the possible biases from adopting a complete case approach will be examined. Where multiple imputation is not appropriate and there are large quantities of missing data, covariates will be used only as part of secondary analysis and biases and limitations will be discussed.

Data on BMI and smoking status are less likely to be missing in the COPD and HF populations than in the general population. Based on previous (unpublished) work, we expect no more than 15% missing data for BMI. With our expected numbers high, we will conduct complete case analysis. Should BMI be missing more than 15%, we will report results for a 'not recorded' category as well. For smoking status, one category of classification is 'never/not recorded', thus all patients will be included in analyses by default.

GG. Patient or user group involvement (if applicable)

The study has been discussed in principle with patients at a 'Breathe Easy' group who feel it is an important topic. We have not involved patients in the design or analysis of this study.

HH. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals, and will be presented both at appropriate conferences and at other meetings; the latter will include scientific meetings externally, for example for the American and European Respiratory Society Meetings and within academic institutions in London.

II. Limitations of the study design, data sources, and analytic methods

We are aware that misclassification of heart failure and AECOPD is likely to occur with respect to recording in CPRD and HES. This will be minimised by the use of validated definitions for AECOPD in HES and CPRD. We have recently completed a major project which validated the recording of AECOPD within the CPRD and we will use a combination of algorithms which resulted in a PPV of 85%. We have also validated the recording of hospitalisations of AECOPD, these will use definitions we have previously developed. We are currently validating the recording of hospitalisations of HF and the coding of different phenotypes of HF in primary care records.

A major limitation of this study is the inability to stratify by or control for severity of HF. Measurements of ejection fraction and biomarkers used to determine the severity of HF are not available in CPRD or HES data.

Stratification by type of HF is dependent on information from a validation study in The Health Care Improvement Network data (THIN) which is currently being conducted. We are aware that this stratification may not be possible depending on the results of this ongoing study.

We have tried to eliminate as many other indications for the prescription of diuretics as described in Section M; however, there may be some indications unrelated to undiagnosed heart failure that we missed.

We are aware that patients are only eligible for linkage if they (i) registered at a participating English practice prior to the transfer of identifiers to the trusted third party for matching (ii) had a valid identifier

for linkage (either NHS number or postcode), (iii) had not opted out or dissented from CPRD or the linkage scheme.

Specific Read codes have been chosen to maximize the sensitivity of diagnosing heart failure and COPD based on previous work. Ultimately, however, we are limited by the acumen of the reviewing clinician recording the diagnosis.

We are aware that the regional distribution of CPRD practices in recent years is not considered to be representative and will take this into consideration in the interpretation of the analysis.

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List of Appendices *(Submit all appendices as separate documents to this application)*

Heart Failure code list
Diuretics code list (including Mineralocorticoid receptor antagonists)
Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker code list
Angiotensin Receptor Neprilysn Inhibitor code list
Beta-blockers code list

Amendment: 21 January 2019

Rationale: Upon describing the patients with incident HF within the COPD population, we found that COPD patients who went on to get a HF diagnosis were significantly older at COPD diagnosis than COPD patients who did not go on to get a HF diagnosis. Contrarily, when we described incident COPD patients within the HF population we found that HF patients who went on to get a COPD diagnosis were significantly younger at HF diagnosis than HF patients who did not go on to get a COPD diagnosis. We also found that COPD patients who did not go on to get a HF diagnosis died at a significantly younger age than the other populations. In order to better describe this relationship in terms of ages at incident diagnoses and death, we wish to conduct the following additional descriptive analyses. All additional analyses will utilise the cohort derived for Specific Aim #1: patients with comorbid COPD-HF, defined as described above (Section M).

Analysis #1: Time-to-comorbidity

- Investigate the median ages of diagnosis of first condition, either COPD or HF
- Investigate the median ages of diagnosis and time-to-diagnosis of second condition (comorbidity), HF or COPD
- Kaplan-Meier survival curves

Exposure: diagnosis of first condition (COPD or HF)
Outcome: diagnosis of second condition (HF or COPD)

Analysis #2: Time-to-death

- Investigate the median age of death and time-to-death following comorbidity diagnosis
- Comparison of median age and time-to-death of COPD patients without HF or HF patients without COPD
- Kaplan-Meier survival curves

Exposure: diagnosis of comorbidity (in comparators: diagnosis of first condition without subsequent diagnosis of second)
Outcome: all-cause mortality

Amendment: 11 November 2019

Rationale for amendment: To further describe the COPD patient group with evidence of undiagnosed HF to see if a diagnosis of HF has possibly been considered in hospital and/or by the GP. To identify the effect of individual cardiovascular drugs on the risk for AECOPD.

N. Data/Statistical Analysis
Methods: To determine the proportion (%) of patients with a history of hospitalisation due to HF. To determine the proportion of patients with a history of echocardiography. To determine the proportion of patients with a history of brain natriuretic peptide (BNP) tests. To determine the time between the most recent of each of these and the end of follow-up to see if there has been enough time for a diagnosis of HF to be made or refuted. These proportions will be described and compared in each of the patient populations: 1) COPD patients with undiagnosed HF, 2) COPD patients without HF, 3) COPD patients with diagnosed HF. Differences in the proportion of patients with evidence of HF hospitalisation or testing between the patient groups will be assessed using Chi-squared.

HF hospitalisations will be identified in HES (linked data already approved and provided by this ISAC) using the International Classification of Disease 10 (ICD-10) codes I11.0, I13.0, I13.2, I50, I50.0, I50.1, or I50.9. History of echocardiography will be identified in CPRD using the echocardiography Read codes from the Quality and Outcomes Framework (QOF- Business Rules for Quality and Outcomes Framework (QOF) 2017/18. In: (SDS) NDPCDSDS, ed. 36.0 ed, 2018.). History of BNP test will be identified in CPRD using medcodes: 14140, 14143, 27097, 40914, and 68734.

The effect of individual cardiovascular drugs on AECOPD risk and severity will be assessed using Cox regression, adjusted for the covariates in section M. Drugs will include Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker, beta-blockers, Angiotensin Receptor Neprilysn Inhibitor, mineralocorticoid receptor antagonist, statins, vasodilators, calcium channel blockers, per the British National Formulary (BNF).

Amendment: 09 December 2019

Rationale for the amendment: To modestly enhance our definition of possible heart failure.
M. Exposures, Health Outcomes[§] and Covariates
Possible HF patients, as identified per Section M above, will be categorised as having been investigated for HF or as not having been investigated for HF, per Amendment 11 November 2019 above.

ICD-10 codes

List of ICD-10 used to identify AECOPD, COPD, lower respiratory tract infection, and heart failure with their descriptions are listed in the table below. AECOPD, COPD, and lower respiratory tract infection codes were validated through the identification of exacerbations in CPRD [263].

ICD-10 CODE	DESCRIPTION
COPD	
J44.9	Chronic obstructive pulmonary disease, unspecified
AECOPD	
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
LOWER RESPIRATORY TRACT INFECTION	
J22	Unspecified acute lower respiratory infection
HEART FAILURE	
I50	Heart failure
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
I11.0	Hypertensive heart disease with (congestive) heart failure
I13.0	Hypertensice heart and renal disease with (congestive) heart failure
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure

Identification of COPD

List of medical codes (medcode) and Read codes (readcode) used to identify COPD and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of COPD [21], the validated code COPD code list from 2014 [261], and/or having been found during a search of the CPRD Code Browser at the time of cohort definition in 2018 (post-2014). The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify COPD are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Validated	Included
11287	66YM.00	Chronic obstructive pulmonary disease annual review	687,574	28.2		1	1
1001	H3…00	Chronic obstructive pulmonary disease	411,447	16.9	1	1	1
28755	9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter	265,409	10.9		1	1
9520	66YB.00	Chronic obstructive pulmonary disease monitoring	224,583	9.2		1	1
998	H3…00	Chronic obstructive pulmonary disease	212,572	8.7	1	1	1
34202	9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter	82,015	3.4		1	1
10863	H36..00	Mild chronic obstructive pulmonary disease	70,287	2.9	1	1	1
10802	H37..00	Moderate chronic obstructive pulmonary disease	69,093	2.8	1	1	1
5710	H3z..00	Chronic obstructive airways disease NOS	63,954	2.6	1	1	1
18621	66YL.00	Chronic obstructive pulmonary disease follow-up	60,895	2.5		1	1
794	H32..00	Emphysema	52,427	2.2	1	1	1
34215	9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter	39,709	1.6		1	1
18476	66YL.11	COPD follow-up	36,891	1.5		1	1
9876	H38..00	Severe chronic obstructive pulmonary disease	30,505	1.3	1	1	1
3243	H31..00	Chronic bronchitis	26421	1.1	1		
42313	679V.00	Health education – chronic obstructive pulmonary disease	21,475	0.9		1	1
38074	9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite	18,028	0.7		1	1
18792	9Oi..00	Chronic obstructive pulmonary disease monitoring admin	16,524	0.7		1	1
45777	8CR1.00	Chronic obstructive pulmonary disease clini management plan	9,294	0.4		1	1
42258	9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite	7,871	0.3		1	1
15157	H31z.00	Chronic bronchitis NOS	3571	0.1	1		
26018	66YS.00	Chronic obstructive pulmonary disease monitoring by nurse	3,534	0.1		1	1
37371	66YD.00	Chronic obstructive pulmonary disease monitoring due	3,465	0.1		1	1
93568	H39..00	Very severe chronic obstructive pulmonary disease	2,627	0.1	1	1	1
5798	H312000	Chronic asthmatic bronchitis	1871	0.1	1		
15626	H310000	Chronic catarrhal bronchitis	1708	0.1	1		
45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep	1,628	0.1		1	1
4084	663K.00	Airways obstructn irreversible	1,465	0.1		1	1
12166	H3y..00	Other specified chronic obstructive airways disease	1,285	0.1	1	1	1
14798	H312100	Emphysematous bronchitis	1,248	0.1	1	1	1
27819	H312.00	Obstructive chronic bronchitis	1204	0.0	1		
37247	H3z..11	Chronic obstructive pulmonary disease NOS	1,167	0.0	1	1	1

33450	H32z.00	Emphysema NOS	1,002	0.0	1	1	1
105457	8CMW500	Chronic obstructive pulmonary disease care pathway	769	0.0			1
25603	H310.00	Simple chronic bronchitis	761	0.0	1		
26306	H320.00	Chronic bullous emphysema	544	0.0	1	1	1
45998	66YT.00	Chronic obstructive pulmonary disease monitoring by doctor	502	0.0		1	1
45770	6Yg.00	Chronic obstructive pulmonary disease disturbs sleep	448	0.0		1	1
109958	H3B..00	Asthma-chronic obstructive pulmonary disease overlap syndrome	440	0.0	1		
11150	H311.00	Mucopurulent chronic bronchitis	371	0.0	1		
10980	H322.00	Centrilobular emphysema	289	0.0	1	1	1
26125	H312300	Bronchiolitis obliterans	207	0.0	1		
104608	H3A..00	End stage chronic obstructive airways disease	135	0.0	1		1
106637	9Nk7000	Seen in chronic obstructive pulmonary disease clinic	122	0.0			1
23492	H320z00	Chronic bullous emphysema NOS	91	0.0	1	1	1
44525	H312z00	Obstructive chronic bronchitis NOS	81	0.0	1	1	1
16410	H32yz00	Other emphysema NOS	74	0.0	1		1
40788	H32y.00	Other emphysema	66	0.0	1		
45089	H31y100	Chronic tracheobronchitis	61	0.0	1		
40159	H311000	Purulent chronic bronchitis	56	0.0	1		
65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease	50	0.0	1		1
104985	9NgP.00	On chronic obstructive pulmonary disease supportv cre pathway	48	0.0			1
104710	9NgP.11	On COPD (chr obstruc pulmonary disease) supportv cre pathway	45	0.0			1
61118	H310z00	Simple chronic bronchitis NOS	43	0.0	1		
106650	H583200	Eosinophilic bronchitis	40	0.0	1		
242748	H313.00	Mixed simple and mucopurulent chronic bronchitis	31	0.0	1		
46578	H321.00	Panlobular emphysema	30	0.0	1		1
61513	H311z00	Mucopurulent chronic bronchitis NOS	30	0.0	1		
63479	H32y200	MacLeod's unilateral emphysema	29	0.0	1		
66043	H31y.00	Other chronic bronchitis	28	0.0	1		
68066	H31yz00	Other chronic bronchitis NOS	21	0.0	1		
60188	H320200	Giant bullous emphysema	18	0.0	1		1
56860	H320000	Segmental bullous emphysema	14	0.0	1		
99536	H3203	Bullous emphysema with collapse	14	0.0	1		
66058	Hyu3000	[X]Other emphysema	13	0.0	1		
68662	H320100	Zonal bullous emphysema	12	0.0	1		
67040	H3y..11	Other specified chronic obstructive pulmonary disease	9	0.0	1		1
64721	H464000	Chronic emphysema due to chemical fumes	5	0.0	1		
63216	H464100	Obliterative bronchiolitis due to chemical fumes	5	0.0	1		
37959	H311100	Fetid chronic bronchitis	4	0.0	1		
70787	H32y100	Atrophic (senile) emphysema	3	0.0	1		
92955	H32y000	Acute vesicular emphysema	1	0.0	1		
			2,438,259	**100.0**			

Identification of smoking status

List of medical codes (medcode) and Read codes (readcode) used to identify smoking status and their descriptions are listed in the table below. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify current or former smokers are identified in the far right columns by a '1'.

medcode	readcode	description	clinical events	% clinical events	Current	Former
90	137S.00	Ex smoker	8,740,903	24.1		1
7622	8CAL.00	Smoking cessation advice	7,579,832	20.9	1	
93	137P.00	Cigarette smoker	7,119,028	19.7	1	
60	137L.00	Current non-smoker	2,976,050	8.2		1
54	137..00	Tobacco consumption	2,947,390	8.1	1	
10558	137R.00	Current smoker	1,215,963	3.4	1	
1878	1374000	Moderate smoker - 10-19 cigs/d	699,898	1.9	1	
12944	1373.00	Light smoker - 1-9 cigs/day	480,381	1.3	1	
776	137K.00	Stopped smoking	389,924	1.1		1
1823	137P.11	Smoker	363,533	1.0	1	
3568	1375.00	Heavy smoker - 20-39 cigs/day	359,999	1.0	1	
12946	137F.00	Ex-smoker - amount unknown	304,938	0.8		1
2111	6791000	Health ed. - smoking	296,932	0.8	1	
12955	1379.00	Ex-moderate smoker (10-19/day)	282,409	0.8		1
11356	9N2k.00	Seen by smoking cessation advisor	276,061	0.8	1	
12240	137G.00	Trying to give up smoking	207,783	0.6	1	
12957	1378.00	Ex-light smoker (1-9/day)	184,425	0.5		1
18573	8H7i.00	Referral to smoking cessation advisor	161,953	0.4	1	
12956	137A.00	Ex-heavy smoker (20-39/day)	147,713	0.4		1
12941	1372.11	Occasional smoker	144,743	0.4	1	
12945	137M.00	Rolls own cigarettes	103,245	0.3	1	
12958	1372.00	Trivial smoker - < 1 cig/day	101,130	0.3	1	
74907	745H.00	Smoking cessation therapy	87,659	0.2	1	
34126	13p0.00	Negotiated date for cessation of smoking	76,386	0.2	1	
10742	8HTK.00	Referral to stop-smoking clinic	75,704	0.2	1	
12943	137J.00	Cigar smoker	68,982	0.2	1	
12947	137H.00	Pipe smoker	66,125	0.2	1	
12878	137T.00	Date ceased smoking	61,404	0.2		1
11713	388B.00	Pack years	57,543	0.2	1	
12961	1377000	Ex-trivial smoker (<1/day)	54,872	0.2		1
12942	137..11	Smoker - amount smoked	54,333	0.1	1	
7130	9OO..12	Stop smoking monitoring admin.	45,991	0.1		1
18926	67H1.00	Lifestyle advice regarding smoking	45,721	0.1	1	
1822	1376000	Very heavy smoker - 40+cigs/d	35,217	0.1	1	

38112	13p5.00	Smoking cessation programme start date	31,839	0.1	1	
12959	137B.00	Ex-very heavy smoker (40+/day)	31,661	0.1		1
30762	137d.00	Not interested in stopping smoking	29,166	0.1	1	
98154	8HkQ.00	Referral to NHS stop smoking service	26,838	0.1	1	
12960	137Z.00	Tobacco consumption NOS	18,968	0.1	1	
30423	137c.00	Thinking about stopping smoking	18,264	0.1	1	
12965	137X.00	Cigarette consumption	17,400	0.0	1	
98137	67H6.00	Brief intervention for smoking cessation	17,078	0.0	1	
31114	137b.00	Ready to stop smoking	17,067	0.0	1	
12964	137C.00	Keeps trying to stop smoking	12,393	0.0	1	
10898	13p4.00	Smoking free weeks	11,866	0.0		1
94958	745H400	Smoking cessation drug therapy	10,821	0.0	1	
12952	137Q.00	Smoking started	9,748	0.0	1	
46300	137g.00	Cigarette pack-years	9,374	0.0	1	
26470	137N.00	Ex pipe smoker	9,094	0.0		1
12967	137a.00	Pipe tobacco consumption	8,876	0.0	1	
12951	137Q.11	Smoking restarted	8,750	0.0	1	
40418	9OO2.00	Refuses stop smoking monitor	8,732	0.0	1	
9045	ZG23300	Advice on smoking	8,319	0.0	1	
97210	137j.00	Ex-cigarette smoker	8,180	0.0		1
62686	137h.00	Minutes from waking to first tobacco consumption	7,968	0.0	1	
106391	8IEo.00	Referral to smoking cessation service declined	7,355	0.0	1	
102361	9NS0200	Referral for smoking cessation service offered	7,238	0.0	1	
90522	745Hz00	Smoking cessation therapy NOS	6,845	0.0	1	
12963	137Y.00	Cigar consumption	6,307	0.0	1	
19488	137O.00	Ex cigar smoker	5,920	0.0		1
12966	137V.00	Smoking reduced	5,765	0.0	1	
106359	8T08.00	Referral to smoking cessation service	5,612	0.0	1	
103507	8CdB.00	Stop smoking service opportunity signposted	5,549	0.0	1	
32687	E251.00	Tobacco dependence	4,970	0.0	1	
100099	8IAj.00	Smoking cessation advice declined	3,759	0.0	1	
10184	67A3.00	Pregnancy smoking advice	3,653	0.0	1	
104310	9ko..11	Current smoker annual review	3,255	0.0	1	
99838	137K000	Recently stopped smoking	2,891	0.0		1
16717	H310100	Smokers' cough	2,690	0.0	1	
91708	745Hy00	Other specified smoking cessation therapy	2,249	0.0	1	
53101	9OO7.00	Stop smoking monitor verb.inv.	2,097	0.0	1	
101338	137m.00	Failed attempt to stop smoking	2,043	0.0	1	
41042	8CAg.00	Smoking cessation advice provided by community pharmacist	1,439	0.0	1	
41979	137e.00	Smoking restarted	1,229	0.0	1	
26096	13cA.00	Smokes drugs	1,141	0.0	1	
100963	9km..11	Ex-smoker annual review	984	0.0		1

42288	ZRb3.00	Pack years	840	0.0	1	
105711	137n.00	Total time smoked	527	0.0		1
100495	137l.00	Ex roll-up cigarette smoker	509	0.0		1
68658	E251z00	Tobacco dependence NOS	350	0.0	1	
46321	137f.00	Reason for restarting smoking	233	0.0	1	
98347	9ko..00	Current smoker annual review - enhanced services admin	179	0.0	1	
98447	9km..00	Ex-smoker annual review - enhanced services administration	175	0.0		1
12954	ZV4K000	[V]Tobacco use	144	0.0	1	
72706	E251300	Tobacco dependence in remission	124	0.0		1
35055	ZV6D800	[V]Tobacco abuse counselling	47	0.0	1	
70746	E251100	Tobacco dependence, continuous	43	0.0	1	
105501	137o.00	Waterpipe tobacco consumption	35	0.0	1	
110692	8B31G00	Varenicline smoking cessation therapy offered	21	0.0	1	
72700	ZV11600	[V]Personal history of tobacco abuse	10	0.0		1
95610	E251000	Tobacco dependence, unspecified	7	0.0	1	
61905	Eu17.00	[X]Mental and behavioural disorder due to use of tobacco	7	0.0	1	
107792	Eu17200	[X]Mental and behav dis due to use tobacco: dependence syndr	5	0.0	1	
108835	E251200	Tobacco dependence, episodic	4	0.0	1	
56144	Eu17100	[X]Mental and behav dis due to use of tobacco: harmful use	4	0.0	1	
103400	9kf1.11	Referred for COPD structured smoking assessment	3	0.0	1	
101519	Eu17300	[X]Mental and behav dis due to use tobacco: withdrawal state	2	0.0	1	
			36,222,832	**100.0**		

Identification of AECOPD

List of medical codes (medcode) and Read codes (readcode) used to identify AECOPD and their descriptions are listed in the table below. AECOPD codes were validated through the identification of exacerbations in CPRD [263]. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify presence of AECOPD are identified in the far right columns by a '1'.

medcode	readcode	description	clinical events	% clinical events	Validated	Included
1446	H312200	Acute exacerbation of chronic obstructive airways disease	215,605	45.6	1	1
28743	66Yf.00	Number of COPD exacerbations in past year	187,430	39.6		
7884	H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec	66,791	14.1	1	1
96931	14OX.00	At risk of chronic obstructive pulmonary diseas exacerbation	2,282	0.5		
100123	8BP8.00	Antibiotic therapy for acute pulmonary exacerbation	364	0.1		
103558	8CeD.00	Preferred place of care for next exacerbation of COPD	255	0.1		
			472,727	**100.0**		

Identification of LRTI

List of medical codes (medcode) and Read codes (readcode) used to identify LRTI and their descriptions are listed in the table below. LRTI codes were validated through the identification of exacerbations in CPRD [263]. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify presence of LRTI are identified in the far right columns by a '1'.

medcode	readcode	description	clinical events	% clinical events	Validated	Included
68	H06z011	Chest infection	2,994,054	52.2	1	1
312	H060.00	Acute bronchitis	863,708	15.1	1	1
2157	H27z.11	Flu like illness	574,593	10.0	1	1
3358	H06z100	Lower resp tract infection	336,795	5.9	1	1
556	H27..00	Influenza	286,641	5.0	1	1
1019	H061.00	Acute bronchiolitis	196,139	3.4	1	1
6124	H062.00	Acute lower respiratory tract infection	151,477	2.6	1	1
5978	H060.11	Acute wheezy bronchitis	133,532	2.3	1	1
16388	H27z.00	Influenza NOS	47,298	0.8	1	1
2476	H07..00	Chest cold	30,023	0.5	1	1
8980	16L..00	Influenza-like symptoms	21,819	0.4	1	1
29669	H06..00	Acute bronchitis and bronchiolitis	13,875	0.2	1	1
2581	H06z000	Chest infection NOS	13,082	0.2	1	1
5947	H27z.12	Influenza like illness	11,936	0.2	1	1
20198	H060z00	Acute bronchitis NOS	10,100	0.2	1	1
1382	H060w00	Acute viral bronchitis unspecified	7,046	0.1	1	1
17359	H30..11	Chest infection - unspecified bronchitis	6,523	0.1	1	1
37447	H06z112	Acute lower respiratory tract infection	5,669	0.1	1	1
21061	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn	4,834	0.1	1	1
98102	H2A..11	Influenza A (H1N1) swine flu	4,264	0.1	1	1
98115	1J72.11	Suspected swine influenza	3,364	0.1	1	1
17917	H061z00	Acute bronchiolitis NOS	3,025	0.1	1	1
14791	H27y100	Influenza with gastrointestinal tract involvement	2,920	0.1	1	1
23488	H271z00	Influenza with respiratory manifestations NOS	2,267	0.0	1	1
17185	H061200	Acute bronchiolitis with bronchospasm	1,983	0.0	1	1
11072	H060300	Acute purulent bronchitis	1,909	0.0	1	1
21145	H060400	Acute croupous bronchitis	1,274	0.0	1	1
43625	H271.00	Influenza with other respiratory manifestation	1,196	0.0	1	1
18451	H061500	Acute bronchiolitis due to respiratory syncytial virus	870	0.0	1	1
29273	H060C00	Acute bronchitis due to parainfluenza virus	842	0.0	1	1
98125	1J72.00	Suspected influenza A virus subtype H1N1 infection	778	0.0	1	1
41137	H06z.00	Acute bronchitis or bronchiolitis NOS	717	0.0	1	1
29617	H271100	Influenza with pharyngitis	504	0.0	1	1

98129	H2A..00	Influenza due to Influenza A virus subtype H1N1	431	0.0	1	1
15774	H271000	Influenza with laryngitis	412	0.0	1	1
9043	H060600	Acute pneumococcal bronchitis	390	0.0	1	1
98103	1W0..00	Possible influenza A virus H1N1 subtype	318	0.0	1	1
97279	Hyu0700	[X]Influenza+other manifestations, virus not identified	234	0.0	1	1
26125	H312300	Bronchiolitis obliterans	207	0.0	1	1
24800	H060x00	Acute bacterial bronchitis unspecified	176	0.0	1	1
41589	H061100	Acute obliterating bronchiolitis	167	0.0	1	1
47472	H27y.00	Influenza with other manifestations	140	0.0	1	1
96019	4JU0.00	Influenza H1 virus detected	133	0.0	1	1
21492	H060800	Acute haemophilus influenzae bronchitis	110	0.0	1	1
66397	Hyu1.00	[X]Other acute lower respiratory infections	99	0.0	1	1
98143	4J3L.00	Influenza A virus H1N1 subtype detected	83	0.0	1	1
6181	H061400	Obliterating fibrous bronchiolitis	78	0.0	1	1
24316	H24..11	Chest infection with infectious disease EC	63	0.0	1	1
97062	4JU4.00	Influenza A virus, other or untyped strain detected	48	0.0	1	1
96017	4JU5.00	Influenza B virus detected	46	0.0	1	1
31363	H27yz00	Influenza with other manifestations NOS	45	0.0	1	1
64890	H060E00	Acute bronchitis due to rhinovirus	44	0.0	1	1
66228	H061600	Acute bronchiolitis due to other specified organisms	37	0.0	1	1
97605	Hyu0600	[X]Influenza+oth respiratory manifestatns,virus not identifd	37	0.0	1	1
48593	H060D00	Acute bronchitis due to respiratory syncytial virus	31	0.0	1	1
69192	H061300	Acute exudative bronchiolitis	22	0.0	1	1
43362	H060700	Acute streptococcal bronchitis	20	0.0	1	1
49794	H060900	Acute neisseria catarrhalis bronchitis	20	0.0	1	1
96286	4JUF.00	Human parainfluenza virus detected	18	0.0	1	1
46157	H27y000	Influenza with encephalopathy	14	0.0	1	1
71370	H060200	Acute pseudomembranous bronchitis	12	0.0	1	1
73100	Hyu1000	[X]Acute bronchitis due to other specified organisms	12	0.0	1	1
94930	H29..00	Avian influenza	12	0.0	1	1
96018	4JU2.00	Influenza H3 virus detected	9	0.0	1	1
98257	Hyu0400	[X]Flu+oth respiratory manifestations,'flu virus identified	7	0.0	1	1
54533	H061000	Acute capillary bronchiolitis	6	0.0	1	1
91123	43jz.00	Parainfluenza type 3 nucleic acid detection	6	0.0	1	1
94130	43jx.00	Parainfluenza type 1 nucleic acid detection	5	0.0	1	1
65916	H060F00	Acute bronchitis due to echovirus	4	0.0	1	1
93153	H060B00	Acute bronchitis due to coxsackievirus	4	0.0	1	1
101775	H060100	Acute membranous bronchitis	4	0.0	1	1
99214	Hyu1100	[X]Acute bronchiolitis due to other specified organisms	3	0.0	1	1
63697	43jQ.00	Avian influenza virus nucleic acid detection	2	0.0	1	1
97936	Hyu0500	[X]Influenza+other manifestations,influenza virus identified	2	0.0	1	1
98156	4JU3.00	Influenza H5 virus detected	1	0.0	1	1

94858	43jy.00	Parainfluenza type 2 nucleic acid detection	-	0.0	1	1
102918	4JU1.00	Influenza H2 virus detected	-	0.0	1	1
			5,738,569	**100.0**		

Identification of OCS

List of product codes (medcode) used to identify OCS and their descriptions are listed in the table below. OCS codes were validated through the identification of exacerbations in CPRD [263]. The final codes to identify presence of OCS are identified in the far right columns by a '1'.

prodcode	productname	validated_ocs	Included
44	prednisolone 5mg gastro-resistant tablets	0	1
95	prednisolone 5mg tablets	1	1
557	prednisolone 2.5mg gastro-resistant tablets	0	1
578	prednisolone 1mg tablets	0	1
955	prednisolone 5mg soluble tablets	0	1
1063	prednesol 5mg tablet (sovereign medical ltd)	1	1
2044	prednisone 2.5 mg tab	1	1
2368	prednisolone 2.5mg tablet	1	1
2390	prednisolone e/c 1 mg tab	1	1
2704	prednisolone 25mg tablets	0	1
2799	prednisolone 10 mg tab	1	1
2949	prednisone 5mg tablets	1	1
3059	prednisolone 50 mg tab	1	1
3345	sintisone tablet (pharmacia ltd)	1	1
3557	prednisone 1mg tablets	1	1
5490	deltacortril 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	0	1
5913	deltacortril 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	0	1
7584	prednisolone 4 mg tab	1	1
7710	prednisolone 15 mg tab	1	1
7934	prednisone 30 mg tab	1	1
9727	prednisolone 50mg tablets	1	1
13522	prednisolone 2 mg tab	1	1
13615	prednisone 10 mg tab	1	1
16724	prednisone 50 mg tab	1	1
19141	prednisolone 5mg soluble tablets (amco)	0	1
20095	precortisyl forte 25mg tablet (aventis pharma)	1	1
20670	prednisolone e/c	1	1
21417	prednisolone 5mg tablets (a a h pharmaceuticals ltd)	0	1
21833	decortisyl 5mg tablet (roussel laboratories ltd)	1	1
23512	precortisyl 5mg tablet (hoechst marion roussel)	1	1
24716	prednisolone e/c	1	1
25272	precortisyl 1mg tablet (hoechst marion roussel)	1	1
27889	prednisolone	1	1
27959	prednisolone	1	1
27962	deltastab 1mg tablet (waymade healthcare plc)	1	1
28375	prednisolone 2.5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	0	1

28376	prednisolone 2.5mg gastro-resistant tablet (biorex laboratories ltd)	1	1
28859	deltastab 5mg tablet (waymade healthcare plc)	1	1
29333	prednisolone 5mg tablets (actavis uk ltd)	0	1
30390	deltastab 2 mg tab	1	1
30971	decortisyl 25 mg tab	1	1
31327	prednisolone steaglate 6.65mg tablet	1	1
31532	prednisolone 5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	0	1
32803	prednisolone 5mg gastro-resistant tablets (actavis uk ltd)	0	1
32835	prednisolone 5mg tablets (wockhardt uk ltd)	0	1
33691	prednisolone 5mg gastro-resistant tablet (biorex laboratories ltd)	1	1
33988	prednisolone 5mg tablet (co-pharma ltd)	1	1
33990	prednisolone 5mg tablet (ivax pharmaceuticals uk ltd)	1	1
34109	prednisolone 5 mg gastro-resistant tablet	1	1
34393	prednisolone 5mg gastro-resistant tablets (teva uk ltd)	0	1
34404	prednisolone 1mg tablets (actavis uk ltd)	0	1
34452	prednisolone 1mg tablets (a a h pharmaceuticals ltd)	0	1
34461	prednisolone 2.5mg gastro-resistant tablets (actavis uk ltd)	0	1
34631	prednisolone 1mg tablet (co-pharma ltd)	1	1
34660	prednisolone 1mg tablets (kent pharmaceuticals ltd)	0	1
34748	prednisolone 1mg tablets (teva uk ltd)	0	1
34781	prednisolone 5mg tablets (kent pharmaceuticals ltd)	0	1
34914	prednisolone 1mg tablet (celltech pharma europe ltd)	1	1
34978	prednisolone 1mg tablets (wockhardt uk ltd)	0	1
38407	prednisolone 20mg tablet	1	1
41515	prednisolone 5mg tablets (teva uk ltd)	0	1
41745	prednisolone 25mg tablets (zentiva)	0	1
43544	prednisone 5mg tablet (knoll ltd)	1	1
44380	prednisone 1mg modified-release tablets	1	1
44723	prednisone 5mg modified-release tablets	1	1
44802	lodotra 5mg modified-release tablets (napp pharmaceuticals ltd)	1	1
44803	lodotra 2mg modified-release tablets (napp pharmaceuticals ltd)	1	1
45302	prednisolone 5mg tablet (biorex laboratories ltd)	1	1
46711	prednisone 2mg modified-release tablets	1	1
47142	prednisolone 5mg soluble tablet (amdipharm plc)	1	1
51753	prednisolone 1mg tablets (strides shasun (uk) ltd)	0	1
53313	prednisolone 20mg/5ml oral suspension	0	1
53336	prednisolone 25mg tablets (a a h pharmaceuticals ltd)	0	1
54118	prednisolone 25mg/5ml oral suspension	0	1
54432	lodotra 1mg modified-release tablets (napp pharmaceuticals ltd)	1	1
54434	prednisolone 2.5mg/5ml oral suspension	0	1
55024	prednisolone 5mg/5ml oral solution	0	1
55480	prednisolone 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	0	1

56891	prednisolone 1mg tablets (waymade healthcare plc)	0	1
58000	prednisolone 5mg tablets (almus pharmaceuticals ltd)	0	1
58061	prednisone 50mg tablets	0	1
58234	prednisolone 10mg/5ml oral solution	0	1
58369	prednisolone 5mg tablets (boston healthcare ltd)	0	1
58384	prednisolone 1mg tablets (almus pharmaceuticals ltd)	0	1
58987	prednisolone 5mg gastro-resistant tablets (phoenix healthcare distribution ltd)	0	1
59229	dilacort 5mg gastro-resistant tablets (auden mckenzie (pharma division) ltd)	0	1
59283	dilacort 2.5mg gastro-resistant tablets (auden mckenzie (pharma division) ltd)	0	1
59338	prednisolone 1mg/5ml oral solution	0	1
59912	prednisolone 5mg gastro-resistant tablets (waymade healthcare plc)	0	1
60421	prednisolone 5mg tablets (strides shasun (uk) ltd)	0	1
61132	prednisolone 1mg tablets (boston healthcare ltd)	0	1
61162	prednisolone 5mg tablets (waymade healthcare plc)	0	1
61689	prednisolone 5mg soluble tablets (a a h pharmaceuticals ltd)	0	1
62656	prednisone 5mg tablet (hillcross pharmaceuticals ltd)	0	1
63066	prednisolone 2.5mg tablets	0	1
63082	prednisolone 20mg tablets	0	1
63172	prednisolone 10mg tablets	0	1
63214	prednisolone 5mg soluble tablets (alliance healthcare (distribution) ltd)	0	1
63549	prednisolone 1mg/ml oral solution (logixx pharma solutions ltd)	0	1
63791	prednisolone 5mg/5ml oral solution unit dose	0	1
64007	pevanti 10mg tablets (amco)	0	1
64008	pevanti 2.5mg tablets (amco)	0	1
64128	pevanti 5mg tablets (amco)	0	1
64221	prednisolone 5mg/5ml oral suspension	0	1
64416	prednisolone 10mg/ml oral solution sugar free	0	1
65020	prednisolone 25mg/5ml oral solution	0	1
65626	prednisolone 10mg/5ml oral suspension	0	1
66015	prednisolone dompe 5mg/5ml oral solution unit dose (logixx pharma solutions ltd)	0	1
66550	prednisolone 5mg gastro-resistant tablets (alliance healthcare (distribution) ltd)	0	1
66645	prednisolone 5mg/5ml oral solution unit dose (logixx pharma solutions ltd)	0	1
66914	prednisolone 1mg gastro-resistant tablets	0	1
67076	prednisolone 20mg/5ml oral solution	0	1
67107	prednisolone 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	0	1
67507	prednisolone 30mg tablets	0	1
67559	prednisolone 5mg/5ml oral solution unit dose (a a h pharmaceuticals ltd)	0	1
68497	prednisolone 2.5mg gastro-resistant tablets (waymade healthcare plc)	0	1
69811	prednisolone 30mg tablets (actavis uk ltd)	0	1
70603	prednisolone 5mg soluble tablets (focus pharmaceuticals ltd)	0	1
72421	prednisolone 1mg gastro-resistant tablets (a a h pharmaceuticals ltd)	0	1
73294	prednisolone 2.5mg/5ml oral solution	0	1

73553	prednisolone 1mg tablets (alliance healthcare (distribution) ltd)	0	1
73678	prednisolone 5mg gastro-resistant tablets (de pharmaceuticals)	0	1

Identification of COPD-specific antibiotics

List of medical codes (medcode) and Read codes (readcode) used to identify COPD-specific antibiotics and their descriptions are listed in the table below. The final codes to identify presence of antibiotics are identified in the far right columns by a '1'.

prodcode	productname	Included
9	amoxicillin 250mg capsules	1
37	trimethoprim 200mg tablets	1
48	amoxicillin 500mg capsules	1
60	flucloxacillin 250mg capsules	1
62	amoxicillin 125mg/5ml oral suspension	1
63	erythromycin 250mg gastro-resistant tablets	1
103	erythromycin 250mg gastro-resistant capsules	1
105	erythroped 250mg/5ml liquid (abbott laboratories ltd)	1
106	ampicillin 250mg/5ml oral suspension	1
108	ampicillin 125 mg cap	1
109	septrin adult 80mg/400mg/5ml oral suspension (aspen pharma trading ltd)	1
115	ampicillin 250mg capsules	1
128	sulfametopyrazine 2g tablet	1
131	septrin for infusion 80mg/400mg/5ml solution for infusion ampoules (aspen pharma trading ltd)	1
133	amoxil 250mg capsules (glaxosmithkline uk ltd)	1
135	septrin tablet (wellcome medical division)	1
153	trimethoprim 100mg/5ml solution for injection ampoules	1
155	cefalexin 250mg capsules	1
161	flucloxacillin 1 gm cap	1
163	ciproxin 250mg/5ml oral suspension (bayer plc)	1
192	ceporex 250mg capsule (galen ltd)	1
201	erythrocin 1g/vial injection (abbott laboratories ltd)	1
226	trimethoprim 100 mg cap	1
232	cefotaxime 500mg powder for solution for injection vials	1
240	rifampicin 150mg capsules	1
244	augmentin intravenous 1.2g powder for solution for injection vials (glaxosmithkline uk ltd)	1
251	erythromycin 50 mg inj	1
260	sulphafurazole 500mg/5ml oral solution	1
264	doxycycline 50mg capsules	1
268	vibramycin 100mg capsules (pfizer ltd)	1
279	vancomycin 125mg capsules	1
280	monotrim 50mg/5ml liquid (solvay healthcare)	1
281	ciprofloxacin 250mg tablets	1
287	co-trimoxazole (trimethoprim with sulfamethoxazole) 320mg/ml im injection	1
290	cefuroxime 1.5g powder for injection vials	1
298	sulfadimidine 333mg/ml injection	1

303	co-trimoxazole 16mg with 80mg/ml concentrate solution for infusion	1
308	magnapen 250mg/250mg capsules (wockhardt uk ltd)	1
318	erymax 250mg capsule (elan pharma)	1
327	erythroped a 500mg tablet (abbott laboratories ltd)	1
331	clarithromycin 125mg/5ml oral suspension	1
340	trimethoprim 100mg tablets	1
343	ampicillin 125 mg tab	1
373	chloramphenicol 250mg capsules	1
397	erythromycin 125mg/5ml oral suspension	1
399	augmentin 375mg tablets (glaxosmithkline uk ltd)	1
400	cefalexin 500mg capsules	1
401	erythromycin 500mg ec gastro-resistant tablets	1
403	sulfadiazine 500mg tablets	1
415	augmentin 125/31 sf oral suspension (glaxosmithkline uk ltd)	1
427	amoxicillin 250mg/5ml oral suspension	1
438	erythromycin stearate 250mg tablets	1
439	amoxicillin with clavulanic acid dispersible tablets	1
457	flucloxacillin 125mg/5ml oral solution	1
477	trimethoprim 50mg/5ml oral suspension sugar free	1
480	erythrocin 250mg tablet (abbott laboratories ltd)	1
485	amoxicillin 125mg/1.25ml oral suspension paediatric	1
498	ciprofloxacin 100mg tablets	1
503	amoxicillin 125mg/5ml oral suspension sugar free	1
509	augmentin 625mg tablets (glaxosmithkline uk ltd)	1
524	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free	1
532	erythroped 250mg/5ml oral suspension (abbott laboratories ltd)	1
537	clarithromycin 250mg tablets	1
545	co-amoxiclav 250mg/125mg tablets	1
553	erythromycin 250mg.5ml oral suspension	1
569	augmentin 250/62 sf oral suspension (glaxosmithkline uk ltd)	1
577	co-amoxiclav 500mg/100mg powder for solution for injection vials	1
579	flucloxacillin 500mg capsules	1
583	ciprofloxacin 500mg tablets	1
585	amoxicillin 250mg/5ml oral suspension sugar free	1
598	amoxicillin 250mg powder for solution for injection vials	1
606	co-trimoxazole 80mg/400mg tablets	1
641	co-amoxiclav 500mg/125mg tablets	1
678	teicoplanin 200mg powder and solvent for solution for injection vials	1
681	clarithromycin 500mg tablets	1
684	ceftriaxone 1g powder for solution for injection vials	1
693	piperacillin 2g / tazobactam 250mg powder for solution for injection vials	1
694	tazocin 4.5g powder for solution for injection (pfizer consumer healthcare ltd)	1

725	cefuroxime 125mg/5ml oral suspension	1
728	ciproxin 500mg tablets (bayer plc)	1
733	erythromycin ethyl succinate 500mg tablets	1
743	azithromycin 500mg tablets	1
765	clarithromycin 250mg granules sachets	1
825	erythroped pi 125mg/5ml oral suspension (abbott laboratories ltd)	1
829	co-amoxiclav 250mg/125mg dispersible tablets sugar free	1
830	keflex 250mg tablets (flynn pharma ltd)	1
835	teicoplanin 400mg powder and solvent for solution for injection vials	1
847	amoxil 500mg capsules (glaxosmithkline uk ltd)	1
857	ampicillin 125mg/5ml oral suspension	1
865	cefalexin 500mg tablets	1
870	amoxicillin 250mg sugar free chewable tablets	1
900	ampicillin 125mg/5ml sugar free suspension	1
926	ampicillin 500mg capsules	1
951	flucloxacillin with ampicillin 125mg+125mg liquid	1
970	doxycycline (as hyclate) 100mg tablets	1
993	erythroped forte 500mg/5ml liquid (abbott laboratories ltd)	1
997	erythroped pi 125mg/5ml liquid (abbott laboratories ltd)	1
1000	flucloxacillin 125mg/5ml oral suspension	1
1001	flucloxacillin 250mg/5ml oral solution	1
1037	erythromycin ethylsuccinate sf 125 mg/5ml sus	1
1046	doxycycline 100mg capsules	1
1072	erythrocin 500 500mg tablet (abbott laboratories ltd)	1
1140	amoxicillin 3g oral powder sachets sugar free	1
1146	cefalexin 250mg tablets	1
1199	co-trimoxazole 40mg/200mg/5ml oral suspension sugar free	1
1202	ciproxin 250mg tablets (bayer plc)	1
1345	rifampicin 100mg/5ml oral suspension	1
1347	rimactane 150mg capsule (novartis pharmaceuticals uk ltd)	1
1376	erythromycin 100 mg syr	1
1384	cefalexin 125mg/5ml suspension	1
1391	amoxicillin 250mg / clavulanic acid 125mg tablets	1
1393	amoxycillin fiztab 250 mg tab	1
1450	ampicillin 250mg / flucloxacillin 250mg capsules	1
1467	co-trimoxazole 160mg/800mg tablets	1
1531	rifampicin 300mg capsules	1
1570	amoxycillin 500 mg tab	1
1604	septrin paediatric oral suspension sugar free (wellcome medical division)	1
1634	septrin paediatric dispersible tablet (wellcome medical division)	1
1637	amoxil fiztab 250mg tablet (bencard)	1
1638	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	1

1693	cefalexin 125mg/5ml oral suspension	1
1694	flucloxacillin 125 mg pow	1
1706	cephalexin 125 mg tab	1
1713	cefalexin 250mg/5ml suspension	1
1722	amoxicillin 500mg dispersible tablets	1
1746	amoxicillin 500mg powder for solution for injection vials	1
1812	amoxil 250mg/5ml syrup sucrose free (glaxosmithkline uk ltd)	1
1837	ciprofloxacin 750mg tablets	1
1860	cefalexin 250mg/5ml oral suspension	1
1969	erythromycin 250 mg mix	1
2153	amoxil 125mg/5ml syrup sucrose free (glaxosmithkline uk ltd)	1
2171	amoxil 125mg/1.25ml paediatric oral suspension (glaxosmithkline uk ltd)	1
2174	amoxil 3g oral powder sachets sucrose free (glaxosmithkline uk ltd)	1
2202	vibramycin 50 capsules (pfizer ltd)	1
2225	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free	1
2226	erythromycin ethyl succinate 500mg/5ml oral suspension	1
2227	cefalexin 500mg/5ml oral suspension	1
2246	pondocillin 500mg tablet (leo pharma)	1
2281	amoxicillin 500mg sugar free chewable tablets	1
2299	fluclomix 250 capsules (ashbourne pharmaceuticals ltd)	1
2326	erythromycin 500mg/5ml oral suspension	1
2350	erythromycin stearate 500mg tablets	1
2376	erythromycin ethyl succinate 250mg/5ml oral suspension	1
2377	pondocillin 175mg/5ml oral suspension sugar free (leo pharma)	1
2429	erythromycin ethyl succinate 125mg/5ml oral suspension	1
2460	septrin forte 160mg/800mg tablets (aspen pharma trading ltd)	1
2507	augmentin 375mg dispersible tablets (glaxosmithkline uk ltd)	1
2642	floxapen 250mg/5ml syrup (actavis uk ltd)	1
2651	ceftazidime 1g powder for solution for injection vials	1
2658	co-trimoxazole 80mg/400mg/5ml oral suspension	1
2661	ceporex 500mg capsule (galen ltd)	1
2719	klaricid 250mg tablets (abbott laboratories ltd)	1
2725	co-trimoxazole 100 mg tab	1
2735	flucloxin 125mg/5ml liquid (opd pharm)	1
2798	rimactane 100mg/5ml syrup (movianto uk ltd)	1
2874	magnapen syrup (wockhardt uk ltd)	1
2884	doxycycline (as hyclate) 100mg dispersible tablets	1
2902	amoxycillin fiztab 125 mg tab	1
3042	erythroped pi 125mg sachets (abbott laboratories ltd)	1
3152	vibramycin 100mg dispersible tablet (pfizer ltd)	1
3209	erythromid 250mg tablet (abbott laboratories ltd)	1
3403	rifinah 150 tablet (aventis pharma)	1

3408	erythromycin 500 mg cap	1
3572	erythroped 250mg powder (abbott laboratories ltd)	1
3583	co-trimoxazole paed 120 mg tab	1
3609	ceporex 125mg/5ml oral solution (galen ltd)	1
3660	septrin dispersible tablet (wellcome medical division)	1
3669	amoxymed 250mg capsule (medipharma ltd)	1
3678	cefuroxime 250mg tablets	1
3704	ceftriaxone 250mg powder for solution for injection vials	1
3736	klaricid 125mg/5ml oral suspension (abbott laboratories ltd)	1
3742	amoxicillin 125mg sugar free chewable tablets	1
3846	zinnat 250mg tablets (glaxosmithkline uk ltd)	1
3877	flucloxacillin 125 mg cap	1
3907	erythromycin sf sach 250 mg	1
4008	fluclomix 500 capsules (ashbourne pharmaceuticals ltd)	1
4010	amoxil 750mg sachets (glaxosmithkline uk ltd)	1
4074	flucloxin 500mg capsule (opd pharm)	1
4091	ciprofloxacin 250mg/5ml oral suspension	1
4153	erythrolar 250mg/5ml liquid (lagap)	1
4154	amoxil fiztab 125mg tablet (bencard)	1
4165	zithromax 250mg capsules (pfizer ltd)	1
4372	erythroped forte 500mg sachets (abbott laboratories ltd)	1
4489	erycen 250mg tablet (berk pharmaceuticals ltd)	1
4522	rifinah 300 tablet (aventis pharma)	1
4555	co-trimoxazole 200 mg sus	1
4582	amoxicillin 750mg soluble tablets	1
4596	erythroped a 1g sachets (abbott laboratories ltd)	1
4610	erythroped forte 500mg/5ml oral suspension (abbott laboratories ltd)	1
4672	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free	1
4895	benzoyl peroxide 5% / erythromycin 3% gel	1
5057	azithromycin 200mg/5ml oral suspension	1
5116	azithromycin 250mg capsules	1
5238	levofloxacin 500mg tablets	1
5280	vancomycin 250mg capsules	1
5335	zithromax 500mg tablets (pfizer ltd)	1
5341	augmentin-duo 400/57 oral suspension (glaxosmithkline uk ltd)	1
5357	clarithromycin 250mg/5ml oral suspension	1
5423	flucloxacillin 250mg/5ml oral suspension	1
5454	co-fluampicil 250mg/250mg capsules	1
5662	amoxicillin 500mg / clarithromycin 500mg / lansoprazole 30mg triple pack	1
5859	ceporex 500mg/5ml oral solution (galen ltd)	1
6121	klaricid xl 500mg tablets (mylan)	1
6206	tavanic 500mg tablets (sanofi)	1

6295	levofloxacin 250mg tablets	1
6396	doxycycline 100mg dispersible tablets sugar free	1
6497	clarithromycin 500mg with metronidazole 400mg with lansoprazole 30mg triple pack	1
6623	klaricid 500 tablets (abbott laboratories ltd)	1
6651	cefalexin 125mg/5ml oral suspension sugar free	1
6671	cefalexin 250mg/5ml oral suspension sugar free	1
6687	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free	1
6803	clarithromycin 500mg modified-release tablets	1
7364	co-amoxiclav 250mg/62mg/5ml oral suspension	1
7420	bactrim 480mg tablet (roche products ltd)	1
7421	bactrim adult 480mg/5ml liquid (roche products ltd)	1
7430	keflex 250mg capsule (eli lilly and company ltd)	1
7485	keflex 125mg/5ml liquid (eli lilly and company ltd)	1
7501	cefotaxime 1g powder for solution for injection vials	1
7502	ceftazidime 2g powder for solution for injection vials	1
7503	cefuroxime (as sodium salt) 1.5g/vial infusion	1
7523	doxycycline (as hyclate) 20mg capsules	1
7531	penbritin 500mg powder for solution for injection vials (chemidex pharma ltd)	1
7560	ceporex 125mg/5ml liquid (galen ltd)	1
7570	pivampicillin 500mg tablet	1
7581	amoxycillin 125mg/62mg clavulanic acid syr	1
7587	cefuroxime 250mg powder for injection vials	1
7592	amoxycillin 125 mg cap	1
7616	trimopan 50mg/5ml liquid (berk pharmaceuticals ltd)	1
7636	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension	1
7737	amoxil fiztab 500mg tablet (bencard)	1
7752	ciproxin 750mg tablets (bayer plc)	1
7792	erythromycin 12 mg syr	1
7818	rifater tablets (sanofi)	1
7962	kelfizine w 2g tablet (pharmacia ltd)	1
8008	ceporex 250mg/5ml oral solution (galen ltd)	1
8019	ceporex 250mg tablet (galen ltd)	1
8073	trimethoprim 300mg tablet	1
8085	ceporex 500mg tablet (galen ltd)	1
8171	monotrim 200mg tablets (abbott healthcare products ltd)	1
8209	ampicillin 125mg/5ml paediatric oral suspension	1
8286	co-trimoxazole (trimethoprim and sulfamethoxazole) 80mg+400mg dispersible tablets	1
8394	co-trimoxazole 80 mg syr	1
8462	targocid 400mg powder and solvent for solution for injection vials (sanofi)	1
8561	bactrim paediatric sugar free oral solution	1
8613	rifampicin 300mg / isoniazid 150mg tablets	1
8614	pivampicillin 175mg/5ml oral solution	1

8625	ceporex 250mg/5ml liquid (galen ltd)	1
8724	doxycycline (as hyclate) 50mg/5ml oral solution	1
8741	bactrim dispersible tablet (roche products ltd)	1
8900	co-trimoxazole 800 mg tab	1
8906	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension	1
8933	floxapen 125mg/5ml syrup (actavis uk ltd)	1
8960	pondocillin plus tablet (edwin burgess ltd)	1
9062	rimactazid 150 tablets (movianto uk ltd)	1
9100	co-trimoxazole (trimethoprim and sulfamethoxazole) 160mg+800mg dispersible tablets	1
9148	erythromid ds 500mg tablet (abbott laboratories ltd)	1
9154	ciproxin 100mg tablets (bayer plc)	1
9157	keflex 250mg tablet (eli lilly and company ltd)	1
9242	flucloxacillin with ampicillin 250mg+250mg capsule	1
9243	amoram 250mg capsules (lpc medical (uk) ltd)	1
9267	vibramycin acne pack 50mg capsules (pfizer ltd)	1
9343	amoxicillin 750mg sugar free powder	1
9434	erymin 250mg/5ml oral suspension (elan pharma)	1
9473	co-fluampicil 125mg/125mg/5ml oral suspension	1
9583	klaricid 250mg/5ml oral suspension (abbott laboratories ltd)	1
9603	keflex 500mg tablet (eli lilly and company ltd)	1
9656	erythromycin 2% gel	1
9664	cefalexin 500mg capsules (ivax pharmaceuticals uk ltd)	1
9689	cefalexin 500mg tablets (teva uk ltd)	1
9690	cefalexin 250mg capsules (teva uk ltd)	1
9691	rifampicin with isoniazid & pyrazinamide tablet	1
9698	cefalexin 250mg tablets (teva uk ltd)	1
9800	flucloxin 250mg capsule (opd pharm)	1
9903	erythromycin estolate 250mg capsules	1
9925	clavulanic acid 125mg with amoxicillin 250mg tablets	1
10046	trimopan 200mg tablets (teva uk ltd)	1
10190	erymax 250mg gastro-resistant capsules (teva uk ltd)	1
10200	co-amoxiclav 125mg/31mg/5ml oral suspension	1
10300	chloramphenicol 1.2g/vial sterile powder	1
10301	sulfadimidine 500mg/5ml paediatric mixture	1
10304	ciprofloxacin 2mg/ml infusion	1
10308	sulfamethoxazole 400mg with trimethoprim 80mg tablet	1
10318	sulfamethoxazole 80mg with trimethoprim 16mg/5ml concentrate solution for infusion	1
10319	levofloxacin 500mg/100ml intravenous infusion	1
10326	clarithromycin 125mg granules straws	1
10369	ampicillin 125mg / flucloxacillin 125mg oral solution	1
10447	chloramphenicol pow	1
10454	vibramycin 50mg/5ml oral solution (pfizer ltd)	1

10455	keflex 250mg/5ml liquid (eli lilly and company ltd)	1
10632	co-trimoxazole f/c 480 mg tab	1
10685	ampicillin 250mg injection	1
10720	co-trimoxazole paed 200 mg syr	1
10745	bactrim double strength 160mg+800mg tablet (roche products ltd)	1
10755	ampiciilin 60mg / cloxacillin 30mg/0.6ml sugar free oral suspension	1
10771	amoxil 250mg powder for solution for injection vials (glaxosmithkline uk ltd)	1
10794	zinnat 125mg tablets (glaxosmithkline uk ltd)	1
10814	flucloxacillin 500mg powder for solution for injection vials	1
11226	rifampicin 600mg powder and solvent for solution for infusion vials	1
11433	clarithromycin 500mg with lansoprazole 30mg and amoxicillin 500mg triple pack	1
11611	rommix 250 ec tablets (ashbourne pharmaceuticals ltd)	1
11613	amix 250 capsules (ashbourne pharmaceuticals ltd)	1
11634	amix 125 oral suspension (ashbourne pharmaceuticals ltd)	1
11883	ciprofloxacin 100mg/50ml solution for infusion vials	1
11989	keflex 250mg capsules (flynn pharma ltd)	1
12235	ceporex 1g tablet (galen ltd)	1
12248	cefalexin 125mg/1.25ml paediatric drops	1
12276	keflex 500mg capsule (eli lilly and company ltd)	1
12329	rifampicin 150mg / isoniazid 100mg tablets	1
12330	erythromycin ethylsuccinate 1g sachets	1
12378	amoram 125mg/5ml oral suspension (lpc medical (uk) ltd)	1
12437	rimactazid 300 tablets (movianto uk ltd)	1
12465	polytrim ophthalmic ointment (pliva pharma ltd)	1
12489	ambaxin 400mg tablet (pharmacia ltd)	1
12540	pivampicillin 250mg with pivmecillinam 200mg tablet	1
12850	cefuroxime 125mg tablets	1
12987	doxycycline (as hyclate) 50mg capsules with microgranules	1
13120	erythromycin ethyl succinate 250mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
13167	erythromycin ethyl succinate 125mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
13216	amoxicillin 500mg / clavulanic acid 125mg tablets	1
13239	clavulanic acid 125mg with amoxicillin 500mg tablets	1
13262	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension	1
13285	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension	1
13306	monotrim 100mg/5ml solution for injection ampoules (abbott healthcare products ltd)	1
13323	clarithromycin 500mg powder for solution for infusion vials	1
13325	monotrim 100mg tablets (abbott healthcare products ltd)	1
13412	zinnat 125mg/5ml oral suspension (glaxosmithkline uk ltd)	1
13438	magnapen 1g/vial injection (c p pharmaceuticals ltd)	1
13531	magnapen 500mg powder for solution for injection vials (wockhardt uk ltd)	1
13635	erythromycin ethylsuccinate 250mg sachets	1
13797	targocid 200mg powder and solvent for solution for injection vials (sanofi)	1

13848	amoxicillin 125mg sugar free powder	1
13908	rifadin 100mg/5ml syrup (sanofi)	1
14137	doxycycline 20mg tablets	1
14171	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free	1
14367	ipral 50mg/5ml liquid (e r squibb and sons ltd)	1
14371	galenamox 250mg capsules (galen ltd)	1
14376	ciproxin 2mg/ml infusion (bayer plc)	1
14386	galenamox 125mg/5ml oral suspension (galen ltd)	1
14396	galenamox 500mg capsules (galen ltd)	1
14407	galenamox 250mg/5ml oral suspension (galen ltd)	1
14429	erythromycin 125mg sprinkle capsules	1
14484	ampicillin / cloxacillin 500mg capsules	1
14485	ampicillin 500mg powder for solution for injection vials	1
14511	erymax sprinkle 125mg capsule (elan pharma)	1
14514	zithromax 200mg/5ml oral suspension (pfizer ltd)	1
14546	chloramphenicol 125mg/ml oral suspension	1
14749	ceftazidime 2g/vial powder for injection solution	1
14816	klaricid adult 250mg granules sachets (mylan)	1
14904	vibramycin-d 100mg dispersible tablets (pfizer ltd)	1
14998	ipral 200mg tablet (e r squibb and sons ltd)	1
15071	nordox 100mg capsule (sankyo pharma uk ltd)	1
15081	ipral 100mg tablet (e r squibb and sons ltd)	1
15148	amoxil 500mg dispersible tablet (smithkline beecham plc)	1
15192	amoxicillin 400mg / clavulanic acid 57mg/5ml sugar free oral suspension	1
15247	flucloxacillin 250mg powder for solution for injection vials	1
15290	lansoprazole with amoxicillin and clarithromycin 30mg + 500mg + 500mg triple pack	1
15386	c0-trimoxazole tab	1
15713	erythromycin ethylsuccinate 500mg sachets	1
15988	trimethoprim with sulfamethoxazole 80mg+400mg tablet	1
16167	ampicillin 250mg/5ml sugar free suspension	1
16191	flucloxacillin 1g powder for solution for injection vials	1
16202	rocephin 1g powder for solution for injection vials (roche products ltd)	1
16589	talampicillin 125mg/5ml syrup	1
16594	piperacillin 1g/vial injection	1
16595	ceftazidime 250mg powder for solution for injection vials	1
16605	erythromycin i/v 1 gm inj	1
16612	clavulanic acid 62mg with amoxicillin 250mg/5ml sugar free suspension	1
16620	co-trimoxazole 80mg/400mg/5ml solution for infusion ampoules	1
16639	rifadin 300mg capsules (sanofi)	1
16746	vancocin 125mg capsule (eli lilly and company ltd)	1
16747	erythroped 250mg sachets (abbott laboratories ltd)	1
16802	isoniazid with rifampicin 150mg + 300mg tablet	1

17015	vancomycin 500mg powder for solution for infusion vials	1
17099	amoxil 1g powder for solution for injection vials (glaxosmithkline uk ltd)	1
17116	vancomycin 1g powder for solution for infusion vials	1
17123	zinacef 1.5g powder for injection vials (glaxosmithkline uk ltd)	1
17150	ceporex 125mg/1.25ml drops (glaxo laboratories ltd)	1
17161	miraxid tablet (rpr / fisons)	1
17181	pivampicillin 175mg sachet	1
17207	ilosone 250mg capsule (dista products ltd)	1
17231	chloramphenicol 300mg/vial sterile powder	1
17282	almodan 125mg/5ml syrup (teva uk ltd)	1
17292	zinacef 750mg powder for injection vials (glaxosmithkline uk ltd)	1
17323	piperacillin 4g / tazobactam 500mg powder for solution for infusion vials	1
17396	chloramphenicol 1g powder for solution for injection vials	1
17509	amoxicillin 1g powder for solution for injection vials	1
17645	clarithromycin 250mg granules straws	1
17693	tavanic 250mg tablets (sanofi)	1
17711	amopen 500mg capsule (yorkshire pharmaceuticals ltd)	1
17729	sulfadimidine 500mg tablet	1
17738	co-trimoxazole 96 mg inj	1
17746	amoxicillin 375mg soluble tablets	1
17852	augmentin intravenous 600mg powder for solution for injection vials (glaxosmithkline uk ltd)	1
17871	fortum 500mg powder for solution for injection vials (glaxosmithkline uk ltd)	1
17873	fortum 1g powder for solution for injection vials (glaxosmithkline uk ltd)	1
18041	periostat 20mg tablets (alliance pharmaceuticals ltd)	1
18313	ceftazidime intermate inf device	1
18451	cefalexin 1g tablets	1
18643	ilosone 500mg tablet (dista products ltd)	1
18682	ilosone 125mg/5ml liquid (dista products ltd)	1
18786	amix 500 capsules (ashbourne pharmaceuticals ltd)	1
18930	flemoxin 375mg soluble tablet (paines & byrne ltd)	1
19133	cefalexin 250mg capsules (ivax pharmaceuticals uk ltd)	1
19138	cefalexin 500mg capsules (actavis uk ltd)	1
19144	cefalexin 125mg/5ml oral suspension sugar free (teva uk ltd)	1
19152	cefalexin 250mg capsules (actavis uk ltd)	1
19160	cefalexin 250mg capsules (mylan)	1
19161	cefalexin 500mg capsules (ranbaxy (uk) ltd)	1
19184	cefalexin 500mg capsules (mylan)	1
19209	co-amoxiclav 250mg/125mg tablets (actavis uk ltd)	1
19330	ilosone 250mg/5ml liquid (dista products ltd)	1
19368	tazocin 2.25g powder for solution for injection vials (pfizer ltd)	1
19414	co-amoxiclav 250mg/125mg tablets (sandoz ltd)	1
19585	ampicillin 250mg/flucloxacillin 250mg	1

19648	co-fluampicil 250mg/250mg capsules (a a h pharmaceuticals ltd)	1
19795	amoxycillin 250mg/clavulanic acid 125mg	1
19838	ceftriaxone 2g powder for solution for injection vials	1
19909	cefuroxime 750mg powder for injection vials	1
20003	ceftazidime 3g powder for solution for injection vials	1
20007	talampicillin 250mg tablets	1
20009	talampicillin 250 mg syr	1
20126	trimethoprim with sulfamethoxazole 160mg+800mg tablet	1
20205	vancomycin oral 10 gm sol	1
20368	sulfamethoxazole 400mg with trimethoprim 80mg/5ml concentrate solution for infusion	1
20432	clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension	1
20516	miraxid liquid (rpr / fisons)	1
20523	thalazole 500mg tablet (may and baker)	1
20524	gx co-trimoxazole 480 mg tab	1
20531	amfipen 250mg capsule (yamanouchi pharma ltd)	1
20569	claforan 1g powder for solution for injection vials (sanofi)	1
20869	flucloxacillin with ampicillin 250mg+250mg injection	1
20920	trimethoprim with sulfamethoxazole 80mg + 400mg/5ml oral suspension	1
21029	miraxid 450 tablet (rpr / fisons)	1
21037	uromide tablet (consolidated chemicals (uk) ltd)	1
21038	doxatet 100mg tablet (manufacturer unknown)	1
21345	bacampicillin hcl 400mg tablets	1
21367	rifadin 150mg capsules (sanofi)	1
21640	trimopan 100mg tablets (teva uk ltd)	1
21737	piperacillin 2g/vial injection	1
21775	clavulanic acid 31mg with amoxicillin 125mg/5ml sugar free oral suspension	1
21799	almodan 250mg capsule (berk pharmaceuticals ltd)	1
21801	vidopen 250mg capsule (berk pharmaceuticals ltd)	1
21805	triprimix 200 tablet (ashbourne pharmaceuticals ltd)	1
21808	rommix 125mg/5ml oral suspension sugar free (ashbourne pharmaceuticals ltd)	1
21809	comixco 80mg+400mg tablet (ashbourne pharmaceuticals ltd)	1
21812	ciproxin infusion 100mg/50ml solution for infusion bottles (bayer plc)	1
21827	almodan 500mg capsule (berk pharmaceuticals ltd)	1
21828	demix 50 capsules (ashbourne pharmaceuticals ltd)	1
21829	zoxycil 250mg capsule (trinity pharmaceuticals ltd)	1
21835	kiflone 250mg capsule (berk pharmaceuticals ltd)	1
21844	amix 250 oral suspension (ashbourne pharmaceuticals ltd)	1
21845	almodan 250mg/5ml oral solution (berk pharmaceuticals ltd)	1
21850	zoxin 250mg capsule (opus pharmaceuticals ltd)	1
21860	cyclodox 100mg capsule (berk pharmaceuticals ltd)	1
21878	demix 100 capsules (ashbourne pharmaceuticals ltd)	1
21926	amfipen 500mg/vial injection (yamanouchi pharma ltd)	1

21963	almodan 250mg/5ml oral solution (berk pharmaceuticals ltd)	1
21967	vidopen 500mg capsule (berk pharmaceuticals ltd)	1
21979	kiflone 250mg/5ml oral solution (berk pharmaceuticals ltd)	1
21982	amoxycillin trihydrate sachet	1
22015	respillin 125mg/5ml oral solution (opd pharm)	1
22016	almodan 125mg/5ml oral solution (berk pharmaceuticals ltd)	1
22017	respillin 125mg/5ml oral solution (opd pharm)	1
22029	amiclav 250mg/125mg tablets (ashbourne pharmaceuticals ltd)	1
22118	pivampicillin 175mg/5ml	1
22293	amoxycillin trihydrate sachet	1
22321	cefalexin 500mg tablets (mylan)	1
22415	amoram 500mg capsules (lpc medical (uk) ltd)	1
22422	galfloxin 250mg capsule (galen ltd)	1
22438	amoram 250mg/5ml oral suspension (lpc medical (uk) ltd)	1
22452	britcin 250mg capsule (ddsa pharmaceuticals ltd)	1
22469	amoxycillin 125mg/31mg clavulanic acid	1
22482	ampicillin	1
22517	isoniazid / pyrazinamide / rifampicin 50 mg tab	1
22544	ampicillin 125mg/flucloxacillin 125mg	1
22991	chemotrim liquid (rosemont pharmaceuticals ltd)	1
23017	erycen 500mg tablet (berk pharmaceuticals ltd)	1
23186	vidopen 125mg/5ml oral solution (berk pharmaceuticals ltd)	1
23238	amoxicillin 125mg/5ml oral suspension (ivax pharmaceuticals uk ltd)	1
23240	flucloxacillin 250mg capsules (a a h pharmaceuticals ltd)	1
23244	ilotycin 250mg tablet (eli lilly and company ltd)	1
23405	doxylar 100mg capsules (sandoz ltd)	1
23432	doxylar 50mg capsules (sandoz ltd)	1
23485	flu-amp 500mg capsule (generics (uk) ltd)	1
23510	kefadim 500mg powder for solution for injection vials (flynn pharma ltd)	1
23583	flucloxacillin	1
23740	amoxicillin 500mg capsules (mylan)	1
23819	doxycycline (as hyclate) 50mg capsules with microgranules	1
23954	erythrolar 500mg tablet (lagap)	1
23967	amoxicillin 250mg capsules (teva uk ltd)	1
24005	co-amoxiclav 1000mg/200mg powder for solution for injection vials	1
24006	clavulanic acid 31mg with amoxcillin 125mg/5ml oral suspension	1
24046	ceftazidime 500mg powder for solution for injection vials	1
24048	vancocin matrigel 250mg capsules (flynn pharma ltd)	1
24090	cefalexin 250mg capsules (pliva pharma ltd)	1
24093	clavulanic acid with amoxicillin dispersible tablets	1
24126	doxycycline 100mg capsules (ivax pharmaceuticals uk ltd)	1
24127	erythromycin 250mg gastro-resistant tablets (a a h pharmaceuticals ltd)	1

24129	erythromycin 250mg gastro-resistant tablets (ivax pharmaceuticals uk ltd)	1
24149	doxycycline 100mg capsules (a a h pharmaceuticals ltd)	1
24150	amoxicillin 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)	1
24200	respillin 500mg capsule (opd pharm)	1
24203	respillin 250mg capsule (opd pharm)	1
24220	arpimycin 250mg/5ml liquid (rosemont pharmaceuticals ltd)	1
24324	trimogal 200mg tablet (lagap)	1
24373	tavanic 500mg/100ml solution for infusion vials (sanofi)	1
24396	flemoxin 750mg soluble tablet (paines & byrne ltd)	1
24483	penbritin 250mg capsules (chemidex pharma ltd)	1
24618	keflex 500mg capsules (flynn pharma ltd)	1
24819	amoxil 500mg powder for solution for injection vials (glaxosmithkline uk ltd)	1
24847	ampicillin 500mg / flucloxacillin 500mg injection	1
24856	sulphamezathine 333mg/ml injection (astrazeneca uk ltd)	1
24974	pivampicillin 250mg/pivmecillinam 200mg	1
25017	tetracycline	1
25034	amoxycillin 125mg/62mg clavulanic acid	1
25269	bactrim im 320mg/ml intramuscular injection (roche products ltd)	1
25277	rimactane 300mg capsule (novartis pharmaceuticals uk ltd)	1
25278	rommix 500mg tablet (ashbourne pharmaceuticals ltd)	1
25280	tiloryth 250mg gastro-resistant capsules (tillomed laboratories ltd)	1
25370	ranclav 375mg tablets (ranbaxy (uk) ltd)	1
25484	amoxicillin 250mg capsules (a a h pharmaceuticals ltd)	1
25497	syraprim 100mg tablet (wellcome medical division)	1
25570	co-fluampicil 250mg/250mg capsules (sandoz ltd)	1
25595	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)	1
25614	cefotaxime 2g powder for solution for injection vials	1
25666	cefuroxime with saline 750mg infusion	1
25667	zinacef 1.5g/vial infusion (glaxo laboratories ltd)	1
25751	erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free	1
25832	pivampicillin 125mg with pivmecillinam100mg tablet	1
25908	sulfamethoxazole 800mg with trimethoprim 160mg tablet	1
25943	erythromycin i/v 300 mg inj	1
26042	rocephin 250mg powder for solution for injection vials (roche products ltd)	1
26059	clarithromycin 187.5mg granules straws	1
26075	oxyphenbutazone 10%/chloramphenicol 1% e	1
26157	amoxicillin 500mg capsules (actavis uk ltd)	1
26174	ampicillin 500mg capsules (a a h pharmaceuticals ltd)	1
26189	erythromycin 1g powder for solution for infusion vials	1
26262	zoxycil 500mg capsule (trinity pharmaceuticals ltd)	1
26326	floxapen 250mg powder for solution for injection vials (glaxosmithkline uk ltd)	1
26329	co-fluampicil 250mg/250mg powder for solution for injection vials	1

26350	floxapen 500mg powder for solution for injection vials (glaxosmithkline uk ltd)	1
26356	amfipen 500mg capsule (yamanouchi pharma ltd)	1
26365	erythromycin 500mg tablet (ivax pharmaceuticals uk ltd)	1
26392	vibrox 100mg capsules (kent pharmaceuticals ltd)	1
26510	ampicillin 250mg / flucloxacillin 250mg injection	1
26558	floxapen 1g powder for solution for injection vials (glaxosmithkline uk ltd)	1
26747	doxycycline 100mg tablet (neo laboratories ltd)	1
26776	isoniazid with rifampicin 100mg + 150mg tablet	1
26840	ciprofloxacin 100mg/50ml solution for infusion bottles	1
26989	kiflone 125mg/5ml oral solution (berk pharmaceuticals ltd)	1
26992	kiflone 500mg tablet (berk pharmaceuticals ltd)	1
27016	ciprofloxacin	1
27017	kiflone 500mg capsule (berk pharmaceuticals ltd)	1
27048	syraprim 300mg tablet (wellcome medical division)	1
27057	flucloxacillin 125mg/5ml oral solution (a a h pharmaceuticals ltd)	1
27072	keflex 125mg/5ml oral suspension (flynn pharma ltd)	1
27203	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (teva uk ltd)	1
27254	tenkorex 500mg capsule (opd pharm)	1
27255	trimethoprim 200mg tablets (a a h pharmaceuticals ltd)	1
27405	vancocin matrigel 125mg capsules (flynn pharma ltd)	1
27417	sulphafurazole 500mg tablet	1
27418	trimethoprim with sulfamethoxazole 40mg + 200mg/5ml oral suspension	1
27445	trimethoprim with sulfamethoxazole 160mg + 800mg/10ml concentrate for solution for infusion	1
27495	arpimycin 125mg/5ml liquid (rosemont pharmaceuticals ltd)	1
27504	primacine 500mg/5ml liquid (pinewood healthcare)	1
27681	ranclav 125mg/31mg/5ml sf oral suspension (ranbaxy (uk) ltd)	1
27714	amrit 250mg capsule (bhr pharmaceuticals ltd)	1
27725	amoxicillin 250mg/5ml oral suspension (teva uk ltd)	1
27768	erythrolar 250mg tablet (lagap)	1
27886	amoxycillin 250/clavulanic acid 125 disp	1
27897	amoxycillin	1
27921	laratrim forte tablet (lagap)	1
27994	vancocin 500mg/vial powder for solution for infusion (eli lilly and company ltd)	1
28004	co-trimoxazole (trimethoprim and sulfamethoxazole) 20mg+100mg paediatric tablets	1
28054	zinacef 250mg powder for injection vials (glaxosmithkline uk ltd)	1
28130	amoxicillin 3g oral powder sachets sugar free (teva uk ltd)	1
28284	flucloxacillin 125mg/5ml oral solution (teva uk ltd)	1
28289	klaricid iv 500mg powder for solution for infusion vials (mylan)	1
28349	clarosip 125mg granules for oral suspension straws (grunenthal ltd)	1
28544	ciprofloxaxin 400mg/200ml in glucose 5% infusion	1
28562	enteromide 500mg tablet (consolidated chemicals (uk) ltd)	1
28685	rocephin 2g powder for solution for injection vials (roche products ltd)	1

28701	ampicillin 50mg / cloxacillin 25mg/vial injection	1
28722	keflex 250mg/5ml oral suspension (flynn pharma ltd)	1
28870	amoxicillin 125mg/5ml oral suspension (teva uk ltd)	1
28871	co-amoxiclav 250mg/125mg tablets (ivax pharmaceuticals uk ltd)	1
28872	amoxicillin 125mg/5ml mixture (crosspharma ltd)	1
28874	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)	1
28875	amoxicillin 125mg/5ml oral suspension (ranbaxy (uk) ltd)	1
28882	amoxicillin 250mg capsule (crosspharma ltd)	1
28919	ampicillin 250mg / cloxacillin 250mg/vial injection	1
29154	erythromycin 250mg capsule (actavis uk ltd)	1
29183	cefuroxime 750mg with metronidazole 500mg infusion	1
29202	cefalexin 500mg tablets (a a h pharmaceuticals ltd)	1
29281	cefalexin 500mg capsules (teva uk ltd)	1
29337	amoxicillin 125mg/5ml oral solution (neo laboratories ltd)	1
29343	ciprofloxacin 250mg tablets (a a h pharmaceuticals ltd)	1
29344	erythromycin 250mg gastro-resistant tablets (actavis uk ltd)	1
29351	trimethoprim 50mg/5ml oral suspension sugar free (teva uk ltd)	1
29353	co-amoxiclav 500mg/125mg tablets (teva uk ltd)	1
29356	co-amoxiclav 500mg/125mg tablets (ivax pharmaceuticals uk ltd)	1
29357	sulphadimethoxine 500mg tablet	1
29458	ciprofloxacin 500mg tablets (a a h pharmaceuticals ltd)	1
29463	amoxicillin 500mg capsules (ivax pharmaceuticals uk ltd)	1
29464	cefalexin 250mg/5ml oral suspension (mylan)	1
29472	ciprofloxacin 750mg tablets (a a h pharmaceuticals ltd)	1
29507	ciprofloxacin 400mg/200ml in sodium chloride 0.9% infusion	1
29532	trimogal 100mg tablet (lagap)	1
29671	flucloxacillin iv 500mg/vial injection	1
29697	amopen 125mg/5ml liquid (yorkshire pharmaceuticals ltd)	1
29748	cefalexin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
29800	phthalylsulfathiazole 500mg tablet	1
29858	amoxicillin 125mg/5ml oral suspension sugar free (sandoz ltd)	1
29907	comox tablet (ivax pharmaceuticals uk ltd)	1
29944	flucloxacillin 250mg capsules (ranbaxy (uk) ltd)	1
29994	sulfaguanidine 500mg tablet	1
30046	claforan 500mg powder for solution for injection vials (sanofi)	1
30177	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)	1
30201	co-trimoxazole 240mg/5ml paediatric mixture (lagap)	1
30234	erythromycin ethylsuccinate 125mg sachets	1
30498	amopen 250mg capsule (yorkshire pharmaceuticals ltd)	1
30520	primacine 125mg/5ml liquid (pinewood healthcare)	1
30528	amoxicillin 250mg capsules (kent pharmaceuticals ltd)	1
30530	ceftazidime with saline 2g infusion	1

30614	sulfamethoxazole 200mg with trimethoprim 40mg/5ml oral suspension	1
30705	co-amoxiclav 500mg/125mg tablets (mylan)	1
30707	ciprofloxacin 500mg tablets (mylan)	1
30739	doxycycline 100mg capsules (teva uk ltd)	1
30743	amoxicillin 250mg capsules (ranbaxy (uk) ltd)	1
30745	amoxicillin 250mg capsules (mylan)	1
30764	co-fluampicil 250mg/250mg capsules (ivax pharmaceuticals uk ltd)	1
30783	co-amoxiclav 250mg/125mg tablets (ranbaxy (uk) ltd)	1
30786	co-amoxiclav 250mg/125mg tablets (a a h pharmaceuticals ltd)	1
30960	kemicetine 1g powder for solution for injection vials (essential pharma ltd)	1
30980	erythromycin ethyl succinate 500mg/5ml oral suspension (kent pharmaceuticals ltd)	1
31000	kefadim 1g injection (eli lilly and company ltd)	1
31014	amoxicillin 125mg/5ml oral suspension sugar free (mylan)	1
31110	keflex 500mg tablets (flynn pharma ltd)	1
31154	ampitrin 500mg capsule (opd pharm)	1
31156	ampitrin 250mg capsule (opd pharm)	1
31174	piperacillin 4g/infusion bottle infusion	1
31227	trimethoprim 200mg tablet (regent laboratories ltd)	1
31281	penbritin 500mg capsules (chemidex pharma ltd)	1
31286	amoxymed 125mg/5ml oral solution (medipharma ltd)	1
31423	amopen 250mg/5ml liquid (yorkshire pharmaceuticals ltd)	1
31428	retcin 250mg tablet (ddsa pharmaceuticals ltd)	1
31463	co-trimoxazole 160mg/800mg/10ml solution for infusion ampoules	1
31471	vidopen 250mg/5ml oral solution (berk pharmaceuticals ltd)	1
31473	vidopen 250mg/vial injection (berk pharmaceuticals ltd)	1
31477	laratrim liquid (lagap)	1
31484	laratrim adult 480mg/5ml liquid (lagap)	1
31514	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (abbott laboratories ltd)	1
31530	erythromycin 250mg gastro-resistant tablets (ranbaxy (uk) ltd)	1
31535	amoxicillin 250mg/5ml oral suspension sugar free (mylan)	1
31571	amoxycillin	1
31661	amoxicillin 250mg capsule (co-pharma ltd)	1
31669	pondocillin 120mg sachets (leo pharma)	1
31689	clarosip 187.5mg granules for oral suspension straws (grunenthal ltd)	1
31690	clarosip 250mg granules for oral suspension straws (grunenthal ltd)	1
31693	vancocin 500mg powder for solution for infusion vials (flynn pharma ltd)	1
31775	flucloxacillin 250mg/5ml oral solution (a a h pharmaceuticals ltd)	1
31801	amoxicillin 500mg capsules (sandoz ltd)	1
31825	cefalexin 250mg tablets (ivax pharmaceuticals uk ltd)	1
31827	cefalexin 500mg tablets (ivax pharmaceuticals uk ltd)	1
31905	trimethoprim with sulfamethoxazole 80mg + 400mg/5ml concentrate for solution for infusion	1
31940	flucloxacillin 250mg/5ml oral solution (lagap)	1

32065	flucloxacillin 250mg/5ml oral solution (teva uk ltd)	1
32066	doxycycline 100mg capsules (mylan)	1
32148	amfipen forte 250mg/5ml oral solution (yamanouchi pharma ltd)	1
32181	cefalexin 125mg/5ml oral suspension (actavis uk ltd)	1
32221	kefadim 2g injection (eli lilly and company ltd)	1
32347	amfipen 125mg/5ml oral solution (yamanouchi pharma ltd)	1
32360	vancomycin 1g powder for solution for infusion (dumex ltd)	1
32361	stafoxil 250mg capsule (yamanouchi pharma ltd)	1
32388	ciproxin 200mg/100ml infusion (bayer plc)	1
32407	rifadin 600mg powder and solvent for solution for infusion vials (sanofi)	1
32419	doxycycline 50mg capsules (teva uk ltd)	1
32441	claforan 2g powder for solution for injection vials (sanofi)	1
32505	amoxycillin	1
32530	ciproxin iv flexibag 400mg/200ml infusion (bayer plc)	1
32564	vancomycin 250mg/vial injection	1
32622	amoxicillin 125mg/5ml oral suspension (mylan)	1
32640	amoxicillin 250mg/5ml oral suspension (ivax pharmaceuticals uk ltd)	1
32642	cefalexin 125mg/5ml oral suspension (kent pharmaceuticals ltd)	1
32643	cefalexin 500mg capsules (a a h pharmaceuticals ltd)	1
32665	galfloxin 500mg capsule (galen ltd)	1
32730	fortum 250mg powder for solution for injection vials (glaxosmithkline uk ltd)	1
32760	ampitrin 125mg/5ml liquid (opd pharm)	1
32872	amoxicillin 250mg capsule (mepra-pharm)	1
32898	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
32901	flucloxacillin 250mg/5ml oral solution (kent pharmaceuticals ltd)	1
32902	erythromycin ethyl succinate 250mg/5ml oral suspension (kent pharmaceuticals ltd)	1
32906	trimethoprim 100mg tablets (a a h pharmaceuticals ltd)	1
32908	trimethoprim 200mg tablets (teva uk ltd)	1
32910	co-amoxiclav 500mg/125mg tablets (sandoz ltd)	1
33109	amrit 125mg/5ml liquid (bhr pharmaceuticals ltd)	1
33110	amrit 250mg/5ml liquid (bhr pharmaceuticals ltd)	1
33112	amrit 500mg capsule (bhr pharmaceuticals ltd)	1
33165	amoxicillin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
33215	ciprofloxacin 200mg/100ml in sodium chloride 0.9% infusion	1
33222	amoxicillin 250mg capsule (lagap)	1
33248	erythromycin 125mg/5ml liquid (ivax pharmaceuticals uk ltd)	1
33304	kerymax 250mg gastro-resistant capsules (kent pharmaceuticals ltd)	1
33329	cefalexin 125mg/5ml oral suspension (teva uk ltd)	1
33334	cefalexin 250mg tablets (a a h pharmaceuticals ltd)	1
33343	amoxicillin 250mg capsules (actavis uk ltd)	1
33383	amoxicillin 3g oral powder sachets sugar free (a a h pharmaceuticals ltd)	1
33570	amoxicillin 250mg/5ml mixture (crosspharma ltd)	1

33671	doxycycline 100mg capsules (kent pharmaceuticals ltd)	1
33685	erythromycin 250mg gastro-resistant tablets (teva uk ltd)	1
33686	erythromycin 250mg gastro-resistant capsules (a a h pharmaceuticals ltd)	1
33689	amoxicillin 250mg/5ml oral suspension (mylan)	1
33690	amoxicillin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
33692	amoxicillin 500mg capsules (a a h pharmaceuticals ltd)	1
33693	co-amoxiclav 250mg/125mg tablets (kent pharmaceuticals ltd)	1
33694	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (mylan)	1
33695	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (mylan)	1
33696	amoxicillin 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
33697	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
33699	amoxicillin 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)	1
33701	co-amoxiclav 500mg/125mg tablets (a a h pharmaceuticals ltd)	1
33703	erythromycin 250mg gastro-resistant tablets (abbott laboratories ltd)	1
33705	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (teva uk ltd)	1
33706	amoxicillin 500mg capsules (kent pharmaceuticals ltd)	1
33794	sulfamethoxazole 400mg with trimethoprim 80mg/5ml oral suspension	1
33802	cefalexin 250mg capsule (berk pharmaceuticals ltd)	1
33840	amoxicillin 500mg powder for solution for injection vials (wockhardt uk ltd)	1
33888	azithromycin 250mg tablets	1
33987	sulfamethoxazole 800mg with trimethoprim 160mg/5ml concentrate solution for infusion	1
33989	ciprofloxacin 250mg tablets (mylan)	1
33993	flucloxacillin 250mg capsules (teva uk ltd)	1
33997	trimethoprim 200mg tablets (ivax pharmaceuticals uk ltd)	1
34001	amoxicillin 500mg capsules (teva uk ltd)	1
34007	flucloxacillin 500mg capsules (teva uk ltd)	1
34042	amoxicillin 250mg capsules (ivax pharmaceuticals uk ltd)	1
34052	flucloxacillin 500mg capsules (ivax pharmaceuticals uk ltd)	1
34057	flucloxacillin 250mg capsules (actavis uk ltd)	1
34130	rifampicin 300mg capsule (approved prescription services ltd)	1
34133	cefalexin 250mg/5ml oral suspension sugar free (teva uk ltd)	1
34175	doxycycline 50mg capsules (a a h pharmaceuticals ltd)	1
34189	erythromycin 250mg tablet (c p pharmaceuticals ltd)	1
34193	vancomycin 250mg capsule (dumex ltd)	1
34194	vancomycin 125mg capsule (dumex ltd)	1
34226	flucloxacillin 500mg capsules (kent pharmaceuticals ltd)	1
34228	ampicillin 250mg capsules (a a h pharmaceuticals ltd)	1
34231	erythromycin 125mg/5ml liquid (berk pharmaceuticals ltd)	1
34232	amoxicillin 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
34234	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (teva uk ltd)	1
34238	amoxicillin 1g powder for solution for injection vials (wockhardt uk ltd)	1
34252	trimethoprim 50mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1

34253	cefalexin 250mg capsules (a a h pharmaceuticals ltd)	1
34259	flucloxacillin 125mg/5ml oral solution (sandoz ltd)	1
34297	co-amoxiclav 250mg/125mg tablets (mylan)	1
34300	doxycycline 100mg capsules (actavis uk ltd)	1
34308	ciprofloxacin 250mg tablets (actavis uk ltd)	1
34313	flucloxacillin 500mg capsules (a a h pharmaceuticals ltd)	1
34322	ciprofloxacin 500mg tablet (niche generics ltd)	1
34330	flucloxacillin 250mg capsules (mylan)	1
34334	erythromycin 250mg gastro-resistant tablets (mylan)	1
34358	co-fluampicil 250mg/250mg capsules (mylan)	1
34364	flucloxacillin 250mg capsules (sandoz ltd)	1
34375	flucloxacillin 250mg capsules (kent pharmaceuticals ltd)	1
34379	trimethoprim 200mg tablets (kent pharmaceuticals ltd)	1
34380	co-fluampicil 250mg/250mg capsules (actavis uk ltd)	1
34384	amoxicillin 125mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)	1
34392	trimethoprim 200mg tablets (actavis uk ltd)	1
34394	clarithromycin 250mg tablets (mylan)	1
34423	doxycycline 100mg capsule (pliva pharma ltd)	1
34435	amoxicillin 250mg capsule (ddsa pharmaceuticals ltd)	1
34448	ciprofloxacin 250mg tablets (niche generics ltd)	1
34455	trimethoprim 200mg tablet (c p pharmaceuticals ltd)	1
34464	flucloxacillin 500mg capsules (actavis uk ltd)	1
34478	ciprofloxacin 250mg tablets (teva uk ltd)	1
34479	erythromycin 250mg gastro-resistant tablets (sovereign medical ltd)	1
34488	trimethoprim 100mg tablets (kent pharmaceuticals ltd)	1
34493	co-amoxiclav 500mg/125mg tablets (ranbaxy (uk) ltd)	1
34494	ciprofloxacin 500mg tablets (wockhardt uk ltd)	1
34512	erythromycin 250mg gastro-resistant capsules (teva uk ltd)	1
34533	clarithromycin 250mg tablets (teva uk ltd)	1
34542	trimethoprim 100mg tablets (teva uk ltd)	1
34559	ciprofloxacin 250mg tablets (sandoz ltd)	1
34594	doxycycline 100mg capsule (neo laboratories ltd)	1
34605	ciprofloxacin 500mg tablets (actavis uk ltd)	1
34608	clarithromycin 500mg tablets (mylan)	1
34617	flucloxacillin 500mg capsules (sandoz ltd)	1
34633	trimethoprim 200mg tablets (sandoz ltd)	1
34638	amoxicillin 125mg/5ml oral suspension sugar free (teva uk ltd)	1
34647	ciprofloxacin 250mg tablet (neo laboratories ltd)	1
34650	clarithromycin 250mg tablets (a a h pharmaceuticals ltd)	1
34653	rifampicin 300mg capsules (a a h pharmaceuticals ltd)	1
34655	ciprofloxacin 250mg tablets (wockhardt uk ltd)	1
34679	amoxicillin 125mg/5ml oral suspension sugar free (actavis uk ltd)	1

34680	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)	1
34683	flucloxacillin 125mg/5ml oral solution (mylan)	1
34694	ciprofloxacin 250mg tablets (pliva pharma ltd)	1
34701	flucloxacillin 125mg/5ml oral solution (ivax pharmaceuticals uk ltd)	1
34714	amoxicillin 250mg capsule (neo laboratories ltd)	1
34721	flucloxacillin 250mg capsules (ivax pharmaceuticals uk ltd)	1
34727	co-trimoxazole 80mg/400mg tablets (actavis uk ltd)	1
34734	co-amoxiclav 250mg/125mg tablets (teva uk ltd)	1
34760	amoxicillin 250mg/5ml oral suspension (actavis uk ltd)	1
34765	doxycycline 50mg capsules (mylan)	1
34766	flucloxacillin 125mg/5ml oral solution (kent pharmaceuticals ltd)	1
34775	amoxicillin 250mg/5ml oral suspension sugar free (teva uk ltd)	1
34776	flucloxacillin 500mg capsules (mylan)	1
34779	erythromycin ethyl succinate 125mg/5ml oral suspension (sandoz ltd)	1
34795	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)	1
34805	vancomycin 125mg capsules (actavis uk ltd)	1
34811	clarithromycin 250mg/5ml oral suspension (ranbaxy (uk) ltd)	1
34837	erythromycin 250mg gastro-resistant tablet (co-pharma ltd)	1
34848	flucloxacillin 500mg capsule (c p pharmaceuticals ltd)	1
34852	amoxicillin 500mg capsules (ranbaxy (uk) ltd)	1
34853	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (teva uk ltd)	1
34855	amoxicillin 250mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)	1
34857	amoxicillin 125mg/5ml oral suspension (actavis uk ltd)	1
34869	erythromycin 500mg tablet (c p pharmaceuticals ltd)	1
34870	flucloxacillin 250mg capsule (c p pharmaceuticals ltd)	1
34873	erythromycin 250mg tablet (berk pharmaceuticals ltd)	1
34878	trimethoprim 100mg tablet (c p pharmaceuticals ltd)	1
34885	amoxicillin 500mg capsule (ddsa pharmaceuticals ltd)	1
34912	amoxicillin 500mg capsule (neo laboratories ltd)	1
34944	flucloxacillin 250mg capsule (co-pharma ltd)	1
34972	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (sandoz ltd)	1
34973	ciprofloxacin 750mg tablet (niche generics ltd)	1
34974	clarithromycin 500mg tablets (teva uk ltd)	1
35191	co-amoxiclav 500mg/100mg powder for solution for injection vials (teva uk ltd)	1
35570	amoxicillin 500mg capsule (crosspharma ltd)	1
36054	amoxicillin 125mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)	1
36330	cefalexin 250mg tablets (actavis uk ltd)	1
36357	rimactane 300mg capsules (sandoz ltd)	1
36514	arpimycin 250mg/5ml oral suspension (rosemont pharmaceuticals ltd)	1
36544	arpimycin 125mg/5ml oral suspension (rosemont pharmaceuticals ltd)	1
36569	cefalexin 500mg capsules (kent pharmaceuticals ltd)	1
36578	cefalexin 125mg/5ml oral suspension (ranbaxy (uk) ltd)	1

36599	cefalexin 250mg capsules (ranbaxy (uk) ltd)	1
36622	monotrim 50mg/5ml oral suspension (chemidex pharma ltd)	1
36667	kefadim 2g infusion (eli lilly and company ltd)	1
36701	cefalexin 250mg tablets (mylan)	1
37022	arpimycin 500mg/5ml liquid (rosemont pharmaceuticals ltd)	1
37304	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)	1
37485	penbritin 125mg/5ml syrup (chemidex pharma ltd)	1
37681	erythrocin iv lactobionate 1g powder for solution for infusion vials (amco)	1
37694	erythromycin estolate 500mg tablets	1
37755	amoxicillin 250mg/5ml oral suspension (sandoz ltd)	1
37796	erythromycin estolate 125mg/5ml suspension	1
37857	cefuroxime 1.5g with 500mg infusion	1
38006	ciproxin 400mg/200ml infusion (bayer plc)	1
38090	co-trimoxazole 480mg/5ml adult mixture (lagap)	1
38091	penbritin forte 250mg/5ml syrup (chemidex pharma ltd)	1
38163	clarithromycin 500mg tablets (a a h pharmaceuticals ltd)	1
38171	ciprofloxacin 200mg/100ml infusion bags	1
38661	rimactane 150mg capsules (sandoz ltd)	1
38684	amoxicillin 500mg capsule (c p pharmaceuticals ltd)	1
38997	klaricid paediatric 125mg/5ml oral suspension (mylan)	1
39010	klaricid paediatric 250mg/5ml oral suspension (mylan)	1
39020	rifinah 300mg/150mg tablets (sanofi)	1
39118	primacine 250mg/5ml liquid (pinewood healthcare)	1
39194	rifinah 150mg/100mg tablets (sanofi)	1
39417	cefalexin 125mg/5ml oral suspension (mylan)	1
39613	erythrocin 500 tablets (amdipharm plc)	1
39616	erythrocin 250 tablets (amdipharm plc)	1
39623	erythroped pi sf 125mg/5ml oral suspension (amco)	1
39632	erythroped a 500mg tablets (amco)	1
39642	erythroped forte sf 500mg/5ml oral suspension (amco)	1
39669	erythroped sf 250mg/5ml oral suspension (amco)	1
39913	ciprofloxacin 100mg tablets (sandoz ltd)	1
39933	trimethoprim 200mg tablets (almus pharmaceuticals ltd)	1
39989	floxapen 250mg capsules (actavis uk ltd)	1
40025	floxapen 500mg capsules (actavis uk ltd)	1
40073	erythromycin estolate 250mg/5ml suspension	1
40108	flucloxacillin 250mg capsules (almus pharmaceuticals ltd)	1
40142	flucloxacillin iv 250mg/vial injection	1
40148	co-amoxiclav 500mg/125mg tablets (kent pharmaceuticals ltd)	1
40155	cefotaxime 1g/vial injection (c p pharmaceuticals ltd)	1
40168	amoxicillin 3g oral powder sachets sugar free (kent pharmaceuticals ltd)	1
40218	azithromycin 500mg tablets (teva uk ltd)	1

40238	amoxicillin 250mg/5ml mixture (mepra-pharm)	1
40243	amoxicillin 250mg/5ml oral suspension sugar free (actavis uk ltd)	1
40320	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)	1
40391	doxycycline 50mg capsules (ivax pharmaceuticals uk ltd)	1
40747	cefalexin 250mg chewable tablets	1
40784	clarithromycin 500mg tablets (sandoz ltd)	1
40796	doxycycline 40mg modified-release capsules	1
40884	ceporex 250mg capsules (strides shasun (uk) ltd)	1
40914	ceporex 500mg tablets (strides shasun (uk) ltd)	1
40915	ceporex 500mg capsules (strides shasun (uk) ltd)	1
40945	ceporex 250mg/5ml syrup (strides shasun (uk) ltd)	1
40980	efracea 40mg modified-release capsules (galderma (uk) ltd)	1
41049	ceporex 250mg tablets (strides shasun (uk) ltd)	1
41090	amoxicillin 250mg/5ml oral suspension (almus pharmaceuticals ltd)	1
41106	ceporex 125mg/5ml syrup (strides shasun (uk) ltd)	1
41163	flucloxacillin 125mg/5ml oral solution sugar free	1
41172	flucloxacillin 250mg/5ml oral solution sugar free	1
41192	cefalexin 250mg/5ml oral suspension (ranbaxy (uk) ltd)	1
41230	ceporex 500mg/5ml syrup (strides shasun (uk) ltd)	1
41389	erythoden 250mg/5ml liquid (stevenden healthcare)	1
41394	cefotaxime 500mg/vial injection (c p pharmaceuticals ltd)	1
41415	co-fluampicil 250mg/250mg capsules (kent pharmaceuticals ltd)	1
41453	clarithromycin 125mg/5ml oral suspension (ranbaxy (uk) ltd)	1
41544	trimethoprim 100mg tablet (ivax pharmaceuticals uk ltd)	1
41560	doxycycline 100mg capsule (ivax pharmaceuticals uk ltd)	1
41561	ciprofloxacin 250mg tablets (ivax pharmaceuticals uk ltd)	1
41579	co-trimoxazole 80mg/400mg tablets (a a h pharmaceuticals ltd)	1
41584	erythromycin 250mg/5ml liquid (ivax pharmaceuticals uk ltd)	1
41604	erythromycin 500mg tablet (hillcross pharmaceuticals ltd)	1
41605	doxycycline 100mg capsule (sandoz ltd)	1
41646	ampicillin 250mg capsule (berk pharmaceuticals ltd)	1
41647	ampicillin 500mg capsules (actavis uk ltd)	1
41734	amoxicillin 3g powder (actavis uk ltd)	1
41736	cefalexin 250mg capsules (kent pharmaceuticals ltd)	1
41744	ampicillin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
41818	amoxicillin 125mg/5ml oral solution (berk pharmaceuticals ltd)	1
41825	cefalexin 250mg/5ml oral solution (c p pharmaceuticals ltd)	1
41835	amoxicillin 125mg powder (ivax pharmaceuticals uk ltd)	1
41967	co-trimoxazole 240mg/5ml oral suspension (hillcross pharmaceuticals ltd)	1
41968	cefalexin 250mg/5ml oral suspension (teva uk ltd)	1
41978	co-trimoxazole 240mg/5ml oral suspension (approved prescription services ltd)	1
41982	fortum 2g/vial powder for solution for injection (glaxo laboratories ltd)	1

41991	co-trimoxazole 80mg+400mg dispersible tablet (approved prescription services ltd)	1
42008	cefalexin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
42070	kefadim 1g powder for solution for injection vials (flynn pharma ltd)	1
42174	ciprofloxacin 500mg tablets (ivax pharmaceuticals uk ltd)	1
42227	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
42240	amoxicillin 125mg/5ml oral solution (co-pharma ltd)	1
42296	erythromycin 250mg gastro-resistant tablets (dr reddy's laboratories (uk) ltd)	1
42485	clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension	1
42496	rifampicin 300mg/vial infusion	1
42507	ciprofloxacin 100mg tablets (a a h pharmaceuticals ltd)	1
42517	co-trimoxazole 40mg+200mg liquid (celltech pharma europe ltd)	1
42545	amoxicillin 125mg/5ml oral suspension (almus pharmaceuticals ltd)	1
42659	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (abbott laboratories ltd)	1
42661	erythromycin 250mg gastro-resistant tablets (almus pharmaceuticals ltd)	1
42688	vancocin 1g powder for solution for infusion vials (flynn pharma ltd)	1
42732	amoxicillin 250mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)	1
42809	amoxicillin 250mg capsule (c p pharmaceuticals ltd)	1
42815	amoxicillin 250mg/5ml mixture (celltech pharma europe ltd)	1
42822	amoxicillin 125mg/5ml mixture (celltech pharma europe ltd)	1
43229	amoxicillin 125mg/5ml oral suspension (sandoz ltd)	1
43262	co-trimoxazole 240mg/5ml oral suspension (c p pharmaceuticals ltd)	1
43274	cefotaxime 2g/vial injection (c p pharmaceuticals ltd)	1
43400	clamelle 500mg tablets (actavis uk ltd)	1
43505	trimethoprim 200mg tablet (numark management ltd)	1
43509	sulfadiazine 500mg tablets (wockhardt uk ltd)	1
43517	ciprofloxacin 750mg tablets (actavis uk ltd)	1
43537	trimethoprim 200mg tablet (celltech pharma europe ltd)	1
43545	trimethoprim 100mg tablets (actavis uk ltd)	1
43546	flucloxacillin 125mg/5ml oral solution (actavis uk ltd)	1
43548	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
43557	ciprofloxacin 500mg tablets (pliva pharma ltd)	1
43797	ciprofloxacin 500mg tablets (sandoz ltd)	1
43814	ciprofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)	1
44075	septrin tablets (aspen pharma trading ltd)	1
44154	co-amoxiclav 500mg/125mg tablets (zentiva)	1
44241	fectrim dispersible tablet (ddsa pharmaceuticals ltd)	1
44286	septrin paediatric 40mg/200mg/5ml oral suspension (aspen pharma trading ltd)	1
44755	cefalexin 500mg capsule (berk pharmaceuticals ltd)	1
44854	amoxicillin 500mg capsule (lagap)	1
44855	flucloxacillin 500mg capsules (ranbaxy (uk) ltd)	1
45221	cefalexin 250mg/5ml oral suspension (actavis uk ltd)	1
45237	co-fluampicil 500mg with 500mg injection	1

45246	trimethoprim 100mg tablets (sandoz ltd)	1
45252	flucloxacillin 500mg capsule (co-pharma ltd)	1
45267	amoxicillin 250mg capsule (regent laboratories ltd)	1
45285	ciprofloxacin 500mg tablets (teva uk ltd)	1
45312	flucloxacillin 125mg/5ml liquid (lagap)	1
45317	amoxicillin 250mg/5ml oral solution (neo laboratories ltd)	1
45341	ciprofloxacin 500mg tablet (neo laboratories ltd)	1
45591	clarie xl 500mg tablets (teva uk ltd)	1
45757	trimethoprim with sulfamethoxazole 16mg + 80mg/ml concentrate for solution for infusion	1
45795	clarithromycin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
45870	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (pinewood healthcare)	1
46154	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (abbott laboratories ltd)	1
46175	ampicillin 125mg/5ml oral suspension (hillcross pharmaceuticals ltd)	1
46488	clarithromycin 500mg tablets (ranbaxy (uk) ltd)	1
46663	bactrim paediatric tablets (roche products ltd)	1
46695	azithromycin 500mg tablet (hillcross pharmaceuticals ltd)	1
46696	erythromycin ethyl succinate 250mg/5ml oral suspension (sandoz ltd)	1
46807	doxycycline 100mg capsules (almus pharmaceuticals ltd)	1
46915	co-amoxiclav 250mg/125mg tablets (zentiva)	1
46917	rifampicin 300mg capsules (mylan)	1
46918	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (sandoz ltd)	1
47125	flucloxacillin 125mg/5ml oral solution sugar free (actavis uk ltd)	1
47126	erythromycin ethyl succinate 125mg/5ml oral suspension (pinewood healthcare)	1
47163	cefalexin 250mg tablets (arrow generics ltd)	1
47184	co-amoxiclav 500mg/100mg powder for solution for injection vials (wockhardt uk ltd)	1
47242	erythromycin 250mg/5ml liquid (c p pharmaceuticals ltd)	1
47582	clarithromycin 250mg tablets (sandoz ltd)	1
47640	amoxicillin 500mg capsules (almus pharmaceuticals ltd)	1
47676	erythromycin 500mg/5ml liquid (c p pharmaceuticals ltd)	1
47785	ciprofloxacin 400mg/200ml infusion bags	1
47983	cefuroxime 250mg tablets (a a h pharmaceuticals ltd)	1
47993	cefuroxime (as axetil) 500mg tablets	1
48006	amoxicillin 250mg capsules (sandoz ltd)	1
48017	erythoden 125mg/5ml liquid (stevenden healthcare)	1
48023	clarithromycin 500mg tablets (actavis uk ltd)	1
48031	ciprofloxacin 100mg tablets (almus pharmaceuticals ltd)	1
48038	amoxicillin 125mg/5ml oral suspension (kent pharmaceuticals ltd)	1
48095	doxycycline 50mg capsules (actavis uk ltd)	1
48101	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (focus pharmaceuticals ltd)	1
48147	co-amoxiclav 250mg/125mg tablets (almus pharmaceuticals ltd)	1
48163	clarithromycin 250mg tablets (actavis uk ltd)	1
48683	augmentin 375mg tablets (lexon (uk) ltd)	1

49048	augmentin 375mg tablets (waymade healthcare plc)	1
49063	augmentin 375mg tablets (de pharmaceuticals)	1
49065	amoxicillin 250mg/5ml oral suspension sugar free (bristol laboratories ltd)	1
49301	erythrolar 500mg tablets (ennogen pharma ltd)	1
49321	augmentin 625mg tablets (sigma pharmaceuticals plc)	1
49349	flucloxacillin 125mg/5ml oral solution sugar free (kent pharmaceuticals ltd)	1
49374	augmentin 375mg tablets (mawdsley-brooks & company ltd)	1
49445	ciprofloxacin 500mg tablets (almus pharmaceuticals ltd)	1
49530	azithromycin 200mg/5ml oral suspension (sandoz ltd)	1
49590	amoxil 500mg capsules (lexon (uk) ltd)	1
49592	trimethoprim 100mg tablets (phoenix healthcare distribution ltd)	1
49610	co-amoxiclav 500mg/125mg tablets (medreich plc)	1
49656	augmentin 625mg tablets (lexon (uk) ltd)	1
49683	augmentin 625mg tablets (waymade healthcare plc)	1
49724	tazocin 4.5g powder for solution for infusion vials (pfizer ltd)	1
49737	doxycycline 100mg capsules (alliance healthcare (distribution) ltd)	1
49839	ciproxin 500mg tablets (waymade healthcare plc)	1
49939	clarithromycin 500mg tablets (alliance healthcare (distribution) ltd)	1
49952	erythromycin 250mg gastro-resistant capsules (phoenix healthcare distribution ltd)	1
49978	erythromycin ethyl succinate 125mg/5ml oral suspension (focus pharmaceuticals ltd)	1
50002	amoxicillin 125mg/5ml oral suspension (bristol laboratories ltd)	1
50055	ciprofloxacin 500mg tablets (de pharmaceuticals)	1
50120	trimethoprim 200mg tablets (accord healthcare ltd)	1
50205	erythrolar 250mg tablets (ennogen pharma ltd)	1
50223	erythrocin 500 tablets (stephar (u.k.) ltd)	1
50279	augmentin 625mg tablets (de pharmaceuticals)	1
50341	co-amoxiclav 500mg/125mg tablets (alliance healthcare (distribution) ltd)	1
50446	co-amoxiclav 250mg/125mg tablets (phoenix healthcare distribution ltd)	1
50580	erythromycin 250mg gastro-resistant capsules (actavis uk ltd)	1
50595	augmentin 125/31 sf oral suspension (mawdsley-brooks & company ltd)	1
50601	ciprofloxacin 250mg tablets (accord healthcare ltd)	1
50693	erythrocin 500 tablets (sigma pharmaceuticals plc)	1
50694	erythromycin 250mg gastro-resistant capsules (alliance healthcare (distribution) ltd)	1
50729	flucloxacillin 250mg/5ml oral solution (de pharmaceuticals)	1
50742	co-amoxiclav 500mg/125mg tablets (actavis uk ltd)	1
50797	trimethoprim 200mg tablets (alliance healthcare (distribution) ltd)	1
50820	flucloxacillin 500mg capsules (medreich plc)	1
50946	clarithromycin 250mg tablets (sigma pharmaceuticals plc)	1
50948	erythromycin ethyl succinate 125mg/5ml oral suspension (phoenix healthcare distribution ltd)	1
51037	flucloxacillin 250mg capsules (alliance healthcare (distribution) ltd)	1
51154	clarithromycin 250mg tablets (kent pharmaceuticals ltd)	1
51164	augmentin 125/31 sf oral suspension (waymade healthcare plc)	1

51194	augmentin-duo 400/57 oral suspension (sigma pharmaceuticals plc)	1
51262	flucloxacillin 125mg/5ml oral solution (alliance healthcare (distribution) ltd)	1
51382	amoxicillin 250mg/5ml oral suspension (phoenix healthcare distribution ltd)	1
51426	clarithromycin 500mg tablets (accord healthcare ltd)	1
51436	amoxil 500mg capsules (mawdsley-brooks & company ltd)	1
51510	trimethoprim 200mg tablets (bristol laboratories ltd)	1
51536	amoxicillin 250mg capsules (milpharm ltd)	1
51537	ciprofloxacin 250mg tablets (alliance healthcare (distribution) ltd)	1
51623	co-amoxiclav 250mg/125mg tablets (alliance healthcare (distribution) ltd)	1
51637	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
51678	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)	1
51725	trimethoprim 20mg/5ml oral suspension	1
51830	flucloxacillin 250mg/5ml oral solution sugar free (accord healthcare ltd)	1
51831	clarithromycin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)	1
51984	erythrocin 500 tablets (mawdsley-brooks & company ltd)	1
52029	zithromax 250mg capsules (mawdsley-brooks & company ltd)	1
52058	amoxicillin 500mg capsules (medreich plc)	1
52099	ciprofloxacin 750mg tablets (bristol laboratories ltd)	1
52122	amoxicillin 125mg/5ml oral suspension sugar free (bristol laboratories ltd)	1
52158	clarithromycin 250mg tablets (alliance healthcare (distribution) ltd)	1
52177	ciproxin 500mg tablets (sigma pharmaceuticals plc)	1
52198	co-trimoxazole 80mg/400mg tablets (sigma pharmaceuticals plc)	1
52207	augmentin 625mg tablets (mawdsley-brooks & company ltd)	1
52281	flucloxacillin 500mg capsules (milpharm ltd)	1
52282	cefalexin 250mg capsules (milpharm ltd)	1
52283	cefalexin 250mg capsules (arrow generics ltd)	1
52309	ciprofloxacin 100mg tablets (sigma pharmaceuticals plc)	1
52340	cloxacillin 30mg with ampicillin 60mg/0.6ml suspension	1
52353	ciproxin 250mg tablets (de pharmaceuticals)	1
52374	flucloxacillin 500mg capsules (almus pharmaceuticals ltd)	1
52411	klaricid 250mg tablets (necessity supplies ltd)	1
52428	erythromycin 250mg gastro-resistant tablets (phoenix healthcare distribution ltd)	1
52501	ciprofloxacin 500mg tablets (accord healthcare ltd)	1
52549	flucloxacillin 250mg/5ml oral solution (phoenix healthcare distribution ltd)	1
52616	ciprofloxacin 500mg tablets (arrow generics ltd)	1
52666	augmentin 250/62 sf oral suspension (sigma pharmaceuticals plc)	1
52669	trimethoprim 200mg/5ml oral solution	1
52685	amoxicillin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)	1
52719	clarithromycin 250mg tablets (apotex uk ltd)	1
52771	amoxicillin 500mg capsules (bristol laboratories ltd)	1
52807	ciproxin 500mg tablets (mawdsley-brooks & company ltd)	1
52820	amoxicillin 500mg capsules (alliance healthcare (distribution) ltd)	1

52851	cefalexin 500mg capsules (alliance healthcare (distribution) ltd)	1
52857	amoxicillin 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)	1
52860	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
52906	erythromycin 250mg gastro-resistant tablets (alliance healthcare (distribution) ltd)	1
52945	ciprofloxacin 200mg/100ml solution for infusion vials	1
52952	erythromycin 250mg gastro-resistant tablets (strides shasun (uk) ltd)	1
52967	vibramycin-d 100mg dispersible tablets (stephar (u.k.) ltd)	1
52990	vancomycin 125mg/5ml oral suspension	1
53004	erythrocin 500 tablets (necessity supplies ltd)	1
53078	amoxicillin 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
53086	clarithromycin 250mg tablets (de pharmaceuticals)	1
53088	ciprofloxacin 500mg tablets (dr reddy's laboratories (uk) ltd)	1
53109	clarithromycin 500mg tablets (somex pharma)	1
53135	vibramycin-d 100mg dispersible tablets (waymade healthcare plc)	1
53144	clarithromycin 250mg tablets (wockhardt uk ltd)	1
53153	clarithromycin 250mg tablets (phoenix healthcare distribution ltd)	1
53168	clarithromycin 125mg/5ml oral suspension (sandoz ltd)	1
53179	clarithromycin 250mg/5ml oral suspension (sandoz ltd)	1
53270	chloramphenicol intrathecal (huddersfield royal infirmary)	1
53275	trimethoprim 50mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
53276	trimethoprim 50mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)	1
53284	trimethoprim 50mg/5ml oral suspension sugar free (sigma pharmaceuticals plc)	1
53310	doxycycline 100mg capsules (sigma pharmaceuticals plc)	1
53398	clarithromycin 500mg powder for concentrate for solution for infusion vials (mercury pharma group ltd)	1
53449	erythrocin 500 tablets (lexon (uk) ltd)	1
53519	ciproxin 250mg tablets (lexon (uk) ltd)	1
53599	trimethoprim 200mg tablets (phoenix healthcare distribution ltd)	1
53609	co-amoxiclav 500mg/125mg tablets (apc pharmaceuticals & chemicals (europe) ltd)	1
53627	amoxicillin 500mg capsules (accord healthcare ltd)	1
53641	ciprofloxacin 500mg tablets (strides shasun (uk) ltd)	1
53673	levofloxacin 500mg/100ml infusion bags	1
53681	vancomycin powder	1
53688	clarithromycin 250mg tablets (ranbaxy (uk) ltd)	1
53703	clarithromycin 500mg tablets (kent pharmaceuticals ltd)	1
53715	clarithromycin 500mg tablets (almus pharmaceuticals ltd)	1
53720	trimethoprim 100mg tablets (almus pharmaceuticals ltd)	1
53776	clarithromycin 500mg tablets (de pharmaceuticals)	1
53793	trimethoprim 50mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)	1
53828	trimethoprim 50mg/5ml oral suspension sugar free (actavis uk ltd)	1
53850	azithromycin 200mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
53851	flucloxacillin 250mg powder for solution for injection vials (wockhardt uk ltd)	1
53875	clarithromycin 500mg tablets (tillomed laboratories ltd)	1

53878	ciprofloxacin 500mg tablets (ranbaxy (uk) ltd)	1
53884	vancomycin 500mg powder for concentrate for solution for infusion vials (pfizer ltd)	1
53924	amoxicillin 250mg/5ml oral suspension (sigma pharmaceuticals plc)	1
53942	amoxicillin 125mg / clavulanic acid 62.5mg/5ml oral suspension	1
53945	cefalexin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
53946	sulfadiazine 500mg tablets (alliance healthcare (distribution) ltd)	1
53973	doxycycline 50mg capsules (alliance healthcare (distribution) ltd)	1
53986	erythromycin 250mg gastro-resistant tablets (medreich plc)	1
53996	co-amoxiclav 500mg/125mg tablets (aurobindo pharma ltd)	1
54052	co-amoxiclav 125mg/31mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
54098	erythroped a 500mg tablets (lexon (uk) ltd)	1
54166	sulfadiazine oral solution	1
54185	amoxicillin 250mg capsules (wockhardt uk ltd)	1
54208	clarithromycin 250mg/5ml oral suspension (sigma pharmaceuticals plc)	1
54222	amoxicillin 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
54241	clarithromycin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
54269	clarithromycin 250mg tablets (somex pharma)	1
54271	amoxicillin 250mg capsules (mawdsley-brooks & company ltd)	1
54302	ciprofloxacin 250mg tablets (medreich plc)	1
54324	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (actavis uk ltd)	1
54393	ciprofloxacin 250mg tablets (arrow generics ltd)	1
54452	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
54471	ampicillin 250mg capsules (kent pharmaceuticals ltd)	1
54472	clarithromycin 250mg tablets (accord healthcare ltd)	1
54491	amoxicillin 250mg capsules (bristol laboratories ltd)	1
54529	clarithromycin 500mg modified-release tablet (hillcross pharmaceuticals ltd)	1
54555	ciprofloxacin 100mg tablets (de pharmaceuticals)	1
54591	co-amoxiclav 500mg/125mg tablets (phoenix healthcare distribution ltd)	1
54663	ciproxin infusion 200mg/100ml solution for infusion bottles (bayer plc)	1
54674	ciprofloxacin 100mg tablets (phoenix healthcare distribution ltd)	1
54701	ciprofloxacin 250mg tablets (bristol laboratories ltd)	1
54708	co-amoxiclav 250mg/62mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
54725	amoxicillin 500mg capsules (milpharm ltd)	1
54732	co-amoxiclav 125mg/31mg/5ml oral suspension (mylan)	1
54780	co-amoxiclav 250mg/62mg/5ml oral suspension (mylan)	1
54796	amoxicillin 250mg capsules (boston healthcare ltd)	1
54808	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)	1
54864	cefalexin 250mg capsules (alliance healthcare (distribution) ltd)	1
54882	clarithromycin 250mg tablets (almus pharmaceuticals ltd)	1
54897	clarithromycin 250mg tablets (tillomed laboratories ltd)	1
54903	clarithromycin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
54907	cloxacillin 250mg with ampicillin 250mg injection	1

54914	co-trimoxazole 80mg/400mg tablets (kent pharmaceuticals ltd)	1
54953	clarithromycin 500mg powder for concentrate for solution for infusion vials (martindale pharmaceuticals ltd)	1
54955	cefalexin 500mg capsules (milpharm ltd)	1
54993	ciprofloxacin 400mg/200ml solution for infusion vials	1
55018	amoxicillin 250mg/5ml oral suspension (bristol laboratories ltd)	1
55047	amoxicillin 125mg/5ml oral suspension (sandoz ltd)	1
55121	sulfadiazine 500mg tablets (a a h pharmaceuticals ltd)	1
55133	erythromycin 250mg gastro-resistant capsules (kent pharmaceuticals ltd)	1
55148	clarithromycin 250mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
55300	erythromycin 500mg tablet (teva uk ltd)	1
55312	co-amoxiclav 250mg/125mg tablets (waymade healthcare plc)	1
55387	cefuroxime 125mg granules sachets	1
55394	amoxicillin 500mg capsules (wockhardt uk ltd)	1
55397	erythromycin 250mg gastro-resistant capsules (waymade healthcare plc)	1
55428	clarithromycin 250mg/5ml oral suspension (waymade healthcare plc)	1
55438	flucloxacillin 250mg/5ml oral solution sugar free (kent pharmaceuticals ltd)	1
55483	erythromycin 250mg gastro-resistant tablets (milpharm ltd)	1
55499	amoxicillin 250mg/5ml oral suspension (ranbaxy (uk) ltd)	1
55519	doxycycline 100mg capsules (waymade healthcare plc)	1
55527	amoxicillin 500mg capsules (boston healthcare ltd)	1
55589	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
55626	amoxicillin 125mg/5ml oral suspension sugar free (waymade healthcare plc)	1
55708	levofloxacin 250mg tablets (actavis uk ltd)	1
55754	flucloxacillin 125mg/5ml oral solution (waymade healthcare plc)	1
55799	flucloxacillin 500mg capsules (sigma pharmaceuticals plc)	1
55827	chloramphenicol 250mg capsules (a a h pharmaceuticals ltd)	1
55846	ampicillin 125mg/5ml liquid (c p pharmaceuticals ltd)	1
55877	ceftazidime 2g powder for solution for injection vials (genus pharmaceuticals ltd)	1
55895	ceftriaxone 1g powder for solution for injection vials (pliva pharma ltd)	1
55897	ceftazidime 1g powder for solution for injection vials (mylan)	1
55917	ciprofloxacin 500mg tablets (medreich plc)	1
55986	trimethoprim 200mg/5ml oral suspension	1
56012	levofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)	1
56027	flucloxacillin 250mg capsules (sigma pharmaceuticals plc)	1
56075	levofloxacin 500mg/100ml solution for infusion vials	1
56189	flucloxacillin 250mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)	1
56198	vibramycin-d 100mg dispersible tablets (mawdsley-brooks & company ltd)	1
56203	erythroped a 500mg tablets (sigma pharmaceuticals plc)	1
56223	amoxicillin 250mg/5ml oral suspension (sandoz ltd)	1
56259	trimethoprim 100mg tablets (sigma pharmaceuticals plc)	1
56267	trimethoprim 100mg tablets (bristol laboratories ltd)	1
56381	ciprofloxacin 250mg tablets (strides shasun (uk) ltd)	1

56384	flucloxacillin 500mg capsules (bristol laboratories ltd)	1
56439	ciprofloxacin 200mg/100ml solution for infusion vials (a a h pharmaceuticals ltd)	1
56444	ceftriaxone 250mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1
56561	amoxicillin 125mg/5ml oral suspension (waymade healthcare plc)	1
56578	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (waymade healthcare plc)	1
56591	augmentin-duo 400/57 oral suspension (lexon (uk) ltd)	1
56700	amoxil 500mg capsules (necessity supplies ltd)	1
56717	flucloxacillin 500mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1
56789	ciprofloxacin 500mg tablets (apc pharmaceuticals & chemicals (europe) ltd)	1
56856	ciprofloxacin 750mg tablets (ranbaxy (uk) ltd)	1
56884	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)	1
57080	trimethoprim 100mg tablets (waymade healthcare plc)	1
57081	co-amoxiclav 500mg/125mg tablets (waymade healthcare plc)	1
57106	flucloxacillin 250mg capsules (medreich plc)	1
57116	trimethoprim 50mg/5ml oral suspension sugar free (waymade healthcare plc)	1
57118	ciprofloxacin 250mg tablets (kent pharmaceuticals ltd)	1
57178	amoxicillin 3g oral powder sachets sugar free (mawdsley-brooks & company ltd)	1
57267	clarithromycin 125mg/5ml oral suspension (waymade healthcare plc)	1
57292	flucloxacillin 250mg/5ml oral solution sugar free (waymade healthcare plc)	1
57331	flucloxacillin 250mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1
57415	flucloxacillin 125mg/5ml oral solution (phoenix healthcare distribution ltd)	1
57485	flucloxacillin 500mg capsules (alliance healthcare (distribution) ltd)	1
57602	rifinah 300mg/150mg tablets (sigma pharmaceuticals plc)	1
57634	flucloxacillin 250mg capsules (milpharm ltd)	1
57642	trimethoprim 20mg/5ml oral solution	1
57660	clarithromycin 250mg tablets (almus pharmaceuticals ltd)	1
57703	ciprofloxacin 200mg/100ml solution for infusion bottles	1
57833	amoxil 500mg capsules (waymade healthcare plc)	1
57842	cefotaxime 500mg powder for solution for injection vials (genus pharmaceuticals ltd)	1
57886	amoxil 500mg capsules (stephar (u.k.) ltd)	1
57960	ciprofloxacin 500mg tablets (tillomed laboratories ltd)	1
57966	amoxicillin 250mg capsules (medreich plc)	1
57981	trimethoprim 200mg tablets (waymade healthcare plc)	1
57997	ampicillin 250mg capsules (waymade healthcare plc)	1
58021	ciprofloxacin 100mg tablets (dr reddy's laboratories (uk) ltd)	1
58037	clarithromycin 500mg tablets (almus pharmaceuticals ltd)	1
58053	amoxicillin 250mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)	1
58057	amoxicillin 250mg/5ml oral suspension sugar free (sandoz ltd)	1
58074	ciprofloxacin 400mg/200ml solution for infusion bottles	1
58097	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)	1
58126	flucloxacillin sodium 125mg/5ml oral suspension	1
58175	clarithromycin 500mg tablets (wockhardt uk ltd)	1

58205	amoxicillin 500mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1
58206	azithromycin 250mg tablets (teva uk ltd)	1
58235	ciprofloxacin 250mg tablets (de pharmaceuticals)	1
58239	ceftriaxone 1g powder for solution for injection vials (a a h pharmaceuticals ltd)	1
58246	ciprofloxacin 400mg/200ml infusion bags (pfizer ltd)	1
58252	vancomycin 125mg capsules (a a h pharmaceuticals ltd)	1
58282	co-trimoxazole 80mg/400mg tablets (waymade healthcare plc)	1
58323	ciprofloxacin 100mg tablets (alliance healthcare (distribution) ltd)	1
58326	doxycycline 50mg capsules (waymade healthcare plc)	1
58343	rifinah 300mg/150mg tablets (lexon (uk) ltd)	1
58345	levofloxacin 250mg tablets (mylan)	1
58426	azithromycin 500mg tablets (sandoz ltd)	1
58463	cefuroxime 250mg tablets (sandoz ltd)	1
58490	trimethoprim 100mg tablets (alliance healthcare (distribution) ltd)	1
58494	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (colorama pharmaceuticals ltd)	1
58520	ampicillin 250mg capsules (alliance healthcare (distribution) ltd)	1
58525	ceftriaxone 2g powder for solution for infusion vials	1
58541	flucloxacillin 250mg capsules (bristol laboratories ltd)	1
58608	ciprofloxacin 100mg tablets (bristol laboratories ltd)	1
58623	cefuroxime 250mg tablets (alliance healthcare (distribution) ltd)	1
58756	erythromycin ethyl succinate 125mg/5ml oral suspension (waymade healthcare plc)	1
58760	erythroped a 500mg tablets (necessity supplies ltd)	1
58771	amoxicillin 250mg capsules (de pharmaceuticals)	1
58803	co-amoxiclav 250mg/125mg tablets (apc pharmaceuticals & chemicals (europe) ltd)	1
58806	ceftazidime 500mg powder for solution for injection vials (genus pharmaceuticals ltd)	1
58824	erythromycin 250mg gastro-resistant tablets (kent pharmaceuticals ltd)	1
58841	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)	1
58902	clarithromycin 500mg tablets (phoenix healthcare distribution ltd)	1
58920	cefuroxime 250mg tablets (tillomed laboratories ltd)	1
58940	levofloxacin 250mg tablets (a a h pharmaceuticals ltd)	1
58955	ciprofloxacin 100mg/50ml solution for infusion vials (a a h pharmaceuticals ltd)	1
58963	ceftriaxone 2g powder for solution for infusion vials (kent pharmaceuticals ltd)	1
58988	doxycycline 100mg capsules (phoenix healthcare distribution ltd)	1
59036	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (pinewood healthcare)	1
59042	amoxicillin 250mg capsules (alliance healthcare (distribution) ltd)	1
59068	cefuroxime 250mg tablets (teva uk ltd)	1
59069	cefalexin 250mg tablets (phoenix healthcare distribution ltd)	1
59100	erythromycin 250mg gastro-resistant tablets (waymade healthcare plc)	1
59112	amoxicillin 125mg/5ml oral suspension sugar free (de pharmaceuticals)	1
59126	erythromycin ethyl succinate 125mg/5ml oral suspension (kent pharmaceuticals ltd)	1
59153	amoxicillin 250mg capsules (waymade healthcare plc)	1
59269	cefalexin 250mg capsules (de pharmaceuticals)	1

59391	amoxicillin 125mg/5ml oral suspension (de pharmaceuticals)	1
59406	cefalexin 500mg tablets (waymade healthcare plc)	1
59422	flucloxacillin 500mg powder for solution for injection vials (wockhardt uk ltd)	1
59432	amoxicillin 250mg capsules (accord healthcare ltd)	1
59441	erythromycin ethyl succinate 125mg/5ml oral suspension (de pharmaceuticals)	1
59444	co-trimoxazole 80mg/400mg tablets (alliance healthcare (distribution) ltd)	1
59481	amoxicillin 250mg capsules (phoenix healthcare distribution ltd)	1
59542	vibramycin-d 100mg dispersible tablets (sigma pharmaceuticals plc)	1
59572	ciprofloxacin 500mg tablets (sigma pharmaceuticals plc)	1
59588	co-amoxiclav 125mg/31mg/5ml oral suspension (waymade healthcare plc)	1
59592	amoxicillin 500mg capsules (pfizer ltd)	1
59653	ciproxin infusion 400mg/200ml solution for infusion bottles (bayer plc)	1
59708	ceftriaxone 1g powder for solution for injection vials (genus pharmaceuticals ltd)	1
59740	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)	1
59879	amoxicillin 500mg capsules (de pharmaceuticals)	1
59908	co-amoxiclav 500mg/125mg tablets (de pharmaceuticals)	1
59937	ciprofloxacin 750mg tablets (accord healthcare ltd)	1
60027	amoxicillin 250mg/5ml oral suspension sugar free (de pharmaceuticals)	1
60032	flucloxacillin 125mg/5ml oral solution (milpharm ltd)	1
60034	co-amoxiclav 250mg/125mg tablets (de pharmaceuticals)	1
60039	cefalexin 250mg capsules (waymade healthcare plc)	1
60134	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)	1
60159	doxycycline 100mg capsules (de pharmaceuticals)	1
60190	erythromycin 250mg gastro-resistant tablets (waymade healthcare plc)	1
60202	cefalexin 250mg/5ml oral suspension (kent pharmaceuticals ltd)	1
60216	bactrim 96mg/ml infusion (roche products ltd)	1
60260	flucloxacillin 500mg capsules (de pharmaceuticals)	1
60263	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
60267	amoxicillin 250mg/5ml oral suspension (de pharmaceuticals)	1
60281	co-amoxiclav 125mg/31mg/5ml oral suspension (cst pharma ltd)	1
60308	erythromycin ethyl succinate 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
60330	flucloxacillin 1g powder for solution for injection vials (wockhardt uk ltd)	1
60382	azithromycin 250mg capsules (de pharmaceuticals)	1
60390	flucloxacillin 1g powder for solution for injection vials (a a h pharmaceuticals ltd)	1
60436	ciprofloxacin 250mg tablets (almus pharmaceuticals ltd)	1
60448	co-trimoxazole 80mg/400mg/5ml solution for infusion ampoules (alliance healthcare (distribution) ltd)	1
60593	flucloxacillin 125mg/5ml oral solution (medreich plc)	1
60749	vancomycin 1g powder for solution for infusion vials (a a h pharmaceuticals ltd)	1
60805	clarithromycin 500mg tablets (waymade healthcare plc)	1
60808	trimethoprim 50mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)	1
60814	azithromycin 500mg tablets (de pharmaceuticals)	1
60817	levofloxacin 500mg tablets (actavis uk ltd)	1

60828	erythromycin 250mg gastro-resistant tablets (bristol laboratories ltd)	1
61001	clarithromycin 125mg/5ml oral suspension (kent pharmaceuticals ltd)	1
61207	amoxicillin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
61264	erythromycin 250mg gastro-resistant tablets (de pharmaceuticals)	1
61268	cefuroxime 250mg tablets (waymade healthcare plc)	1
61299	co-amoxiclav 125mg/31mg/5ml oral suspension (mawdsley-brooks & company ltd)	1
61302	ciprofloxacin 100mg tablets (almus pharmaceuticals ltd)	1
61355	doxycycline 50mg capsules (chanelle medical uk ltd)	1
61407	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (colorama pharmaceuticals ltd)	1
61560	voractiv tablets (thornton & ross ltd)	1
61561	erythromycin ethyl succinate 250mg/5ml oral suspension (waymade healthcare plc)	1
61612	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (waymade healthcare plc)	1
61661	cefalexin 125mg/5ml oral suspension (waymade healthcare plc)	1
61714	trimethoprim 50mg/5ml oral suspension sugar free (pinewood healthcare)	1
61783	ciprofloxacin 250mg tablets (waymade healthcare plc)	1
61810	azithromycin 500mg tablets (a a h pharmaceuticals ltd)	1
61830	clarithromycin 125mg/5ml oral suspension (sigma pharmaceuticals plc)	1
61850	levofloxacin 500mg tablets (a a h pharmaceuticals ltd)	1
61860	cefuroxime 50mg powder for solution for injection vials	1
61869	ciproxin 250mg/5ml oral suspension (waymade healthcare plc)	1
61881	ceftazidime 500mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1
61896	flucloxacillin 125mg/5ml oral solution sugar free (waymade healthcare plc)	1
61906	amoxicillin 500mg capsules (mawdsley-brooks & company ltd)	1
62008	doxycycline 50mg capsules (de pharmaceuticals)	1
62025	doxycycline 100mg capsules (chanelle medical uk ltd)	1
62074	amoxicillin 250mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
62102	amoxicillin 250mg/5ml oral suspension (waymade healthcare plc)	1
62143	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (de pharmaceuticals)	1
62188	cefalexin 250mg capsules (phoenix healthcare distribution ltd)	1
62332	co-amoxiclav 875mg/125mg tablets	1
62442	amoxicillin 250mg/5ml oral suspension sugar free (waymade healthcare plc)	1
62466	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
62597	augmentin-duo 400/57 oral suspension (mawdsley-brooks & company ltd)	1
62630	trimethoprim 200mg tablets (ranbaxy (uk) ltd)	1
62686	co-amoxiclav 125mg/31mg/5ml oral suspension (pharma-z ltd)	1
62762	amoxicillin 250mg/5ml oral suspension (kent pharmaceuticals ltd)	1
62785	azithromycin 250mg capsules (a a h pharmaceuticals ltd)	1
62786	amoxicillin 250mg powder for solution for injection vials (wockhardt uk ltd)	1
62897	clarithromycin 250mg/5ml oral suspension (phoenix healthcare distribution ltd)	1
62898	cefalexin 125mg/5ml oral suspension sugar free (pliva pharma ltd)	1
62995	erythromycin ethyl succinate 500mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
63032	erythromycin ethyl succinate 250mg/5ml oral suspension (de pharmaceuticals)	1

63033	clarithromycin 250mg tablets (waymade healthcare plc)	1
63063	co-amoxiclav 250mg/62mg/5ml oral suspension (de pharmaceuticals)	1
63236	klaricid 500 tablets (necessity supplies ltd)	1
63244	vancomycin 500mg powder for concentrate for solution for infusion vials (kent pharmaceuticals ltd)	1
63306	flucloxacillin 500mg capsules (waymade healthcare plc)	1
63458	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)	1
63501	ciprofloxacin 750mg tablets (medreich plc)	1
63566	vancomycin 50mg/5ml oral solution	1
63567	vancomycin 500mg/100ml infusion bags	1
63596	cefuroxime 1.5g powder for injection vials (a a h pharmaceuticals ltd)	1
63660	doxycycline 50mg capsules (kent pharmaceuticals ltd)	1
63733	co-trimoxazole 80mg/400mg tablets (essential generics ltd)	1
63830	vancomycin 250mg/5ml oral suspension	1
63911	amoxicillin 250mg capsules (almus pharmaceuticals ltd)	1
63931	rifampicin 150mg capsules (a a h pharmaceuticals ltd)	1
64301	ciprofloxacin 500mg tablets (kent pharmaceuticals ltd)	1
64312	erythromycin ethyl succinate 250mg/5ml oral suspension (pinewood healthcare)	1
64355	amoxicillin 125mg/5ml oral suspension (sigma pharmaceuticals plc)	1
64357	amoxicillin 500mg capsules (waymade healthcare plc)	1
64375	flucloxacillin 250mg/5ml oral solution (actavis uk ltd)	1
64446	ciprofloxacin 250mg tablets (tillomed laboratories ltd)	1
64615	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (waymade healthcare plc)	1
64732	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)	1
64794	amoxicillin 250mg capsules (sigma pharmaceuticals plc)	1
64814	ciprofloxacin 400mg/200ml solution for infusion vials (genus pharmaceuticals ltd)	1
64903	ceftriaxone 1g powder for solution for injection vials (wockhardt uk ltd)	1
64986	co-amoxiclav 500mg/100mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1
64991	levofloxacin 500mg tablets (accord healthcare ltd)	1
65056	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (sandoz ltd)	1
65072	cefalexin 250mg/5ml oral suspension (mawdsley-brooks & company ltd)	1
65095	amoxicillin 250mg/5ml oral suspension sugar free (sigma pharmaceuticals plc)	1
65189	doxycycline 50mg/5ml oral suspension	1
65215	co-amoxiclav 250mg/125mg tablets (sigma pharmaceuticals plc)	1
65259	klaricid 500 tablets (sigma pharmaceuticals plc)	1
65343	co-trimoxazole 160mg/800mg tablets (tillomed laboratories ltd)	1
65360	doxycycline 50mg capsules (phoenix healthcare distribution ltd)	1
65486	azithromycin 200mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
65487	trimethoprim 200mg tablets (de pharmaceuticals)	1
65497	trimethoprim 200mg tablets (mawdsley-brooks & company ltd)	1
65533	co-amoxiclav 250mg/62mg/5ml oral suspension (cst pharma ltd)	1
65667	erythroped a 500mg tablets (mawdsley-brooks & company ltd)	1
65855	azithromycin 200mg/5ml oral suspension sugar free	1

65885	levofloxacin 500mg tablets (waymade healthcare plc)	1
65896	ciproxin 250mg tablets (waymade healthcare plc)	1
65945	flucloxacillin 125mg/5ml oral solution (de pharmaceuticals)	1
65953	cefalexin 250mg capsules (mawdsley-brooks & company ltd)	1
65956	erythromycin ethyl succinate 125mg/5ml oral suspension (sigma pharmaceuticals plc)	1
65958	amoxicillin 500mg capsules (sigma pharmaceuticals plc)	1
66034	azithromycin 250mg tablets (sandoz ltd)	1
66062	amoxicillin 125mg/5ml oral suspension sugar free (mawdsley-brooks & company ltd)	1
66092	clarithromycin 500mg powder for solution for infusion vials (a a h pharmaceuticals ltd)	1
66179	cefalexin 500mg capsules (waymade healthcare plc)	1
66211	levofloxacin 500mg/100ml solution for infusion bottles	1
66214	ciprofloxacin 250mg tablets (ranbaxy (uk) ltd)	1
66349	cefalexin 500mg/5ml oral suspension (waymade healthcare plc)	1
66483	ciprofloxacin 170mg/5ml oral suspension	1
66650	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (waymade healthcare plc)	1
66727	ciprofloxacin 500mg/5ml oral suspension	1
66747	co-amoxiclav 250mg/125mg tablets (brown & burk uk ltd)	1
66789	vancomycin 250mg capsules (a a h pharmaceuticals ltd)	1
66852	ceftazidime 2g powder for solution for injection vials (a a h pharmaceuticals ltd)	1
66905	co-amoxiclav 1000mg/200mg powder for solution for injection vials (wockhardt uk ltd)	1
66971	ciprofloxacin 400mg/200ml solution for infusion vials (a a h pharmaceuticals ltd)	1
67071	vancomycin 500mg powder for solution for infusion vials (a a h pharmaceuticals ltd)	1
67147	trimethoprim 100mg tablets (mawdsley-brooks & company ltd)	1
67361	trimethoprim 50mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)	1
67466	co-amoxiclav 500mg/125mg tablets (brown & burk uk ltd)	1
67560	clarithromycin 250mg/5ml oral suspension (almus pharmaceuticals ltd)	1
67572	levofloxacin 250mg tablets (accord healthcare ltd)	1
67596	trimethoprim 100mg tablets (de pharmaceuticals)	1
67613	co-trimoxazole 80mg+400mg dispersible tablet (ivax pharmaceuticals uk ltd)	1
67656	ciprofloxacin 500mg tablets (bristol laboratories ltd)	1
67694	co-amoxiclav 250mg/125mg tablets (mawdsley-brooks & company ltd)	1
67710	flucloxacillin 500mg capsules (mawdsley-brooks & company ltd)	1
67746	cefalexin 500mg tablets (pliva pharma ltd)	1
67749	cefalexin 250mg tablets (pliva pharma ltd)	1
67771	co-amoxiclav 1000mg/200mg powder for solution for injection vials (pliva pharma ltd)	1
67787	ampicillin 250mg/5ml oral suspension (sigma pharmaceuticals plc)	1
67794	cefalexin 250mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
67797	ceftazidime 1g powder for solution for injection vials (wockhardt uk ltd)	1
67828	cefalexin 500mg capsules (phoenix healthcare distribution ltd)	1
68001	flucloxacillin 250mg capsules (mawdsley-brooks & company ltd)	1
68027	co-trimoxazole 160mg+800mg tablet (c p pharmaceuticals ltd)	1
68101	co-trimoxazole 40mg/200mg/5ml oral suspension sugar free (aspen pharma trading ltd)	1

68110	doxycycline 100mg/5ml oral suspension	1
68226	erythromycin ethyl succinate 250mg/5ml oral suspension (sigma pharmaceuticals plc)	1
68274	ciproxin 500mg tablets (de pharmaceuticals)	1
68367	erythromycin ethyl succinate 500mg tablets (dawa ltd)	1
68408	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (brown & burk uk ltd)	1
68409	ciprofloxacin 750mg tablets (phoenix healthcare distribution ltd)	1
68416	amoxicillin 500mg capsules (phoenix healthcare distribution ltd)	1
68444	fortum 2g powder for solution for injection vials (glaxosmithkline uk ltd)	1
68476	amoxil 500mg capsules (sigma pharmaceuticals plc)	1
68521	cefalexin 125mg/5ml oral suspension (arrow generics ltd)	1
68545	amoxicillin 1g powder for solution for injection vials (a a h pharmaceuticals ltd)	1
68690	doxycycline 100mg capsules (mawdsley-brooks & company ltd)	1
68696	flucloxacillin 250mg capsules (de pharmaceuticals)	1
68723	clarithromycin 125mg/5ml oral suspension (de pharmaceuticals)	1
68726	co-trimoxazole 80mg/400mg tablets (sigma pharmaceuticals plc)	1
68826	co-trimoxazole 160mg/800mg tablets (alliance healthcare (distribution) ltd)	1
68943	clarithromycin 500mg tablets (sigma pharmaceuticals plc)	1
68990	comox forte tablet (ivax pharmaceuticals uk ltd)	1
69107	cefalexin 250mg capsules (sigma pharmaceuticals plc)	1
69118	amoxicillin 500mg capsules (brown & burk uk ltd)	1
69140	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (mawdsley-brooks & company ltd)	1
69171	vancomycin 500mg/vial injection (antigen pharmaceuticals)	1
69172	vancomycin oral liquid	1
69292	co-amoxiclav 500mg/125mg tablets (sigma pharmaceuticals plc)	1
69330	erythromycin 250mg/5ml liquid (rosemont pharmaceuticals ltd)	1
69340	amoxicillin 125mg/5ml mixture (mepra-pharm)	1
69362	septrin im 320mg/ml intramuscular injection (wellcome medical division)	1
69398	respillin 250mg capsules (kent pharmaceuticals ltd)	1
69403	erythromycin 250mg gastro-resistant tablets (genesis pharmaceuticals ltd)	1
69438	zithromax 200mg/5ml oral suspension (waymade healthcare plc)	1
69472	cefalexin 500mg capsules (lupin healthcare (uk) ltd)	1
69480	erythromycin 250mg gastro-resistant tablets (mawdsley-brooks & company ltd)	1
69493	co-trimoxazole 80mg/400mg tablets (phoenix healthcare distribution ltd)	1
69532	amoxil 500mg capsules (de pharmaceuticals)	1
69613	azithromycin 250mg capsules (teva uk ltd)	1
69709	flucloxacillin 250mg/5ml oral solution sugar free (alliance healthcare (distribution) ltd)	1
69711	amoxicillin 250mg capsules (brown & burk uk ltd)	1
69814	co-trimoxazole 80mg/400mg/5ml solution for infusion ampoules (aspen pharma trading ltd)	1
69881	co-trimoxazole 80mg/400mg tablets (aspen pharma trading ltd)	1
69893	ciprofloxacin 400mg/200ml solution for infusion bottles (kent pharmaceuticals ltd)	1
69901	amoxicillin 125mg/5ml oral suspension sugar free (arrow generics ltd)	1
69920	co-amoxiclav 125mg/31mg/5ml oral suspension (ennogen healthcare ltd)	1

70023	co-trimoxazole 160mg/800mg tablets (a a h pharmaceuticals ltd)	1
70275	amoxicillin 3g oral powder sachets sugar free (brown & burk uk ltd)	1
70311	erythromycin ethyl succinate 250mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
70402	cefalexin 500mg capsules (mawdsley-brooks & company ltd)	1
70641	generic rifater tablets	1
70783	azithromycin 500mg tablets (kent pharmaceuticals ltd)	1
70869	doxycycline 36.4mg/260mg periodontal gel cartridge	1
70998	ciprofloxacin 100mg/5ml oral suspension (special order)	1
71001	ampicillin 250mg capsules (phoenix healthcare distribution ltd)	1
71011	ciprofloxacin 250mg tablets (apc pharmaceuticals & chemicals (europe) ltd)	1
71024	vancomycin 125mg capsules (alliance healthcare (distribution) ltd)	1
71066	erythromycin ethyl succinate 500mg tablets (sigma pharmaceuticals plc)	1
71086	co-fluampicil 250mg/250mg capsules (almus pharmaceuticals ltd)	1
71091	chloramphenicol 250mg capsules (special order)	1
71092	ampicillin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)	1
71154	klaricid paediatric 125mg/5ml oral suspension (dowelhurst ltd)	1
71271	ceftazidime 2g powder for solution for injection vials (stravencon ltd)	1
71420	co-fluampicil 125mg/125mg/5ml oral suspension (alliance healthcare (distribution) ltd)	1
71423	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (focus pharmaceuticals ltd)	1
71435	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (focus pharmaceuticals ltd)	1
71473	piperacillin 2g / tazobactam 250mg powder for solution for infusion vials (bowmed ibisqus ltd)	1
71541	co-amoxiclav 125mg/31mg/5ml oral suspension (sigma pharmaceuticals plc)	1
71572	ciprofloxacin 200mg/100ml solution for infusion bottles (kent pharmaceuticals ltd)	1
71576	vancomycin 500mg powder for concentrate for solution for infusion vials (flynn pharma ltd)	1
71582	ciproxin 250mg/5ml oral suspension (lexon (uk) ltd)	1
71609	amoxicillin 250mg capsules (mawdsley-brooks & company ltd)	1
71680	clarithromycin 250mg/5ml oral suspension (de pharmaceuticals)	1
71819	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
71820	ampicillin 250mg/5ml oral suspension (kent pharmaceuticals ltd)	1
71937	co-amoxiclav 500mg/125mg tablets (almus pharmaceuticals ltd)	1
72041	piperacillin 2g / tazobactam 250mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1
72108	clarithromycin 500mg powder for solution for infusion vials (bowmed ibisqus ltd)	1
72126	clarithromycin 125mg/5ml oral suspension (almus pharmaceuticals ltd)	1
72157	levofloxacin 250mg tablets (de pharmaceuticals)	1
72219	flucloxacillin 125mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)	1
72224	cefalexin 125mg/5ml oral suspension sugar free (milpharm ltd)	1
72318	clarithromycin 500mg tablets (milpharm ltd)	1
72439	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (pinewood healthcare)	1
72447	co-trimoxazole 80mg/400mg tablets (genesis pharmaceuticals ltd)	1
72454	flucloxacillin 250mg capsules (waymade healthcare plc)	1
72595	co-trimoxazole 40mg/200mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
72685	rifampicin 150mg/5ml oral suspension	1

72784	cefotaxime 1g powder for solution for injection vials (wockhardt uk ltd)	1
72884	ciprofloxacin 500mg tablets (alliance healthcare (distribution) ltd)	1
73039	co-amoxiclav 500mg/100mg powder for solution for injection vials (bowmed ibisqus ltd)	1
73065	zinnat 250mg tablets (lexon (uk) ltd)	1
73070	doxycycline 50mg capsules (almus pharmaceuticals ltd)	1
73125	co-fluampicil 250mg/250mg capsules (waymade healthcare plc)	1
73301	ciprofloxacin 250mg tablets (phoenix healthcare distribution ltd)	1
73335	levofloxacin 250mg tablets (teva uk ltd)	1
73388	ciprofloxacin 400mg/200ml infusion bags (a a h pharmaceuticals ltd)	1
73431	levofloxacin 500mg tablets (de pharmaceuticals)	1
73452	rifampicin 150mg capsules (waymade healthcare plc)	1
73461	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)	1
73462	flucloxacillin 250mg/5ml oral solution (waymade healthcare plc)	1
73464	levofloxacin 500mg tablets (mylan)	1
73468	co-trimoxazole 80mg+400mg tablet (approved prescription services ltd)	1
73510	amoxicillin 500mg/50ml infusion bags	1
73536	doxycycline 50mg capsules (sigma pharmaceuticals plc)	1
73626	trimethoprim 7mg/5ml oral solution	1
73645	ciprofloxacin 750mg tablets (almus pharmaceuticals ltd)	1
73663	erythromycin ethyl succinate 500mg/5ml oral suspension (pinewood healthcare)	1
73695	co-trimoxazole 80mg/400mg tablets (de pharmaceuticals)	1
73702	co-trimoxazole 40mg/200mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
73744	co-trimoxazole 160mg/800mg tablets (aspen pharma trading ltd)	1
73859	levofloxacin 100mg/ml nebuliser liquid ampoules	1
73933	ciprofloxacin 400mg/200ml solution for infusion vials (intrapharm laboratories ltd)	1
73965	flucloxacillin 250mg/5ml oral solution (alliance healthcare (distribution) ltd)	1
73979	amoxicillin 250mg/5ml oral suspension sugar free (rx farma)	1
73983	augmentin 375mg tablets (dowelhurst ltd)	1
74060	cefalexin 125mg/5ml oral suspension (dowelhurst ltd)	1
74202	cefuroxime 250mg powder for injection vials (bowmed ibisqus ltd)	1
74293	azithromycin 250mg tablets (alliance healthcare (distribution) ltd)	1
74309	amoxicillin 250mg/5ml oral suspension sugar free (dowelhurst ltd)	1
74355	erythromycin 250mg gastro-resistant tablets (sigma pharmaceuticals plc)	1
74365	amoxicillin 125mg/5ml oral suspension sugar free (dowelhurst ltd)	1
74382	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (sigma pharmaceuticals plc)	1
74505	cefalexin 500mg capsules (sigma pharmaceuticals plc)	1
74523	azithromycin 500mg tablets (aspire pharma ltd)	1
74550	amoxicillin 125mg/5ml oral suspension sugar free (sigma pharmaceuticals plc)	1
74616	clarithromycin 250mg tablets (milpharm ltd)	1
74637	cefalexin 250mg tablets (ranbaxy (uk) ltd)	1
74651	erythromycin ethyl succinate 250mg/5ml oral suspension (actavis uk ltd)	1
74658	ciprofloxacin 750mg tablets (sandoz ltd)	1

74893	cefalexin 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
74937	amoxicillin 3g oral powder sachets sugar free (waymade healthcare plc)	1
75084	rifampicin 150mg/5ml oral solution	1
75085	trimethoprim 240mg/5ml oral solution	1
75097	vancomycin 1g powder for solution for infusion vials (pfizer ltd)	1
75243	co-amoxiclav 1000mg/200mg powder for solution for injection vials (peckforton pharmaceuticals ltd)	1
75269	co-amoxiclav 250mg/125mg tablets (rivopharm (uk) ltd)	1
75275	ciprofloxacin 400mg/200ml infusion bags (bowmed ibisqus ltd)	1
75298	levofloxacin 250mg tablets (macleods pharma uk ltd)	1
75316	klaricid xl 500mg tablets (dowelhurst ltd)	1
75317	co-amoxiclav 500mg/125mg tablets (consilient health ltd)	1
75331	co-amoxiclav 500mg/125mg tablets (bristol laboratories ltd)	1
75358	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (mawdsley-brooks & company ltd)	1
75386	cefalexin 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
75422	erythromycin ethyl succinate 500mg tablets (alliance healthcare (distribution) ltd)	1
75547	co-amoxiclav 250mg/62mg/5ml oral suspension (ennogen healthcare ltd)	1
75579	cefalexin 250mg/5ml oral solution (lagap)	1
75595	erythromycin 250mg/5ml liquid (berk pharmaceuticals ltd)	1
75663	co-amoxiclav 250mg/125mg tablets (bristol laboratories ltd)	1
75738	pivmecillinam 200mg with pivampicillin 250mg tablet	1
75766	trimethoprim 100mg tablet (celltech pharma europe ltd)	1
75782	co-amoxiclav 125mg/31mg/5ml oral suspension (de pharmaceuticals)	1
75783	cefalexin 250mg capsules (lupin healthcare (uk) ltd)	1
75871	clarithromycin 500mg powder for concentrate for solution for infusion vials (hameln pharmaceuticals ltd)	1
75944	flucloxacillin 2g powder for solution for injection vials	1
75961	amoxicillin 125mg/5ml oral suspension sugar free (medreich plc)	1
75978	co-fluampicil 125mg/125mg/5ml oral suspension (a a h pharmaceuticals ltd)	1
76071	erythromycin ethyl succinate 250mg/5ml oral suspension (focus pharmaceuticals ltd)	1
76155	azithromycin 500mg powder for solution for infusion vials	1
76188	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (teva uk ltd)	1
76233	amoxicillin 500mg capsules (rx farma)	1
76263	azithromycin 200mg/5ml oral suspension (waymade healthcare plc)	1
76347	amoxicillin 500mg capsules (mawdsley-brooks & company ltd)	1
76430	ciprofloxacin 750mg tablets (apc pharmaceuticals & chemicals (europe) ltd)	1
76434	amoxicillin 250mg powder for solution for injection vials (a a h pharmaceuticals ltd)	1

Identification of breathlessness

List of medical codes (medcode) and Read codes (readcode) used to identify breathlessness and their descriptions are listed in the table below. Breathlessness codes were validated through the identification of exacerbations in CPRD [263]. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify presence or absence of breathlessness are identified in the far right columns by a '1'.

medcode	readcode	description	clinical events	% clinical events	Validated	Absence	Present	Absent
4822	1739.00	Shortness of breath	676,052	19.8	1		1	
741	R060800	[D]Shortness of breath	406,978	11.9	1		1	
1429	173..00	Breathlessness	338,098	9.9	1		1	
19427	173I.00	MRC Breathlessness Scale: grade 2	317,830	9.3			1	
19432	173H.00	MRC Breathlessness Scale: grade 1	225,162	6.6		1		1
19426	173J.00	MRC Breathlessness Scale: grade 3	209,285	6.1			1	
5349	173..13	Shortness of breath symptom	189,439	5.6	1		1	
5175	173..11	Breathlessness symptom	171,252	5.0	1		1	
3092	R060A00	[D]Dyspnoea	135,063	4.0	1		1	
19430	173K.00	MRC Breathlessness Scale: grade 4	121,904	3.6			1	
19346	1731.00	No breathlessness	114,619	3.4		1		1
2575	173C.00	Short of breath on exertion	100,546	3.0	1		1	
5896	173..12	Dyspnoea - symptom	88,685	2.6	1		1	
6326	1732.00	Breathless - moderate exertion	86,815	2.5	1		1	
2931	1738.00	Difficulty breathing	85,252	2.5	1		1	
7932	1733.00	Breathless - mild exertion	39,292	1.2	1		1	
19429	173L.00	MRC Breathlessness Scale: grade 5	29,358	0.9			1	
735	R060D00	[D]Breathlessness	14,961	0.4	1		1	
6434	1736.00	Paroxysmal nocturnal dyspnoea	11,311	0.3	1		1	
7000	2322.00	O/E - dyspnoea	9,908	0.3	1		1	
31143	1734.00	Breathless - at rest	7,072	0.2	1		1	
7683	1735.00	Breathless - lying flat	5,501	0.2	1		1	
21801	173Z.00	Breathlessness NOS	3,588	0.1	1		1	
24889	173G.00	Breathless - strenuous exertion	3,511	0.1	1		1	
2563	R060600	[D]Respiratory distress	3,275	0.1	1		1	
7534	2324.00	O/E - respiratory distress	3,252	0.1	1		1	
2737	Q30..00	Respiratory distress syndrome	2,737	0.1	1		1	
18116	173D.00	Nocturnal dyspnoea	2,422	0.1	1		1	
53771	173C.11	Dyspnoea on exertion	980	0.0	1		1	
24848	H585300	Adult respiratory distress syndrome	582	0.0			1	
9297	R060700	[D]Respiratory insufficiency	250	0.0	1		1	
22094	173F.00	Short of breath dressing/undressing	188	0.0	1		1	
65353	173M.00	Borg Breathlessness Score: 0 none at all	140	0.0		1		1

57193	173R.00	Borg Breathlessness Score: 3 moderate	134	0.0			1	
57759	173Q.00	Borg Breathlessness Score: 2 slight	99	0.0			1	
107410	173f.00	Anxiety about breathlessness	96	0.0			1	
55791	1757.00	Breath normal	94	0.0		1		1
40813	173b.00	Unable to complete a sentence in one breath	91	0.0	1		1	
59860	173S.00	Borg Breathlessness Score: 4 somewhat severe	63	0.0			1	
68707	173P.00	Borg Breathlessness Score: 1 very slight	42	0.0		1		1
64049	173T.00	Borg Breathlessness Score: 5 severe	34	0.0			1	
70818	173N.00	Borg Breathlessness Score: 0.5 very, very slight	20	0.0		1		1
57678	H585.11	Adult respiratory distress syndrome	19	0.0			1	
70061	173W.00	Borg Breathlessness Score: 7 very severe	13	0.0			1	
72334	173X.00	Borg Breathlessness Score: 8 very severe (+)	10	0.0			1	
42287	173V.00	Borg Breathlessness Score: 6 severe (+)	10	0.0			1	
108650	173g.00	Breathlessness causing difficulty eating	6	0.0			1	
67566	173Y.00	Borg Breathlessness Score: 9 very, very sev (almost maximal)	2	0.0			1	
101843	173a.00	Borg Breathlessness Score: 10 maximal	1	0.0			1	
			3,406,042	**100.0**				

Identification of cough

List of medical codes (medcode) and Read codes (readcode) used to identify cough and their descriptions are listed in the table below. Cough codes were validated through the identification of exacerbations in CPRD [263]. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify presence of cough are identified in the far right columns by a '1'.

medcode	readcode	description	clinical events	% clinical events	Validated	Included
92	171..00	Cough	5,924,060	42.3	1	1
1273	171..11	C/O - cough	4,226,829	30.2	1	1
3068	1717	Night cough present	1,338,205	9.6	1	1
292	1719	Chesty cough	1,005,454	7.2	1	1
1160	R062.00	[D]Cough	544,785	3.9	1	1
4931	1712	Dry cough	232,519	1.7	1	1
4836	173B.00	Nocturnal cough / wheeze	231,225	1.7	1	1
7773	1714	Productive cough -green sputum	147,545	1.1	1	1
1234	1716	Productive cough NOS	147,364	1.1	1	1
7706	1713	Productive cough -clear sputum	64,751	0.5	1	1
7708	1715	Productive cough-yellow sputum	57,478	0.4	1	1
7707	171Z.00	Cough symptom NOS	27,400	0.2	1	1
3645	1716.11	Coughing up phlegm	18,355	0.1	1	1
1025	1719.11	Bronchial cough	15,212	0.1	1	1
4070	171C.00	Morning cough	6,261	0.0	1	1
18907	171F.00	Cough with fever	2,996	0.0	1	1
29318	171D.00	Evening cough	1,213	0.0	1	1
8239	R063000	[D]Cough with haemorrhage	1,121	0.0	1	1
22318	171H.00	Difficulty in coughing up sputum	897	0.0	1	1
60903	1D87.00	Cough aggravates symptom	188	0.0	1	1
100515	4I2G.00	Cough swab	17	0.0	1	1
			13,993,875	**100.0**		

Identification of sputum

List of medical codes (medcode) and Read codes (readcode) used to identify sputum and their descriptions are listed in the table below. Sputum codes were validated through the identification of exacerbations in CPRD [263]. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify presence of sputum are identified in the far right columns by a '1'.

medcode	readcode	desc	clinical events	% clinical events	Validated	Included
292	1719.00	Chesty cough	1,005,454	65.1	1	1
7773	1714.00	Productive cough -green sputum	147,545	9.5	1	1
1234	1716.00	Productive cough NOS	147,364	9.5	1	1
7706	1713.00	Productive cough -clear sputum	64,751	4.2	1	1
7708	1715.00	Productive cough-yellow sputum	57,478	3.7	1	1
9807	171..12	Sputum - symptom	24,228	1.6	1	1
3645	1716.11	Coughing up phlegm	18,355	1.2	1	1
14804	4E3Z.12	Sputum appears infected	16,517	1.1	1	1
1025	1719.11	Bronchial cough	15,212	1.0	1	1
3727	4JF5.00	Sputum sent for C/S	12,547	0.8	1	1
24181	4E23.00	Sputum: mucopurulent	12,067	0.8	1	1
1251	R064.00	[D]Abnormal sputum	4,623	0.3	1	1
8760	R153100	[D]Positive culture findings in sputum	3,326	0.2	1	1
15430	R064100	[D]Sputum abnormal - colour	3,325	0.2	1	1
14269	4E...00	Sputum examination	2,508	0.2		
8287	41D4.00	Sputum sample obtained	2,293	0.1	1	1
11072	H060300	Acute purulent bronchitis	1,909	0.1	1	1
14273	4E2A.00	Sputum appearance	1,289	0.1	1	1
20086	R064000	[D]Sputum abnormal - amount	1,112	0.1	1	1
22318	171H.00	Difficulty in coughing up sputum	897	0.1	1	1
36880	4E29.00	Green sputum	581	0.0	1	1
30754	4E28.00	Yellow sputum	561	0.0	1	1
16026	4E13.00	Sputum examination: abnormal	295	0.0	1	1
36515	R064300	[D]Abnormal sputum - tenacious	218	0.0	1	1
14518	4KC..00	Sputum cytology	207	0.0		
18964	Z691.11	Sputum clearance	179	0.0	1	1
23582	R064z00	[D]Abnormal sputum NOS	165	0.0	1	1
14271	4E4..00	Sputum culture	154	0.0	1	1
100629	4E2D.00	White sputum	69	0.0	1	1
42573	4E27.00	Clear sputum	52	0.0		
30904	4E11.00	Sputum sent for examination	34	0.0	1	1
40202	4E...11	Mucoid sputum - O/E	33	0.0		
100484	4E2E.00	Volume of sputum	23	0.0	1	1

100931	4E2C.00	Brown sputum	22	0.0	1	1
14272	4E3..00	Sputum microscopy	19	0.0	1	1
56133	4E2..00	Sputum inspection	13	0.0		
35577	4E1..00	Sputum examination - general	10	0.0		
54177	4E22.00	Sputum: excessive - mucoid	9	0.0	1	1
44214	R064200	[D]Sputum abnormal - odour	8	0.0	1	1
49144	4E36.00	Sputum: pus cells present	8	0.0	1	1
100647	4E2E000	Copious sputum	8	0.0	1	1
101782	4E2E011	Profuse sputum	3	0.0	1	1
103209	4E2F.00	Grey sputum	3	0.0	1	1
52806	4E25.00	Sputum: frothy/watery	3	0.0		
43272	4EZ..00	Sputum examination NOS	3	0.0		
49029	4E1Z.00	Sputum gen. exam. NOS	3	0.0		
23252	4E3Z.00	Sputum microscopy NOS	1	0.0	1	1
100524	4E2E100	Moderate sputum	1	0.0	1	1
61079	4E2Z.00	Sputum inspection NOS	1	0.0		
43270	5E3Z.11	Sputum evidence of infection	-	0.0	1	1
49694	4E37.00	Sputum: organism on gram stain	-	0.0	1	1
107359	4E29000	Dark green sputum	-	0.0		1
109879	4E29100	Pale green sputum	-	0.0		1
			1,545,486	**100.0**		

Identification of HF

List of medical codes (medcode) and Read codes (readcode) used to identify HF and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of HF [21] and/or code list used by Conrad et al. [61]. Codes not identified as being QOF [21] or Conrad et al. [61] were additional codes added through searching the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify HF and LVF are identified in the far right columns by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Conrad	Included	LVF
398	G580.00	congestive heart failure	203,027	26.3	1	1	1	
884	G581.00	left ventricular failure	173,060	22.5	1	1	1	1
2062	G58..00	heart failure	107,422	13.9	1	1	1	
2906	G580.11	congestive cardiac failure	81,706	10.6	1	1	1	
12627	9N0k.00	seen in heart failure clinic	21,975	2.9			1	
3204	G55..00	cardiomyopathy	21,521	2.8		1		
8966	G5yy900	Left ventricular systolic dysfunction	19,978	2.6	1	1	1	1
4024	G58z.00	heart failure nos	16,134	2.1	1	1	1	
17851	8HBE.00	heart failure follow-up	12,042	1.6			1	
12366	662T.00	congestive heart failure monitoring	10,241	1.3			1	
30779	662W.00	heart failure annual review	9,777	1.3			1	
1223	G58..11	cardiac failure	9,414	1.2	1	1	1	
9913	1O1..00	heart failure confirmed	7,277	0.9		1	1	
5695	G41z.11	Chronic cor pulmonale	7,192	0.9		1	1	
13189	662g.00	New York Heart Association classification - class II	6,456	0.8	1	1	1	
11284	585f.00	Echocardiogram shows left ventricular systolic dysfunction	6,357	0.8	1	1	1	1
5942	G581.13	impaired left ventricular function	6,236	0.8	1	1	1	1
7251	33BA.00	Impaired Left Ventricular Function	6,220	0.8		1	1	1
18853	662f.00	New York Heart Association classification - class I	3,757	0.5	1	1	1	
7535	G554400	Primary dilated cardiomyopathy	3,638	0.5		1		
19066	662h.00	New York Heart Association classification - class III	3,500	0.5	1	1	1	
8464	G400.00	Acute cor pulmonale	2,366	0.3			1	
7320	G343.00	Ischaemic cardiomyopathy	2,180	0.3		1		
3499	G554300	Hypertrophic non-obstructive cardiomyopathy	2,106	0.3		1		
46672	388D.00	New York Heart Assoc classification heart failure symptoms	2,087	0.3				
12550	G5yyA00	Left ventricular diastolic dysfunction	1,975	0.3		1	1	1
5255	G581000	acute left ventricular failure	1,687	0.2	1	1	1	1
83502	662p.00	heart failure 6 month review	1,353	0.2			1	
32671	G580100	chronic congestive heart failure	1,342	0.2	1	1	1	
32945	8CL3.00	heart failure care plan discussed with patient	1,319	0.2			1	
9524	G580.14	Biventricular failure	1,234	0.2		1	1	
10079	G580.12	Right heart failure	1,192	0.2		1	1	

11351	585g.00	Echocardiogram shows left ventricular diastolic dysfunction	1,189	0.2		1	1	1
24503	8B29.00	Cardiac failure therapy	1,167	0.2			1	
22993	G55z.00	Cardiomyopathy NOS	1,142	0.1		1		
4915	G555.00	Alcoholic cardiomyopathy	1,061	0.1		1		
27884	G580200	decompensated cardiac failure	985	0.1	1	1	1	
107397	G5yyD00	Left ventricular cardiac dysfunction	909	0.1	1	1	1	1
103732	8CMK.00	has heart failure management plan	898	0.1		1	1	
17278	G58z.12	cardiac failure nos	816	0.1	1	1	1	
9402	G55y.11	Secondary dilated cardiomyopathy	799	0.1		1		
23707	G580000	acute congestive heart failure	688	0.1			1	
5141	G554000	Congestive cardiomyopathy	624	0.1		1		
27964	G582.00	acute heart failure	563	0.1	1	1	1	
10154	G580.13	Right ventricular failure	525	0.1		1	1	
26242	Zrad.00	New York Heart Assoc classification heart failure symptoms	451	0.1			1	
8010	G551.00	Hypertrophic obstructive cardiomyopathy	398	0.1		1		
51214	662i.00	New York Heart Association classification - class IV	375	0.0	1	1	1	
101138	G583.00	heart failure with normal ejection fraction	315	0.0		1	1	
32898	8H2S.00	admit heart failure emergency	290	0.0		1	1	
11424	G580300	compensated cardiac failure	196	0.0	1	1	1	
21852	G221200	Familial cardiomyopathy	188	0.0		1		
104275	G584.00	Right ventricular failure	188	0.0		1	1	
106897	G583.12	heart failure with preserved ejection fraction	187	0.0	1	1	1	
22262	G1yz100	Rheumatic left ventricular failure	152	0.0		1	1	
70648	Gyu5M00	[X]Other hypertrophic cardiomyopathy	142	0.0		1		
27683	G558100	Cardiomyopathy in myotonic dystrophy	118	0.0		1		
97780	G559.00	Arrhythmogenic right ventricular cardiomyopathy	94	0.0		1		
106198	661M500	Heart failure self-management plan agreed	82	0.0		1		
101137	G583.11	hfnef - heart failure with normal ejection fraction	79	0.0	1	1	1	
94870	G580400	congestive heart failure due to valvular disease	78	0.0	1	1	1	
106008	8CMW800	heart failure clinical pathway	77	0.0		1	1	
62718	G21z100	hypertensive heart disease nos with ccf	72	0.0		1	1	
21837	G232.00	hypertensive heart&renal dis wth (congestive) heart failure	31	0.0		1	1	
52127	G211100	benign hypertensive heart disease with ccf	24	0.0		1	1	
57987	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail	8	0.0			1	
105542	8CeC.00	preferred place of care for next exacerbation heart failure	7	0.0		1	1	
72668	G210100	malignant hypertensive heart disease with ccf	5	0.0			1	
66306	SP11111	heart failure as a complication of care	1	0.0			1	
111428	2JZ..00	On optimal heart failure therapy	1	0.0				
			770,696	**100.0**				

Identification of LABA

List of product codes (prodcode) used to identify LABA and their descriptions are listed in the table below. The final codes to identify presence of LABA are identified in the far right columns by a '1'.

prodcode	productname	Included
465	salmeterol 25micrograms/dose inhaler	1
549	serevent 25micrograms/dose inhaler (glaxosmithkline uk ltd)	1
638	seretide 250 accuhaler (glaxosmithkline uk ltd)	1
665	seretide 100 accuhaler (glaxosmithkline uk ltd)	1
719	salmeterol 50micrograms/dose dry powder inhaler	1
910	serevent diskhaler 50microgram inhalation powder (glaxo wellcome uk ltd)	1
1974	oxis 12 turbohaler (astrazeneca uk ltd)	1
1975	oxis 6 turbohaler (astrazeneca uk ltd)	1
2224	serevent 50micrograms/dose accuhaler (glaxosmithkline uk ltd)	1
3297	salmeterol 50micrograms disc	1
3666	seretide 500 accuhaler (glaxosmithkline uk ltd)	1
5143	seretide 50 evohaler (glaxosmithkline uk ltd)	1
5161	seretide 125 evohaler (glaxosmithkline uk ltd)	1
5172	seretide 250 evohaler (glaxosmithkline uk ltd)	1
5558	salmeterol 50micrograms with fluticasone 500micrograms cfc free inhaler	1
5864	salmeterol 25micrograms with fluticasone 250micrograms cfc free inhaler	1
5942	salmeterol 50micrograms with fluticasone 250micrograms cfc free inhaler	1
6325	symbicort 200/6 turbohaler (astrazeneca uk ltd)	1
6526	formoterol 12microgram inhalation powder capsules with device	1
6569	salmeterol 25micrograms with fluticasone 125micrograms cfc free inhaler	1
6616	salmeterol 25micrograms with fluticasone 50micrograms cfc free inhaler	1
6746	budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler	1
6780	symbicort 400/12 turbohaler (astrazeneca uk ltd)	1
6796	budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
6938	salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler	1
7013	symbicort 100/6 turbohaler (astrazeneca uk ltd)	1
7133	formoterol 12micrograms/dose dry powder inhaler	1
7268	serevent 25micrograms/dose evohaler (glaxosmithkline uk ltd)	1
7270	salmeterol 25micrograms/dose inhaler cfc free	1
9711	formoterol 6micrograms/dose dry powder inhaler	1
10218	budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
10968	foradil 12microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	1
11410	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	1
11588	fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	1
11618	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	1
12994	fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	1

13040	fluticasone propionate 250micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	1
13273	fluticasone propionate 100micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	1
14306	formoterol 12micrograms/dose inhaler cfc free	1
19799	tulobuterol 2mg	1
22663	respacal 2mg tablet (ucb pharma ltd)	1
25784	atimos modulite 12micrograms/dose inhaler (chiesi ltd)	1
26829	brelomax 2mg tablet (abbott laboratories ltd)	1
35165	serevent 50microgram disks with diskhaler (glaxosmithkline uk ltd)	1
35503	salmeterol 50microgram inhalation powder blisters	1
35542	salmeterol 50microgram inhalation powder blisters with device	1
35725	formoterol easyhaler 12micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
35825	serevent 50microgram disks (glaxosmithkline uk ltd)	1
37432	fostair 100micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	1
37470	beclometasone 100micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	1
43738	indacaterol 150microgram inhalation powder capsules with device	1
43893	onbrez breezhaler 150microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	1
44064	onbrez breezhaler 300microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	1
45610	indacaterol 300microgram inhalation powder capsules with device	1
47638	neovent 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)	1
48666	flutiform 250micrograms/dose / 10micrograms/dose inhaler (napp pharmaceuticals ltd)	1
48739	seretide 250 evohaler (de pharmaceuticals)	1
49000	seretide 250 evohaler (waymade healthcare plc)	1
49114	symbicort 100/6 turbohaler (sigma pharmaceuticals plc)	1
49868	fluticasone 250micrograms/dose / formoterol 10micrograms/dose inhaler cfc free	1
50036	flutiform 125micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	1
50051	serevent 25micrograms/dose evohaler (waymade healthcare plc)	1
50560	seretide 250 accuhaler (sigma pharmaceuticals plc)	1
50689	flutiform 50micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	1
50739	symbicort 400/12 turbohaler (mawdsley-brooks & company ltd)	1
50886	seretide 250 evohaler (stephar (u.k.) ltd)	1
50945	symbicort 100/6 turbohaler (mawdsley-brooks & company ltd)	1
51027	seretide 125 evohaler (de pharmaceuticals)	1
51151	seretide 125 evohaler (lexon (uk) ltd)	1
51209	fluticasone 125micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	1
51270	fluticasone 50micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	1
51394	seretide 500 accuhaler (waymade healthcare plc)	1
51570	symbicort 200/6 turbohaler (de pharmaceuticals)	1
51593	seretide 500 accuhaler (de pharmaceuticals)	1
51759	symbicort 200/6 turbohaler (mawdsley-brooks & company ltd)	1
51861	seretide 500 accuhaler (mawdsley-brooks & company ltd)	1
51909	seretide 250 evohaler (necessity supplies ltd)	1
53230	seretide 250 accuhaler (de pharmaceuticals)	1

53237	symbicort 400/12 turbohaler (de pharmaceuticals)	1
53283	seretide 100 accuhaler (waymade healthcare plc)	1
53491	symbicort 200/6 turbohaler (sigma pharmaceuticals plc)	1
54742	salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)	1
55677	seretide 500 accuhaler (lexon (uk) ltd)	1
56478	serevent 50micrograms/dose accuhaler (de pharmaceuticals)	1
56482	oxis 12 turbohaler (waymade healthcare plc)	1
57544	serevent 50micrograms/dose accuhaler (waymade healthcare plc)	1
57558	oxis 6 turbohaler (lexon (uk) ltd)	1
57694	vertine 25micrograms/dose inhaler cfc free (teva uk ltd)	1
59327	relvar ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
59439	fluticasone furoate 92micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	1
59573	relvar ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
59899	fluticasone furoate 184micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	1
61176	anoro ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
61280	seretide 250 accuhaler (waymade healthcare plc)	1
61490	umeclidinium bromide 65micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	1
61644	fostair nexthaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	1
61666	duoresp spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (teva uk ltd)	1
61782	duoresp spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (teva uk ltd)	1
62030	beclometasone 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
62126	seretide 100 accuhaler (de pharmaceuticals)	1
62535	duaklir 340micrograms/dose / 12micrograms/dose genuair (astrazeneca uk ltd)	1
62662	olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free	1
62667	ultibro breezhaler 85microgram/43microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	1
62739	indacaterol 85micrograms/dose / glycopyrronium bromide 54micrograms/dose inhalation powder capsules with device	1
62838	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler	1
63252	seretide 250 evohaler (lexon (uk) ltd)	1
63945	seretide 250 accuhaler (lexon (uk) ltd)	1
64372	sirdupla 25micrograms/dose / 125micrograms/dose inhaler (mylan)	1
64373	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (mylan)	1
64509	tiotropium bromide 2.5micrograms/dose / olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free	1
64523	spiolto respimat 2.5micrograms/dose / 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)	1
64638	flutiform 125micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)	1
65117	seretide 125 evohaler (mawdsley-brooks & company ltd)	1
65431	striverdi respimat 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)	1
65596	fostair 200micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	1
65658	fostair nexthaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	1
65677	airflusal forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (sandoz ltd)	1
65758	beclometasone 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	1
65894	beclometasone 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
66448	flutiform 250micrograms/dose / 10micrograms/dose inhaler (waymade healthcare plc)	1

66453	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (waymade healthcare plc)	1
66547	oxis 12 turbohaler (de pharmaceuticals)	1
67055	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)	1
67101	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler (a a h pharmaceuticals ltd)	1
67238	foradil 12microgram inhalation powder capsules with device (sigma pharmaceuticals plc)	1
67677	symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (astrazeneca uk ltd)	1
67800	serevent 25micrograms/dose evohaler (lexon (uk) ltd)	1
67823	salmeterol 50microgram diskhaler (dowelhurst ltd)	1
67958	budesonide 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	1
68034	symbicort 200/6 turbohaler (necessity supplies ltd)	1
68175	flutiform 50micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)	1
68260	serevent 50micrograms/dose accuhaler (mawdsley-brooks & company ltd)	1
68453	seretide 125 evohaler (waymade healthcare plc)	1
68483	soltel 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)	1
68495	seretide 500 accuhaler (necessity supplies ltd)	1
68983	aerivio spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (teva uk ltd)	1
69436	sereflo 25micrograms/dose / 125micrograms/dose inhaler (kent pharmaceuticals ltd)	1
69538	sereflo 25micrograms/dose / 250micrograms/dose inhaler (kent pharmaceuticals ltd)	1
69556	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler (colorama pharmaceuticals ltd)	1
69827	airflusal 25micrograms/dose / 250micrograms/dose inhaler (sandoz ltd)	1
70250	airflusal 25micrograms/dose / 125micrograms/dose inhaler (sandoz ltd)	1
70711	trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler (chiesi ltd)	1
71260	generic trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler	1
71284	fobumix easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
71354	symbicort 400/12 turbohaler (necessity supplies ltd)	1
71371	symbicort 100/6 turbohaler (waymade healthcare plc)	1
71394	serevent 50microgram disks with diskhaler (dowelhurst ltd)	1
71409	seretide 50 evohaler (waymade healthcare plc)	1
71597	serevent 25micrograms/dose evohaler (sigma pharmaceuticals plc)	1
71763	trelegy ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
71915	fobumix easyhaler 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
72310	generic trelegy ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler	1
72400	fobumix easyhaler 80micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
72564	aloflute 25micrograms/dose / 125micrograms/dose inhaler (mylan)	1
72949	serevent 25micrograms/dose evohaler (de pharmaceuticals)	1
73527	aloflute 25micrograms/dose / 250micrograms/dose inhaler (mylan)	1
73849	fusacomb easyhaler 50micrograms/dose / 500micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1

Identification of LAMA

List of product codes (prodcode) used to identify LAMA and their descriptions are listed in the table below. The final codes to identify presence of LAMA are identified in the far right columns by a '1'.

prodcode	productname	Included
746	tiotropium 18 microgram capsule	1
6050	spiriva 18 microgram capsule (boehringer ingelheim ltd)	1
34995	spiriva 18microgram inhalation powder capsules with handihaler (boehringer ingelheim ltd)	1
35000	spiriva 18microgram inhalation powder capsules (boehringer ingelheim ltd)	1
35011	tiotropium bromide 18microgram inhalation powder capsules	1
35014	tiotropium bromide 18microgram inhalation powder capsules with device	1
36864	tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free	1
36869	spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)	1
49227	aclidinium bromide 375micrograms/dose dry powder inhaler	1
49228	eklira 322micrograms/dose genuair (astrazeneca uk ltd)	1
50103	spiriva 18microgram inhalation powder capsules with handihaler (waymade healthcare plc)	1
50292	spiriva 18microgram inhalation powder capsules (sigma pharmaceuticals plc)	1
50577	spiriva 18microgram inhalation powder capsules with handihaler (de pharmaceuticals)	1
51967	spiriva 18microgram inhalation powder capsules (mawdsley-brooks & company ltd)	1
53761	glycopyrronium bromide 55microgram inhalation powder capsules with device	1
53982	seebri breezhaler 44microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)	1
59638	spiriva 18microgram inhalation powder capsules with handihaler (sigma pharmaceuticals plc)	1
61176	anoro ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
61490	umeclidinium bromide 65micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	1
61582	spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (waymade healthcare plc)	1
61879	incruse ellipta 55micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
62109	umeclidinium bromide 65micrograms/dose dry powder inhaler	1
62535	duaklir 340micrograms/dose / 12micrograms/dose genuair (astrazeneca uk ltd)	1
62838	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler	1
63992	eklira 322micrograms/dose genuair (waymade healthcare plc)	1
64232	tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free (am distributions (yorkshire) ltd)	1
64509	tiotropium bromide 2.5micrograms/dose / olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free	1
64523	spiolto respimat 2.5micrograms/dose / 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)	1
67531	glycopyrronium bromide 55microgram inhalation powder capsules with device (j m mcgill ltd)	1
68530	tiotropium bromide 10microgram inhalation powder capsules with device	1
68729	braltus 10microgram inhalation powder capsules with zonda inhaler (teva uk ltd)	1
69109	glycopyrronium bromide 400micrograms/ml oral solution sugar free	1
69556	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler (colorama pharmaceuticals ltd)	1
72031	glycopyrronium bromide 55microgram inhalation powder capsules with device (ennogen healthcare ltd)	1

Identification of ICS

List of product codes (prodcode) used to identify ICS and their descriptions are listed in the table below. The final codes to identify presence of ICS are identified in the far right columns by a '1'.

prodcode	productname	Included
38	beclometasone 100micrograms/dose inhaler	1
99	becotide 100 inhaler (glaxosmithkline uk ltd)	1
454	pulmicort 200microgram inhaler (astrazeneca uk ltd)	1
638	seretide 250 accuhaler (glaxosmithkline uk ltd)	1
665	seretide 100 accuhaler (glaxosmithkline uk ltd)	1
883	becodisks 200microgram disc (allen & hanburys ltd)	1
895	beclazone 100 easi-breathe inhaler (teva uk ltd)	1
896	becotide easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd)	1
908	pulmicort 400 turbohaler (astrazeneca uk ltd)	1
909	budesonide 200micrograms/dose inhaler	1
911	flixotide accuhaler 250 250microgram/inhalation inhalation powder (allen & hanburys ltd)	1
947	budesonide 50micrograms/actuation refill canister	1
956	pulmicort 200 turbohaler (astrazeneca uk ltd)	1
959	budesonide 50micrograms/dose inhaler	1
960	pulmicort 100 turbohaler (astrazeneca uk ltd)	1
1100	beclazone 100 inhaler (teva uk ltd)	1
1236	becloforte 250micrograms/dose inhaler (glaxosmithkline uk ltd)	1
1242	beclometasone 250micrograms/dose inhaler	1
1243	beclazone 250 easi-breathe inhaler (teva uk ltd)	1
1258	becotide 200 inhaler (glaxosmithkline uk ltd)	1
1259	beclometasone 200micrograms/dose inhaler	1
1406	becotide 50 inhaler (glaxosmithkline uk ltd)	1
1412	flixotide 250microgram/actuation inhalation powder (allen & hanburys ltd)	1
1424	flixotide 250microgram disc (allen & hanburys ltd)	1
1426	flixotide 500microgram disc (allen & hanburys ltd)	1
1518	flixotide 50microgram/actuation inhalation powder (allen & hanburys ltd)	1
1537	becotide 200microgram rotacaps (glaxosmithkline uk ltd)	1
1551	beclazone 250 inhaler (teva uk ltd)	1
1552	becloforte easi-breathe 250microgram/actuation pressurised inhalation (allen & hanburys ltd)	1
1642	budesonide 400micrograms/dose dry powder inhaler	1
1676	flixotide 125microgram/actuation inhalation powder (allen & hanburys ltd)	1
1680	pulmicort ls 50micrograms/dose inhaler (astrazeneca uk ltd)	1
1725	beclazone 50 easi-breathe inhaler (teva uk ltd)	1
1727	becotide easi-breathe 50microgram/actuation pressurised inhalation (allen & hanburys ltd)	1
1734	beclometasone 100micrograms/dose breath actuated inhaler	1
1801	ventide inhaler (glaxosmithkline uk ltd)	1

1861	aerobec 100 autohaler (meda pharmaceuticals ltd)	1
1885	beclazone 200 inhaler (teva uk ltd)	1
1951	becodisks 400microgram disc (allen & hanburys ltd)	1
1956	pulmicort 1mg respules (astrazeneca uk ltd)	1
1959	pulmicort 0.5mg respules (astrazeneca uk ltd)	1
2092	budesonide 200micrograms/dose dry powder inhaler	1
2124	pulmicort refil 200 mcg inh	1
2125	pulmicort 200microgram refill canister (astrazeneca uk ltd)	1
2148	beclometasone 400microgram disc	1
2159	aerobec 50 autohaler (meda pharmaceuticals ltd)	1
2160	beclometasone 50micrograms/dose breath actuated inhaler	1
2229	becodisks 100microgram disc (allen & hanburys ltd)	1
2282	fluticasone propionate 500micrograms/dose dry powder inhaler	1
2335	qvar 100 inhaler (teva uk ltd)	1
2440	flixotide accuhaler 500 500microgram/inhalation inhalation powder (allen & hanburys ltd)	1
2600	beclometasone 250micrograms/dose breath actuated inhaler	1
2723	fluticasone 25micrograms/dose inhaler	1
2892	becloforte 400microgram disks (glaxosmithkline uk ltd)	1
2893	beclometasone 200micrograms disc	1
2951	fluticasone 250microgram/actuation pressurised inhalation	1
2992	beclazone 50 inhaler (teva uk ltd)	1
3018	beclometasone 50micrograms/dose inhaler	1
3065	bextasol inhalation powder (allen & hanburys ltd)	1
3075	becotide 400microgram rotacaps (glaxosmithkline uk ltd)	1
3119	becloforte integra 250microgram/actuation inhaler with compact spacer (glaxo laboratories ltd)	1
3150	beclometasone 100micrograms/actuation extrafine particle cfc free inhaler	1
3188	pulmicort complete 50 mcg inh	1
3220	qvar 50 autohaler (teva uk ltd)	1
3289	flixotide 25micrograms/dose inhaler (glaxosmithkline uk ltd)	1
3993	filair forte 250micrograms/dose inhaler (meda pharmaceuticals ltd)	1
4131	fluticasone 100microgram disc	1
4132	fluticasone 125microgram/actuation pressurised inhalation	1
4365	beclometasone 100micrograms disc	1
4413	qvar 100 autohaler (teva uk ltd)	1
4499	aerobec 250microgram/actuation pressurised inhalation (meda pharmaceuticals ltd)	1
4545	pulmicort ls 50microgram refill canister (astrazeneca uk ltd)	1
4601	asmabec 100 clickhaler (focus pharmaceuticals ltd)	1
4688	fluticasone 50microgram/actuation pressurised inhalation	1
4759	beclometasone 100microgram inhalation powder capsules	1
4803	beclazone 250microgram/actuation inhalation powder (actavis uk ltd)	1
4926	flixotide accuhaler 100 100microgram/inhalation inhalation powder (allen & hanburys ltd)	1
5143	seretide 50 evohaler (glaxosmithkline uk ltd)	1

5161	seretide 125 evohaler (glaxosmithkline uk ltd)	1
5172	seretide 250 evohaler (glaxosmithkline uk ltd)	1
5223	fluticasone 50micrograms/dose inhaler cfc free	1
5309	flixotide 50micrograms/dose evohaler (glaxosmithkline uk ltd)	1
5521	beclometasone 200micrograms/dose dry powder inhaler	1
5522	beclometasone 100micrograms/dose dry powder inhaler	1
5551	flixotide 0.5mg/2ml nebules (glaxosmithkline uk ltd)	1
5558	salmeterol 50micrograms with fluticasone 500micrograms cfc free inhaler	1
5580	flixotide accuhaler 50 50microgram/inhalation inhalation powder (allen & hanburys ltd)	1
5683	flixotide 250micrograms/dose evohaler (glaxosmithkline uk ltd)	1
5718	flixotide 125micrograms/dose evohaler (glaxosmithkline uk ltd)	1
5804	beclometasone 250micrograms/dose dry powder inhaler	1
5822	fluticasone 250micrograms/dose inhaler cfc free	1
5864	salmeterol 25micrograms with fluticasone 250micrograms cfc free inhaler	1
5885	fluticasone propionate 100micrograms/dose dry powder inhaler	1
5942	salmeterol 50micrograms with fluticasone 250micrograms cfc free inhaler	1
5975	fluticasone 125micrograms/dose inhaler cfc free	1
5992	beclometasone 50micrograms/dose dry powder inhaler	1
6095	budesonide 3mg gastro-resistant capsules	1
6325	symbicort 200/6 turbohaler (astrazeneca uk ltd)	1
6569	salmeterol 25micrograms with fluticasone 125micrograms cfc free inhaler	1
6616	salmeterol 25micrograms with fluticasone 50micrograms cfc free inhaler	1
6746	budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler	1
6780	symbicort 400/12 turbohaler (astrazeneca uk ltd)	1
6796	budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
6938	salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler	1
7013	symbicort 100/6 turbohaler (astrazeneca uk ltd)	1
7602	fluticasone 50microgram disc	1
7638	fluticasone 250microgram disc	1
7653	beclometasone 400microgram inhalation powder capsules	1
7724	betamethasone valerate 100micrograms/actuation inhaler	1
7788	budesonide 100micrograms/dose dry powder inhaler	1
7891	fluticasone 500microgram disc	1
7948	fluticasone propionate 250micrograms/dose dry powder inhaler	1
8111	becloforte vm 250microgram/actuation vm pack (allen & hanburys ltd)	1
8251	pulmicort refil 50 mg inh	1
8433	budesonide 100micrograms/actuation inhaler	1
8450	flixotide diskhaler-community pack 50 mcg	1
8635	flixotide 50microgram disc (allen & hanburys ltd)	1
9164	fluticasone propionate 50micrograms/dose dry powder inhaler	1
9233	beclometasone 200microgram inhalation powder capsules	1
9356	becotide rotahaler insufflator inhalation powder (allen and hanburys ltd)	1

9477	asmabec 100microgram/actuation spacehaler (celltech pharma europe ltd)	1
9571	beclometasone 250micrograms/actuation vortex inhaler	1
9577	asmabec 50 clickhaler (focus pharmaceuticals ltd)	1
9599	beclazone 50microgram/actuation inhalation powder (actavis uk ltd)	1
9921	beclometasone 100micrograms/dose breath actuated inhaler cfc free	1
10090	beclometasone 50micrograms/actuation extrafine particle cfc free inhaler	1
10218	budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
10254	mometasone 400micrograms/dose dry powder inhaler	1
10321	budesonide 400microgram inhalation powder capsules	1
11149	betnelan 500microgram tablets (focus pharmaceuticals ltd)	1
11198	beclometasons 50 micrograms/actuation vortex inhaler	1
11307	salbutamol 100micrograms/dose / beclometasone 50micrograms/dose inhaler	1
11410	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	1
11497	beclometasone 400micrograms/dose dry powder inhaler	1
11588	fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	1
11618	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	1
11732	beclometasone 50micrograms/dose breath actuated inhaler cfc free	1
12994	fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	1
13037	pulvinal beclometasone dipropionate 200micrograms/dose dry powder inhaler (chiesi ltd)	1
13040	fluticasone propionate 250micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	1
13273	fluticasone propionate 100micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	1
13290	clenil modulite 100micrograms/dose inhaler (chiesi ltd)	1
13815	beclazone 100microgram/actuation inhalation powder (actavis uk ltd)	1
14294	qvar 50micrograms/dose easi-breathe inhaler (teva uk ltd)	1
14321	beclometasone 200micrograms/dose inhaler cfc free	1
14524	bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)	1
14561	salbutamol 400microgram / beclometasone 200microgram inhalation powder capsules	1
14567	asmabec 250 clickhaler (focus pharmaceuticals ltd)	1
14590	asmabec 250microgram/actuation spacehaler (celltech pharma europe ltd)	1
14700	budesonide 400micrograms/actuation inhaler	1
14736	pulvinal beclometasone dipropionate 400micrograms/dose dry powder inhaler (chiesi ltd)	1
14757	pulvinal beclometasone dipropionate 100micrograms/dose dry powder inhaler (chiesi ltd)	1
15326	beclometasone 100micrograms/dose inhaler cfc free	1
15706	beclometasone 100 micrograms/actuation vortex inhaler	1
16018	mometasone 200micrograms/dose dry powder inhaler	1
16054	budesonide 200micrograms/actuation breath actuated powder inhaler	1
16148	clenil modulite 250micrograms/dose inhaler (chiesi ltd)	1
16151	clenil modulite 200micrograms/dose inhaler (chiesi ltd)	1
16158	clenil modulite 50micrograms/dose inhaler (chiesi ltd)	1
16305	flixotide 2mg/2ml nebules (glaxosmithkline uk ltd)	1
16584	beclometasone 50micrograms/dose inhaler cfc free	1
16625	ventide rotacaps (glaxosmithkline uk ltd)	1

17654	easyhaler beclometasone 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
17670	easyhaler budesonide 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
18394	bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)	1
18456	salbutamol 200microgram / beclometasone 100microgram inhalation powder capsules	1
18484	ventide paediatric rotacaps (glaxosmithkline uk ltd)	1
18537	budesonide 200microgram inhalation powder capsules	1
18848	qvar 100micrograms/dose easi-breathe inhaler (teva uk ltd)	1
19031	bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)	1
19121	beclometasone 100micrograms with salbutamol 200micrograms inhalation capsules	1
19376	beclometasone 200micrograms with salbutamol 400micrograms inhalation capsules	1
19389	asmabec 50microgram/actuation spacehaler (celltech pharma europe ltd)	1
19401	beclometasone 250micrograms/actuation inhaler and compact spacer	1
19736	becotide susp for nebulisation	1
20707	becotide 100	1
20763	becloforte	1
20812	pulmicort refill	1
20825	spacehaler bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)	1
21005	beclometasone 250micrograms/dose inhaler cfc free	1
21482	beclometasone 100micrograms/dose inhaler (mylan)	1
23675	pulmicort l.s. refil	1
23741	novolizer budesonide 200microgram/actuation pressurised inhalation (meda pharmaceuticals ltd)	1
24219	becotide rotacaps	1
24660	betamethasone valerate	1
24898	spacehaler bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)	1
25204	beclometasone 100micrograms/dose inhaler (a a h pharmaceuticals ltd)	1
26063	beclometasone 100micrograms/dose inhaler (teva uk ltd)	1
26665	pulmicort complete	1
27188	easyhaler budesonide 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
27525	becotide 50	1
27583	pulmicort	1
27679	beclometasone 100microgram/actuation pressurised inhalation (approved prescription services ltd)	1
27915	fluticasone prop disk refill	1
28073	beclometasone 250microgram/actuation pressurised inhalation (approved prescription services ltd)	1
28640	beclometasone 100microgram/actuation inhalation powder (actavis uk ltd)	1
28761	spacehaler bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)	1
29325	beclometasone 250micrograms/dose inhaler (mylan)	1
30210	beclometasone 250micrograms/dose inhaler (teva uk ltd)	1
30238	beclometasone 50microgram/actuation pressurised inhalation (approved prescription services ltd)	1
30649	easyhaler budesonide 400micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
31774	beclometasone 50micrograms/dose inhaler (mylan)	1
32874	beclometasone 50microgram/actuation inhalation powder (actavis uk ltd)	1
33258	beclometasone 250micrograms/dose inhaler (a a h pharmaceuticals ltd)	1

33849	beclometasone 100microgram/actuation inhalation powder (neo laboratories ltd)	1
34315	beclometasone 250microgram/actuation inhalation powder (actavis uk ltd)	1
34428	beclometasone 50microgram/actuation inhalation powder (neo laboratories ltd)	1
34739	beclometasone 50micrograms/dose inhaler (teva uk ltd)	1
34794	beclometasone 200micrograms/dose inhaler (a a h pharmaceuticals ltd)	1
34859	beclometasone 250microgram/actuation inhalation powder (neo laboratories ltd)	1
34919	beclometasone 50micrograms/dose inhaler (a a h pharmaceuticals ltd)	1
35071	becodisks 200microgram (glaxosmithkline uk ltd)	1
35106	becodisks 100microgram with diskhaler (glaxosmithkline uk ltd)	1
35107	beclometasone 400microgram inhalation powder blisters with device	1
35113	beclometasone 200microgram inhalation powder blisters	1
35118	becodisks 400microgram with diskhaler (glaxosmithkline uk ltd)	1
35225	flixotide 100microgram disks with diskhaler (glaxosmithkline uk ltd)	1
35288	beclometasone 400microgram inhalation powder blisters	1
35293	beclometasone 200microgram inhalation powder blisters with device	1
35299	becodisks 400microgram (glaxosmithkline uk ltd)	1
35374	flixotide 500microgram disks (glaxosmithkline uk ltd)	1
35392	flixotide 500microgram disks with diskhaler (glaxosmithkline uk ltd)	1
35408	becodisks 100microgram (glaxosmithkline uk ltd)	1
35430	becodisks 200microgram with diskhaler (glaxosmithkline uk ltd)	1
35461	flixotide 250microgram disks with diskhaler (glaxosmithkline uk ltd)	1
35510	budesonide 200micrograms/dose dry powder inhalation cartridge with device	1
35580	beclometasone 100microgram inhalation powder blisters with device	1
35602	budesonide 200micrograms/dose dry powder inhalation cartridge	1
35611	flixotide 250microgram disks (glaxosmithkline uk ltd)	1
35631	budelin novolizer 200micrograms/dose inhalation powder (meda pharmaceuticals ltd)	1
35638	fluticasone propionate 100microgram inhalation powder blisters with device	1
35652	beclometasone 100microgram inhalation powder blisters	1
35700	fluticasone propionate 500microgram inhalation powder blisters with device	1
35724	budelin novolizer 200micrograms/dose inhalation powder refill (meda pharmaceuticals ltd)	1
35772	fluticasone propionate 100microgram inhalation powder blisters	1
35905	fluticasone propionate 250microgram inhalation powder blisters	1
35986	flixotide 50microgram disks (glaxosmithkline uk ltd)	1
36021	fluticasone propionate 50microgram inhalation powder blisters with device	1
36090	flixotide 100microgram disks (glaxosmithkline uk ltd)	1
36290	flixotide 50microgram disks with diskhaler (glaxosmithkline uk ltd)	1
36401	fluticasone propionate 250microgram inhalation powder blisters with device	1
36462	fluticasone propionate 500microgram inhalation powder blisters	1
37203	beclometasone 5mg gastro-resistant modified-release tablets	1
37432	fostair 100micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	1
37447	fluticasone propionate 50microgram inhalation powder blisters	1
37470	beclometasone 100micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	1

39067	clipper 5mg gastro-resistant modified-release tablets (chiesi ltd)	1
39099	pulmicort 100micrograms/dose inhaler cfc free (astrazeneca uk ltd)	1
39102	budesonide 100micrograms/dose inhaler cfc free	1
39200	aerobec forte 250 autohaler (meda pharmaceuticals ltd)	1
39879	budesonide 200micrograms/dose inhaler cfc free	1
40057	pulmicort 200micrograms/dose inhaler cfc free (astrazeneca uk ltd)	1
41269	beclometasone 400 cyclocaps (teva uk ltd)	1
41412	beclometasone 400micrograms/actuation inhaler	1
42928	flixotide 100micrograms/dose accuhaler (glaxosmithkline uk ltd)	1
42985	flixotide 50micrograms/dose accuhaler (glaxosmithkline uk ltd)	1
42994	flixotide 250micrograms/dose accuhaler (glaxosmithkline uk ltd)	1
43074	flixotide 500micrograms/dose accuhaler (glaxosmithkline uk ltd)	1
46157	beclometasone 200 cyclocaps (teva uk ltd)	1
47225	budesonide 9mg gastro-resistant granules sachets	1
47943	beclazone easi-breathe (roi) 100microgram/actuation pressurised inhalation (ivax pharmaceuticals ireland)	1
48088	budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd)	1
48340	clenil modulite 100micrograms/dose inhaler (mawdsley-brooks & company ltd)	1
48666	flutiform 250micrograms/dose / 10micrograms/dose inhaler (napp pharmaceuticals ltd)	1
48709	qvar 100micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)	1
48739	seretide 250 evohaler (de pharmaceuticals)	1
49000	seretide 250 evohaler (waymade healthcare plc)	1
49114	symbicort 100/6 turbohaler (sigma pharmaceuticals plc)	1
49367	clenil modulite 50micrograms/dose inhaler (mawdsley-brooks & company ltd)	1
49412	clenil modulite 200micrograms/dose inhaler (mawdsley-brooks & company ltd)	1
49711	pulmicort 200micrograms/dose inhaler (astrazeneca uk ltd)	1
49772	fluticasone 250micrograms/dose evohaler (sigma pharmaceuticals plc)	1
49868	fluticasone 250micrograms/dose / formoterol 10micrograms/dose inhaler cfc free	1
50036	flutiform 125micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	1
50037	pulmicort 0.5mg respules (waymade healthcare plc)	1
50129	qvar 100micrograms/dose easi-breathe inhaler (de pharmaceuticals)	1
50287	qvar 100 inhaler (de pharmaceuticals)	1
50560	seretide 250 accuhaler (sigma pharmaceuticals plc)	1
50689	flutiform 50micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	1
50701	becotide rotahaler (glaxosmithkline uk ltd)	1
50739	symbicort 400/12 turbohaler (mawdsley-brooks & company ltd)	1
50886	seretide 250 evohaler (stephar (u.k.) ltd)	1
50945	symbicort 100/6 turbohaler (mawdsley-brooks & company ltd)	1
51027	seretide 125 evohaler (de pharmaceuticals)	1
51151	seretide 125 evohaler (lexon (uk) ltd)	1
51209	fluticasone 125micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	1
51234	qvar 100 inhaler (waymade healthcare plc)	1
51270	fluticasone 50micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	1

51394	seretide 500 accuhaler (waymade healthcare plc)	1
51415	qvar 50 inhaler (mawdsley-brooks & company ltd)	1
51480	qvar 100 autohaler (de pharmaceuticals)	1
51570	symbicort 200/6 turbohaler (de pharmaceuticals)	1
51593	seretide 500 accuhaler (de pharmaceuticals)	1
51681	qvar 100 inhaler (sigma pharmaceuticals plc)	1
51759	symbicort 200/6 turbohaler (mawdsley-brooks & company ltd)	1
51815	flixotide 250micrograms/dose evohaler (waymade healthcare plc)	1
51861	seretide 500 accuhaler (mawdsley-brooks & company ltd)	1
51909	seretide 250 evohaler (necessity supplies ltd)	1
51997	budesonide 9mg gastro-resistant granules sachets	1
52732	pulmicort 0.5mg respules (necessity supplies ltd)	1
52806	qvar 100 autohaler (lexon (uk) ltd)	1
53057	flixotide 50micrograms/dose evohaler (lexon (uk) ltd)	1
53230	seretide 250 accuhaler (de pharmaceuticals)	1
53237	symbicort 400/12 turbohaler (de pharmaceuticals)	1
53283	seretide 100 accuhaler (waymade healthcare plc)	1
53480	qvar 100 autohaler (stephar (u.k.) ltd)	1
53491	symbicort 200/6 turbohaler (sigma pharmaceuticals plc)	1
54207	qvar 50 inhaler (de pharmaceuticals)	1
54399	qvar 100 autohaler (sigma pharmaceuticals plc)	1
55677	seretide 500 accuhaler (lexon (uk) ltd)	1
56144	budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd)	1
56462	becodisks 400microgram (waymade healthcare plc)	1
56471	becodisks 200microgram (mawdsley-brooks & company ltd)	1
56474	flixotide 125micrograms/dose evohaler (de pharmaceuticals)	1
56475	flixotide 50micrograms/dose accuhaler (sigma pharmaceuticals plc)	1
56477	flixotide 100micrograms/dose accuhaler (waymade healthcare plc)	1
56484	flixotide 250micrograms/dose accuhaler (waymade healthcare plc)	1
56493	qvar 50micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)	1
56498	pulmicort 200 turbohaler (waymade healthcare plc)	1
56499	flixotide 500micrograms/dose accuhaler (waymade healthcare plc)	1
57525	flixotide 250micrograms/dose accuhaler (stephar (u.k.) ltd)	1
57555	flixotide 125micrograms/dose evohaler (dowelhurst ltd)	1
57579	flixotide 50micrograms/dose accuhaler (de pharmaceuticals)	1
57589	becloforte 250micrograms/dose inhaler (dowelhurst ltd)	1
59327	relvar ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
59439	fluticasone furoate 92micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	1
59573	relvar ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
59899	fluticasone furoate 184micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler	1
60937	pulmicort 200 turbohaler (dowelhurst ltd)	1
60946	entocort cr 3mg capsules (waymade healthcare plc)	1

61280	seretide 250 accuhaler (waymade healthcare plc)	1
61644	fostair nexthaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	1
61664	clenil modulite 250micrograms/dose inhaler (waymade healthcare plc)	1
61666	duoresp spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (teva uk ltd)	1
61782	duoresp spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (teva uk ltd)	1
62030	beclometasone 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
62126	seretide 100 accuhaler (de pharmaceuticals)	1
62341	becotide 50 inhaler (dowelhurst ltd)	1
62518	beclometasone 100micrograms/dose inhaler cfc free (ennogen healthcare ltd)	1
63252	seretide 250 evohaler (lexon (uk) ltd)	1
63585	beclometasone 50micrograms/dose inhaler (almus pharmaceuticals ltd)	1
63893	budesonide 9mg modified-release tablets	1
63945	seretide 250 accuhaler (lexon (uk) ltd)	1
64372	sirdupla 25micrograms/dose / 125micrograms/dose inhaler (mylan)	1
64373	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (mylan)	1
64557	cortiment 9mg modified-release tablets (ferring pharmaceuticals ltd)	1
64638	flutiform 125micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)	1
65117	seretide 125 evohaler (mawdsley-brooks & company ltd)	1
65596	fostair 200micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	1
65658	fostair nexthaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)	1
65677	airflusal forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (sandoz ltd)	1
65758	beclometasone 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	1
65894	beclometasone 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	1
66448	flutiform 250micrograms/dose / 10micrograms/dose inhaler (waymade healthcare plc)	1
66453	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (waymade healthcare plc)	1
67055	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)	1
67101	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler (a a h pharmaceuticals ltd)	1
67234	becotide 100 inhaler (waymade healthcare plc)	1
67237	flixotide 125micrograms/dose evohaler (lexon (uk) ltd)	1
67239	pulmicort 400 turbohaler (waymade healthcare plc)	1
67253	flixotide 50micrograms/dose accuhaler (mawdsley-brooks & company ltd)	1
67261	pulmicort 1mg respules (sigma pharmaceuticals plc)	1
67265	becodisks 200microgram (lexon (uk) ltd)	1
67315	budesonide 400micrograms/dose turbohaler (waymade healthcare plc)	1
67319	flixotide 0.5mg/2ml nebules (waymade healthcare plc)	1
67322	pulmicort 100 turbohaler (waymade healthcare plc)	1
67677	symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (astrazeneca uk ltd)	1
67735	beclazone easi-breathe (roi) 250microgram/actuation pressurised inhalation (ivax pharmaceuticals ireland)	1
67958	budesonide 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free	1
68034	symbicort 200/6 turbohaler (necessity supplies ltd)	1
68175	flutiform 50micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)	1
68453	seretide 125 evohaler (waymade healthcare plc)	1

68495	seretide 500 accuhaler (necessity supplies ltd)	1
68983	aerivio spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (teva uk ltd)	1
69436	sereflo 25micrograms/dose / 125micrograms/dose inhaler (kent pharmaceuticals ltd)	1
69538	sereflo 25micrograms/dose / 250micrograms/dose inhaler (kent pharmaceuticals ltd)	1
69827	airflusal 25micrograms/dose / 250micrograms/dose inhaler (sandoz ltd)	1
70015	beclometasone 100micrograms/dose inhaler (almus pharmaceuticals ltd)	1
70250	airflusal 25micrograms/dose / 125micrograms/dose inhaler (sandoz ltd)	1
70711	trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler (chiesi ltd)	1
70749	budesonide 400micrograms/dose turbohaler (dowelhurst ltd)	1
71109	flixotide 250micrograms/dose accuhaler (de pharmaceuticals)	1
71260	generic trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler	1
71284	fobumix easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
71337	qvar 100 inhaler (mawdsley-brooks & company ltd)	1
71338	pulmicort 200 turbohaler (de pharmaceuticals)	1
71341	flixotide 100micrograms/dose accuhaler (necessity supplies ltd)	1
71345	budesonide 200micrograms/dose turbohaler (dowelhurst ltd)	1
71347	pulmicort 400 turbohaler (sigma pharmaceuticals plc)	1
71354	symbicort 400/12 turbohaler (necessity supplies ltd)	1
71356	clenil modulite 250micrograms/dose inhaler (mawdsley-brooks & company ltd)	1
71366	flixotide 500micrograms/dose accuhaler (de pharmaceuticals)	1
71368	pulmicort 200 turbohaler (lexon (uk) ltd)	1
71371	symbicort 100/6 turbohaler (waymade healthcare plc)	1
71380	flixotide 250micrograms/dose accuhaler (necessity supplies ltd)	1
71409	seretide 50 evohaler (waymade healthcare plc)	1
71427	budesonide 100micrograms/dose turbohaler (dowelhurst ltd)	1
71467	beclometasone 50micrograms/dose inhaler cfc free (j m mcgill ltd)	1
71763	trelegy ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)	1
71915	fobumix easyhaler 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
72292	flixotide 250micrograms/dose accuhaler (mawdsley-brooks & company ltd)	1
72310	generic trelegy ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler	1
72400	fobumix easyhaler 80micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1
72564	aloflute 25micrograms/dose / 125micrograms/dose inhaler (mylan)	1
73527	aloflute 25micrograms/dose / 250micrograms/dose inhaler (mylan)	1
73691	flixotide 100micrograms/dose accuhaler (de pharmaceuticals)	1
73849	fusacomb easyhaler 50micrograms/dose / 500micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	1

Identification of ACE$_i$-ARB

List of product codes (prodcode) used to identify ACE$_i$-ARB and their descriptions are listed in the table below. The final codes to identify presence of ACE$_i$-ARB are identified in the far right columns by a '1'.

prodcode	productname	acei	arb	Included
65	lisinopril 10mg tablets	1	0	1
69	lisinopril 20mg tablets	1	0	1
78	lisinopril 5mg tablets	1	0	1
80	ramipril 5mg capsules	1	0	1
82	ramipril 10mg capsules	1	0	1
97	perindopril erbumine 4mg tablets	1	0	1
147	ramipril 1.25mg capsules	1	0	1
196	enalapril 5mg tablets	1	0	1
217	captopril 4 mg/ml liq	1	0	1
277	lisinopril 2.5mg tablets	1	0	1
448	enalapril 2.5mg tablets	1	0	1
520	losartan 25mg tablets	0	1	1
529	candesartan 2mg tablets	0	1	1
531	candesartan 4mg tablets	0	1	1
575	valsartan 40mg capsules	0	1	1
593	perindopril erbumine 2mg tablets	1	0	1
624	losartan 100mg tablets	0	1	1
633	fosinopril 10mg tablets	1	0	1
654	ramipril 2.5/5mg/10mg capsule	1	0	1
709	ramipril 2.5mg capsules	1	0	1
756	ramipril 10mg tablets	1	0	1
761	ramipril 1.25mg tablets	1	0	1
764	co-diovan 80mg/12.5mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
828	irbesartan 75mg tablets	0	1	1
1021	innozide 20mg/12.5mg tablets (merck sharp & dohme ltd)	1	0	1
1121	captopril 12.5mg tablets	1	0	1
1143	captopril 25mg tablets	1	0	1
1144	capoten 25mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
1293	irbesartan 150mg tablets	0	1	1
1299	enalapril 10mg tablets	1	0	1
1520	capozide 25mg/50mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
1780	losartan 50mg tablets	0	1	1
1807	captopril 50mg tablets	1	0	1
1904	enalapril 20mg tablets	1	0	1
2927	perindopril/tert-butylamine 2 mg tab	1	0	1
2971	irbesartan 300mg tablets	0	1	1

2982	zestoretic 20- 20mg+12.5mg tablet (astrazeneca uk ltd)	1	0	1
3069	acepril 25mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
3203	capozide ls tablet (e r squibb and sons ltd)	1	0	1
3222	valsartan 80mg capsules	0	1	1
3310	capoten 12.5mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
3509	enalapril maleate 40 mg tab	1	0	1
3720	zestril 2.5mg tablets (astrazeneca uk ltd)	1	0	1
3839	capoten 50mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
3929	quinapril 10mg tablets	1	0	1
4155	amias 2mg tablets (takeda uk ltd)	0	1	1
4226	cozaar 25mg tablets (merck sharp & dohme ltd)	0	1	1
4540	cozaar-comp 50mg/12.5mg tablets (merck sharp & dohme ltd)	0	1	1
4571	staril 10mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
4645	valsartan 160mg capsules	0	1	1
4685	amias 4mg tablets (takeda uk ltd)	0	1	1
4741	candesartan 16mg tablets	0	1	1
4818	candesartan 8mg tablets	0	1	1
5013	amias 8mg tablets (takeda uk ltd)	0	1	1
5117	amias 16mg tablets (takeda uk ltd)	0	1	1
5159	quinapril 20mg tablets	1	0	1
5189	enalapril 20mg / hydrochlorothiazide 12.5mg tablets	1	0	1
5275	tritace 2.5mg capsules (sanofi)	1	0	1
5612	coversyl 2mg tablets (servier laboratories ltd)	1	0	1
5723	cozaar 50mg tablets (merck sharp & dohme ltd)	0	1	1
5735	tritace 5mg capsules (sanofi)	1	0	1
5800	coversyl 4mg tablets (servier laboratories ltd)	1	0	1
5861	fosinopril 20mg tablets	1	0	1
5988	telmisartan 40mg tablets	0	1	1
6078	perindopril erbumine 8mg tablets	1	0	1
6217	olmesartan medoxomil 10mg tablets	0	1	1
6243	telmisartan 20mg tablets	0	1	1
6261	tritace 1.25mg tablets (sanofi)	1	0	1
6285	olmesartan medoxomil 20mg tablets	0	1	1
6288	ramipril 5mg tablets	1	0	1
6314	ramipril 2.5mg tablets	1	0	1
6351	olmesartan medoxomil 40mg tablets	0	1	1
6359	zestoretic 10- 10mg+12.5mg tablet (astrazeneca uk ltd)	1	0	1
6362	tritace 5mg tablets (sanofi)	1	0	1
6364	tritace 2.5mg tablets (sanofi)	1	0	1
6408	tanatril 5mg tablets (mitsubishi tanabe pharma europe ltd)	1	0	1
6437	losartan 50mg / hydrochlorothiazide 12.5mg tablets	0	1	1
6468	lisinopril 20mg / hydrochlorothiazide 12.5mg tablets	1	0	1

6518	diovan 160mg capsules (novartis pharmaceuticals uk ltd)	0	1	1
6765	quinapril 5mg tablets	1	0	1
6786	lisinopril 10mg / hydrochlorothiazide 12.5mg tablets	1	0	1
6794	perindopril erbumine 4mg / indapamide 1.25mg tablets	1	0	1
6806	zestril 10mg tablets (astrazeneca uk ltd)	1	0	1
6807	zestril 5mg tablets (astrazeneca uk ltd)	1	0	1
6877	co-diovan 160mg/12.5mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
6939	eprosartan 300mg tablets	0	1	1
7043	candesartan 32mg tablets	0	1	1
7314	accupro 5mg tablets (pfizer ltd)	1	0	1
7338	aprovel 75mg tablets (sanofi)	0	1	1
8105	innovace 20mg tablets (merck sharp & dohme ltd)	1	0	1
8106	innovace 2.5mg tablets (merck sharp & dohme ltd)	1	0	1
8268	zestril 20mg tablets (astrazeneca uk ltd)	1	0	1
8800	innovace 5mg tablets (merck sharp & dohme ltd)	1	0	1
8830	innovace 10mg tablets (merck sharp & dohme ltd)	1	0	1
8923	captopril 100 mg tab	1	0	1
9196	aprovel 150mg tablets (sanofi)	0	1	1
9646	tritace 1.25mg capsules (aventis pharma)	1	0	1
9693	tritace 10mg capsules (sanofi)	1	0	1
9731	quinapril 40mg tablets	1	0	1
9745	teveten 300mg tablets (mylan)	0	1	1
9764	carace 20 tablet (bristol-myers squibb pharmaceuticals ltd)	1	0	1
9915	tritace 10mg tablets (sanofi)	1	0	1
10316	coaprovel 150mg/12.5mg tablets (sanofi)	0	1	1
10323	losartan 100mg / hydrochlorothiazide 25mg tablets	0	1	1
10882	carace 2.5mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
10902	captopril 50mg with hydrochlorothiazide 25mg tablets	1	0	1
11133	hydrochlorothiazide with captopril 25mg with 50mg tablet	1	0	1
11197	innovace melt 5mg wafer (merck sharp & dohme ltd)	1	0	1
11251	diovan 40mg capsules (novartis pharmaceuticals uk ltd)	0	1	1
11252	diovan 80mg capsules (novartis pharmaceuticals uk ltd)	0	1	1
11348	aprovel 300mg tablets (sanofi)	0	1	1
11351	co-zidocapt 25mg/50mg tablets	1	0	1
11448	irbesartan 150mg / hydrochlorothiazide 12.5mg tablets	0	1	1
11469	irbesartan 300mg / hydrochlorothiazide 12.5mg tablets	0	1	1
11526	coaprovel 300mg/12.5mg tablets (sanofi)	0	1	1
11561	co-zidocapt 12.5mg/25mg tablets	1	0	1
11567	ramipril 5mg with felodipine 5mg modified-release tablet	1	0	1
11641	captopril 25mg with hydrochlorothiazide 12.5mg tablets	1	0	1
11864	valsartan 160mg / hydrochlorothiazide 12.5mg tablets	0	1	1
11937	ramipril 2.5mg/5ml oral suspension	1	0	1

11965	ramipril 2.5mg with felodipine 2.5mg modified-release tablet	1	0	1
11983	perindopril erbumine 4mg/5ml oral suspension	1	0	1
11987	lisinopril 5mg/5ml oral solution	1	0	1
12313	carace 20mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
12815	tanatril 10mg tablets (mitsubishi tanabe pharma europe ltd)	1	0	1
12836	eprosartan 600mg tablets	0	1	1
12858	imidapril 10mg tablets	1	0	1
12874	telmisartan 80mg tablets	0	1	1
13123	eprosartan 400mg tablets	0	1	1
13589	staril 20mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
13755	enalapril 10mg wafer	1	0	1
13821	micardis 40mg tablets (boehringer ingelheim ltd)	0	1	1
14228	coversyl plus tablets (servier laboratories ltd)	1	0	1
14283	valsartan 160mg / hydrochlorothiazide 25mg tablets	0	1	1
14387	carace 5mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
14477	accupro 10mg tablets (pfizer ltd)	1	0	1
14478	accupro 20mg tablets (pfizer ltd)	1	0	1
14738	hydrochlorothiazide with losartan 12.5mg with 50mg tablet	0	1	1
14870	telmisartan 40mg / hydrochlorothiazide 12.5mg tablets	0	1	1
14943	valsartan 40mg tablets	0	1	1
14960	coversyl 8mg tablets (servier laboratories ltd)	1	0	1
14965	cozaar 100mg tablets (merck sharp & dohme ltd)	0	1	1
14983	olmetec 10mg tablets (daiichi sankyo uk ltd)	0	1	1
15031	accuretic 12.5mg/10mg tablets (pfizer ltd)	1	0	1
15085	innovace titration pack (merck sharp & dohme ltd)	1	0	1
15096	accupro 40mg tablets (pfizer ltd)	1	0	1
15108	quinapril 10mg / hydrochlorothiazide 12.5mg tablets	1	0	1
15135	hydrochlorothiazide with captopril 12.5mg with 25mg tablet	1	0	1
15958	captopril 2mg tablets	1	0	1
16060	valsartan 80mg / hydrochlorothiazide 12.5mg tablets	0	1	1
16161	telmisartan 80mg / hydrochlorothiazide 12.5mg tablets	0	1	1
16285	teveten 400mg tablets (abbott healthcare products ltd)	0	1	1
16371	teveten 600mg tablets (mylan)	0	1	1
16701	carace 10mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
16708	enalapril titration pack	1	0	1
16924	imidapril 5mg tablets	1	0	1
17006	triapin 5mg/5mg modified-release tablets (sanofi)	1	0	1
17474	felodipine 5mg modified-release / ramipril 5mg tablets	1	0	1
17545	micardis 80mg tablets (boehringer ingelheim ltd)	0	1	1
17624	captopril 5mg/5ml oral suspension	1	0	1
17633	captopril 3mg/5ml oral solution	1	0	1
17655	carace 10 tablet (bristol-myers squibb pharmaceuticals ltd)	1	0	1

17686	micardis 20mg tablets (boehringer ingelheim ltd)	0	1	1
17689	micardisplus 80mg/12.5mg tablets (boehringer ingelheim ltd)	0	1	1
18200	olmesartan medoxomil 20mg / hydrochlorothiazide 12.5mg tablets	0	1	1
18202	micardisplus 40mg/12.5mg tablets (boehringer ingelheim ltd)	0	1	1
18219	imidapril 20mg tablets	1	0	1
18263	acezide 25mg/50mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
18269	acepril 12.5mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
18325	acepril 50mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
18903	olmesartan medoxomil 20mg / hydrochlorothiazide 25mg tablets	0	1	1
18910	olmetec 20mg tablets (daiichi sankyo uk ltd)	0	1	1
19198	lisinopril 20mg tablets (teva uk ltd)	1	0	1
19204	lisinopril 5mg tablets (teva uk ltd)	1	0	1
19208	enalapril 10mg tablets (actavis uk ltd)	1	0	1
19223	lisinopril 10mg tablets (teva uk ltd)	1	0	1
20117	olmetec 40mg tablets (daiichi sankyo uk ltd)	0	1	1
20188	enalapril 2.5mg wafer	1	0	1
20849	tensopril 12.5mg tablets (teva uk ltd)	1	0	1
20975	lisinopril 7.5mg/5ml oral suspension	1	0	1
21162	felodipine 2.5mg modified-release / ramipril 2.5mg tablets	1	0	1
21231	caralpha 20mg/12.5mg tablets (actavis uk ltd)	1	0	1
21423	cozaar-comp 100mg/25mg tablets (merck sharp & dohme ltd)	0	1	1
21943	kaplon 12.5mg tablets (teva uk ltd)	1	0	1
22439	ednyt 20mg tablet (dominion pharma)	1	0	1
22708	enalapril 5mg wafer	1	0	1
22882	ramipril	1	0	1
23252	pralenal 10 tablets (opus pharmaceuticals ltd)	1	0	1
23456	hydrochlorothiazide with valsartan 25mg with 160mg tablet	0	1	1
23478	tensopril 50mg tablets (teva uk ltd)	1	0	1
24041	enalapril 20mg wafer	1	0	1
24268	hydrochlorothiazide with valsartan 12.5mg with 80mg tablet	0	1	1
24359	diovan 40mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
24482	captomex 50mg tablets (actavis uk ltd)	1	0	1
24484	hydrochlorothiazide with valsartan 12.5mg with 160mg tablet	0	1	1
24632	hydrochlorothiazide with losartan 25mg with 100mg tablet	0	1	1
25382	co-diovan 160mg/25mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
25998	captomex 12.5mg tablets (actavis uk ltd)	1	0	1
26995	kaplon 25mg tablets (teva uk ltd)	1	0	1
27520	olmetec plus 20mg/25mg tablets (daiichi sankyo uk ltd)	0	1	1
27871	innovace melt 10mg wafer (merck sharp & dohme ltd)	1	0	1
27890	enalapril maleate	1	0	1
28127	enalapril 2.5mg tablets (teva uk ltd)	1	0	1
28438	triapin 2.5mg/2.5mg modified-release tablets (sanofi)	1	0	1

28486	captopril 6.25mg/5ml oral suspension	1	0	1
28586	lopace 5mg capsules (discovery pharmaceuticals)	1	0	1
28820	captomex 25mg tablets (actavis uk ltd)	1	0	1
29530	innovace melt 2.5mg wafer (merck sharp & dohme ltd)	1	0	1
29627	lopace 2.5mg capsules (discovery pharmaceuticals)	1	0	1
29634	olmetec plus 20mg/12.5mg tablets (daiichi sankyo uk ltd)	0	1	1
30039	tensopril 25mg tablets (teva uk ltd)	1	0	1
30921	lisinopril 2.5mg tablets (teva uk ltd)	1	0	1
31072	amias 32mg tablets (takeda uk ltd)	0	1	1
31160	irbesartan	0	1	1
31587	innovace melt 20mg wafer (merck sharp & dohme ltd)	1	0	1
31716	enalapril 20mg tablets (actavis uk ltd)	1	0	1
32048	kaplon 50mg tablets (teva uk ltd)	1	0	1
32166	capto-co 25mg+50mg tablet (ivax pharmaceuticals uk ltd)	1	0	1
32241	enalapril 10mg tablets (a a h pharmaceuticals ltd)	1	0	1
32514	ecopace 25mg tablets (amco)	1	0	1
32560	tanatril 20mg tablets (mitsubishi tanabe pharma europe ltd)	1	0	1
32597	lisinopril 10mg tablets (sandoz ltd)	1	0	1
32857	ramipril 1.25mg capsules (teva uk ltd)	1	0	1
32934	lopace 10mg capsules (discovery pharmaceuticals)	1	0	1
33057	ednyt 5mg tablet (dominion pharma)	1	0	1
33078	enalapril 20mg tablets (a a h pharmaceuticals ltd)	1	0	1
33095	perindopril erbumine 4mg tablets (a a h pharmaceuticals ltd)	1	0	1
33336	captopril 5mg/5ml oral suspension (eldon laboratories)	1	0	1
33353	lisinopril 20mg / hydrochlorothiazide 12.5mg tablets (teva uk ltd)	1	0	1
33646	captopril 12.5mg tablet (generics (uk) ltd)	1	0	1
33811	ramipril 2.5mg capsules (ranbaxy (uk) ltd)	1	0	1
33894	ramipril 10mg capsules (teva uk ltd)	1	0	1
33977	lisinopril 10mg tablets (mylan)	1	0	1
34357	ramipril 10mg capsules (genus pharmaceuticals ltd)	1	0	1
34382	ramipril 5mg capsules (zentiva)	1	0	1
34390	ramipril 5mg capsules (genus pharmaceuticals ltd)	1	0	1
34400	enalapril 5mg tablet (dowelhurst ltd)	1	0	1
34412	ramipril 5mg capsules (teva uk ltd)	1	0	1
34429	ramipril 5mg capsules (mylan)	1	0	1
34431	ramipril 2.5mg capsules (zentiva)	1	0	1
34432	ramipril 2.5mg capsules (genus pharmaceuticals ltd)	1	0	1
34453	enalapril 20mg tablets (mylan)	1	0	1
34471	lisinopril 5mg tablets (mylan)	1	0	1
34490	ramipril 2.5mg capsules (teva uk ltd)	1	0	1
34505	ramipril 2.5mg capsules (sandoz ltd)	1	0	1
34528	ramipril 2.5mg capsules (a a h pharmaceuticals ltd)	1	0	1

34539	ramipril 5mg capsules (sandoz ltd)	1	0	1
34540	ramipril 5mg capsules (a a h pharmaceuticals ltd)	1	0	1
34544	captopril 12.5mg tablet (ivax pharmaceuticals uk ltd)	1	0	1
34562	captopril 25mg tablet (ivax pharmaceuticals uk ltd)	1	0	1
34567	ramipril 2.5mg capsules (mylan)	1	0	1
34583	ramipril 10mg capsule (dexcel-pharma ltd)	1	0	1
34589	ramipril 5mg capsule (dexcel-pharma ltd)	1	0	1
34651	ramipril 10mg capsules (mylan)	1	0	1
34652	ramipril 5mg capsule (sovereign medical ltd)	1	0	1
34657	ramipril 10mg capsules (zentiva)	1	0	1
34696	lisinopril 20mg tablets (mylan)	1	0	1
34698	ramipril 1.25mg capsules (zentiva)	1	0	1
34710	ramipril 10mg capsules (sandoz ltd)	1	0	1
34712	enalapril 20mg tablets (kent pharmaceuticals ltd)	1	0	1
34719	captopril 50mg tablet (generics (uk) ltd)	1	0	1
34732	ramipril 2.5mg capsule (dexcel-pharma ltd)	1	0	1
34768	enalapril 20mg tablets (ivax pharmaceuticals uk ltd)	1	0	1
34798	enalapril 20mg tablets (sandoz ltd)	1	0	1
34799	lisinopril 20mg tablets (zentiva)	1	0	1
34877	ramipril 10mg capsule (sovereign medical ltd)	1	0	1
34893	ramipril 10mg capsule (ivax pharmaceuticals uk ltd)	1	0	1
34936	captopril 25mg tablet (lagap)	1	0	1
34937	captopril 50mg tablet (ivax pharmaceuticals uk ltd)	1	0	1
34943	ramipril 10mg capsules (a a h pharmaceuticals ltd)	1	0	1
34952	enalapril 10mg tablets (mylan)	1	0	1
34953	enalapril 20mg tablets (zentiva)	1	0	1
35007	ramipril 10mg/5ml oral suspension	1	0	1
35096	exforge 10mg/160mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
35173	valsartan 160mg with amlodipine 5mg tablets	0	1	1
35174	valsartan 80mg with amlodipine 5mg tablets	0	1	1
35189	amlodipine 10mg / valsartan 160mg tablets	0	1	1
35196	coaprovel 300mg/25mg tablets (sanofi)	0	1	1
35302	captopril 12.5mg/5ml oral suspension	1	0	1
35304	valsartan 160mg with amlodipine 10mg tablets	0	1	1
35317	exforge 5mg/80mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
35329	amlodipine 5mg / valsartan 80mg tablets	0	1	1
35343	amlodipine 5mg / valsartan 160mg tablets	0	1	1
35380	hydrochlorothiazide with olmesartan medoxomil 12.5mg with 20mg tablet	0	1	1
35481	irbesartan 300mg / hydrochlorothiazide 25mg tablets	0	1	1
35697	exforge 5mg/160mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
35731	perindopril erbumine 8mg tablets (a a h pharmaceuticals ltd)	1	0	1
35794	enalapril 5mg tablets (a a h pharmaceuticals ltd)	1	0	1

36742	captopril 2mg/5ml oral suspension	1	0	1
36753	ednyt 10mg tablet (dominion pharma)	1	0	1
36939	irbesartan 300mg/5ml oral suspension	0	1	1
37080	enalapril 5mg/5ml oral solution	1	0	1
37087	enalapril 5mg/5ml oral suspension	1	0	1
37573	valsartan 320mg tablets	0	1	1
37650	losartan 100mg / hydrochlorothiazide 12.5mg tablets	0	1	1
37655	captopril 25mg tablets (teva uk ltd)	1	0	1
37710	lisinopril 10mg / hydrochlorothiazide 12.5mg tablets (teva uk ltd)	1	0	1
37747	cozaar-comp 100mg/12.5mg tablets (merck sharp & dohme ltd)	0	1	1
37778	lisinopril 5mg/5ml oral suspension	1	0	1
37908	coversyl arginine plus 5mg/1.25mg tablets (servier laboratories ltd)	1	0	1
37930	perindopril arginine 5mg tablets	1	0	1
37964	perindopril arginine 2.5mg tablets	1	0	1
37965	coversyl arginine 5mg tablets (servier laboratories ltd)	1	0	1
37971	perindopril arginine 10mg tablets	1	0	1
37978	perindopril arginine 5mg / indapamide 1.25mg tablets	1	0	1
38026	coversyl arginine 10mg tablets (servier laboratories ltd)	1	0	1
38034	coversyl arginine 2.5mg tablets (servier laboratories ltd)	1	0	1
38285	perindopril erbumine 4mg tablets (teva uk ltd)	1	0	1
38308	ramipril 2.5/5mg/10mg tablet	1	0	1
38367	hydrochlorothiazide with losartan 12.5mg with 100mg tablet	0	1	1
38395	valsartan 80mg tablets	0	1	1
38459	telmisartan 80mg / hydrochlorothiazide 25mg tablets	0	1	1
38510	perindopril erbumine 4mg tablets (apotex uk ltd)	1	0	1
38854	quinapril 20mg/5ml oral solution	1	0	1
38889	micardisplus 80mg/25mg tablets (boehringer ingelheim ltd)	0	1	1
38899	quinil 10mg tablets (tillomed laboratories ltd)	1	0	1
38995	zestoretic 20 tablets (astrazeneca uk ltd)	1	0	1
39021	hydrochlorothiazide with olmesartan medoxomil 25mg with 20mg tablet	0	1	1
39137	zestoretic 10 tablets (astrazeneca uk ltd)	1	0	1
39147	carace 20 plus tablets (merck sharp & dohme ltd)	1	0	1
39199	diovan 320mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
39227	capozide ls 12.5mg/25mg tablets (bristol-myers squibb pharmaceuticals ltd)	1	0	1
39242	carace 10 plus tablets (merck sharp & dohme ltd)	1	0	1
39355	tritace 10mg tablet (sterwin medicines)	1	0	1
39512	captopril 25mg/5ml oral suspension	1	0	1
39786	olmesartan medoxomil 10mg/5ml oral suspension	0	1	1
39944	losartan 12.5mg tablets	0	1	1
39984	sevikar 20mg/5mg tablets (daiichi sankyo uk ltd)	0	1	1
40316	olmesartan medoxomil 20mg / amlodipine 5mg tablets	0	1	1
40355	quinil 5mg tablets (tillomed laboratories ltd)	1	0	1

40384	ramipril 10mg tablets (a a h pharmaceuticals ltd)	1	0	1
40571	cozaar 12.5mg tablets (merck sharp & dohme ltd)	0	1	1
40639	olmesartan medoxomil 40mg / amlodipine 5mg tablets	0	1	1
40668	olmesartan medoxomil 40mg / amlodipine 10mg tablets	0	1	1
40711	losartan 2.5mg/ml oral suspension sugar free	0	1	1
41203	sevikar 40mg/10mg tablets (daiichi sankyo uk ltd)	0	1	1
41205	sevikar 40mg/5mg tablets (daiichi sankyo uk ltd)	0	1	1
41232	cozaar 2.5mg/ml oral suspension (merck sharp & dohme ltd)	0	1	1
41417	enalapril 2.5mg tablets (a a h pharmaceuticals ltd)	1	0	1
41522	lisopress 20mg tablets (teva uk ltd)	1	0	1
41532	lisopress 5mg tablets (teva uk ltd)	1	0	1
41538	lisopress 2.5mg tablets (teva uk ltd)	1	0	1
41573	lisopress 10mg tablets (teva uk ltd)	1	0	1
41617	captopril 25mg tablets (actavis uk ltd)	1	0	1
41633	captopril 12.5mg tablets (actavis uk ltd)	1	0	1
41694	enalapril 2.5mg tablets (ivax pharmaceuticals uk ltd)	1	0	1
41743	captopril 50mg tablets (teva uk ltd)	1	0	1
41746	enalapril 10mg tablets (sandoz ltd)	1	0	1
42081	tritace 1.25mg tablet (sterwin medicines)	1	0	1
42285	quinil 40mg tablets (tillomed laboratories ltd)	1	0	1
42723	pralenal 5 tablets (opus pharmaceuticals ltd)	1	0	1
42894	enalapril 10mg tablets (teva uk ltd)	1	0	1
42901	enalapril 5mg tablets (teva uk ltd)	1	0	1
42902	enalapril 20mg tablets (teva uk ltd)	1	0	1
42908	enalapril 5mg tablets (ivax pharmaceuticals uk ltd)	1	0	1
43012	perindopril erbumine oral solution	1	0	1
43322	olmesartan medoxomil 40mg / hydrochlorothiazide 12.5mg tablets	0	1	1
43411	enalapril 5mg tablets (sandoz ltd)	1	0	1
43412	lisinopril 2.5mg tablets (a a h pharmaceuticals ltd)	1	0	1
43413	lisinopril 20mg tablets (a a h pharmaceuticals ltd)	1	0	1
43416	lisinopril 10mg tablets (a a h pharmaceuticals ltd)	1	0	1
43418	lisinopril 5mg tablets (a a h pharmaceuticals ltd)	1	0	1
43432	captopril 6.25mg tablets	1	0	1
43507	captopril 25mg tablet (generics (uk) ltd)	1	0	1
43563	enalapril 2.5mg tablets (zentiva)	1	0	1
43566	lisinopril 2.5mg tablets (sandoz ltd)	1	0	1
43649	captopril 25mg tablets (a a h pharmaceuticals ltd)	1	0	1
43813	perindopril erbumine 2mg tablets (actavis uk ltd)	1	0	1
43915	olmetec plus 40mg/12.5mg tablets (daiichi sankyo uk ltd)	0	1	1
44527	captopril 5mg/ml oral solution sugar free	1	0	1
44657	ednyt 2.5mg tablet (dominion pharma)	1	0	1
44778	valsartan 160mg tablets	0	1	1

45217	enalapril 5mg tablets (kent pharmaceuticals ltd)	1	0	1
45228	captopril capsules	1	0	1
45264	ramipril 1.25mg capsules (actavis uk ltd)	1	0	1
45300	lisinopril 10mg tablets (actavis uk ltd)	1	0	1
45319	perindopril erbumine 2mg tablets (a a h pharmaceuticals ltd)	1	0	1
45324	lisinopril 20mg tablets (actavis uk ltd)	1	0	1
45337	lisinopril 5mg tablets (actavis uk ltd)	1	0	1
45340	ramipril 10mg capsule (actavis uk ltd)	1	0	1
45554	ramipril 5mg/5ml oral solution	1	0	1
45600	diovan 160mg tablet (novartis pharmaceuticals uk ltd)	0	1	1
45816	lisinopril 5mg tablets (almus pharmaceuticals ltd)	1	0	1
45938	perindopril erbumine 8mg tablets (teva uk ltd)	1	0	1
46355	sevikar hct 20mg/5mg/12.5mg tablets (daiichi sankyo uk ltd)	0	1	1
46365	quinil 20mg tablets (tillomed laboratories ltd)	1	0	1
46687	olmesartan medoxomil with amlodipine and hydrochlorothiazide 20mg + 5mg + 12.5mg tablet	0	1	1
46715	olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 10mg + 12.5mg tablet	0	1	1
46792	olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 5mg + 12.5mg tablet	0	1	1
46851	captopril 5mg/5ml oral solution	1	0	1
46890	ramipril 5mg/5ml oral suspension	1	0	1
46951	captopril 12.5mg tablets (a a h pharmaceuticals ltd)	1	0	1
46957	captopril 12.5mg tablets (tillomed laboratories ltd)	1	0	1
46974	enalapril 5mg tablets (mylan)	1	0	1
46975	lisinopril 5mg tablets (sandoz ltd)	1	0	1
46979	lisinopril 20mg tablets (sandoz ltd)	1	0	1
47006	losartan 100mg tablets (teva uk ltd)	0	1	1
47021	ramipril 2.5mg/5ml oral solution sugar free	1	0	1
47159	lisinopril 10mg tablets (almus pharmaceuticals ltd)	1	0	1
47467	olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 5mg + 25mg tablet	0	1	1
47573	sevikar hct 40mg/5mg/12.5mg tablets (daiichi sankyo uk ltd)	0	1	1
47616	sevikar hct 40mg/10mg/12.5mg tablets (daiichi sankyo uk ltd)	0	1	1
47727	sevikar hct 40mg/5mg/25mg tablets (daiichi sankyo uk ltd)	0	1	1
47998	ramipril 2.5mg capsules (actavis uk ltd)	1	0	1
48008	ramipril 5mg capsules (actavis uk ltd)	1	0	1
48039	losartan 100mg / hydrochlorothiazide 12.5mg tablets (teva uk ltd)	0	1	1
48049	perindopril erbumine 2mg tablets (mylan)	1	0	1
48053	ramipril 2.5mg capsules (almus pharmaceuticals ltd)	1	0	1
48098	perindopril arginine 4mg with indapamide 1.25mg tablet	1	0	1
48180	perindopril erbumine 4mg tablets (sandoz ltd)	1	0	1
48214	perindopril erbumine 4mg tablets (actavis uk ltd)	1	0	1
48398	losartan 25mg tablets (dexcel-pharma ltd)	0	1	1
49164	ramipril 10mg capsules (actavis uk ltd)	1	0	1
49491	perindopril erbumine 2mg tablets (consilient health ltd)	1	0	1

49492	losartan 25mg tablets (mylan)	0	1	1
49588	losartan 100mg tablets (a a h pharmaceuticals ltd)	0	1	1
50185	candesartan 8mg tablets (teva uk ltd)	0	1	1
50334	enalapril 4mg/5ml oral suspension	1	0	1
50347	coversyl arginine 5mg tablets (waymade healthcare plc)	1	0	1
50402	perindopril 2mg tablet (servier laboratories ltd)	1	0	1
50509	ramipril 10mg/5ml oral solution	1	0	1
50607	perindopril arginine 2mg with indapamide 625 micrograms tablet	1	0	1
50780	enalapril 2mg/5ml oral solution	1	0	1
50863	enalapril 5mg/5ml oral solution (drug tariff special order)	1	0	1
50971	losartan 25mg tablets (a a h pharmaceuticals ltd)	0	1	1
51117	candesartan 8mg tablets (de pharmaceuticals)	0	1	1
51186	losartan 25mg tablets (arrow generics ltd)	0	1	1
51258	coversyl arginine plus 5mg/1.25mg tablets (de pharmaceuticals)	1	0	1
51368	azilsartan medoxomil 80mg tablets	0	1	1
51433	lisinopril 20mg tablets (tillomed laboratories ltd)	1	0	1
51519	candesartan 8mg tablets (a a h pharmaceuticals ltd)	0	1	1
51601	losartan 50mg tablets (actavis uk ltd)	0	1	1
51647	candesartan 4mg tablets (mawdsley-brooks & company ltd)	0	1	1
51701	ramipril 5mg capsules (bristol laboratories ltd)	1	0	1
51714	ramipril 2.5mg capsules (alliance healthcare (distribution) ltd)	1	0	1
51807	coversyl arginine 5mg tablets (de pharmaceuticals)	1	0	1
51897	edarbi 20mg tablets (takeda uk ltd)	0	1	1
52010	enalapril 10mg tablets (alliance healthcare (distribution) ltd)	1	0	1
52088	lisinopril 5mg tablets (phoenix healthcare distribution ltd)	1	0	1
52189	losartan 100mg / hydrochlorothiazide 25mg tablets (a a h pharmaceuticals ltd)	0	1	1
52197	ramipril 5mg capsules (sigma pharmaceuticals plc)	1	0	1
52208	candesartan 16mg tablets (a a h pharmaceuticals ltd)	0	1	1
52293	captopril 2mg capsules	1	0	1
52399	ramipril 1.25mg capsules (kent pharmaceuticals ltd)	1	0	1
52407	ramipril 10mg capsules (kent pharmaceuticals ltd)	1	0	1
52427	cozaar 100mg tablets (necessity supplies ltd)	0	1	1
52499	captopril 25mg/5ml oral solution	1	0	1
52559	candesartan 8mg tablets (zentiva)	0	1	1
52658	losartan 100mg/5ml oral suspension	0	1	1
52659	losartan 50mg/5ml oral solution	0	1	1
52858	co-diovan 80mg/12.5mg tablets (sigma pharmaceuticals plc)	0	1	1
52882	enalapril 5mg/5ml oral suspension sugar free	1	0	1
52886	losartan 12.5mg tablets (a a h pharmaceuticals ltd)	0	1	1
52972	irbesartan 300mg tablets (sigma pharmaceuticals plc)	0	1	1
53058	perindopril erbumine 8mg tablets (sandoz ltd)	1	0	1
53220	sevikar hct 40mg/10mg/25mg tablets (daiichi sankyo uk ltd)	0	1	1

53271	lisinopril 10mg tablets (alliance healthcare (distribution) ltd)	1	0	1
53551	lisinopril 20mg tablets (phoenix healthcare distribution ltd)	1	0	1
53612	ramipril 10mg tablets (alliance healthcare (distribution) ltd)	1	0	1
53621	ramipril 2.5mg capsules (bristol laboratories ltd)	1	0	1
53680	candesartan 16mg tablets (teva uk ltd)	0	1	1
53719	enalapril 20mg tablets (alliance healthcare (distribution) ltd)	1	0	1
53755	candesartan 4mg tablets (teva uk ltd)	0	1	1
53820	lisinopril 5mg tablets (arrow generics ltd)	1	0	1
53833	valsartan 160mg capsules (mylan)	0	1	1
53915	enalapril 5mg tablets (dexcel-pharma ltd)	1	0	1
54037	lisinopril 10mg tablets (relonchem ltd)	1	0	1
54049	losartan 50mg tablets (accord healthcare ltd)	0	1	1
54057	losartan 50mg tablets (teva uk ltd)	0	1	1
54201	lisinopril 20mg / hydrochlorothiazide 12.5mg tablets (almus pharmaceuticals ltd)	1	0	1
54283	lisinopril 5mg/5ml oral suspension (special order)	1	0	1
54288	lisinopril 10mg tablets (arrow generics ltd)	1	0	1
54298	ramipril 2.5mg capsules (arrow generics ltd)	1	0	1
54326	candesartan 32mg tablets (teva uk ltd)	0	1	1
54404	losartan 100mg tablets (actavis uk ltd)	0	1	1
54414	candesartan 16mg tablets (consilient health ltd)	0	1	1
54512	lisinopril oral solution	1	0	1
54544	captopril 25mg/5ml oral suspension	1	0	1
54620	ramipril 2.5mg capsules (sigma pharmaceuticals plc)	1	0	1
54726	valsartan 40mg capsules (teva uk ltd)	0	1	1
54733	perindopril erbumine 8mg tablets (consilient health ltd)	1	0	1
54735	losartan 50mg tablets (alliance healthcare (distribution) ltd)	0	1	1
54740	losartan 25mg tablets (actavis uk ltd)	0	1	1
54843	losartan 50mg tablets (dexcel-pharma ltd)	0	1	1
54899	perindopril erbumine 2mg tablets (teva uk ltd)	1	0	1
54928	lisinopril 10mg tablets (bristol laboratories ltd)	1	0	1
54941	ramipril 5mg capsules (alliance healthcare (distribution) ltd)	1	0	1
54942	perindopril erbumine 8mg tablets (mylan)	1	0	1
54986	perindopril erbumine 8mg/5ml oral suspension	1	0	1
55002	lisinopril 20mg tablets (accord healthcare ltd)	1	0	1
55017	irbesartan 300mg tablets (accord healthcare ltd)	0	1	1
55160	cozaar-comp 50mg/12.5mg tablets (sigma pharmaceuticals plc)	0	1	1
55187	valsartan 160mg capsules (arrow generics ltd)	0	1	1
55296	losartan 50mg tablets (mylan)	0	1	1
55299	ramipril 1.25mg capsules (a a h pharmaceuticals ltd)	1	0	1
55358	olmesartan medoxomil with amlodipine and hydrochlorothiazide 40mg + 10mg + 25mg tablet	0	1	1
55399	lisinopril 20mg / hydrochlorothiazide 12.5mg tablets (a a h pharmaceuticals ltd)	1	0	1
55446	losartan 100mg tablets (bristol laboratories ltd)	0	1	1

55456	lisinopril 5mg tablets (alliance healthcare (distribution) ltd)	1	0	1
55588	lisinopril 20mg tablets (sigma pharmaceuticals plc)	1	0	1
55639	lisinopril 10mg tablets (accord healthcare ltd)	1	0	1
55718	losartan 25mg tablets (phoenix healthcare distribution ltd)	0	1	1
55798	ramipril 5mg capsules (waymade healthcare plc)	1	0	1
55821	valsartan 160mg capsules (teva uk ltd)	0	1	1
55896	lisinopril 2.5mg tablets (actavis uk ltd)	1	0	1
55903	enalapril 10mg tablets (dexcel-pharma ltd)	1	0	1
56013	ramipril 2.5mg capsules (waymade healthcare plc)	1	0	1
56038	ramipril 10mg tablets (pfizer ltd)	1	0	1
56079	perindopril tosilate 10mg tablets	1	0	1
56104	losartan 50mg tablets (a a h pharmaceuticals ltd)	0	1	1
56129	ramipril 5mg capsules (kent pharmaceuticals ltd)	1	0	1
56148	ramipril 1.25mg tablets (kent pharmaceuticals ltd)	1	0	1
56157	perindopril tosilate 5mg / indapamide 1.25mg tablets	1	0	1
56162	perindopril erbumine 4mg tablets (consilient health ltd)	1	0	1
56169	ramipril 10mg capsules (arrow generics ltd)	1	0	1
56204	losartan 50mg / hydrochlorothiazide 12.5mg tablets (actavis uk ltd)	0	1	1
56244	lisinopril 20mg / hydrochlorothiazide 12.5mg tablets (tillomed laboratories ltd)	1	0	1
56279	lisinopril 2.5mg/5ml oral solution	1	0	1
56356	ramipril 10mg capsules (alliance healthcare (distribution) ltd)	1	0	1
56472	perindopril erbumine 4mg tablets (kent pharmaceuticals ltd)	1	0	1
56473	perindopril erbumine 2mg tablets (sigma pharmaceuticals plc)	1	0	1
56505	zestril 5mg tablets (lexon (uk) ltd)	1	0	1
56506	coversyl 2mg tablets (dowelhurst ltd)	1	0	1
56508	coversyl 4mg tablets (dowelhurst ltd)	1	0	1
56509	capoten 12.5mg tablets (dowelhurst ltd)	1	0	1
56510	zestril 20mg tablets (sigma pharmaceuticals plc)	1	0	1
56516	perindopril erbumine 2mg tablets (sandoz ltd)	1	0	1
56606	azilsartan medoxomil 40mg tablets	0	1	1
56704	ramipril 1.25mg capsules (alliance healthcare (distribution) ltd)	1	0	1
56763	ramipril 10mg capsules (phoenix healthcare distribution ltd)	1	0	1
56850	ecopace 12.5mg tablets (amco)	1	0	1
56855	ramipril 10mg capsules (sigma pharmaceuticals plc)	1	0	1
56970	losartan 100mg tablets (pfizer ltd)	0	1	1
56975	losartan 50mg / hydrochlorothiazide 12.5mg tablets (a a h pharmaceuticals ltd)	0	1	1
57026	candesartan 8mg tablets (waymade healthcare plc)	0	1	1
57028	losartan 100mg tablets (mylan)	0	1	1
57048	lisinopril 10mg tablets (zentiva)	1	0	1
57073	ramipril 1.25mg capsules (waymade healthcare plc)	1	0	1
57235	ramipril 1.25mg tablets (sandoz ltd)	1	0	1
57266	candesartan 2mg tablets (actavis uk ltd)	0	1	1

57273	candesartan 8mg tablets (actavis uk ltd)	0	1	1
57333	perindopril tosilate 5mg tablets	1	0	1
57346	ramipril 10mg capsules (waymade healthcare plc)	1	0	1
57378	enalapril 2mg/5ml oral suspension	1	0	1
57539	zestoretic 10 tablets (sigma pharmaceuticals plc)	1	0	1
57588	zestril 2.5mg tablets (mawdsley-brooks & company ltd)	1	0	1
57658	ramipril 1.25mg tablets (a a h pharmaceuticals ltd)	1	0	1
57701	perindopril erbumine 8mg tablets (actavis uk ltd)	1	0	1
57796	cozaar-comp 50mg/12.5mg tablets (de pharmaceuticals)	0	1	1
57801	perindopril erbumine 4mg tablets (glenmark pharmaceuticals europe ltd)	1	0	1
57864	ramipril 5mg tablets (sigma pharmaceuticals plc)	1	0	1
57882	enalapril 2.5mg/5ml oral suspension	1	0	1
57944	perindopril tosilate 2.5mg tablets	1	0	1
57977	candesartan 16mg tablets (alliance healthcare (distribution) ltd)	0	1	1
58108	irbesartan 150mg tablets (a a h pharmaceuticals ltd)	0	1	1
58195	captopril 12.5mg/5ml oral solution	1	0	1
58201	irbesartan 150mg tablets (actavis uk ltd)	0	1	1
58258	lisinopril 2.5mg/5ml oral suspension	1	0	1
58274	losartan 25mg tablets (accord healthcare ltd)	0	1	1
58294	lisinopril 5mg tablets (accord healthcare ltd)	1	0	1
58451	lisinopril 2.5mg tablets (almus pharmaceuticals ltd)	1	0	1
58461	lisinopril 2.5mg tablets (kent pharmaceuticals ltd)	1	0	1
58646	candesartan 4mg tablets (actavis uk ltd)	0	1	1
58649	losartan 25mg tablets (bristol laboratories ltd)	0	1	1
58669	valsartan 40mg capsules (teva uk ltd)	0	1	1
58682	lisinopril 2.5mg tablets (mylan)	1	0	1
58751	enalapril 1.25mg/5ml oral suspension	1	0	1
58843	perindopril erbumine 2mg tablets (kent pharmaceuticals ltd)	1	0	1
58863	lisinopril 10mg tablets (phoenix healthcare distribution ltd)	1	0	1
58871	lisinopril 10mg tablets (waymade healthcare plc)	1	0	1
58874	perindopril erbumine 2mg tablets (somex pharma)	1	0	1
58910	valsartan 80mg capsules (sigma pharmaceuticals plc)	0	1	1
58967	losartan 12.5mg tablets (alliance healthcare (distribution) ltd)	0	1	1
59029	valsartan 3mg/1ml oral solution	0	1	1
59086	losartan 25mg tablets (wockhardt uk ltd)	0	1	1
59109	lisinopril 5mg tablets (tillomed laboratories ltd)	1	0	1
59111	lisinopril 20mg tablets (alliance healthcare (distribution) ltd)	1	0	1
59271	losartan 25mg tablets (sandoz ltd)	0	1	1
59340	losartan 12.5mg tablets (dexcel-pharma ltd)	0	1	1
59351	losartan 50mg tablets (pfizer ltd)	0	1	1
59393	irbesartan 300mg tablets (sandoz ltd)	0	1	1
59448	valsartan 80mg capsules (a a h pharmaceuticals ltd)	0	1	1

59557	ramipril 2.5mg capsules (kent pharmaceuticals ltd)	1	0	1
59603	ramipril 2.5mg capsules (phoenix healthcare distribution ltd)	1	0	1
59690	candesartan 8mg tablets (consilient health ltd)	0	1	1
59699	captopril 5mg/5ml oral solution sugar free	1	0	1
59750	losartan 50mg tablets (aptil pharma ltd)	0	1	1
59770	perindopril erbumine 4mg tablets (aurobindo pharma ltd)	1	0	1
59788	ramipril 10mg capsules (bristol laboratories ltd)	1	0	1
59790	perindopril erbumine 8mg tablets (accord healthcare ltd)	1	0	1
59802	candesartan 2mg tablets (teva uk ltd)	0	1	1
59903	losartan 50mg/5ml oral suspension	0	1	1
59915	captopril 25mg/5ml oral solution sugar free	1	0	1
59972	perindopril erbumine 2mg tablets (alliance healthcare (distribution) ltd)	1	0	1
59996	enalapril 20mg tablets (milpharm ltd)	1	0	1
60007	generic sevikar hct 40mg/10mg/12.5mg tablets	0	1	1
60010	lisinopril 10mg tablets (kent pharmaceuticals ltd)	1	0	1
60065	perindopril erbumine 4mg tablets (sigma pharmaceuticals plc)	1	0	1
60067	perindopril erbumine 4mg / amlodipine 5mg tablets	1	0	1
60076	valsartan 160mg capsules (waymade healthcare plc)	0	1	1
60097	lisinopril 2.5mg tablets (zentiva)	1	0	1
60143	enalapril 5mg tablets (medreich plc)	1	0	1
60232	lisinopril 5mg tablets (zentiva)	1	0	1
60309	lisinopril 5mg tablets (relonchem ltd)	1	0	1
60349	noyada 25mg/5ml oral solution (martindale pharmaceuticals ltd)	1	0	1
60506	losartan 100mg tablets (dexcel-pharma ltd)	0	1	1
60597	irbesartan 150mg tablets (teva uk ltd)	0	1	1
60684	perindopril erbumine 4mg / amlodipine 10mg tablets	1	0	1
60730	ramipril 5mg capsules (phoenix healthcare distribution ltd)	1	0	1
60744	perindopril erbumine 8mg / amlodipine 5mg tablets	1	0	1
60780	generic sevikar hct 20mg/5mg/12.5mg tablets	0	1	1
60823	noyada 5mg/5ml oral solution (martindale pharmaceuticals ltd)	1	0	1
61053	losartan 100mg tablets (alliance healthcare (distribution) ltd)	0	1	1
61067	ramipril 5mg capsules (almus pharmaceuticals ltd)	1	0	1
61117	perindopril erbumine 4mg/5ml oral solution	1	0	1
61133	enalapril 10mg tablets (phoenix healthcare distribution ltd)	1	0	1
61177	telmisartan 20mg tablets (sigma pharmaceuticals plc)	0	1	1
61262	lisinopril 20mg tablets (bristol laboratories ltd)	1	0	1
61270	perindopril erbumine 4mg tablets (accord healthcare ltd)	1	0	1
61288	losartan 100mg tablets (accord healthcare ltd)	0	1	1
61292	quinapril 40mg tablets (mylan)	1	0	1
61339	ramipril 10mg capsules (almus pharmaceuticals ltd)	1	0	1
61442	valsartan 160mg capsules (teva uk ltd)	0	1	1
61495	losartan 25mg tablets (aptil pharma ltd)	0	1	1

61499	ramipril 2.5mg tablets (actavis uk ltd)	1	0	1
61693	perindopril erbumine 8mg tablets (aurobindo pharma ltd)	1	0	1
61694	ramipril 5mg tablets (zentiva)	1	0	1
61754	losartan 25mg/5ml oral suspension	0	1	1
61781	irbesartan 300mg tablets (teva uk ltd)	0	1	1
61985	ramipril 1.25mg tablets (teva uk ltd)	1	0	1
62035	candesartan 16mg tablets (waymade healthcare plc)	0	1	1
62036	ramipril 5mg tablets (waymade healthcare plc)	1	0	1
62039	ramipril 1.25mg tablets (zentiva)	1	0	1
62140	candesartan 4mg tablets (sandoz ltd)	0	1	1
62337	irbesartan 300mg / hydrochlorothiazide 12.5mg tablets (actavis uk ltd)	0	1	1
62376	actelsar hct 80mg/12.5mg tablets (actavis uk ltd)	0	1	1
62388	losartan 12.5mg tablets (de pharmaceuticals)	0	1	1
62415	irbesartan 300mg tablets (a a h pharmaceuticals ltd)	0	1	1
62564	lisinopril 10mg/5ml oral solution	1	0	1
62860	enalapril 5mg tablets (de pharmaceuticals)	1	0	1
62911	losartan 50mg / hydrochlorothiazide 12.5mg tablets (teva uk ltd)	0	1	1
62918	ramipril 2.5mg/5ml oral solution	1	0	1
62958	ramipril 5mg tablets (teva uk ltd)	1	0	1
63010	ramipril 10mg tablets (phoenix healthcare distribution ltd)	1	0	1
63030	lisinopril 10mg tablets (de pharmaceuticals)	1	0	1
63149	perindopril erbumine 8mg / amlodipine 10mg tablets	1	0	1
63222	losartan 25mg tablets (pfizer ltd)	0	1	1
63322	enalapril 10mg tablets (almus pharmaceuticals ltd)	1	0	1
63337	eprosartan 600mg tablets (a a h pharmaceuticals ltd)	0	1	1
63385	sabervel 75mg tablets (aspire pharma ltd)	0	1	1
63411	irbesartan 300mg tablets (alliance healthcare (distribution) ltd)	0	1	1
63442	ramipril 2.5mg tablets (teva uk ltd)	1	0	1
63559	lisinopril 20mg tablets (kent pharmaceuticals ltd)	1	0	1
63717	irbesartan 300mg tablets (de pharmaceuticals)	0	1	1
63824	lisinopril 10mg/5ml oral suspension	1	0	1
63890	micardisplus 80mg/12.5mg tablets (waymade healthcare plc)	0	1	1
63918	losartan 25mg tablets (teva uk ltd)	0	1	1
64055	ramipril 2.5mg/5ml oral solution sugar free (waymade healthcare plc)	1	0	1
64062	enalapril 1mg/5ml oral suspension	1	0	1
64359	candesartan 4mg tablets (de pharmaceuticals)	0	1	1
64602	perindopril erbumine 2mg tablets (waymade healthcare plc)	1	0	1
64739	captopril 25mg/5ml oral solution (special order)	1	0	1
64877	enalapril 2.5mg tablets (dexcel-pharma ltd)	1	0	1
64888	losartan 12.5mg tablets (sigma pharmaceuticals plc)	0	1	1
64902	lisinopril 5mg/5ml oral solution sugar free	1	0	1
65065	irbesartan 75mg tablets (a a h pharmaceuticals ltd)	0	1	1

65094	losartan 50mg tablets (sandoz ltd)	0	1	1
65102	lisinopril 10mg tablets (sigma pharmaceuticals plc)	1	0	1
65228	candesartan 16mg tablets (mawdsley-brooks & company ltd)	0	1	1
65273	perindopril erbumine 4mg tablets (mylan)	1	0	1
65274	telmisartan 40mg tablets (actavis uk ltd)	0	1	1
65416	lisinopril 5mg tablets (lupin (europe) ltd)	1	0	1
65443	ramipril 1.25mg tablet (sovereign medical ltd)	1	0	1
65479	candesartan 2mg tablets (a a h pharmaceuticals ltd)	0	1	1
65536	lisinopril 2.5mg tablets (alliance healthcare (distribution) ltd)	1	0	1
65599	ramipril 5mg tablets (a a h pharmaceuticals ltd)	1	0	1
65749	ramipril 5mg capsules (ennogen pharma ltd)	1	0	1
65936	ramipril 5mg capsules (de pharmaceuticals)	1	0	1
65983	lisinopril 2.5mg tablets (lupin (europe) ltd)	1	0	1
65985	lisinopril 2.5mg tablets (de pharmaceuticals)	1	0	1
66060	perindopril erbumine 2mg tablets (de pharmaceuticals)	1	0	1
66114	losartan 12.5mg tablets (mawdsley-brooks & company ltd)	0	1	1
66162	ramipril 10mg tablets (teva uk ltd)	1	0	1
66197	sacubitril 49mg / valsartan 51mg tablets	0	1	1
66205	entresto 49mg/51mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
66261	entresto 24mg/26mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
66329	ramipril oral solution	1	0	1
66551	losartan 50mg tablets (bristol laboratories ltd)	0	1	1
66558	lisinopril 5mg tablets (de pharmaceuticals)	1	0	1
66597	captopril 10mg/5ml oral suspension	1	0	1
66598	losartan 50mg / hydrochlorothiazide 12.5mg tablets (lupin (europe) ltd)	0	1	1
66622	lisinopril 20mg tablets (de pharmaceuticals)	1	0	1
66624	candesartan 16mg tablets (sandoz ltd)	0	1	1
66669	ramipril 10mg capsules (de pharmaceuticals)	1	0	1
66702	sacubitril 24mg / valsartan 26mg tablets	0	1	1
66772	lisinopril 2.5mg tablets (waymade healthcare plc)	1	0	1
66829	entresto 97mg/103mg tablets (novartis pharmaceuticals uk ltd)	0	1	1
66895	enalapril 10mg/5ml oral suspension	1	0	1
66931	sacubitril 97mg / valsartan 103mg tablets	0	1	1
66958	candesartan 8mg tablets (sandoz ltd)	0	1	1
66997	micardisplus 40mg/12.5mg tablets (waymade healthcare plc)	0	1	1
67075	lisinopril 2.5mg tablets (mawdsley-brooks & company ltd)	1	0	1
67194	lisinopril 2.5mg tablets (bristol laboratories ltd)	1	0	1
67269	coversyl 2mg tablets (waymade healthcare plc)	1	0	1
67307	staril 20mg tablets (dowelhurst ltd)	1	0	1
67663	valsartan 160mg capsules (dexcel-pharma ltd)	0	1	1
67664	valsartan 160mg / hydrochlorothiazide 12.5mg tablets (teva uk ltd)	0	1	1
67719	ramipril 5mg capsules (mawdsley-brooks & company ltd)	1	0	1

67741	ramipril 1.25mg capsules (almus pharmaceuticals ltd)	1	0	1
67767	lisinopril 10mg / hydrochlorothiazide 12.5mg tablets (almus pharmaceuticals ltd)	1	0	1
67789	perindopril erbumine 2mg tablets (accord healthcare ltd)	1	0	1
67795	lisinopril 20mg tablets (almus pharmaceuticals ltd)	1	0	1
67902	losartan 100mg tablets (sandoz ltd)	0	1	1
67929	candesartan 16mg tablets (tillomed laboratories ltd)	0	1	1
68021	perindopril erbumine 4mg tablets (alliance healthcare (distribution) ltd)	1	0	1
68094	lisinopril 5mg tablets (sigma pharmaceuticals plc)	1	0	1
68192	ramipril 5mg capsules (brown & burk uk ltd)	1	0	1
68247	lisinopril 5mg tablets (bristol laboratories ltd)	1	0	1
68340	losartan 12.5mg tablets (consilient health ltd)	0	1	1
68372	ramipril 5mg tablets (actavis uk ltd)	1	0	1
68381	perindopril erbumine 4mg tablets (mawdsley-brooks & company ltd)	1	0	1
68480	ramipril 10mg capsules (mawdsley-brooks & company ltd)	1	0	1
68496	enalapril 10mg tablets (kent pharmaceuticals ltd)	1	0	1
68603	losartan 50mg tablets (wockhardt uk ltd)	0	1	1
68647	candesartan 8mg tablets (genesis pharmaceuticals ltd)	0	1	1
68718	candesartan 4mg tablets (a a h pharmaceuticals ltd)	0	1	1
68751	candesartan 16mg tablets (genesis pharmaceuticals ltd)	0	1	1
68759	perindopril erbumine 2mg tablets (aurobindo pharma ltd)	1	0	1
68948	valsartan 160mg capsules (actavis uk ltd)	0	1	1
69016	perindopril erbumine 8mg tablets (de pharmaceuticals)	1	0	1
69074	lisinopril 20mg tablets (relonchem ltd)	1	0	1
69192	captopril oral solution	1	0	1
69269	lisinopril 20mg tablets (waymade healthcare plc)	1	0	1
69288	ramipril 10mg capsules (brown & burk uk ltd)	1	0	1
69599	captopril 500micrograms/5ml oral suspension	1	0	1
69600	captopril 1mg/5ml oral suspension	1	0	1
69667	losartan 100mg/5ml oral solution	0	1	1
69802	candesartan 4mg tablets (mylan)	0	1	1
69858	losartan 25mg tablets (alliance healthcare (distribution) ltd)	0	1	1
70072	ramipril 1.25mg capsules (mawdsley-brooks & company ltd)	1	0	1
70251	telmisartan 20mg tablets (teva uk ltd)	0	1	1
70325	losartan 50mg tablets (almus pharmaceuticals ltd)	0	1	1
70431	irbesartan 150mg tablets (lupin (europe) ltd)	0	1	1
70455	candesartan 4mg/5ml oral suspension	0	1	1
70628	diovan 3mg/1ml oral solution (novartis pharmaceuticals uk ltd)	0	1	1
70667	lisinopril 5mg tablets (mawdsley-brooks & company ltd)	1	0	1
70709	ramipril 10mg tablets (actavis uk ltd)	1	0	1
70754	losartan 50mg / hydrochlorothiazide 12.5mg tablets (ranbaxy (uk) ltd)	0	1	1
70765	losartan 100mg tablets (almus pharmaceuticals ltd)	0	1	1
70805	candesartan 8mg tablets (crescent pharma ltd)	0	1	1

70916	perindopril erbumine 8mg tablets (glenmark pharmaceuticals europe ltd)	1	0	1
70917	perindopril erbumine 2mg tablets (glenmark pharmaceuticals europe ltd)	1	0	1
70922	losartan 100mg / hydrochlorothiazide 12.5mg tablets (phoenix healthcare distribution ltd)	0	1	1
70955	irbesartan 300mg/5ml oral suspension (martindale pharmaceuticals ltd)	0	1	1
70994	captopril 12.5mg tablets (sandoz ltd)	1	0	1
71004	perindopril erbumine 8mg tablets (accord healthcare ltd)	1	0	1
71019	irbesartan 75mg tablets (dr reddy's laboratories (uk) ltd)	0	1	1
71025	ramipril 1.25mg tablets (apc pharmaceuticals & chemicals (europe) ltd)	1	0	1
71028	valsartan 80mg capsules (arrow generics ltd)	0	1	1
71040	ramipril 5mg tablets (pfizer ltd)	1	0	1
71068	ramipril 2.5mg tablets (apc pharmaceuticals & chemicals (europe) ltd)	1	0	1
71080	candesartan 4mg tablets (zentiva)	0	1	1
71096	irbesartan 150mg tablets (dr reddy's laboratories (uk) ltd)	0	1	1
71115	zestoretic 10 tablets (waymade healthcare plc)	1	0	1
71215	irbesartan 75mg tablets (actavis uk ltd)	0	1	1
71277	captopril 7.5mg/5ml oral suspension	1	0	1
71491	ramipril 2.5mg capsules (ennogen pharma ltd)	1	0	1

Identification of beta-blockers

List of product codes (prodcode) used to identify beta-blockers and their descriptions are listed in the table below. Codes used to identify cardioselective beta-blockers are flagged. Cardioselective beta-blockers were identified as acebutolol, atenolol, bisoprolol, metoprolol, and nebivolol per NICE [271]. The final codes to identify presence of beta-blockers and cardioselective beta-blockers are identified in the far right columns by a '1'.

prodcode	productname	Included	Cardioselective
5	atenolol 50mg tablets	1	1
24	atenolol 100mg tablets	1	1
26	atenolol 25mg tablets	1	1
197	atenolol 5mg/10ml solution for injection ampoules	1	1
220	propranolol 5mg/5ml oral solution	1	0
297	propranolol 10mg tablets	1	0
472	bisoprolol 5mg tablets	1	1
581	atenolol 50mg with chlortalidone 12.5mg tablets	1	1
594	bisoprolol 2.5mg tablets	1	1
599	bisoprolol 1.25mg tablets	1	1
707	propranolol 40mg tablets	1	0
739	metoprolol 50mg tablets	1	1
751	nebivolol 5mg tablets	1	1
753	metoprolol 100mg tablets	1	1
769	propranolol 80mg modified-release capsules	1	0
817	carvedilol 3.125mg tablets	1	0
822	bisoprolol 1.5mg/5ml oral suspension	1	1
940	propranolol 80mg tablets	1	0
1006	half inderal la 80mg capsules (astrazeneca uk ltd)	1	0
1048	inderal 80mg tablets (astrazeneca uk ltd)	1	0
1050	inderal 40mg tablets (astrazeneca uk ltd)	1	0
1124	tenoretic 100mg/25mg tablets (astrazeneca uk ltd)	1	1
1288	tenoret 50mg/12.5mg tablets (astrazeneca uk ltd)	1	1
1290	bisoprolol 10mg tablets	1	1
1448	propranolol 160mg modified-release capsules	1	0
1684	beta-adalat modified-release capsules (bayer plc)	1	1
1788	atenolol 100mg with chlortalidone 25mg tablets	1	1
2414	inderal 10mg tablets (astrazeneca uk ltd)	1	0
2432	tenormin ls 50mg tablets (astrazeneca uk ltd)	1	1
2499	nadolol 80mg tablets	1	0
2587	tenormin 100mg tablets (astrazeneca uk ltd)	1	1
2590	tenormin 25mg tablets (astrazeneca uk ltd)	1	1
2629	carvedilol 12.5mg tablets	1	0

3005	inderal la 160mg capsules (astrazeneca uk ltd)	1	0
3087	propranolol 40mg/5ml oral solution sugar free	1	0
3167	propranolol 160mg tablets	1	0
3344	betaloc 100mg tablets (astrazeneca uk ltd)	1	1
3474	betaloc-sa 200mg tablets (astrazeneca uk ltd)	1	1
3526	amiloride with atenolol with hydrochlorothiazide capsules	1	1
3588	monocor 5mg tablets (wyeth pharmaceuticals)	1	1
3827	propanix 40mg tablet (ashbourne pharmaceuticals ltd)	1	0
4021	propranolol 20 mg tab	1	0
4410	carvedilol 6.25mg tablets	1	0
4542	atenolol 50mg / nifedipine 20mg modified-release capsules	1	1
4588	visken 5mg tablet (sovereign medical ltd)	1	0
4771	emcor ls 5mg tablets (merck serono ltd)	1	1
4796	inderetic 80mg/2.5mg capsules (astrazeneca uk ltd)	1	0
4983	atenolol with amiloride and hydrochlorothiazide capsules	1	1
5284	pindolol 5mg tablets	1	0
5330	corgaretic 40mg tablets (sanofi-synthelabo ltd)	1	0
5478	propranolol 10mg/5ml oral solution sugar free	1	0
5713	bisoprolol 7.5mg tablets	1	1
5721	co-tenidone 100mg/25mg tablets	1	1
5968	monocor 10mg tablets (wyeth pharmaceuticals)	1	1
6066	atenolol 25mg/5ml oral solution sugar free	1	1
7049	carvedilol 25mg tablets	1	0
7066	metoprolol 100mg / hydrochlorothiazide 12.5mg tablets	1	1
7091	bisoprolol 3.75mg tablets	1	1
7429	tenormin 5mg/10ml solution for injection ampoules (astrazeneca uk ltd)	1	1
7528	nebilet 5mg tablets (a. menarini farmaceutica internazionale srl)	1	1
7543	kalten capsules (m & a pharmachem ltd)	1	1
7553	bisoprolol 5mg/5ml oral suspension	1	1
7620	acebutolol 400mg tablets	1	1
8023	sectral 400mg tablets (sanofi)	1	1
8068	metoprolol 200mg modified-release tablets	1	1
8071	betaloc 50mg tablets (astrazeneca uk ltd)	1	1
8113	acebutolol 200mg capsules	1	1
8147	lopresoretic tablet (novartis pharmaceuticals uk ltd)	1	1
8172	acebutolol 100mg capsules	1	1
8189	secadrex 200mg/12.5mg tablets (sanofi)	1	1
8331	inderal 160mg tablet (astrazeneca uk ltd)	1	0
8369	inderex 160mg/5mg modified-release capsules (astrazeneca uk ltd)	1	0
8555	sectral 200mg capsules (sanofi)	1	1
8642	tenif 50mg/20mg modified-release capsules (astrazeneca uk ltd)	1	1
8765	atenolol/chlorthalidone 50 mg tab	1	1

8935	nadolol 40mg tablets	1	0
8978	propanix 160mg modified-release capsule (ashbourne pharmaceuticals ltd)	1	0
8987	propranolol 160mg modified-release / bendroflumethiazide 5mg capsules	1	0
9143	viskaldix tablets (amco)	1	0
9178	atenolol 25mg / bendroflumethiazide 1.25mg capsules	1	1
9185	propranolol 80mg/5ml oral solution	1	0
9783	co-tenidone 50mg/12.5mg tablets	1	1
10191	atenix 50 tablets (ashbourne pharmaceuticals ltd)	1	1
10294	inderal 1mg/1ml solution for injection ampoules (astrazeneca uk ltd)	1	0
10429	lopresor 50mg tablet (novartis pharmaceuticals uk ltd)	1	1
10627	co-betaloc tablets (pfizer ltd)	1	1
10716	corgard 80mg tablets (sanofi)	1	0
10892	emcor 10mg tablets (merck serono ltd)	1	1
11338	bendroflumethiazide 5mg with nadolol 40mg tablets	1	0
11711	propranolol 50mg/5ml oral solution	1	0
11793	metoprolol 50mg/5ml oral suspension	1	1
12054	propranolol 80mg / bendroflumethiazide 2.5mg capsules	1	0
12141	betaxolol 20mg tablets	1	0
12296	sectral 100mg capsules (sanofi)	1	1
12495	berkolol 10mg tablet (berk pharmaceuticals ltd)	1	0
12519	kerlone 20mg tablets (sanofi-synthelabo ltd)	1	0
13394	tenormin 25mg/5ml syrup (astrazeneca uk ltd)	1	1
13415	corgard 40mg tablets (sanofi-synthelabo ltd)	1	0
13499	lopresor 100mg tablet (novartis pharmaceuticals uk ltd)	1	1
13526	atenix co 100 tablets (ashbourne pharmaceuticals ltd)	1	1
14030	cardicor 2.5mg tablets (merck serono ltd)	1	1
14057	pindolol 10mg / clopamide 5mg tablets	1	0
14058	cardicor 1.25mg tablets (merck serono ltd)	1	1
14117	eucardic 3.125mg tablets (roche products ltd)	1	0
14126	acebutolol 200mg / hydrochlorothiazide 12.5mg tablets	1	1
14146	eucardic 6.25mg tablets (roche products ltd)	1	0
14438	corgaretic 80mg tablets (sanofi-synthelabo ltd)	1	0
14502	metoprolol 5mg/5ml solution for injection ampoules	1	1
14552	propanix 10mg tablet (ashbourne pharmaceuticals ltd)	1	0
14673	pindolol 15mg tablets	1	0
14808	bedranol sr 80mg capsules (sandoz ltd)	1	0
15117	nifedipine with atenolol 20mg + 50mg capsule	1	1
15176	totamol 50mg tablet (c p pharmaceuticals ltd)	1	1
15488	metoprolol tartrate with chlortalidone tablet	1	1
15619	half-betadur cr 80mg capsule (monmouth pharmaceuticals ltd)	1	0
15730	totamol 100mg tablet (c p pharmaceuticals ltd)	1	1
16786	chlortalidone 25mg with atenolol 100mg tablets	1	1

17082	syprol 5mg/5ml oral solution (rosemont pharmaceuticals ltd)	1	0
17149	monozide 10 tablets (wyeth pharmaceuticals)	1	1
17322	atenix 25 tablets (ashbourne pharmaceuticals ltd)	1	1
17462	bisoprolol 10mg / hydrochlorothiazide 6.25mg tablets	1	1
17615	cardicor 5mg tablets (merck serono ltd)	1	1
17783	spiroprop tablet (pharmacia ltd)	1	0
17876	metoprolol fumarate 190 mg tab	1	1
18185	cardicor 7.5mg tablets (merck serono ltd)	1	1
18287	co-betaloc sa tablets (pfizer ltd)	1	1
18414	eucardic 12.5mg tablets (roche products ltd)	1	0
18722	carvedilol	1	0
18743	tenben 25mg/1.25mg capsules (galen ltd)	1	1
18950	totamol 25mg tablet (c p pharmaceuticals ltd)	1	1
19003	spironolactone/propranolol 50 mg tab	1	0
19055	chlortalidone 12.5mg with atenolol 50mg tablets	1	1
19172	atenolol 25mg tablets (ivax pharmaceuticals uk ltd)	1	1
19178	bisoprolol 10mg tablets (ranbaxy (uk) ltd)	1	1
19182	atenolol 50mg tablets (ivax pharmaceuticals uk ltd)	1	1
19191	atenolol 100mg tablets (teva uk ltd)	1	1
19200	bisoprolol 5mg tablets (ivax pharmaceuticals uk ltd)	1	1
19202	carvedilol 6.25mg tablets (teva uk ltd)	1	0
19437	eucardic 25mg tablets (roche products ltd)	1	0
19624	betaxolol hydrochloride eye	1	0
19853	cardicor 3.75mg tablets (merck serono ltd)	1	1
19858	cardicor 10mg tablets (merck serono ltd)	1	1
20012	visken 15mg tablet (sovereign medical ltd)	1	0
20082	lopresor sr 200mg tablets (recordati pharmaceuticals ltd)	1	1
20093	metoprolol 200mg modified-release / hydrochlorothiazide 25mg tablets	1	1
20468	half beta-prograne 80mg modified-release capsules (tillomed laboratories ltd)	1	0
20502	atenix 100 tablets (ashbourne pharmaceuticals ltd)	1	1
20728	atenamin 25mg tablet (opd pharm)	1	1
21133	atenamin 50mg tablet (opd pharm)	1	1
21838	propanix 80mg tablet (ashbourne pharmaceuticals ltd)	1	0
21839	berkolol 80mg tablet (berk pharmaceuticals ltd)	1	0
21866	berkolol 40mg tablet (berk pharmaceuticals ltd)	1	0
21873	atenix co 50 tablets (ashbourne pharmaceuticals ltd)	1	1
21905	bipranix 10mg tablets (ashbourne pharmaceuticals ltd)	1	1
21966	bipranix 5mg tablets (ashbourne pharmaceuticals ltd)	1	1
22151	metoprolol 100mg/chlorthalidone 12.5mg	1	1
22167	betaxolol hydrochloride	1	0
22208	half propanix la 80mg modified-release capsule (ashbourne pharmaceuticals ltd)	1	0
22634	propranolol 10 mg sus	1	0

22796	carvedilol 3.125 mg	1	0
22912	bendroflumethiazide 2.5mg with propanolol 80mg capsules	1	0
23131	bendroflumethiazide 5mg with propanolol 160mg modified-release capsules	1	0
23134	nadolol 40mg / bendroflumethiazide 5mg tablets	1	0
23326	betadur cr 160mg modified-release capsule (monmouth pharmaceuticals ltd)	1	0
23587	sloprolol 160mg capsule (c p pharmaceuticals ltd)	1	0
23604	propranolol s/r	1	0
24083	bisoprolol 5mg tablets (teva uk ltd)	1	1
24191	antipressan 50mg tablets (teva uk ltd)	1	1
24195	antipressan 100mg tablets (teva uk ltd)	1	1
24218	berkolol 160mg tablet (berk pharmaceuticals ltd)	1	0
24280	totaretic 100mg+25mg tablet (c p pharmaceuticals ltd)	1	1
24461	betaloc i.v. 5mg/5ml solution for injection ampoules (astrazeneca uk ltd)	1	1
24520	hydrochlorothiazide /metoprolol tartrate 25 mg tab	1	1
24677	atenolol	1	1
25037	atenolol	1	1
25359	rapranol sr 160mg capsules (ranbaxy (uk) ltd)	1	0
25367	rapranol sr 80mg capsules (ranbaxy (uk) ltd)	1	0
25462	clopamide 5mg with pindolol 10mg tablets	1	0
25764	pindolol 10mg/clopamide 5mg	1	0
25818	propranolol 30 mg sus	1	0
26105	propranolol paed 4 mg tab	1	0
26211	antipressan 25mg tablets (teva uk ltd)	1	1
26228	propanix la 160mg modified-release capsule (ashbourne pharmaceuticals ltd)	1	0
26229	beta-prograne 160mg modified-release capsules (tillomed laboratories ltd)	1	0
26248	tenchlor 100mg/25mg tablets (teva uk ltd)	1	1
26255	lopranol la 160mg capsule (opus pharmaceuticals ltd)	1	0
26741	totaretic 50mg+12.5mg tablet (c p pharmaceuticals ltd)	1	1
26788	propranolol 2.5 mg eli	1	0
26895	syprol 10mg/5ml oral solution (rosemont pharmaceuticals ltd)	1	0
26922	brevibloc premixed 100mg/10ml solution for injection vials (baxter healthcare ltd)	1	0
27036	propranolol powders 5 mg pow	1	0
27086	nadolol 80mg/bendrofluazide 5mg mg tab	1	0
27486	propranolol 1mg/1ml solution for injection ampoules	1	0
27700	propranolol 40mg tablets (actavis uk ltd)	1	0
27719	metoros ls 95mg tablet (geigy pharmaceuticals)	1	1
27946	nadolol 80mg / bendroflumethiazide 5mg tablets	1	0
27964	apsolol 40mg tablet (approved prescription services ltd)	1	0
28048	angilol 10mg tablet (ddsa pharmaceuticals ltd)	1	0
28128	propranolol 80mg modified-release capsule (actavis uk ltd)	1	0
28177	hydrochlorothiazide with atenolol and amiloride capsule	1	1
28493	metoprolol fumarate 95 mg tab	1	1

28788	half propatard la 80mg modified-release capsule (galen ltd)	1	0
28996	bedranol sr 160mg capsules (sandoz ltd)	1	0
29368	atenolol 25mg tablets (teva uk ltd)	1	1
29398	atenamin 100mg tablet (opd pharm)	1	1
29427	hydrochlorothiazide with metoprolol tartrate 12.5mg with 100mg tablet	1	1
29762	mepranix 50mg tablet (ashbourne pharmaceuticals ltd)	1	1
29763	propanix 160mg tablet (ashbourne pharmaceuticals ltd)	1	0
29803	propranolol 3 mg eli	1	0
29998	metoros 190mg tablet (novartis pharmaceuticals uk ltd)	1	1
30400	mepranix 100mg tablet (ashbourne pharmaceuticals ltd)	1	1
30541	esmolol hcl 250mg/ml concentrate solution for infusion	1	0
30636	vasaten 50mg tablet (shire pharmaceuticals ltd)	1	1
31214	propranolol 80mg tablets (mylan)	1	0
31470	tenchlor 50mg/12.5mg tablets (teva uk ltd)	1	1
31536	atenolol 25mg tablets (kent pharmaceuticals ltd)	1	1
31708	co-tenidone 50mg/12.5mg tablets (actavis uk ltd)	1	1
31776	propranolol 40mg tablets (mylan)	1	0
31833	angilol 80mg tablet (ddsa pharmaceuticals ltd)	1	0
31934	atenolol 100mg tablets (ivax pharmaceuticals uk ltd)	1	1
32094	co-tenidone 50mg/12.5mg tablets (a a h pharmaceuticals ltd)	1	1
32114	bisoprolol 5mg tablets (mylan)	1	1
32135	brevibloc concentrate 2.5g/10ml solution for infusion ampoules (baxter healthcare ltd)	1	0
32162	propranolol 80mg modified-release capsule (lagap)	1	0
32470	propranolol 1 mg liq	1	0
32552	congescor 2.5mg tablets (tillomed laboratories ltd)	1	1
32630	vivacor 10mg tablets (lexon (uk) ltd)	1	1
32787	visken 15mg tablets (amco)	1	0
32836	metoprolol 50mg tablets (mylan)	1	1
33079	atenolol 100mg tablets (mylan)	1	1
33085	atenolol 100mg tablets (a a h pharmaceuticals ltd)	1	1
33092	atenolol 50mg tablets (a a h pharmaceuticals ltd)	1	1
33184	atenolol 100mg tablets (wockhardt uk ltd)	1	1
33374	carvedilol 12.5mg tablets (genus pharmaceuticals ltd)	1	0
33376	probeta la 160mg capsule (trinity pharmaceuticals ltd)	1	0
33602	slo-pro 160mg capsules (mylan)	1	0
33644	propranolol 80mg tablets (a a h pharmaceuticals ltd)	1	0
33650	atenolol 50mg tablets (mylan)	1	1
33657	atenolol 25mg tablets (a a h pharmaceuticals ltd)	1	1
33659	hydrochlorothiazide with metoprolol tartrate 25mg with 200mg modified-release tablet	1	1
33836	apsolol 160mg tablet (approved prescription services ltd)	1	0
33839	bisoprolol 10mg tablets (actavis uk ltd)	1	1
33850	atenolol 50mg tablets (actavis uk ltd)	1	1

33909	congescor 1.25mg tablets (tillomed laboratories ltd)	1	1
34012	co-tenidone 100mg/25mg tablets (ivax pharmaceuticals uk ltd)	1	1
34034	co-tenidone 50mg/12.5mg tablets (ivax pharmaceuticals uk ltd)	1	1
34092	metoprolol 100mg tablets (teva uk ltd)	1	1
34094	metoprolol 50mg tablets (a a h pharmaceuticals ltd)	1	1
34125	metoprolol 100mg tablets (a a h pharmaceuticals ltd)	1	1
34185	propranolol la 80mg modified-release capsule (approved prescription services ltd)	1	0
34208	propranolol sr 160mg modified-release capsule (c p pharmaceuticals ltd)	1	0
34214	propranolol 160mg tablets (actavis uk ltd)	1	0
34265	atenolol 50mg tablets (sandoz ltd)	1	1
34365	atenolol 50mg tablets (teva uk ltd)	1	1
34378	propranolol 10mg tablets (a a h pharmaceuticals ltd)	1	0
34407	metoprolol 50mg tablets (teva uk ltd)	1	1
34430	metoprolol 50mg tablets (actavis uk ltd)	1	1
34443	atenolol 50mg tablets (wockhardt uk ltd)	1	1
34449	co-tenidone 50mg/12.5mg tablets (mylan)	1	1
34492	atenolol 25mg tablets (mylan)	1	1
34501	carvedilol 12.5mg tablets (actavis uk ltd)	1	0
34509	metoprolol 100mg tablets (mylan)	1	1
34575	atenolol 25mg tablets (wockhardt uk ltd)	1	1
34584	metoprolol 50mg tablets (ivax pharmaceuticals uk ltd)	1	1
34585	atenolol 25mg tablets (sandoz ltd)	1	1
34695	atenolol 50mg tablets (kent pharmaceuticals ltd)	1	1
34740	carvedilol 6.25mg tablets (actavis uk ltd)	1	0
34741	carvedilol 3.125mg tablets (ivax pharmaceuticals uk ltd)	1	0
34754	atenolol 100mg tablets (sandoz ltd)	1	1
34783	propranolol 10mg tablets (actavis uk ltd)	1	0
34804	propranolol 10mg tablets (teva uk ltd)	1	0
34821	bisoprolol 10mg tablets (mylan)	1	1
34825	co-tenidone 50mg/12.5mg tablets (teva uk ltd)	1	1
34854	metoprolol 100mg tablets (actavis uk ltd)	1	1
34867	propranolol 80mg capsule (ivax pharmaceuticals uk ltd)	1	0
34868	propranolol 40mg tablets (teva uk ltd)	1	0
34882	atenolol 50mg tablet (berk pharmaceuticals ltd)	1	1
34884	propranolol 160mg modified-release capsule (sandoz ltd)	1	0
34890	metoprolol 50mg tablet (berk pharmaceuticals ltd)	1	1
34899	co-tenidone 100mg/25mg tablets (a a h pharmaceuticals ltd)	1	1
34925	metoprolol 50mg tablets (sandoz ltd)	1	1
34945	propranolol 160mg modified-release capsule (lagap)	1	0
34949	propranolol 160mg modified-release capsule (actavis uk ltd)	1	0
34963	bisoprolol 5mg tablets (actavis uk ltd)	1	1
34976	atenolol 25mg tablets (tillomed laboratories ltd)	1	1

35695	visken 5mg tablets (amco)	1	0
35938	propranolol 80mg modified-release capsules (a a h pharmaceuticals ltd)	1	0
36261	atenolol 50mg tablets (tillomed laboratories ltd)	1	1
36576	propranolol 10mg tablets (mylan)	1	0
36603	propranolol sr 160mg modified-release capsule (hillcross pharmaceuticals ltd)	1	0
37118	bisoprolol 2.5mg tablets (a a h pharmaceuticals ltd)	1	1
37725	co-tenidone 100mg/25mg tablets (mylan)	1	1
37837	bisoprolol 2.5mg tablet (teva uk ltd)	1	1
38433	propranolol 50mg/5ml oral solution (rosemont pharmaceuticals ltd)	1	0
38991	bisoprolol 7.5mg tablets (a a h pharmaceuticals ltd)	1	1
39233	propranolol 80mg modified-release capsules (teva uk ltd)	1	0
39646	bisoprolol 0.625mg/5ml oral solution	1	1
39819	esmolol 2.5g/250ml infusion bags	1	0
39846	vivacor 5mg tablets (lexon (uk) ltd)	1	1
40167	metoprolol 100mg tablets (ivax pharmaceuticals uk ltd)	1	1
40241	propranolol la 160mg capsule (approved prescription services ltd)	1	0
40761	nebivolol 2.5mg tablets	1	1
41555	propranolol 40mg tablets (a a h pharmaceuticals ltd)	1	0
41572	co-tenidone 100mg/25mg tablets (teva uk ltd)	1	1
41591	bisoprolol 10mg tablets (teva uk ltd)	1	1
41892	metoprolol 100mg/hydrochlorothiaz.12.5mg	1	1
42152	syprol 50mg/5ml oral solution (rosemont pharmaceuticals ltd)	1	0
43251	bisoprolol 1.25mg tablets (mylan)	1	1
43525	propranolol 10mg tablets (ivax pharmaceuticals uk ltd)	1	0
43564	bisoprolol 5mg tablet (pliva pharma ltd)	1	1
44000	bisoprolol 2.5mg/5ml oral suspension	1	1
44808	nebivolol 2.5mg tablets (a a h pharmaceuticals ltd)	1	1
44858	atenolol 25mg tablets (actavis uk ltd)	1	1
45289	metoprolol tartrate oral solution	1	1
45297	propranolol 40mg tablets (ivax pharmaceuticals uk ltd)	1	0
45309	acebutolol 400mg tablets (a a h pharmaceuticals ltd)	1	1
45343	propranolol sr 80mg modified-release capsule (c p pharmaceuticals ltd)	1	0
45494	propranolol 10mg tablets (almus pharmaceuticals ltd)	1	0
45765	syprol 40mg/5ml oral solution (rosemont pharmaceuticals ltd)	1	0
45877	beta-prograne 160mg modified-release capsules (teva uk ltd)	1	0
46363	half beta-prograne 80mg modified-release capsules (teva uk ltd)	1	0
46493	propranolol 15 mg syr	1	0
46614	lopresor 50mg tablets (recordati pharmaceuticals ltd)	1	1
46740	lopresor 100mg tablets (recordati pharmaceuticals ltd)	1	1
46908	atenolol 100mg tablets (kent pharmaceuticals ltd)	1	1
46931	atenolol 100mg tablets (actavis uk ltd)	1	1
46935	carvedilol 3.125mg tablets (actavis uk ltd)	1	0

46936	carvedilol 3.125mg tablets (a a h pharmaceuticals ltd)	1	0
46952	co-tenidone 100mg/25mg tablets (actavis uk ltd)	1	1
47041	bisoprolol 2.5mg tablets (mylan)	1	1
47107	carvedilol 5mg/5ml oral suspension	1	0
47300	nebivolol 2.5mg tablets (glenmark pharmaceuticals europe ltd)	1	1
47536	metoprolol tartrate 12.5mg/5ml oral suspension	1	1
47543	half beta-prograne 80mg modified-release capsules (actavis uk ltd)	1	0
47833	bedranol sr 80mg capsules (almus pharmaceuticals ltd)	1	0
47870	atenolol 25mg tablets (almus pharmaceuticals ltd)	1	1
47907	bedranol sr 160mg capsules (almus pharmaceuticals ltd)	1	0
48682	propranolol 50mg/5ml oral solution sugar free	1	0
49142	carvedilol 3.125mg/5ml oral suspension	1	0
49863	propranolol 5mg/5ml oral solution sugar free	1	0
49953	atenolol 25mg tablets (bristol laboratories ltd)	1	1
50224	congescor 2.5mg tablets (teva uk ltd)	1	1
50300	congescor 1.25mg tablets (teva uk ltd)	1	1
50403	bisoprolol 1.25mg tablet (teva uk ltd)	1	1
50514	bisoprolol 2.5mg tablets (chanelle medical uk ltd)	1	1
50702	atenolol 25mg tablets (alliance healthcare (distribution) ltd)	1	1
51447	metoprolol 12.5mg/5ml oral suspension	1	1
51528	bisoprolol 1.25mg tablets (actavis uk ltd)	1	1
51643	atenolol 25mg/5ml oral solution sugar free (alliance healthcare (distribution) ltd)	1	1
51998	atenolol 25mg tablets (strides shasun (uk) ltd)	1	1
52136	bedranol sr 160mg capsule (lagap)	1	0
52310	atenolol 25mg tablets (crescent pharma ltd)	1	1
52500	atenolol 50mg tablets (almus pharmaceuticals ltd)	1	1
52548	bisoprolol 1.25mg tablets (almus pharmaceuticals ltd)	1	1
52609	inderal la 160mg capsules (sigma pharmaceuticals plc)	1	0
52611	bisoprolol 10mg/5ml oral solution	1	1
52635	bisoprolol 5mg tablets (alliance healthcare (distribution) ltd)	1	1
52686	bisoprolol 2.5mg/5ml oral solution	1	1
52728	beta-adalat modified-release capsules (lexon (uk) ltd)	1	1
52777	propranolol 40mg tablets (kent pharmaceuticals ltd)	1	0
53177	propranolol oral solution	1	0
53204	atenolol 50mg tablets (alliance healthcare (distribution) ltd)	1	1
53215	atenolol 50mg tablets (bristol laboratories ltd)	1	1
53334	bisoprolol 10mg tablets (a a h pharmaceuticals ltd)	1	1
53414	atenolol 50mg tablets (accord healthcare ltd)	1	1
53664	bisoprolol 2.5mg tablets (sandoz ltd)	1	1
53802	atenolol 25mg tablets (sigma pharmaceuticals plc)	1	1
53826	atenolol 25mg tablets (boston healthcare ltd)	1	1
53885	bisoprolol 1.25mg tablets (a a h pharmaceuticals ltd)	1	1

53916	bisoprolol 2.5mg tablets (almus pharmaceuticals ltd)	1	1
54106	carvedilol 1.5mg/5ml oral suspension	1	0
54297	propranolol 50mg/5ml oral solution	1	0
54479	bisoprolol 1.25mg tablets (alliance healthcare (distribution) ltd)	1	1
54487	nebivolol 2.5mg tablets (sigma pharmaceuticals plc)	1	1
54542	atenolol 25mg tablets (zanza laboratories ltd)	1	1
54623	beta-prograne 160mg modified-release capsules (actavis uk ltd)	1	0
54752	atenolol 50mg tablets (strides shasun (uk) ltd)	1	1
55228	propranolol 40mg tablets (boston healthcare ltd)	1	0
55298	bisoprolol 10mg tablets (sigma pharmaceuticals plc)	1	1
55416	propranolol 40mg tablets (almus pharmaceuticals ltd)	1	0
55778	atenolol 50mg tablets (phoenix healthcare distribution ltd)	1	1
55791	bisoprolol 3.75mg tablets (actavis uk ltd)	1	1
55849	propranolol 160mg tablets (mylan)	1	0
55853	pindolol 15mg tablet (hillcross pharmaceuticals ltd)	1	0
55929	bisoprolol 5mg tablets (accord healthcare ltd)	1	1
55949	propranolol 40mg/5ml oral solution	1	0
55979	metoprolol 25mg/5ml oral suspension	1	1
56173	half beta-prograne 80mg modified-release capsules (actavis uk ltd)	1	0
56240	bisoprolol 3.75mg tablets (sandoz ltd)	1	1
56445	atenolol 25mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)	1	1
56459	bisoprolol 2.5mg tablets (accord healthcare ltd)	1	1
56486	monocor 10mg tablets (dowelhurst ltd)	1	1
56764	propranolol 40mg tablets (waymade healthcare plc)	1	0
56768	bisoprolol 2.5mg tablets (niche generics ltd)	1	1
57023	bisoprolol 2.5mg tablets (almus pharmaceuticals ltd)	1	1
57063	bedranol sr 80mg capsules (almus pharmaceuticals ltd)	1	0
57176	bisoprolol 10mg tablets (accord healthcare ltd)	1	1
57240	metoprolol 50mg/5ml oral suspension (special order)	1	1
57342	propranolol 40mg tablets (phoenix healthcare distribution ltd)	1	0
57567	propranolol 10mg/5ml oral suspension	1	0
57578	cardicor 2.5mg tablets (necessity supplies ltd)	1	1
57626	bisoprolol 1.25mg/5ml oral solution	1	1
57817	atenolol 50mg tablets (zentiva)	1	1
57934	bisoprolol 5mg tablets (sandoz ltd)	1	1
58109	bisoprolol 1.25mg/5ml oral suspension	1	1
58297	propranolol 10mg tablets (kent pharmaceuticals ltd)	1	0
58407	propranolol 80mg tablets (teva uk ltd)	1	0
58455	bisoprolol 7.5mg tablets (sandoz ltd)	1	1
58491	propranolol 40mg tablets (alliance healthcare (distribution) ltd)	1	0
58498	bisoprolol 2.5mg tablets (medreich plc)	1	1
58511	bisoprolol 1.25mg tablets (sandoz ltd)	1	1

58763	bisoprolol 2.5mg tablets (waymade healthcare plc)	1	1
58973	bisoprolol 10mg tablets (niche generics ltd)	1	1
58974	bisoprolol 2.5mg tablets (alliance healthcare (distribution) ltd)	1	1
58982	bisoprolol 10mg tablets (medreich plc)	1	1
59037	bisoprolol 5mg tablets (a a h pharmaceuticals ltd)	1	1
59148	bisoprolol 2.5mg tablets (zentiva)	1	1
59415	propranolol 40mg tablets (accord healthcare ltd)	1	0
59495	bisoprolol 1.25mg tablets (teva uk ltd)	1	1
59549	carvedilol 5mg/5ml oral suspension	1	0
59597	propranolol 160mg modified-release capsules (a a h pharmaceuticals ltd)	1	0
59695	atenolol 50mg tablets (boston healthcare ltd)	1	1
59961	nebivolol 10mg tablets	1	1
59969	bisoprolol 5mg tablets (almus pharmaceuticals ltd)	1	1
59982	atenolol 25mg tablets (accord healthcare ltd)	1	1
60502	bisoprolol 3.75mg tablets (de pharmaceuticals)	1	1
60565	propranolol 40mg tablets (ranbaxy (uk) ltd)	1	0
60761	bisoprolol 1.25mg tablets (medreich plc)	1	1
60896	bisoprolol 5mg tablets (medreich plc)	1	1
60934	propranolol 80mg modified-release capsules (kent pharmaceuticals ltd)	1	0
61115	bisoprolol 5mg/5ml oral solution	1	1
61340	bisoprolol 5mg tablets (de pharmaceuticals)	1	1
61564	bisoprolol 3.75mg tablets (waymade healthcare plc)	1	1
61573	atenolol 25mg/5ml oral solution	1	1
61651	bisoprolol 7.5mg tablets (almus pharmaceuticals ltd)	1	1
61663	carvedilol 3.125mg tablets (teva uk ltd)	1	0
61719	beta-adalat modified-release capsules (waymade healthcare plc)	1	1
61727	propranolol 10mg tablets (accord healthcare ltd)	1	0
62325	atenolol 25mg tablets (waymade healthcare plc)	1	1
62361	bisoprolol 1.25mg tablets (chanelle medical uk ltd)	1	1
62407	bisoprolol oral solution	1	1
62537	co-tenidone 100mg/25mg tablets (de pharmaceuticals)	1	1
62711	propranolol 80mg modified-release capsules (waymade healthcare plc)	1	0
63422	carvedilol 12.5mg tablets (waymade healthcare plc)	1	0
63493	bisoprolol 2.5mg tablets (actavis uk ltd)	1	1
63535	bisoprolol 5mg tablets (relonchem ltd)	1	1
63724	metoprolol 100mg tablets (waymade healthcare plc)	1	1
63850	bisoprolol 2.5mg tablets (teva uk ltd)	1	1
64160	propranolol 5mg/5ml oral solution sugar free (am distributions (yorkshire) ltd)	1	0
64538	bisoprolol 3.75mg tablets (teva uk ltd)	1	1
64703	nebivolol 5mg tablets (glenmark pharmaceuticals europe ltd)	1	1
64784	bisoprolol 5mg tablets (niche generics ltd)	1	1
64850	bisoprolol 2.5mg tablets (de pharmaceuticals)	1	1

64973	atenolol 50mg tablets (sigma pharmaceuticals plc)	1	1
65027	bisoprolol 5mg / aspirin 100mg capsules	1	1
65227	metoprolol 12.5mg/5ml oral solution	1	1
65435	propranolol 10mg tablets (waymade healthcare plc)	1	0
65438	acebutolol 100mg capsules (a a h pharmaceuticals ltd)	1	1
65805	bisoprolol 1.25mg tablets (waymade healthcare plc)	1	1
65821	bisoprolol 7.5mg/5ml oral suspension	1	1
65986	propranolol 10mg tablets (alliance healthcare (distribution) ltd)	1	0
66464	nadolol 40mg/5ml oral solution	1	0
66548	atenolol 50mg tablets (de pharmaceuticals)	1	1
66555	propranolol 10mg tablets (boston healthcare ltd)	1	0
66559	nebilet 5mg tablets (waymade healthcare plc)	1	1
66670	metoprolol 100mg tablets (alliance healthcare (distribution) ltd)	1	1
66779	nadolol 30mg/5ml oral suspension	1	0
67124	bisoprolol 10mg / aspirin 75mg capsules	1	1
67424	nadolol 80mg/5ml oral suspension	1	0
67595	nebivolol 5mg tablets (almus pharmaceuticals ltd)	1	1
67661	carvedilol 6.25mg tablets (sigma pharmaceuticals plc)	1	0
68020	beta-adalat modified-release capsules (sigma pharmaceuticals plc)	1	1
68400	propranolol 160mg tablets (de pharmaceuticals)	1	0
68677	nebivolol 5mg tablets (actavis uk ltd)	1	1
68881	metoprolol 12.5mg capsules	1	1
69115	nebivolol 5mg tablets (a a h pharmaceuticals ltd)	1	1
69156	bisoprolol 3.75mg tablets (medreich plc)	1	1
69334	bendroflumethiazide 5mg with nadolol 80mg tablets	1	0
69526	atenolol 50mg/5ml oral solution	1	1
69661	propranolol 3mg/5ml oral solution	1	0
70116	metoprolol 50mg/5ml oral solution	1	1
70135	atenolol 25mg tablets (de pharmaceuticals)	1	1
70680	propranolol 6mg/5ml oral suspension	1	0
70681	propranolol 3mg/5ml oral suspension	1	0
71026	atenolol 100mg tablets (almus pharmaceuticals ltd)	1	1
71032	nebivolol 5mg tablets (sandoz ltd)	1	1
71098	metoprolol 50mg tablets (accord healthcare ltd)	1	1
71150	propranolol 5mg/5ml oral solution	1	0
71173	propranolol 80mg modified-release capsules (mawdsley-brooks & company ltd)	1	0
71472	bisoprolol 5mg tablets (waymade healthcare plc)	1	1

Identification of calcium channel blockers

List of product codes (prodcode) used to identify calcium channel blockers and their descriptions are listed in the table below. The final codes to identify presence of calcium channel blockers are identified in the far right columns by a '1'.

prodcode	productname	Included
219	diltiazem 120mg modified-release tablets	1
269	nifedipine 5mg capsules	1
410	nifedipine 10mg modified-release tablets	1
452	nifedipine 10mg capsules	1
491	felodipine 2.5mg modified-release tablets	1
501	felodipine 5mg modified-release tablets	1
517	adizem sr 120mg modified-release capsule (napp pharmaceuticals ltd)	1
536	tildiem la 200mg modified-release capsule (sanofi)	1
541	adalat la 20mg tablets (bayer plc)	1
568	felodipine 10mg modified-release tablets	1
636	diltiazem 60mg modified-release capsules	1
662	adalat 5mg capsules (bayer plc)	1
700	vera-til sr 120mg tablets (tillomed laboratories ltd)	1
737	nifedipine 20mg modified-release capsules	1
793	adizem xl 240mg capsule (napp pharmaceuticals ltd)	1
939	tildiem retard 90mg tablets (sanofi)	1
1118	verapamil 40mg tablets	1
1120	verapamil 80mg tablets	1
1130	viazem xl 300mg capsules (thornton & ross ltd)	1
1262	nifedipine 12 20mg modified-release tablet	1
1289	tildiem retard 120mg tablets (sanofi)	1
1298	verapamil 240mg modified-release tablets	1
1300	nifensar xl 20mg modified-release tablet (rhone-poulenc rorer ltd)	1
1449	nifedipine 24 30mg modified-release tablet	1
1538	diltiazem 60mg tablets	1
1574	verapamil 120mg modified-release capsules	1
1684	beta-adalat modified-release capsules (bayer plc)	1
1686	diltiazem 90mg modified-release capsules	1
1747	verapamil 120mg tablets	1
1748	cordilox 120mg tablets (ivax pharmaceuticals uk ltd)	1
1836	diltiazem 60mg modified-release tablets	1
1854	adalat la 30mg tablet (bayer plc)	1
1995	diltiazem 12hr 120mg modified-release capsules	1
2280	adalat retard 10mg tablets (bayer plc)	1
2343	adalat retard 20mg tablets (bayer plc)	1
2453	diltiazem 60mg modified-release capsules	1

2521	adalat 10mg capsules (bayer plc)	1
2528	slozem 120mg capsules (merck serono ltd)	1
2592	viazem xl 120mg capsules (thornton & ross ltd)	1
2605	nifedipine 10mg modified-release capsules	1
2663	diltiazem 240mg modified-release capsules	1
2686	dilzem xl mr 240mg modified-release capsule (elan pharma)	1
2746	coracten sr 10mg capsules (ucb pharma ltd)	1
2811	adizem sr 180mg modified-release capsule (napp pharmaceuticals ltd)	1
2888	tildiem 60mg modified-release tablets (sanofi)	1
2926	nicardipine 20mg capsules	1
3057	securon 120mg tablets (abbott laboratories ltd)	1
3061	diltiazem 12hr 180mg modified-release capsules	1
3118	adizem sr 90mg modified-release capsule (napp pharmaceuticals ltd)	1
3302	cardene sr 30mg capsules (astellas pharma ltd)	1
3342	securon sr 240mg tablets (mylan)	1
3343	half securon sr 120mg tablets (mylan)	1
3370	dilzem xl mr 120mg modified-release capsule (elan pharma)	1
3676	dilzem xl mr 180mg modified-release capsule (elan pharma)	1
3711	adipine mr 20 tablets (chiesi ltd)	1
3712	coracten xl 30mg capsules (ucb pharma ltd)	1
3930	nifedipine 60mg modified-release tablets	1
3943	verapamil 240mg modified-release capsules	1
4227	adalat la 60mg tablet (bayer plc)	1
4239	adipine mr 10 tablets (chiesi ltd)	1
4308	dilzem sr 90mg capsule (elan pharma)	1
4408	slozem 240mg capsules (merck serono ltd)	1
4542	atenolol 50mg / nifedipine 20mg modified-release capsules	1
4635	diltiazem 200mg modified-release capsules	1
4732	diltiazem 90mg modified-release tablets	1
4808	diltiazem 240mg modified-release capsules	1
4852	adizem sr 120mg modified-release tablet (napp pharmaceuticals ltd)	1
4856	coracten sr 20mg capsules (ucb pharma ltd)	1
4923	diltiazem 24hr 180mg modified-release capsules	1
4939	coracten xl 60mg capsules (ucb pharma ltd)	1
5054	angitil sr 180 capsules (ethypharm uk ltd)	1
5162	nifedipine 30mg modified-release capsules	1
5181	angiopine mr 20mg tablets (ashbourne pharmaceuticals ltd)	1
5194	dilzem sr 120mg capsule (elan pharma)	1
5234	slozem 180mg capsules (merck serono ltd)	1
5277	fortipine la 40 tablets (amco)	1
5296	tildiem la 300mg modified-release capsule (sanofi)	1
5326	diltiazem 24hr 300mg modified-release capsules	1

5348	diltiazem 300mg modified-release capsules	1
5477	nicardipine 30mg modified-release capsules	1
5513	dilzem sr 60mg capsule (elan pharma)	1
5570	zanidip 10mg tablets (recordati pharmaceuticals ltd)	1
5593	lercanidipine 10mg tablets	1
5806	tensipine mr 20 tablets (thornton & ross ltd)	1
6309	adizem xl 300mg capsule (napp pharmaceuticals ltd)	1
6510	univer 120mg modified-release capsules (teva uk ltd)	1
7280	plendil 10mg modified-release tablets (astrazeneca uk ltd)	1
7398	viazem xl 360mg capsules (thornton & ross ltd)	1
7541	nifopress retard 20mg tablets (amco)	1
7562	cardene 30mg capsules (astellas pharma ltd)	1
7823	nifedipine tab 5 mg	1
8024	diltiazem hcl xl 300 mg cap	1
8201	nicardipine 30mg capsules	1
8213	nifedipine 24 20mg modified-release tablet	1
8257	prescal 2.5mg tablets (novartis pharmaceuticals uk ltd)	1
8310	isradipine 2.5mg tablets	1
8524	securon 40mg tablet (abbott laboratories ltd)	1
8558	adizem xl 120mg capsule (napp pharmaceuticals ltd)	1
8642	tenif 50mg/20mg modified-release capsules (astrazeneca uk ltd)	1
8759	verapamil hcl 120mg modified release tablets	1
8884	cordilox 40mg tablets (ivax pharmaceuticals uk ltd)	1
8945	univer 240mg modified-release capsules (teva uk ltd)	1
8975	verapamil 180mg modified-release capsules	1
9094	diltiazem hcl sr 300 mg cap	1
9240	adizem xl 180mg capsule (napp pharmaceuticals ltd)	1
9269	nifedipine 40mg modified-release tablets	1
9334	plendil 2.5mg modified-release tablets (astrazeneca uk ltd)	1
9374	adizem 60mg modified-release tablet (napp pharmaceuticals ltd)	1
9386	nicardipine 45mg modified-release capsules	1
9410	angitil sr 120 capsules (ethypharm uk ltd)	1
9437	plendil 5mg modified-release tablets (astrazeneca uk ltd)	1
9485	hypolar retard 20 tablets (sandoz ltd)	1
9553	slofedipine xl 60 tablets (zentiva)	1
9569	verapamil 120mg modified-release tablets	1
9573	slofedipine xl 30mg tablets (zentiva)	1
9708	diltiazem 24hr 120mg modified-release capsules	1
9723	calcicard cr 90mg tablets (teva uk ltd)	1
9750	nifedipine 60mg modified-release capsules	1
9919	diltiazem 2% cream	1
10135	nifedipress mr 10mg modified-release tablet (sandoz ltd)	1

10136	nifedipress mr 20 tablets (dexcel-pharma ltd)	1
10153	felendil xl 5mg modified-release tablet (ratiopharm uk ltd)	1
10246	adipine xl 60mg tablets (chiesi ltd)	1
10267	adizem-xl 200mg capsules (napp pharmaceuticals ltd)	1
10688	verapamil 160mg tablets	1
10832	securon 80mg tablet (abbott laboratories ltd)	1
11223	angitil sr 90 capsules (ethypharm uk ltd)	1
11512	nifedipress mr 10 tablets (dexcel-pharma ltd)	1
11567	ramipril 5mg with felodipine 5mg modified-release tablet	1
11769	calchan mr 20 tablets (ranbaxy (uk) ltd)	1
11770	dilzem sr 60 capsules (teva uk ltd)	1
11777	verapamil 40mg/5ml oral solution sugar free	1
11922	diltiazem 60mg/5ml oral suspension	1
11943	cardene 20mg capsules (astellas pharma ltd)	1
11965	ramipril 2.5mg with felodipine 2.5mg modified-release tablet	1
11972	vertab sr 240 tablets (chiesi ltd)	1
11973	calcicard cr 120mg tablets (teva uk ltd)	1
12104	cordilox 160mg tablets (ivax pharmaceuticals uk ltd)	1
12392	univer 180mg modified-release capsules (teva uk ltd)	1
12606	nifelease 20mg modified-release tablet (eastern pharmaceuticals ltd)	1
12613	unipine xl 30mg modified-release tablet (genus pharmaceuticals ltd)	1
12639	diltiazem hcl 90mg modified-release tablet (actavis uk ltd)	1
12705	angiozem cr 90mg tablets (ashbourne pharmaceuticals ltd)	1
12875	cardene sr 45mg capsules (astellas pharma ltd)	1
13027	viazem xl 240mg capsules (thornton & ross ltd)	1
13033	angitil xl 240 capsules (ethypharm uk ltd)	1
13075	dilzem xl 180 capsules (teva uk ltd)	1
13127	dilzem xl 240 capsules (teva uk ltd)	1
13139	adipine xl 30mg tablets (chiesi ltd)	1
13240	dilzem xl 120 capsules (teva uk ltd)	1
13243	lercanidipine 20mg tablets	1
13251	vera-til sr 240mg tablets (tillomed laboratories ltd)	1
13302	dilzem sr 90 capsules (teva uk ltd)	1
13410	angiozem 60mg modified-release tablets (ashbourne pharmaceuticals ltd)	1
13672	angiopine mr 10mg tablets (ashbourne pharmaceuticals ltd)	1
13699	angiopine la 40mg tablet (ashbourne pharmaceuticals ltd)	1
13856	verapress mr 240mg tablets (actavis uk ltd)	1
13926	diltiazem 360mg modified-release capsules	1
13965	cordilox mr 240mg tablets (teva uk ltd)	1
14300	zanidip 20mg tablets (recordati pharmaceuticals ltd)	1
14305	vascalpha 10mg modified-release tablets (actavis uk ltd)	1
14861	calchan mr 10 tablets (ranbaxy (uk) ltd)	1

14892	anoheal 2% cream (s.l.a. pharma (uk) ltd)	1
15117	nifedipine with atenolol 20mg + 50mg capsule	1
15221	dilcardia xl 180mg modified-release capsule (generics (uk) ltd)	1
15288	angitil xl 300 capsules (ethypharm uk ltd)	1
15659	diltiazem hcl s/r 180 cap	1
15715	genalat retard 20mg modified-release tablet (wyeth pharmaceuticals)	1
16038	dilzem sr 120 capsules (teva uk ltd)	1
16073	nifedipress mr 10 tablets (teva uk ltd)	1
16328	verapress mr 240mg tablets (dexcel-pharma ltd)	1
16677	cordilox 80mg tablets (ivax pharmaceuticals uk ltd)	1
16850	angiozem cr 120mg tablets (ashbourne pharmaceuticals ltd)	1
17006	triapin 5mg/5mg modified-release tablets (sanofi)	1
17325	cardilate mr 10mg tablets (teva uk ltd)	1
17338	nifedotard 20 mr 20mg modified-release tablet (galen ltd)	1
17342	nivaten retard 10mg modified-release tablet (actavis uk ltd)	1
17406	zemtard 180 xl capsules (galen ltd)	1
17425	zemtard 120 xl capsules (galen ltd)	1
17448	nifedipress mr 10mg modified-release tablet (sterwin medicines)	1
17474	felodipine 5mg modified-release / ramipril 5mg tablets	1
17492	zemtard 300 xl capsules (galen ltd)	1
17557	felotens xl 5mg tablets (thornton & ross ltd)	1
17566	felotens xl 10mg tablets (thornton & ross ltd)	1
17586	slozem 300mg capsules (merck serono ltd)	1
17599	verapress mr 240mg tablets (sandoz ltd)	1
17666	viazem xl 180mg capsules (thornton & ross ltd)	1
18223	trandolapril with verapamil 2mg + 180mg modified-release capsule	1
18379	dilcardia sr 90mg capsules (mylan)	1
18403	diltiazem hcl 180mg modified-release capsule (hillcross pharmaceuticals ltd)	1
18404	diltiazem 60mg modified-release capsules (a a h pharmaceuticals ltd)	1
18606	diltiazem and hydrochlorothiazide 150mg+12.5mg modified-release capsules	1
18830	disogram sr 90mg capsules (ranbaxy (uk) ltd)	1
18834	disogram sr 60mg capsules (ranbaxy (uk) ltd)	1
18852	disogram sr 120mg capsules (ranbaxy (uk) ltd)	1
18874	disogram sr 180mg capsules (ranbaxy (uk) ltd)	1
18975	calcicard 60mg tablet (3m health care ltd)	1
19170	tensipine mr 10 tablets (thornton & ross ltd)	1
19175	verapamil 40mg tablets (ivax pharmaceuticals uk ltd)	1
19325	cordilox 2.5mg/ml injection (ivax pharmaceuticals uk ltd)	1
19426	disogram sr 240mg capsules (ranbaxy (uk) ltd)	1
19440	disogram sr 300mg capsules (ranbaxy (uk) ltd)	1
19457	ranvera mr 240mg tablets (ranbaxy (uk) ltd)	1
19459	verapamil 240mg modified-release tablets (a a h pharmaceuticals ltd)	1

19690	verapamil 180mg modified-release / trandolapril 2mg capsules	1
20257	cardilate mr 20mg tablets (ivax pharmaceuticals uk ltd)	1
20311	nifedipress mr 20mg modified-release tablet (generics (uk) ltd)	1
20459	felendil xl 10mg modified-release tablet (ratiopharm uk ltd)	1
20579	tarka modified-release capsules (abbott laboratories ltd)	1
20591	nifedipress mr 20 tablets (teva uk ltd)	1
20642	bi-carzem sr 60mg modified-release capsule (tillomed laboratories ltd)	1
20878	angiopine 10 capsules (ashbourne pharmaceuticals ltd)	1
20890	zemtard 240 xl capsules (galen ltd)	1
21145	dilcardia sr 60mg capsules (mylan)	1
21162	felodipine 2.5mg modified-release / ramipril 2.5mg tablets	1
21216	hypolar retard 10mg tablets (sandoz ltd)	1
21245	nifedipress mr 10mg modified-release tablet (actavis uk ltd)	1
21763	diltiazem 60mg modified-release tablets (a a h pharmaceuticals ltd)	1
21773	diltiazem hcl 60mg tablet (generics (uk) ltd)	1
21778	diltiazem 60mg modified-release tablets (teva uk ltd)	1
21795	retalzem 60 modified-release tablets (kent pharmaceuticals ltd)	1
21872	angiopine 5mg capsule (ashbourne pharmaceuticals ltd)	1
21886	nifedipress mr 20 tablets (actavis uk ltd)	1
21918	optil 60mg modified-release tablets (opus pharmaceuticals ltd)	1
22019	calanif 10mg capsule (berk pharmaceuticals ltd)	1
22142	calcilat 10mg capsule (eastern pharmaceuticals ltd)	1
22217	nimodrel 10mg modified-release tablet (opus pharmaceuticals ltd)	1
22619	britiazim 60mg modified-release tablet (thames laboratories ltd)	1
22696	slofedipine 20mg tablets (sterwin medicines)	1
22826	securon 160mg tablet (abbott laboratories ltd)	1
23233	bi-carzem sr 90mg modified-release capsule (tillomed laboratories ltd)	1
23505	adizem xl plus 150mg+12.5mg modified-release capsule (napp pharmaceuticals ltd)	1
23733	optil sr 90mg modified-release capsule (opus pharmaceuticals ltd)	1
23736	hypolar xl 30 tablets (sandoz ltd)	1
23872	berkatens 40mg tablet (berk pharmaceuticals ltd)	1
24228	nimodrel 20mg modified-release tablet (opus pharmaceuticals ltd)	1
24365	cardioplen xl 5mg tablets (chiesi ltd)	1
24366	cardioplen xl 10mg tablets (chiesi ltd)	1
25026	nifedipine retard	1
25044	nifedipine retard	1
25055	nifedipine	1
25059	berkatens 80mg tablet (berk pharmaceuticals ltd)	1
25132	nifopress mr 20mg tablets (teva uk ltd)	1
25572	felogen xl 5mg tablets (mylan)	1
25646	nivaten retard 20mg modified-release tablet (actavis uk ltd)	1
25777	dilcardia sr 120mg capsules (mylan)	1

25919	nifedipine 20mg modified-release tablets (a a h pharmaceuticals ltd)	1
26252	berkatens 160mg tablet (berk pharmaceuticals ltd)	1
26265	calanif 5mg capsule (berk pharmaceuticals ltd)	1
26267	optil sr 120mg modified-release capsule (opus pharmaceuticals ltd)	1
26269	optil sr 180mg modified-release capsule (opus pharmaceuticals ltd)	1
26270	optil xl 300mg modified-release capsule (opus pharmaceuticals ltd)	1
26309	optil xl 240mg modified-release capsule (opus pharmaceuticals ltd)	1
26337	cabren 10mg modified-release tablets (teva uk ltd)	1
26460	dilcardia xl 240mg modified-release capsule (generics (uk) ltd)	1
26463	zemret xl 240mg capsule (neo laboratories ltd)	1
26674	verapamil 5mg/2ml solution for injection ampoules	1
26759	zildil sr 60mg capsules (chanelle medical uk ltd)	1
26774	nifedipine 10mg/5ml oral suspension	1
27135	diltiazem sr 90mg capsule (hillcross pharmaceuticals ltd)	1
27136	diltiazem 90mg modified-release tablets (a a h pharmaceuticals ltd)	1
27295	securon iv 5mg/2ml solution for injection ampoules (mylan)	1
27401	kenzem sr 90mg capsules (kent pharmaceuticals ltd)	1
27685	diltiazem hcl 300mg capsule (pliva pharma ltd)	1
28438	triapin 2.5mg/2.5mg modified-release tablets (sanofi)	1
28688	nifedipine 10mg modified-release tablets (a a h pharmaceuticals ltd)	1
28721	neofel xl 5mg tablets (kent pharmaceuticals ltd)	1
28843	verapamil hc 80mg tablet (celltech pharma europe ltd)	1
28844	berkatens 120mg tablet (berk pharmaceuticals ltd)	1
28949	bi-carzem sr 120mg modified-release capsule (tillomed laboratories ltd)	1
29044	neofel xl 10mg tablets (kent pharmaceuticals ltd)	1
29145	felendil xl 2.5mg modified-release tablet (ratiopharm uk ltd)	1
29637	verapress mr 240mg tablets (teva uk ltd)	1
29676	calazem 60mg modified-release tablet (berk pharmaceuticals ltd)	1
30197	diltiazem 120mg modified-release capsules	1
30199	nifedipine 30mg modified-release tablets	1
30242	diltiazem 180mg modified-release capsules	1
30462	ethimil mr 240mg tablets (genus pharmaceuticals ltd)	1
30473	coroday mr 20mg tablets (mylan)	1
30491	diltiazem hydrochloride	1
30557	felogen xl 10mg tablets (mylan)	1
30915	cabren 2.5mg modified-release tablets (teva uk ltd)	1
30991	cabren 5mg modified-release tablets (teva uk ltd)	1
31489	bi-carzem xl 240mg capsule (tillomed laboratories ltd)	1
31490	zolvera 40mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
31676	diltiazem hcl 120mg modified-release tablet (actavis uk ltd)	1
31711	verapamil 80mg tablets (a a h pharmaceuticals ltd)	1
31737	zildil sr 120mg capsules (chanelle medical uk ltd)	1

32089	diltiazem hcl 120mg modified-release capsule (hillcross pharmaceuticals ltd)	1
32262	diltiazem hcl 60mg tablet (c p pharmaceuticals ltd)	1
32590	verapamil 40mg tablets (mylan)	1
32658	dilcardia xl 120mg modified-release capsule (generics (uk) ltd)	1
32870	diltiazem 60mg modified-release tablets (sterwin medicines)	1
32922	felodipine 10mg modified-release tablet (sandoz ltd)	1
33025	nimodrel xl 30mg tablets (zurich pharmaceuticals)	1
33091	felodipine 10mg modified-release tablets (a a h pharmaceuticals ltd)	1
33471	verapamil 40mg tablets (actavis uk ltd)	1
33932	parmid xl 5mg tablets (sandoz ltd)	1
34101	nifedipine mr 20mg modified-release tablet (ivax pharmaceuticals uk ltd)	1
34115	nifedipine 60mg modified-release tablet	1
34146	nifedipine mr 10mg modified-release tablet (ivax pharmaceuticals uk ltd)	1
34187	nifedipine 10mg modified-release tablet (generics (uk) ltd)	1
34247	nifedipine 10mg capsule (berk pharmaceuticals ltd)	1
34377	diltiazem hcl 90mg modified-release capsule (hillcross pharmaceuticals ltd)	1
34475	diltiazem hcl 90mg modified-release tablet (ivax pharmaceuticals uk ltd)	1
34522	nifedipine 5mg capsules (a a h pharmaceuticals ltd)	1
34581	diltiazem hcl 60mg modified-release tablet (kent pharmaceuticals ltd)	1
34607	nifedipine 5mg capsules (ivax pharmaceuticals uk ltd)	1
34824	diltiazem hcl 120mg modified-release tablet (ivax pharmaceuticals uk ltd)	1
34959	verapamil 40mg tablets (a a h pharmaceuticals ltd)	1
34975	nifedipine 5mg capsules (teva uk ltd)	1
35084	vascalpha 5mg modified-release tablets (actavis uk ltd)	1
35592	cardioplen xl 2.5mg tablets (chiesi ltd)	1
35646	neozipine xl 60mg tablets (kent pharmaceuticals ltd)	1
35696	kenzem sr 120mg capsules (kent pharmaceuticals ltd)	1
35729	verapamil 80mg tablets (teva uk ltd)	1
36583	zemret xl 180mg capsule (neo laboratories ltd)	1
36620	parmid xl 10mg tablets (sandoz ltd)	1
36664	zemret xl 300mg capsule (neo laboratories ltd)	1
37025	nifedipine 20mg modified-release tablets	1
37184	valni xl 30mg tablets (zentiva)	1
37530	neozipine xl 30mg tablets (kent pharmaceuticals ltd)	1
37726	nifedipine 100mg/5ml oral suspension	1
37774	kenzem sr 60mg capsules (kent pharmaceuticals ltd)	1
37897	felotens xl 2.5mg tablets (thornton & ross ltd)	1
38066	diltiazem hcl 60mg modified-release tablet (lagap)	1
38107	nifedipine sr 30mg tablet (hillcross pharmaceuticals ltd)	1
38434	keloc sr 10mg tablets (teva uk ltd)	1
38545	tildiem la 200 capsules (sanofi)	1
38632	adizem-sr 90mg capsules (napp pharmaceuticals ltd)	1

38634	adizem-xl 300mg capsules (napp pharmaceuticals ltd)	1
38818	adizem-sr 120mg capsules (napp pharmaceuticals ltd)	1
38831	adizem-sr 180mg capsules (napp pharmaceuticals ltd)	1
38855	adizem-xl 180mg capsules (napp pharmaceuticals ltd)	1
38865	adizem-xl 120mg capsules (napp pharmaceuticals ltd)	1
38876	tildiem la 300 capsules (sanofi)	1
38882	adizem-xl 240mg capsules (napp pharmaceuticals ltd)	1
38964	adizem-sr 120mg tablets (napp pharmaceuticals ltd)	1
39009	verapamil 40mg tablets (teva uk ltd)	1
39171	bi-carzem sr 60mg capsules (tillomed laboratories ltd)	1
39298	bi-carzem sr 90mg capsules (tillomed laboratories ltd)	1
39357	neofel xl 2.5mg tablets (kent pharmaceuticals ltd)	1
39800	valni xl 60mg tablets (zentiva)	1
40074	nifedipine 20mg capsule	1
40405	verapamil 120mg tablets (teva uk ltd)	1
40633	vascalpha 5mg modified-release tablets (almus pharmaceuticals ltd)	1
41489	bi-carzem sr 120mg capsules (tillomed laboratories ltd)	1
41586	verapamil 80mg tablets (actavis uk ltd)	1
41635	diltiazem 60mg modified-release tablets (ivax pharmaceuticals uk ltd)	1
41679	verapamil 80mg tablets (ivax pharmaceuticals uk ltd)	1
41693	verapamil 120mg tablets (mylan)	1
41979	adipine la 30mg modified-release tablet (chiesi ltd)	1
42625	vera-til sr 120mg tablets (actavis uk ltd)	1
42731	diltiazem sr 120mg capsule (hillcross pharmaceuticals ltd)	1
42804	diltiazem hcl 180mg capsule (pliva pharma ltd)	1
42819	diltiazem xl 240mg capsule (hillcross pharmaceuticals ltd)	1
42912	nifedipine 10mg capsules (teva uk ltd)	1
43222	valni 20 retard tablets (tillomed laboratories ltd)	1
43394	pinefeld xl 10mg tablets (tillomed laboratories ltd)	1
43410	nifedipine extra 60mg modified-release tablet	1
43430	diltiazem 120mg modified-release tablets (a a h pharmaceuticals ltd)	1
43511	nifedipine 10mg capsules (a a h pharmaceuticals ltd)	1
43512	felodipine 5mg modified-release tablets (a a h pharmaceuticals ltd)	1
43515	nifedipine 10mg capsules (actavis uk ltd)	1
43753	adalat la 30mg tablets (bayer plc)	1
43790	vascalpha 10mg modified-release tablets (almus pharmaceuticals ltd)	1
43818	adalat la 60mg tablets (bayer plc)	1
43879	vera-til sr 240mg tablets (actavis uk ltd)	1
44192	zemret 240 xl capsules (tillomed laboratories ltd)	1
44859	felodipine sr 5mg tablet (approved prescription services ltd)	1
44887	bi-carzem xl 300mg capsule (tillomed laboratories ltd)	1
45051	verapamil hc 240mg modified-release tablet (actavis uk ltd)	1

45292	nicardipine 30mg capsules (a a h pharmaceuticals ltd)	1
45308	verapamil 240mg modified-release tablets (mylan)	1
45564	diltiazem 2% ointment	1
45685	adanif xl 30mg tablets (focus pharmaceuticals ltd)	1
45759	diltiazem hcl 240mg capsule (pliva pharma ltd)	1
46009	verapamil 120mg tablets (kent pharmaceuticals ltd)	1
46445	nifedipine 10mg capsules (ivax pharmaceuticals uk ltd)	1
46884	verapamil hc 240mg modified-release tablet (sandoz ltd)	1
46887	adanif xl 60mg tablets (focus pharmaceuticals ltd)	1
46937	diltiazem 60mg modified-release tablets (actavis uk ltd)	1
46955	verapamil 80mg tablets (mylan)	1
47027	nifedipine 10mg modified-release tablet (kent pharmaceuticals ltd)	1
47217	adipine la 60mg modified-release tablet (chiesi ltd)	1
47222	verapamil 120mg modified-release tablets (a a h pharmaceuticals ltd)	1
47230	verapamil 240mg modified-release tablets (teva uk ltd)	1
47285	nifedipine xl 60mg tablet (hillcross pharmaceuticals ltd)	1
47331	lercanidipine 10mg tablets (mylan)	1
47415	diltiazem sr 60mg capsule (hillcross pharmaceuticals ltd)	1
47529	nifedipine 20mg/ml oral drops	1
47530	horizem sr 60mg capsules (horizon lifecare)	1
47608	zemret 300 xl capsules (tillomed laboratories ltd)	1
47614	nifedipine 30mg modified-release tablets (a a h pharmaceuticals ltd)	1
47707	nifedipine oral solution	1
47724	bi-carzem xl 240mg capsules (tillomed laboratories ltd)	1
47732	zemret 180 xl capsules (tillomed laboratories ltd)	1
47887	nimodrel xl 60mg tablets (zurich pharmaceuticals)	1
47996	diltiazem 2% gel	1
48009	felodipine 5mg modified-release tablet (sandoz ltd)	1
48272	diltiazem 60mg modified-release capsules (alliance healthcare (distribution) ltd)	1
48282	diltiazem 90mg modified-release capsules (a a h pharmaceuticals ltd)	1
48288	diltiazem 120mg modified-release capsules (a a h pharmaceuticals ltd)	1
48457	diltiazem 90mg modified-release capsules (alliance healthcare (distribution) ltd)	1
48870	adizem-sr 90mg capsules (de pharmaceuticals)	1
49001	diltiazem 120mg modified-release tablets (alliance healthcare (distribution) ltd)	1
49237	diltiazem 0.2% cream	1
49289	diltiazem 120mg modified-release capsules (alliance healthcare (distribution) ltd)	1
49338	nifedipine 20mg modified-release tablets (alliance healthcare (distribution) ltd)	1
49390	diltiazem 90mg modified-release tablets (alliance healthcare (distribution) ltd)	1
49500	diltiazem 2% ointment (drug tariff special order)	1
49762	nifedipine 10mg modified-release tablets (alliance healthcare (distribution) ltd)	1
51261	tildiem retard 120mg tablets (mawdsley-brooks & company ltd)	1
51461	securon sr 240mg tablets (waymade healthcare plc)	1

51489	anoheal 2% cream (s.l.a. pharma (uk) ltd)	1
51917	adalat la 60 tablets (sigma pharmaceuticals plc)	1
52017	adalat la 30 tablets (mawdsley-brooks & company ltd)	1
52276	adizem-xl 180mg capsules (de pharmaceuticals)	1
52701	tildiem la 200 capsules (mawdsley-brooks & company ltd)	1
52728	beta-adalat modified-release capsules (lexon (uk) ltd)	1
53278	adalat la 30 tablets (necessity supplies ltd)	1
53357	nifedipine 10mg/5ml oral suspension	1
53500	adalat la 30 tablets (de pharmaceuticals)	1
53629	adalat retard 20mg tablets (lexon (uk) ltd)	1
53990	nifedipine 5mg/5ml oral suspension	1
54799	tildiem la 300 capsules (mawdsley-brooks & company ltd)	1
55257	diltiazem 60mg/5ml oral solution	1
55306	folpik xl 5mg tablets (teva uk ltd)	1
55455	nifedipine 10mg capsules (strides shasun (uk) ltd)	1
55740	neofel xl 2.5mg tablets (actavis uk ltd)	1
55824	nifedipine 20mg modified-release tablet (berk pharmaceuticals ltd)	1
56271	diltiazem 0.2% cream (special order)	1
56467	tildiem 60mg modified-release tablets (de pharmaceuticals)	1
56469	adalat la 60 tablets (necessity supplies ltd)	1
56758	diltiazem 90mg modified-release capsules (cubic pharmaceuticals ltd)	1
56767	lercanidipine 20mg tablets (mylan)	1
57208	diltiazem 120mg modified-release capsules (cubic pharmaceuticals ltd)	1
57444	lercanidipine 10mg tablets (aptil pharma ltd)	1
57531	adalat la 60 tablets (waymade healthcare plc)	1
57594	tildiem 60mg modified-release tablets (waymade healthcare plc)	1
57653	adalat la 20 tablets (sigma pharmaceuticals plc)	1
57859	diltiazem 90mg modified-release tablets (cubic pharmaceuticals ltd)	1
58339	neofel xl 2.5mg tablets (almus pharmaceuticals ltd)	1
58557	adalat la 20 tablets (necessity supplies ltd)	1
58990	nifedipine 10mg modified-release tablets (cubic pharmaceuticals ltd)	1
59098	dilzem xl 180 capsules (lexon (uk) ltd)	1
59163	nifedipine 20mg modified-release tablets (cubic pharmaceuticals ltd)	1
59233	lercanidipine 20mg tablets (actavis uk ltd)	1
59264	securon sr 240mg tablets (de pharmaceuticals)	1
59585	uard 120xl capsules (ennogen healthcare ltd)	1
59863	dilzem xl 240 capsules (lexon (uk) ltd)	1
60415	dilzem xl 180 capsules (sigma pharmaceuticals plc)	1
60569	felodipine 2.5mg modified-release tablets (waymade healthcare plc)	1
60620	adizem-xl 240mg capsules (waymade healthcare plc)	1
60652	parmid xl 2.5mg tablets (sandoz ltd)	1
60856	nifedipine 10mg modified-release tablets (sigma pharmaceuticals plc)	1

60884	felodipine 2.5mg modified-release tablets (phoenix healthcare distribution ltd)	1
61010	diltiazem 120mg modified-release tablets (cubic pharmaceuticals ltd)	1
61245	diltiazem 60mg modified-release capsules (sigma pharmaceuticals plc)	1
61532	diltiazem 120mg modified-release capsules (sigma pharmaceuticals plc)	1
61611	lercanidipine 10mg tablets (de pharmaceuticals)	1
61719	beta-adalat modified-release capsules (waymade healthcare plc)	1
62064	diltiazem 120mg modified-release tablets (mawdsley-brooks & company ltd)	1
62065	diltiazem 90mg modified-release tablets (colorama pharmaceuticals ltd)	1
62207	adizem-sr 120mg capsules (waymade healthcare plc)	1
62552	verapamil 80mg tablets (alliance healthcare (distribution) ltd)	1
62912	diltiazem 120mg modified-release capsules (am distributions (yorkshire) ltd)	1
63041	nifedipine 10mg capsules (mylan)	1
63246	nifedipine 10mg modified-release tablets (am distributions (yorkshire) ltd)	1
63331	folpik xl 2.5mg tablets (teva uk ltd)	1
63917	lercanidipine 20mg tablets (a a h pharmaceuticals ltd)	1
64227	lercanidipine 10mg tablets (actavis uk ltd)	1
64424	lercanidipine 20mg tablets (zentiva)	1
64474	felodipine 2.5mg modified-release tablets (a a h pharmaceuticals ltd)	1
64504	plendil 5mg modified-release tablets (necessity supplies ltd)	1
64624	diltiazem 4% cream	1
64719	felodipine 2.5mg modified-release tablets (sigma pharmaceuticals plc)	1
64760	felodipine 10mg modified-release tablets (phoenix healthcare distribution ltd)	1
64890	diltiazem cream	1
64917	felodipine 10mg modified-release tablets (waymade healthcare plc)	1
65349	folpik xl 10mg tablets (teva uk ltd)	1
65504	adizem-sr 180mg capsules (lexon (uk) ltd)	1
65602	adizem-xl 120mg capsules (waymade healthcare plc)	1
65636	adizem-xl 120mg capsules (lexon (uk) ltd)	1
65659	lercanidipine 20mg tablets (teva uk ltd)	1
65970	nifedipine 2% ointment	1
66048	tildiem retard 120mg tablets (de pharmaceuticals)	1
66095	felodipine 5mg modified-release tablets (mawdsley-brooks & company ltd)	1
66172	uard 180xl capsules (ennogen healthcare ltd)	1
66191	adalat retard 20mg tablets (de pharmaceuticals)	1
66236	nifedipine 20mg modified-release tablet (kent pharmaceuticals ltd)	1
66635	dilzem xl 180 capsules (de pharmaceuticals)	1
66701	diltiazem 240mg modified-release capsules (de pharmaceuticals)	1
66834	uard 240xl capsules (ennogen healthcare ltd)	1
66850	diltiazem 240mg modified-release capsules (icarus pharmaceuticals ltd)	1
66910	felodipine 2.5mg modified-release tablets (de pharmaceuticals)	1
67074	adalat 10mg capsules (de pharmaceuticals)	1
67293	half securon sr 120mg tablets (mawdsley-brooks & company ltd)	1

67317	dilzem xl 120 capsules (mawdsley-brooks & company ltd)	1
67344	diltiazem 300mg modified-release capsules (ennogen pharma ltd)	1
67890	uard 300xl capsules (ennogen healthcare ltd)	1
68020	beta-adalat modified-release capsules (sigma pharmaceuticals plc)	1
68054	diltiazem 60mg modified-release tablets (alliance healthcare (distribution) ltd)	1
69028	diltiazem 60mg modified-release capsules (de pharmaceuticals)	1
69108	adizem-xl 300mg capsules (lexon (uk) ltd)	1
69116	diltiazem 60mg modified-release tablets (de pharmaceuticals)	1
69202	nifedipine 2mg/5ml oral suspension	1
69206	felodipine 2.5mg/5ml oral solution	1
69239	lercanidipine 10mg tablets (a a h pharmaceuticals ltd)	1
69277	adizem-xl 240mg capsules (lexon (uk) ltd)	1
69668	nifedipine 30mg/5ml oral suspension	1
69818	diltiazem 0.5% ointment	1
70306	diltiazem 180mg modified-release capsules (mawdsley-brooks & company ltd)	1
70732	lercanidipine 20mg tablets (alliance healthcare (distribution) ltd)	1
70827	lercanidipine 10mg tablets (teva uk ltd)	1
70961	tildiem retard 90mg tablets (de pharmaceuticals)	1
71009	verapamil 40mg tablets (kent pharmaceuticals ltd)	1
71018	lercanidipine 10mg tablets (arrow generics ltd)	1
71030	lercanidipine 20mg tablets (arrow generics ltd)	1
71339	adalat la 30 tablets (dowelhurst ltd)	1
71342	dilzem xl 240 capsules (waymade healthcare plc)	1
71413	diltiazem 120mg modified-release capsules (a a h pharmaceuticals ltd)	1

Identification of loop diuretics

List of product codes (prodcode) used to identify loop diuretics and their descriptions are listed in the table below. The final codes to identify presence of loop diuretics are identified in the far right columns by a '1'.

prodcode	productname	Included
6	furosemide 40mg tablets	1
55	furosemide 20mg tablets	1
56	co-amilofruse 5mg/40mg tablets	1
193	co-amilofruse 2.5mg/20mg tablets	1
211	frumil 40mg+5mg tablet (helios healthcare ltd)	1
562	furosemide 10mg/ml injection	1
814	bumetanide 1mg tablets	1
1301	frumil ls 20mg+2.5mg tablet (helios healthcare ltd)	1
1369	furosemide with amiloride 40mg+5mg tablet	1
1776	burinex k modified-release tablets (leo pharma)	1
2493	burinex a 5mg/1mg tablets (leo pharma)	1
2495	bumetanide with amiloride tablets	1
2772	lasoride 5mg/40mg tablets (sanofi)	1
2788	burinex 1mg tablets (leo pharma)	1
2961	frusene 50mg/40mg tablets (orion pharma (uk) ltd)	1
3050	furosemide with triamterene 40mgwith50mg tablet	1
3248	furosemide 500mg tablets	1
3287	furosemide 1mg/ml oral solution	1
3793	co-amilofruse 10mg/80mg tablets	1
4182	lasix 5mg/5ml oral solution (borg medicare)	1
4211	furosemide with amiloride 20mg+2.5mg tablet	1
4258	lasix 20mg/2ml solution for injection ampoules (sanofi)	1
4661	spironolactone 50mg / furosemide 20mg capsules	1
4705	furosemide 20mg/2ml injection	1
4873	fru-co 5mg/40mg tablets (teva uk ltd)	1
5218	bumetanide 1mg/5ml oral solution sugar free	1
5220	furosemide with amiloride 80mg+10mg tablet	1
5249	furosemide 50mg/5ml oral solution sugar free	1
5728	furosemide 40mg/5ml oral solution sugar free	1
5868	frusol 20mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
6118	furosemide 20mg/5ml oral solution sugar free	1
6160	bumetanide 500microgram / potassium chloride 573mg (potassium 7.7mmol) modified-release tablets	1
7441	lasilactone 20mg/50mg capsules (sanofi)	1
7582	lasikal modified-release tablets (borg medicare)	1
7606	lasix 40mg tablets (sanofi)	1
7734	diumide-k continus tablets (teofarma)	1

7799	lasix 20mg tablets (borg medicare)	1
7806	bumetanide 5mg tablets	1
8052	torasemide 5mg tablets	1
8102	furosemide 40mg / potassium chloride 600mg (potassium 8mmol) modified-release tablets	1
9431	frusemek 40mg+5mg tablet (approved prescription services ltd)	1
9456	amiloride 5mg / furosemide 40mg tablets	1
9680	frusol 40mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
10066	torem 5mg tablets (meda pharmaceuticals ltd)	1
10392	lasix 500mg tablets (sanofi)	1
10422	lasix 50mg/5ml injection (hoechst uk ltd)	1
10781	lasix with k tablet (hoechst marion roussel)	1
11265	triamterene 50mg / furosemide 40mg tablets	1
11268	torem 2.5mg tablets (meda pharmaceuticals ltd)	1
11487	torasemide 2.5mg tablets	1
12226	burinex 1mg/5ml oral solution (leo pharma)	1
12294	burinex 5mg tablets (leo pharma)	1
12318	lasix 250mg/25ml injection (hoechst marion roussel)	1
13435	frumil forte 10mg/80mg tablets (sanofi)	1
14587	amiloride 5mg / bumetanide 1mg tablets	1
14761	frusid 40mg tablets (dr reddy's laboratories (uk) ltd)	1
14837	frusol 50mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
15341	burinex 0.5mg/ml injection (leo pharma)	1
15874	amiloride 2.5mg / furosemide 20mg tablets	1
16206	froop 40mg tablets (ashbourne pharmaceuticals ltd)	1
17960	furosemide 20mg / potassium chloride 750mg (potassium 10mmol) modified-release tablets	1
18096	torasemide 10mg tablets	1
18332	aridil 20mg+2.5mg tablet (c p pharmaceuticals ltd)	1
18497	amiloride 10mg / furosemide 80mg tablets	1
18716	dryptal 10mg/ml injection (berk pharmaceuticals ltd)	1
19056	furosemide 50mg/5ml sugar free oral solution (rosemont pharmaceuticals ltd)	1
19192	furosemide 40mg tablet (m & a pharmachem ltd)	1
19194	furosemide 20mg tablets (teva uk ltd)	1
19258	furosemide 50mg/5ml solution for injection ampoules	1
19300	bumetanide 2mg/4ml solution for injection ampoules	1
20513	lasix 10 mg inj	1
20538	frumax 40mg tablet (ashbourne pharmaceuticals ltd)	1
21849	dryptal 40mg tablet (berk pharmaceuticals ltd)	1
21938	froop co 5mg/40mg tablets (ashbourne pharmaceuticals ltd)	1
22539	lasix (2ml)	1
22658	torem 10mg tablets (meda pharmaceuticals ltd)	1
23256	lasix paed	1
24832	lasipressin tablet (hoechst uk ltd)	1

24835	min-i-jet furosemide 10mg/ml injection (celltech pharma europe ltd)	1
25334	furosemide 500mg tablets (a a h pharmaceuticals ltd)	1
25717	furosemide 40mg tablets (mylan)	1
25965	co-amilofruse 2.5mg/20mg tablets (wockhardt uk ltd)	1
26292	diuresal 40mg tablet (lagap)	1
26328	lasix (25ml)	1
26529	furosemide with penbutolol tablet	1
27447	furosemide 40mg tablets (wockhardt uk ltd)	1
27690	furosemide 40mg tablets (a a h pharmaceuticals ltd)	1
27696	furosemide 40mg tablets (kent pharmaceuticals ltd)	1
27926	furosemide 20mg tablets (mylan)	1
28129	co-amilofruse 5mg/40mg tablets (teva uk ltd)	1
29780	furosemide 20mg tablet (c p pharmaceuticals ltd)	1
30625	furosemide 20mg tablets (a a h pharmaceuticals ltd)	1
30773	co-amilofruse 5mg+40mg tablet (berk pharmaceuticals ltd)	1
30875	furosemide 250mg/25ml solution for injection ampoules	1
30913	betinex 1mg tablet (berk pharmaceuticals ltd)	1
31548	furosemide 20mg tablets (actavis uk ltd)	1
31773	co-amilofruse 5mg/40mg tablets (wockhardt uk ltd)	1
31932	bumetanide 1mg tablets (c p pharmaceuticals ltd)	1
32091	bumetanide 1mg tablets (a a h pharmaceuticals ltd)	1
32277	furosemide 80mg/8ml solution for injection pre-filled syringes	1
32896	furosemide 40mg tablets (ranbaxy (uk) ltd)	1
32918	furosemide 20mg tablets (sandoz ltd)	1
33527	co-amilofruse 5mg/40mg tablets (mylan)	1
33658	co-amilofruse 5mg/40mg tablets (a a h pharmaceuticals ltd)	1
34006	furosemide 40mg tablets (actavis uk ltd)	1
34280	co-amilofruse 2.5mg/20mg tablets (sandoz ltd)	1
34374	furosemide 40mg tablets (teva uk ltd)	1
34557	furosemide 40mg tablets (ivax pharmaceuticals uk ltd)	1
34613	bumetanide 5mg tablets (teva uk ltd)	1
34622	co-amilofruse 10mg/80mg tablets (wockhardt uk ltd)	1
34934	bumetanide 1mg tablets (mylan)	1
35162	furosemide 20mg/2ml solution for injection ampoules	1
36190	furosemide 5mg/5ml oral solution sugar free	1
36767	bumetanide 1mg tablets (ivax pharmaceuticals uk ltd)	1
38901	frumil ls 20mg/2.5mg tablets (sanofi)	1
39602	bumetanide 1mg tablets (actavis uk ltd)	1
39807	frumil 40mg/5mg tablets (sanofi)	1
40190	torasemide iv 20mg/4ml intravenous injection	1
40247	furosemide 10mg/ml injection (martindale pharmaceuticals ltd)	1
40738	torem iv 10mg/2ml intravenous injection (boehringer mannheim uk ltd)	1

40898	torasemide 5mg tablets (a a h pharmaceuticals ltd)	1
41292	furosemide 20mg tablets (wockhardt uk ltd)	1
41405	furosemide 500mg tablets (teva uk ltd)	1
41533	co-amilofruse 2.5mg/20mg tablets (teva uk ltd)	1
41719	co-amilofruse 5mg/40mg tablets (actavis uk ltd)	1
41828	furosemide 500mg tablets (actavis uk ltd)	1
42388	furosemide 40mg/5ml oral solution sugar free (focus pharmaceuticals ltd)	1
42488	furosemide 40mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)	1
43508	co-amilofruse 5mg/40mg tablets (sandoz ltd)	1
45305	bumetanide 1mg tablets (teva uk ltd)	1
46116	furosemide 10mg/ml injection (antigen pharmaceuticals)	1
46525	torasemide 5mg tablets (teva uk ltd)	1
46699	furosemide 40mg tablets (almus pharmaceuticals ltd)	1
46948	furosemide 40mg tablets (arrow generics ltd)	1
47647	co-amilofruse oral liquid	1
47815	furosemide 20mg tablet (celltech pharma europe ltd)	1
49268	furosemide 50mg/5ml oral suspension	1
51983	furosemide 5mg/5ml oral suspension	1
52045	furosemide 250mg/5ml solution for injection vials	1
52887	furosemide 20mg/2ml solution for injection ampoules (a a h pharmaceuticals ltd)	1
52900	furosemide 80mg/8ml solution for injection minijet pre-filled syringes (ucb pharma ltd)	1
53967	furosemide 20mg tablets (bristol laboratories ltd)	1
54825	furosemide 20mg tablets (sigma pharmaceuticals plc)	1
55548	bumetanide 1mg tablets (alliance healthcare (distribution) ltd)	1
55738	furosemide 50mg/5ml solution for injection ampoules (hameln pharmaceuticals ltd)	1
56051	furosemide 20mg tablets (kent pharmaceuticals ltd)	1
56375	furosemide 40mg tablets (accord healthcare ltd)	1
57600	furosemide 20mg/2ml solution for injection ampoules (alliance healthcare (distribution) ltd)	1
57610	furosemide 20mg/5ml oral solution sugar free (focus pharmaceuticals ltd)	1
57908	co-amilofruse 5mg/40mg tablets (kent pharmaceuticals ltd)	1
58078	furosemide 8mg/5ml oral solution	1
58224	furosemide 10mg/5ml oral solution	1
59030	furosemide 20mg/5ml oral solution	1
59290	furosemide 20mg tablets (alliance healthcare (distribution) ltd)	1
59412	co-amilofruse 5mg/40mg tablets (waymade healthcare plc)	1
59884	furosemide 20mg tablets (phoenix healthcare distribution ltd)	1
59911	furosemide 40mg tablets (alliance healthcare (distribution) ltd)	1
59939	furosemide 20mg/5ml oral suspension	1
60258	co-amilofruse 2.5mg/20mg tablets (aurobindo pharma ltd)	1
60291	furosemide 40mg tablets (amco)	1
60465	furosemide 5mg/5ml oral solution	1
61365	furosemide 40mg/5ml oral suspension	1

61475	furosemide 20mg tablets (de pharmaceuticals)	1
62024	bumetanide 5mg tablets (a a h pharmaceuticals ltd)	1
63237	furosemide 20mg tablets (boston healthcare ltd)	1
63555	bumetanide 1mg tablets (phoenix healthcare distribution ltd)	1
64255	furosemide 2mg/5ml oral solution	1
64677	furosemide 40mg tablets (de pharmaceuticals)	1
64745	furosemide 8mg/5ml oral suspension	1
65583	furosemide 3mg/5ml oral solution	1
66017	furosemide 20mg tablets (almus pharmaceuticals ltd)	1
66149	furosemide 4.5mg/5ml oral solution	1
66195	bumetanide 1mg tablets (almus pharmaceuticals ltd)	1
67910	furosemide 40mg/5ml oral solution	1
68068	furosemide 4mg/5ml oral solution	1
69338	furosemide 40mg/5ml sugar free oral solution (rosemont pharmaceuticals ltd)	1
69445	furosemide 40mg/5ml oral solution sugar free (sigma pharmaceuticals plc)	1
70650	furosemide 50mg/5ml solution for injection ampoules (peckforton pharmaceuticals ltd)	1
71348	frumil 40mg/5mg tablets (waymade healthcare plc)	1
71377	frumil ls 20mg/2.5mg tablets (waymade healthcare plc)	1
71406	furosemide 1mg/5ml oral solution	1

Identification of MRA

List of product codes (prodcode) used to identify MRA and their descriptions are listed in the table below. The final codes to identify presence of MRA are identified in the far right columns by a '1'.

prodcode	productname	Included
692	spironolactone 25mg tablets	1
708	spironolactone 50mg tablets	1
787	spironolactone 100mg capsule	1
1297	aldactide 50 tablets (pfizer ltd)	1
2001	aldactide 25 tablets (pfizer ltd)	1
2142	spironolactone 100mg tablets	1
2389	aldactone 25mg tablets (pfizer ltd)	1
3902	frusemide 20mg/spironolactone 50mg mg cap	1
4161	spiroctan 25mg tablet (roche products ltd)	1
4661	spironolactone 50mg / furosemide 20mg capsules	1
4960	aldactone 50mg tablets (pfizer ltd)	1
6815	spironolactone 50mg/5ml oral suspension sugar free	1
7441	lasilactone 20mg/50mg capsules (sanofi)	1
7952	aldactone 100mg tablets (pfizer ltd)	1
7961	spironolactone 50mg with hydroflumethiazide 50mg tablet	1
7991	spiroctan 100mg capsule (roche products ltd)	1
8521	spironolactone 25mg with hydroflumethiazide 25mg tablet	1
10214	spironolactone 5mg/5ml oral suspension sugar free	1
10251	eplerenone 25mg tablets	1
11156	spirolone 25mg tablet (berk pharmaceuticals ltd)	1
11384	co-flumactone 50mg/50mg tablets	1
11519	spironolactone 25mg/5ml oral suspension sugar free	1
12946	spironolactone 10mg/5ml oral suspension sugar free	1
13264	spironolactone 15mg/5ml oral suspension	1
14109	spironolactone 100mg/5ml oral solution sugar free	1
14144	inspra 25mg tablets (pfizer ltd)	1
15052	spiroctan 50mg tablet (roche products ltd)	1
15053	spironolactone 10 mg/5ml liq	1
15811	co-flumactone 25mg/25mg tablets	1
16531	eplerenone 50mg tablets	1
17783	spiroprop tablet (pharmacia ltd)	1
17902	spirolone 100mg tablet (berk pharmaceuticals ltd)	1
17950	spirolone 50mg tablet (berk pharmaceuticals ltd)	1
19003	spironolactone/propranolol 50 mg tab	1
19195	spironolactone 50mg tablet (wyeth pharmaceuticals)	1
21911	spirospare 25mg tablet (ashbourne pharmaceuticals ltd)	1

23091	spirospare 100 tablets (ashbourne pharmaceuticals ltd)	1
25086	spironolactone	1
25494	diatensec 50mg tablet (pharmacia ltd)	1
25505	spiro-co 50mg+50mg tablet (ivax pharmaceuticals uk ltd)	1
29397	spiretic 100mg tablet (ddsa pharmaceuticals ltd)	1
29529	hydroflumethiazide with spironolactone 25mg+25mg tablet	1
29694	inspra 50mg tablets (pfizer ltd)	1
30034	chlorothiazide / spironolactone 100 mg pow	1
30035	chlorothiazide 40mg /spironolactone 4mg pow	1
30365	chlorothiazide/spironolactone/lactose mg pow	1
30367	chlorothiazide 60mg / spironolactone 6mg pow	1
30368	chlorothiazide/spironolactone sachets 100 mg	1
30592	chlorothiazide / spironolactone / glucos 60 mg pow	1
31131	spiro-co 25mg+25mg tablet (ivax pharmaceuticals uk ltd)	1
31219	spironolactone 100mg tablets (a a h pharmaceuticals ltd)	1
31529	spironolactone 25mg tablets (teva uk ltd)	1
32837	spironolactone 50mg tablets (teva uk ltd)	1
34296	spironolactone 25mg tablets (a a h pharmaceuticals ltd)	1
34347	spironolactone 25mg tablets (actavis uk ltd)	1
34908	spironolactone 25mg tablets (ivax pharmaceuticals uk ltd)	1
35789	spironolactone 25mg tablet (celltech pharma europe ltd)	1
41074	spironolactone 25mg tablets (almus pharmaceuticals ltd)	1
41592	spironolactone 100mg tablets (actavis uk ltd)	1
41660	spironolactone 100mg tablets (teva uk ltd)	1
41706	spironolactone 50mg tablets (ivax pharmaceuticals uk ltd)	1
43514	spironolactone 50mg tablets (a a h pharmaceuticals ltd)	1
45078	spironolactone 25mg/5ml oral solution sugar free (rosemont pharmaceuticals ltd)	1
45916	hydroflumethiazide with spironolactone 50mg+50mg tablet	1
46674	spironolactone 50mg/5ml oral suspension sugar free (rosemont pharmaceuticals ltd)	1
46990	spironolactone 50mg/5ml oral suspension	1
47018	spironolactone 25mg/5ml oral suspension	1
47687	spiretic 25mg tablet (ddsa pharmaceuticals ltd)	1
49388	spironolactone 100mg/5ml oral suspension	1
50079	spironolactone 10mg/5ml oral suspension	1
50370	spironolactone 5mg/5ml oral suspension	1
51652	spironolactone 25mg tablets (de pharmaceuticals)	1
51720	spironolactone 25mg/5ml oral solution	1
51933	spironolactone 50mg/5ml oral solution	1
52366	spironolactone 5mg/5ml oral solution	1
52970	spironolactone 10mg/5ml oral solution	1
53253	spironolactone 50mg/5ml oral suspension (drug tariff special order)	1
53508	spironolactone 5mg/5ml / chlorothiazide 50mg/5ml oral suspension	1

54120	spironolactone 4mg/5ml oral suspension	1
55050	chlorothiazide/spironolactone/lact sach 50 mg	1
56067	spironolactone 4mg/5ml oral solution	1
56274	spironolactone 4.5mg/5ml oral suspension	1
56536	spironolactone 100mg/5ml oral solution	1
57104	spironolactone 200mg/5ml oral suspension	1
57556	spironolactone 12mg/5ml oral solution	1
57933	spironolactone 40mg/5ml oral suspension	1
58077	spironolactone 8mg/5ml oral suspension	1
58225	spironolactone 2.5mg/5ml oral suspension	1
58757	spironolactone 20mg/5ml oral suspension	1
60343	spironolactone 25mg tablets (kent pharmaceuticals ltd)	1
60660	spironolactone 3mg/5ml oral suspension	1
61025	spironolactone 20mg/5ml oral solution	1
63309	spironolactone 6mg/5ml oral suspension	1
65582	spironolactone 3mg/5ml oral solution	1
65822	spironolactone 12.5mg/5ml oral suspension	1
66011	eplerenone 50mg tablets (a a h pharmaceuticals ltd)	1
67913	spironolactone 50mg tablets (kent pharmaceuticals ltd)	1
69473	spironolactone 3.5mg/5ml oral suspension	1
70370	eplerenone 25mg tablets (actavis uk ltd)	1
70543	eplerenone 50mg tablets (actavis uk ltd)	1
70918	eplerenone 25mg tablets (alliance healthcare (distribution) ltd)	1
71010	spironolactone 25mg tablets (genesis pharmaceuticals ltd)	1
71398	spironolactone 12.5mg/5ml oral solution	1

Identification of statins

List of product codes (prodcode) used to identify statins and their descriptions are listed in the table below. The final codes to identify presence of statins are identified in the far right columns by a '1'.

prodcode	productname	Included
25	simvastatin 20mg tablets	1
28	atorvastatin 10mg tablets	1
42	simvastatin 10mg tablets	1
51	simvastatin 40mg tablets	1
75	atorvastatin 20mg tablets	1
379	fluvastatin 20mg capsules	1
490	pravastatin 10mg tablets	1
713	rosuvastatin 10mg tablets	1
730	pravastatin 20mg tablets	1
745	atorvastatin 40mg tablets	1
802	simvador 40mg tablets (discovery pharmaceuticals)	1
818	simvastatin 20mg/5ml oral solution sugar free	1
1219	pravastatin 40mg tablets	1
1221	lipostat 10mg tablets (bristol-myers squibb pharmaceuticals ltd)	1
1223	lipostat 40mg tablets (bristol-myers squibb pharmaceuticals ltd)	1
2137	fluvastatin 40mg capsules	1
2718	zocor 10mg tablets (merck sharp & dohme ltd)	1
2955	lipitor 40mg tablets (pfizer ltd)	1
3411	lipitor 10mg tablets (pfizer ltd)	1
3690	lipostat 20mg tablets (bristol-myers squibb pharmaceuticals ltd)	1
5148	simvastatin 80mg tablets	1
5775	atorvastatin 80mg tablets	1
5985	lescol xl 80mg tablets (novartis pharmaceuticals uk ltd)	1
6168	zocor 40mg tablets (merck sharp & dohme ltd)	1
6213	rosuvastatin 20mg tablets	1
7196	zocor 20mg tablets (merck sharp & dohme ltd)	1
7347	crestor 10mg tablets (astrazeneca uk ltd)	1
7374	lipitor 20mg tablets (pfizer ltd)	1
7552	simvastatin 20mg / ezetimibe 10mg tablets	1
7554	rosuvastatin 5mg tablets	1
8380	lescol 20mg capsules (novartis pharmaceuticals uk ltd)	1
9153	lescol 40mg capsules (novartis pharmaceuticals uk ltd)	1
9897	rosuvastatin 40mg tablets	1
9920	simvador 20mg tablets (discovery pharmaceuticals)	1
9930	crestor 40mg tablets (astrazeneca uk ltd)	1
10172	simvastatin 40mg / ezetimibe 10mg tablets	1

10183	simvastatin 40mg with ezetimibe 10mg tablet	1
10206	simvastatin 80mg with ezetimibe 10mg tablet	1
11627	fluvastatin 80mg modified-release tablets	1
11815	simvastatin 20mg with ezetimibe 10mg tablet	1
13041	simvador 10mg tablets (discovery pharmaceuticals)	1
14219	simvastatin 80mg / ezetimibe 10mg tablets	1
15252	crestor 20mg tablets (astrazeneca uk ltd)	1
16186	inegy 10mg/80mg tablets (merck sharp & dohme ltd)	1
17059	inegy 10mg/40mg tablets (merck sharp & dohme ltd)	1
17683	lipitor 80mg tablets (pfizer ltd)	1
17688	crestor 5mg tablets (astrazeneca uk ltd)	1
21020	inegy 10mg/20mg tablets (merck sharp & dohme ltd)	1
22579	zocor 80mg tablets (merck sharp & dohme ltd)	1
24509	simvastatin	1
29438	simvastatin	1
31930	zocor heart-pro 10mg tablet (mcneil products ltd)	1
32909	simvastatin 80mg tablets (a a h pharmaceuticals ltd)	1
32921	pravastatin 10mg tablet (dr reddy's laboratories (uk) ltd)	1
33082	simvastatin 20mg tablets (a a h pharmaceuticals ltd)	1
34312	simvastatin 20mg tablets (mylan)	1
34316	simvastatin 20mg tablets (teva uk ltd)	1
34353	simvastatin 40mg tablets (mylan)	1
34366	simvastatin 20mg tablets (ivax pharmaceuticals uk ltd)	1
34376	simvastatin 40mg tablets (teva uk ltd)	1
34381	simvastatin 40mg tablets (ivax pharmaceuticals uk ltd)	1
34476	simvastatin 20mg tablet (ratiopharm uk ltd)	1
34481	simvastatin 10mg tablets (ivax pharmaceuticals uk ltd)	1
34502	simvastatin 40mg tablets (a a h pharmaceuticals ltd)	1
34535	simvastatin 10mg tablets (mylan)	1
34545	simvastatin 40mg tablet (ratiopharm uk ltd)	1
34560	simvastatin 10mg tablet (ratiopharm uk ltd)	1
34746	simvastatin 20mg tablet (niche generics ltd)	1
34814	simvastatin 20mg tablets (wockhardt uk ltd)	1
34820	pravastatin 40mg tablets (a a h pharmaceuticals ltd)	1
34879	simvastatin 40mg tablet (niche generics ltd)	1
34891	simvastatin 20mg tablets (kent pharmaceuticals ltd)	1
34907	simvastatin 40mg tablets (wockhardt uk ltd)	1
34955	simvastatin 10mg tablets (a a h pharmaceuticals ltd)	1
34969	simvastatin 40mg tablets (actavis uk ltd)	1
36377	pravastatin 20mg tablets (teva uk ltd)	1
37434	simvastatin 40mg tablets (sandoz ltd)	1
39060	simvastatin 20mg tablets (dexcel-pharma ltd)	1

39652	simvastatin 40mg/5ml oral solution sugar free	1
39675	simvastatin 20mg/5ml oral suspension (martindale pharmaceuticals ltd)	1
39870	simvador 80mg tablets (discovery pharmaceuticals)	1
40340	simvastatin 10mg tablets (teva uk ltd)	1
40382	pravastatin 20mg tablets (a a h pharmaceuticals ltd)	1
40601	simvastatin 20mg tablets (ranbaxy (uk) ltd)	1
41657	simvastatin 80mg tablets (teva uk ltd)	1
43218	pravastatin 10mg tablets (teva uk ltd)	1
44528	simvastatin 20mg/5ml oral suspension sugar free (rosemont pharmaceuticals ltd)	1
44650	simvastatin 40mg tablets (dexcel-pharma ltd)	1
44878	ranzolont 10mg tablets (ranbaxy (uk) ltd)	1
45219	simvastatin 40mg tablets (kent pharmaceuticals ltd)	1
45235	simvastatin 20mg tablets (sandoz ltd)	1
45245	simvastatin 20mg tablets (actavis uk ltd)	1
45346	simvastatin 40mg tablets (arrow generics ltd)	1
46878	simvastatin 40mg tablets (almus pharmaceuticals ltd)	1
46956	simvastatin 80mg tablets (arrow generics ltd)	1
47065	atorvastatin 20mg chewable tablets sugar free	1
47090	atorvastatin 10mg chewable tablets sugar free	1
47630	lipitor 20mg chewable tablets (pfizer ltd)	1
47721	lipitor 10mg chewable tablets (pfizer ltd)	1
47774	simvastatin 10mg tablets (arrow generics ltd)	1
47948	simvastatin 10mg tablets (tillomed laboratories ltd)	1
47988	pravastatin 40mg tablets (mylan)	1
48018	simvastatin 20mg tablets (arrow generics ltd)	1
48051	simvastatin 10mg tablets (kent pharmaceuticals ltd)	1
48058	simvastatin 10mg tablets (ranbaxy (uk) ltd)	1
48078	simvastatin 10mg tablets (actavis uk ltd)	1
48097	pravastatin 40mg tablets (teva uk ltd)	1
48221	simvastatin 20mg/5ml oral suspension sugar free	1
48346	atorvastatin 60mg tablets	1
48431	simvastatin 40mg/5ml oral suspension sugar free	1
48518	atorvastatin 10mg/5ml oral solution	1
48867	simvastatin 40mg tablets (alliance healthcare (distribution) ltd)	1
48973	atorvastatin 30mg tablets	1
49061	simvastatin 40mg tablets (bristol laboratories ltd)	1
49062	simvastatin 20mg tablets (alliance healthcare (distribution) ltd)	1
49558	atorvastatin 20mg tablets (a a h pharmaceuticals ltd)	1
49587	simvastatin 80mg tablets (almus pharmaceuticals ltd)	1
49751	atorvastatin 40mg tablets (alliance healthcare (distribution) ltd)	1
50236	atorvastatin 10mg tablets (zentiva)	1
50272	atorvastatin 40mg tablets (pfizer ltd)	1

50483	simvastatin 40mg tablets (relonchem ltd)	1
50564	simvastatin 20mg tablets (relonchem ltd)	1
50670	simvastatin 40mg tablets (aurobindo pharma ltd)	1
50703	simvastatin 40mg tablets (accord healthcare ltd)	1
50754	simvastatin 20mg tablets (medreich plc)	1
50788	atorvastatin 20mg tablets (pfizer ltd)	1
50790	atorvastatin 20mg tablets (dexcel-pharma ltd)	1
50882	simvastatin 40mg tablets (somex pharma)	1
50925	pravastatin 10mg tablets (sigma pharmaceuticals plc)	1
50963	atorvastatin 40mg tablets (teva uk ltd)	1
51085	simvastatin 10mg tablets (medreich plc)	1
51134	atorvastatin 10mg tablets (a a h pharmaceuticals ltd)	1
51166	simvastatin 40mg tablets (medreich plc)	1
51200	atorvastatin 40mg tablets (arrow generics ltd)	1
51233	simvastatin 10mg tablets (alliance healthcare (distribution) ltd)	1
51359	atorvastatin 20mg tablets (arrow generics ltd)	1
51483	simvastatin 20mg tablets (aurobindo pharma ltd)	1
51622	atorvastatin 20mg tablets (consilient health ltd)	1
51676	pravastatin 40mg tablets (medreich plc)	1
51715	simvastatin 10mg tablets (sigma pharmaceuticals plc)	1
51876	atorvastatin 40mg tablets (consilient health ltd)	1
51890	pravastatin 20mg tablets (medreich plc)	1
52097	atorvastatin 40mg tablets (wockhardt uk ltd)	1
52098	simvastatin 40mg tablets (ranbaxy (uk) ltd)	1
52168	atorvastatin 20mg tablets (aspire pharma ltd)	1
52211	atorvastatin 20mg tablets (actavis uk ltd)	1
52257	simvastatin 20mg tablets (accord healthcare ltd)	1
52397	atorvastatin 40mg tablets (dr reddy's laboratories (uk) ltd)	1
52398	atorvastatin 40mg tablets (a a h pharmaceuticals ltd)	1
52459	atorvastatin 80mg tablets (actavis uk ltd)	1
52460	atorvastatin 40mg tablets (aspire pharma ltd)	1
52625	simvastatin 10mg tablets (wockhardt uk ltd)	1
52676	simvastatin 10mg/5ml oral suspension	1
52755	pravastatin 20mg tablets (alliance healthcare (distribution) ltd)	1
52812	simvastatin 20mg tablets (sigma pharmaceuticals plc)	1
52821	atorvastatin 80mg tablets (dr reddy's laboratories (uk) ltd)	1
52953	simvastatin 20mg tablets (bristol laboratories ltd)	1
52962	simvastatin 80mg tablets (medreich plc)	1
53087	simvastatin 20mg tablets (somex pharma)	1
53340	zocor 40mg tablets (lexon (uk) ltd)	1
53415	simvastatin 10mg tablets (aurobindo pharma ltd)	1
53460	crestor 10mg tablets (de pharmaceuticals)	1

53594	lipitor 80mg tablets (mawdsley-brooks & company ltd)	1
53676	simvastatin 20mg tablets (tillomed laboratories ltd)	1
53770	fluvastatin 40mg capsules (a a h pharmaceuticals ltd)	1
53772	atorvastatin 80mg tablets (alliance healthcare (distribution) ltd)	1
53822	simvastatin 10mg tablets (bristol laboratories ltd)	1
53887	atorvastatin 40mg tablets (actavis uk ltd)	1
53890	atorvastatin 80mg tablets (pfizer ltd)	1
53908	simvastatin 10mg tablets (dexcel-pharma ltd)	1
53966	simvastatin 40mg tablets (phoenix healthcare distribution ltd)	1
54240	simvastatin 40mg tablets (sigma pharmaceuticals plc)	1
54266	simvastatin 20mg/5ml oral suspension	1
54435	pravastatin 40mg tablets (almus pharmaceuticals ltd)	1
54493	simvastatin 10mg tablets (relonchem ltd)	1
54535	atorvastatin 10mg tablets (pfizer ltd)	1
54606	simvastatin 20mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1
54607	pravastatin 20mg tablets (almus pharmaceuticals ltd)	1
54655	simvastatin 10mg tablets (accord healthcare ltd)	1
54819	simvastatin 40mg/5ml oral suspension sugar free (rosemont pharmaceuticals ltd)	1
54947	simvastatin 20mg tablets (almus pharmaceuticals ltd)	1
54976	simvastatin 10mg tablets (somex pharma)	1
54985	simvastatin 40mg/5ml oral suspension	1
54992	atorvastatin 10mg/5ml oral suspension	1
55032	atorvastatin 10mg tablets (dexcel-pharma ltd)	1
55034	atorvastatin 40mg/5ml oral suspension	1
55444	atorvastatin 40mg tablets (zentiva)	1
55452	simvastatin 20mg tablets (phoenix healthcare distribution ltd)	1
55727	atorvastatin 10mg tablets (actavis uk ltd)	1
55912	pravastatin 40mg tablets (alliance healthcare (distribution) ltd)	1
56016	lipitor 20mg chewable tablets (pfizer ltd)	1
56065	simvastatin 20mg/5ml oral suspension sugar free (waymade healthcare plc)	1
56097	atorvastatin 10mg chewable tablets sugar free	1
56146	pravastatin 10mg tablets (waymade healthcare plc)	1
56165	atorvastatin 20mg chewable tablets sugar free	1
56182	atorvastatin 80mg tablets (zentiva)	1
56248	atorvastatin 20mg tablets (sigma pharmaceuticals plc)	1
56481	zocor 10mg tablets (sigma pharmaceuticals plc)	1
56494	zocor 20mg tablets (sigma pharmaceuticals plc)	1
56564	atorvastatin 20mg tablets (almus pharmaceuticals ltd)	1
56607	pravastatin 20mg tablets (waymade healthcare plc)	1
56735	pravastatin 20mg tablets (mylan)	1
56841	atorvastatin 40mg tablets (dexcel-pharma ltd)	1
56893	pravastatin 40mg tablets (accord healthcare ltd)	1

56916	pravastatin 40mg tablets (pliva pharma ltd)	1
57108	pravastatin 40mg tablets (waymade healthcare plc)	1
57117	atorvastatin 80mg tablets (waymade healthcare plc)	1
57137	pravastatin 10mg tablets (almus pharmaceuticals ltd)	1
57296	pravastatin 20mg tablets (phoenix healthcare distribution ltd)	1
57329	simvastatin 25mg/5ml oral suspension	1
57348	atorvastatin 10mg tablets (consilient health ltd)	1
57397	pravastatin 10mg tablets (accord healthcare ltd)	1
57568	zocor 10mg tablets (lexon (uk) ltd)	1
57763	rosuvastatin 10mg tablets (waymade healthcare plc)	1
57834	atorvastatin 40mg tablets (de pharmaceuticals)	1
57836	atorvastatin 80mg tablets (teva uk ltd)	1
57999	crestor 40mg tablets (lexon (uk) ltd)	1
58041	atorvastatin 20mg tablets (teva uk ltd)	1
58110	atorvastatin 20mg tablets (zentiva)	1
58315	simvastatin 20mg tablets (waymade healthcare plc)	1
58394	atorvastatin 20mg tablets (alliance healthcare (distribution) ltd)	1
58418	atorvastatin 80mg tablets (a a h pharmaceuticals ltd)	1
58617	rosuvastatin 20mg/5ml oral suspension	1
58742	atorvastatin 80mg tablets (arrow generics ltd)	1
58755	simvastatin 10mg tablets (phoenix healthcare distribution ltd)	1
58834	atorvastatin 10mg tablets (de pharmaceuticals)	1
58868	atorvastatin 10mg tablets (sigma pharmaceuticals plc)	1
59272	atorvastatin 20mg tablets (waymade healthcare plc)	1
59278	fluvastatin 20mg capsules (zentiva)	1
59331	lipitor 10mg tablets (de pharmaceuticals)	1
59357	atorvastatin 10mg tablets (ranbaxy (uk) ltd)	1
59446	atorvastatin 40mg tablets (almus pharmaceuticals ltd)	1
59447	crestor 20mg tablets (waymade healthcare plc)	1
59452	rosuvastatin 5mg tablets (waymade healthcare plc)	1
59508	pravastatin 20mg tablets (accord healthcare ltd)	1
59776	atorvastatin 80mg tablets (aspire pharma ltd)	1
59859	atorvastatin 10mg tablets (teva uk ltd)	1
60160	rosuvastatin 5mg tablets (mawdsley-brooks & company ltd)	1
60251	pravastatin 10mg tablets (sandoz ltd)	1
60464	atorvastatin 20mg/5ml oral suspension	1
60511	atorvastatin 40mg tablets (ranbaxy (uk) ltd)	1
60607	atorvastatin 80mg tablets (de pharmaceuticals)	1
60989	atorvastatin 80mg tablets (phoenix healthcare distribution ltd)	1
61134	pravastatin 20mg tablets (sigma pharmaceuticals plc)	1
61149	atorvastatin 10mg tablets (waymade healthcare plc)	1
61155	simvastatin 40mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)	1

61321	simvastatin 10mg tablets (sandoz ltd)	1
61360	simvastatin 10mg tablets (almus pharmaceuticals ltd)	1
61665	simvastatin 10mg tablets (waymade healthcare plc)	1
62137	simvastatin 40mg tablets (waymade healthcare plc)	1
62148	fluvastatin 20mg capsules (actavis uk ltd)	1
62219	atorvastatin 20mg tablets (de pharmaceuticals)	1
62429	atorvastatin 20mg tablets (de pharmaceuticals)	1
62476	atorvastatin 80mg tablets (almus pharmaceuticals ltd)	1
62979	pravastatin 40mg tablets (kent pharmaceuticals ltd)	1
63074	pravastatin 20mg tablets (pliva pharma ltd)	1
63140	atorvastatin 10mg tablets (alliance healthcare (distribution) ltd)	1
63249	atorvastatin 80mg tablets (consilient health ltd)	1
63469	atorvastatin 30mg tablets (consilient health ltd)	1
63787	pravastatin 10mg tablets (tillomed laboratories ltd)	1
64067	atorvastatin 20mg/5ml oral solution	1
64104	simvastatin 20mg tablets (crescent pharma ltd)	1
64180	simvastatin 10mg tablets (crescent pharma ltd)	1
64307	simvastatin 40mg tablets (crescent pharma ltd)	1
64702	atorvastatin 30mg tablets (a a h pharmaceuticals ltd)	1
64810	atorvastatin 40mg tablets (phoenix healthcare distribution ltd)	1
64825	atorvastatin 10mg tablets (phoenix healthcare distribution ltd)	1
64868	atorvastatin 40mg tablets (sigma pharmaceuticals plc)	1
64968	simvastatin 10mg tablets (de pharmaceuticals)	1
65181	simvastatin 40mg tablets (de pharmaceuticals)	1
65193	atorvastatin 20mg tablets (ranbaxy (uk) ltd)	1
65679	simvastatin 20mg tablets (de pharmaceuticals)	1
65901	simvastatin 40mg tablets (zentiva)	1
65925	simvastatin 20mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)	1
66505	fenofibrate 145mg / simvastatin 40mg tablets	1
66780	fenofibrate 145mg / simvastatin 20mg tablets	1
66963	atorvastatin 80mg tablets (sigma pharmaceuticals plc)	1
67098	simvastatin 10mg tablets (brown & burk uk ltd)	1
67328	lescol xl 80mg tablets (mawdsley-brooks & company ltd)	1
67402	atorvastatin 40mg tablets (kent pharmaceuticals ltd)	1
67573	atorvastatin 10mg tablets (de pharmaceuticals)	1
67660	atorvastatin 80mg tablets (ranbaxy (uk) ltd)	1
67745	simvastatin 10mg tablets (zentiva)	1
67773	simvastatin 20mg tablets (zentiva)	1
67829	pravastatin 20mg tablets (sandoz ltd)	1
67846	atorvastatin 10mg tablets (almus pharmaceuticals ltd)	1
68023	atorvastatin 10mg tablets (aspire pharma ltd)	1
68048	atorvastatin 20mg tablets (phoenix healthcare distribution ltd)	1

68156	pravastatin 10mg tablets (a a h pharmaceuticals ltd)	1
68467	atorvastatin 20mg tablets (kent pharmaceuticals ltd)	1
68563	simvastatin 40mg tablets (brown & burk uk ltd)	1
68686	simvastatin 20mg tablets (genesis pharmaceuticals ltd)	1
68785	atorvastatin 10mg tablets (mylan)	1
68827	atorvastatin 20mg tablets (mylan)	1
69093	atorvastatin 80mg tablets (wockhardt uk ltd)	1
69413	simvastatin 20mg tablets (brown & burk uk ltd)	1
69427	atorvastatin 40mg tablets (mylan)	1
69528	cholib 145mg/20mg tablets (mylan)	1
70308	crestor 20mg tablets (sigma pharmaceuticals plc)	1
70486	cholib 145mg/40mg tablets (mylan)	1
70693	atorvastatin 10mg tablets (sigma pharmaceuticals plc)	1
70987	atorvastatin 10mg tablets (dr reddy's laboratories (uk) ltd)	1
71014	rosuvastatin 20mg tablets (waymade healthcare plc)	1
71015	pravastatin 10mg tablets (medreich plc)	1
71017	atorvastatin 20mg tablets (dr reddy's laboratories (uk) ltd)	1
71029	fluvastatin 40mg capsules (sandoz ltd)	1

Identification of vasodilators

List of product codes (prodcode) used to identify vasodilators and their descriptions are listed in the table below. The final codes to identify presence of vasodilators are identified in the far right columns by a '1'.

prodcode	productname	Included
91	isosorbide mononitrate 20mg tablets	1
119	doxazosin 1mg tablets	1
214	hydralazine 1 mg syr	1
338	clonidine 25microgram tablets	1
445	prazosin 1mg tablets and prazosin 500microgram tablets	1
493	doxazosin 2mg tablets	1
504	hydralazine 20mg powder for solution for injection ampoules	1
521	isosorbide mononitrate 25mg modified-release capsules	1
573	hydralazine 25mg tablets	1
582	doxazosin 4mg modified-release tablets	1
591	prazosin 1mg tablets	1
621	isosorbide mononitrate 60mg modified-release tablets	1
632	imdur 60mg modified-release tablets (astrazeneca uk ltd)	1
726	prazosin 2mg tablets	1
755	cardura xl 4mg tablets (pfizer ltd)	1
776	isosorbide mononitrate 60mg modified-release capsules	1
779	isosorbide mononitrate 10mg tablets	1
1292	hypovase 1mg tablets (pfizer ltd)	1
1294	doxazosin 4mg tablets	1
1296	hydralazine 50mg tablets	1
1455	prazosin 500microgram tablets	1
1707	methyldopa 250mg tablets	1
1753	isordil 10mg tablets (shire pharmaceuticals ltd)	1
1754	isosorbide dinitrate 10mg tablets	1
1782	isosorbide mononitrate 60 mg cap	1
1993	isosorbide mononitrate 40 mg cap	1
1994	isosorbide mononitrate 40mg tablets	1
2362	apresoline 25mg tablets (amco)	1
2619	isosorbide mononitrate 40mg modified-release tablets	1
2630	dixarit 25microgram tablets (boehringer ingelheim ltd)	1
2633	ismo 10- tablet (roche products ltd)	1
2649	methyldopa 250 mg cap	1
2680	apresoline 50mg tablet (sovereign medical ltd)	1
2878	clonidine 100microgram tablets	1
2933	isosorbide dinitrate 20mg tablets	1
2967	minoxidil 5mg tablets	1

2968	minoxidil 10mg tablets	1
2970	minoxidil 2.5mg tablets	1
3049	methyldopa 125mg tablets	1
3070	methyldopa 500mg tablets	1
3715	prazosin 5mg tablets	1
4111	hypovase 500microgram tablets (pfizer ltd)	1
4215	catapres 100microgram tablets (boehringer ingelheim ltd)	1
4449	cardura 1mg tablets (pfizer ltd)	1
4507	hydralazine hcl 12.5 mg tab	1
4508	isosorbide dinitrate 30mg tablets	1
4609	isosorbide mononitrate 40mg modified-release capsules	1
4802	cardura 2mg tablets (pfizer ltd)	1
4843	isosorbide dinitrate 20mg modified-release capsules	1
4993	moxonidine 200microgram tablets	1
5004	isosorbide dinitrate 20mg modified-release tablets	1
5183	hypovase 2mg tablets (pfizer ltd)	1
5289	clonidine 250microgram modified-release capsules	1
5496	doxazosin 8mg modified-release tablets	1
5618	cardura xl 8mg tablets (pfizer ltd)	1
6099	monosorb xl 60 tablets (teva uk ltd)	1
6111	isosorbide dinitrate 40mg modified-release tablets	1
6159	nyzamac sr 60mg capsules (ethypharm uk ltd)	1
6343	monomax xl 60mg tablets (chiesi ltd)	1
6694	clonidine 300microgram tablets	1
6821	isotard 60xl tablets (kyowa kirin ltd)	1
7174	moxonidine 400microgram tablets	1
7327	isosorbide mononitrate 25mg modified-release tablets	1
7416	aldomet 50mg/ml injection (merck sharp & dohme ltd)	1
7433	monit ls 10mg tablets (sanofi-synthelabo ltd)	1
7547	doxadura 2mg tablets (discovery pharmaceuticals)	1
7549	doxadura 1mg tablets (discovery pharmaceuticals)	1
7626	aldomet 250mg tablet (merck sharp & dohme ltd)	1
7642	aldomet 500mg tablet (merck sharp & dohme ltd)	1
7702	sorbitrate 10mg tablet (astrazeneca uk ltd)	1
7746	ismo 20- tablet (roche products ltd)	1
7762	elantan 10 tablets (ucb pharma ltd)	1
7790	minoxidil 1 % lot	1
8033	aldomet 125mg tablet (merck sharp & dohme ltd)	1
8037	monit 20mg tablets (sanofi-synthelabo ltd)	1
8086	cardura 4mg tablet (pfizer ltd)	1
8198	hypovase 5mg tablet (pfizer ltd)	1
8296	catapres pl perlongets 250microgram capsules (boehringer ingelheim ltd)	1

8324	isosorbide mononitrate 50mg modified-release capsules	1
8428	sorbid-40 sa capsules (astrazeneca uk ltd)	1
8539	sorbichew 5mg tablet (astrazeneca uk ltd)	1
8790	isosorbide dinitrate 5mg sublingual tablet	1
8793	monit sr 40mg tablets (sanofi-synthelabo ltd)	1
8863	hypovase benign prostatic hyperplasia 1mg tablet (pfizer ltd)	1
8902	elantan la 25mg capsule (ucb pharma ltd)	1
8940	ismo 40 tablets (roche products ltd)	1
9088	ismo retard 40mg tablet (roche products ltd)	1
9225	methyldopa 250mg capsule	1
9282	nyzamac sr 40mg capsules (ethypharm uk ltd)	1
9295	elantan la 50mg capsule (ucb pharma ltd)	1
9335	isosorbide dinitrate 5mg tablets	1
9463	loniten 5mg tablets (pfizer ltd)	1
9492	modisal 60 xl tablets (sandoz ltd)	1
9497	isosorbide dinitrate 40mg modified-release capsules	1
9622	cedocard retard 40 tablets (pfizer ltd)	1
9660	isotard 40xl tablets (kyowa kirin ltd)	1
9697	loniten 2.5mg tablets (pfizer ltd)	1
9703	isotard 25xl tablets (kyowa kirin ltd)	1
9719	isib 60xl tablets (alliance pharmaceuticals ltd)	1
9744	isoket retard 40 tablets (aspire pharma ltd)	1
9749	physiotens 400microgram tablets (mylan)	1
9876	physiotens 300microgram tablets (mylan)	1
9908	chemydur 60xl tablets (amco)	1
10088	doxadura 4mg tablets (discovery pharmaceuticals)	1
10147	trangina xl 60mg tablets (actavis uk ltd)	1
10253	moxonidine 300microgram tablets	1
10459	cedocard 5 tablets (pfizer ltd)	1
10587	cedocard retard 20 tablets (pfizer ltd)	1
10607	isordil 5mg tablets (shire pharmaceuticals ltd)	1
10700	isordil 30mg tablets (shire pharmaceuticals ltd)	1
11177	physiotens 200microgram tablets (mylan)	1
11596	xismox xl 60 tablets (thornton & ross ltd)	1
11616	isosorbide mononitrate 50mg modified-release tablets	1
11957	isosorbide dinitrate 100mg/100ml solution for infusion bottles	1
11978	isosorbide dinitrate 25mg/50ml infusion bottles	1
12017	sorbitrate 20mg tablet (astrazeneca uk ltd)	1
12063	isordil tembids 40mg modified-release capsules (shire pharmaceuticals ltd)	1
12151	vascardin 10mg tablet (nicholas laboratories ltd)	1
12284	mono-cedocard -40 tablet (pharmacia ltd)	1
12804	mcr-50 modified-release capsules (pfizer ltd)	1

13090	isosorbide dinitrate 1.25mg/dose sublingual spray sugar free	1
13317	apresoline 20mg powder for solution for injection ampoules (amco)	1
13446	elantan 20mg tablet (ucb pharma ltd)	1
13610	alphavase 2 tablets (ashbourne pharmaceuticals ltd)	1
13882	imazin xl tablets (napp pharmaceuticals ltd)	1
14390	aldomet 250mg/5ml liquid (merck sharp & dohme ltd)	1
14495	loniten 10mg tablets (pfizer ltd)	1
14679	cibral xl 60mg tablet (ranbaxy (uk) ltd)	1
14685	monit xl 60 60mg modified-release tablet (sterwin medicines)	1
14731	isodur 25xl capsules (galen ltd)	1
14896	cibral 10 tablets (ranbaxy (uk) ltd)	1
15034	cedocard -10 tablet (pharmacia ltd)	1
15069	elantan 40mg tablet (ucb pharma ltd)	1
15083	ismo starter pack (roche products ltd)	1
15998	eumon xl 40mg tablet (neo laboratories ltd)	1
16248	clonidine 150micrograms/1ml solution for injection ampoules	1
16256	modisal la25 capsules (sandoz ltd)	1
16630	mono-cedocard -10 tablet (pharmacia ltd)	1
16940	zemon 60 xl tablets (fannin uk ltd)	1
17256	isoket -20 tablet (schwarz pharma ltd)	1
17867	imtack 1.25mg/actuation spray (astrazeneca uk ltd)	1
18030	imazin xl forte tablets (napp pharmaceuticals ltd)	1
18252	metalpha 250mg tablet (ashbourne pharmaceuticals ltd)	1
18787	angeze sr 40mg modified-release capsule (opus pharmaceuticals ltd)	1
18861	hydralazine 10mg/5ml oral suspension	1
18889	isoket retard 20 tablets (aspire pharma ltd)	1
18938	minoxidil 1 % tab	1
18964	sorbid-20 sa capsules (astrazeneca uk ltd)	1
19193	doxazosin 2mg tablets (teva uk ltd)	1
19216	doxazosin 4mg tablets (ivax pharmaceuticals uk ltd)	1
19823	alphavase 5 tablets (ashbourne pharmaceuticals ltd)	1
19839	eumon xl 60mg tablet (neo laboratories ltd)	1
20322	monomil xl 60mg tablets (teva uk ltd)	1
20369	doxazosin 1mg/5ml oral suspension	1
20500	soni-slo sr 20mg capsules (lipha pharmaceuticals ltd)	1
20530	cedocard -20 tablet (pharmacia ltd)	1
20879	isotard 50xl tablets (kyowa kirin ltd)	1
21066	mono-cedocard -20 tablet (pharmacia ltd)	1
21346	hydromet tablet (msd thomas morson pharmaceuticals)	1
21380	aspirin 75mg / isosorbide mononitrate 60mg modified-release tablets	1
21382	aspirin 150mg / isosorbide mononitrate 60mg modified-release tablets	1
21749	hydralazine hcl 100 mg tab	1

21764	monodur 60mg modified-release tablet (waymade healthcare plc)	1
22358	monigen xl 60 tablets (mylan)	1
22427	isosorbide dinitrate 30mg/dose transdermal spray	1
22726	monosorb xl 60mg modified-release tablet (generics (uk) ltd)	1
22752	isodur 50xl capsules (galen ltd)	1
22876	cedocard -40 tablet (pharmacia ltd)	1
23011	isotrate 20mg tablet (bioglan laboratories ltd)	1
23380	catapres 300microgram tablets (boehringer ingelheim ltd)	1
23459	hypovase benign prostatic hyperplasia 2mg tablet (pfizer ltd)	1
23683	minoxidil liquid	1
23746	hydralazine hcl 10 mg tab	1
23761	methyldopa 250mg/5ml oral suspension	1
24196	dopamet 250mg tablet (berk pharmaceuticals ltd)	1
24557	dynamin xl25 capsules (teva uk ltd)	1
24651	angitak 1.25mg/dose spray (lpc medical (uk) ltd)	1
24671	isib 50 xl 50mg modified-release capsule (ashbourne pharmaceuticals ltd)	1
24683	isib 40mg tablet (ashbourne pharmaceuticals ltd)	1
25047	hypovase benign prostatic hyperplasia 500microgram tablet (pfizer ltd)	1
25061	isosorbide mononitrate	1
25100	modisal la50 capsules (sandoz ltd)	1
25175	monosorb xl 60mg modified-release tablet (ivax pharmaceuticals uk ltd)	1
25275	metalpha 500mg tablet (ashbourne pharmaceuticals ltd)	1
25276	isib 20mg tablet (ashbourne pharmaceuticals ltd)	1
25289	dopamet 500mg tablet (berk pharmaceuticals ltd)	1
25487	cascor 2mg tablets (ranbaxy (uk) ltd)	1
25551	cascor 4mg tablets (ranbaxy (uk) ltd)	1
25795	isocard 30mg/dose transdermal spray (lpc medical (uk) ltd)	1
25836	methyldopa 200 mg tab	1
25878	isosorbide mononitrate 60mg modified-release tablet (ivax pharmaceuticals uk ltd)	1
26043	monosorb xl 60 tablets (almus pharmaceuticals ltd)	1
26221	angitate 20mg tablet (berk pharmaceuticals ltd)	1
26222	angeze 20 tablets (opus pharmaceuticals ltd)	1
26237	alphavase 500microgram tablet (ashbourne pharmaceuticals ltd)	1
26238	alphavase 1 tablets (ashbourne pharmaceuticals ltd)	1
26246	angeze 40mg tablet (opus pharmaceuticals ltd)	1
26251	dynamin 20mg tablets (teva uk ltd)	1
26253	angeze 10 tablets (opus pharmaceuticals ltd)	1
26260	angitate 10mg tablet (berk pharmaceuticals ltd)	1
26266	monosorb xl 60 tablets (dexcel-pharma ltd)	1
26271	angeze sr 60mg modified-release capsule (opus pharmaceuticals ltd)	1
26279	dynamin 10mg tablets (teva uk ltd)	1
26583	vascardin 30mg tablet (nicholas laboratories ltd)	1

26693	hypovase benign prostatic hyperplasia bd bd starter pack (pfizer ltd)	1
26853	monosorb xl 60mg modified-release tablet (ratiopharm uk ltd)	1
26919	methyldopa 50mg/ml injection	1
27485	soni-slo sr 40mg capsules (lipha pharmaceuticals ltd)	1
27545	isosorbide mononitrate	1
27774	isosorbide mononitrate mr	1
27894	clonidine hydrochloride	1
28719	zemon 40 xl tablets (kent pharmaceuticals ltd)	1
28738	methyldopa with hydrochlorothiazide tablet	1
29072	cedocard iv 1mg/ml injection (pharmacia ltd)	1
29570	dopamet 125mg tablet (berk pharmaceuticals ltd)	1
29777	isotard 25 xl 25mg modified-release capsule (prostrakan ltd)	1
30293	catapres 150micrograms/1ml solution for injection ampoules (boehringer ingelheim ltd)	1
30409	cibral 20 tablets (ranbaxy (uk) ltd)	1
31220	hydralazine 25mg tablets (a a h pharmaceuticals ltd)	1
31475	jeridin 10mg tablet (berk pharmaceuticals ltd)	1
31971	hydralazine 6.25 mg syr	1
32059	slomon xl 60 tablets (zurich pharmaceuticals)	1
32253	carmil xl 60mg tablets (mylan)	1
32442	isosorbide mononitrate 25mg modified-release capsules (a a h pharmaceuticals ltd)	1
32666	isosorbide mononitrate mr	1
32841	isosorbide mononitrate 10mg tablets (dexcel-pharma ltd)	1
32913	methyldopa 250mg tablets (actavis uk ltd)	1
33093	clonidine 25microgram tablets (sandoz ltd)	1
33094	doxazosin 2mg tablets (mylan)	1
33148	isoket 0.1% solution for infusion 100ml bottles (schwarz pharma ltd)	1
33322	moxonidine 200microgram tablets (sandoz ltd)	1
33354	cibral 40 tablets (ranbaxy (uk) ltd)	1
33660	isosorbide mononitrate 60mg modified-release tablet (actavis uk ltd)	1
33661	isosorbide mononitrate 60mg modified-release tablets (a a h pharmaceuticals ltd)	1
33992	isosorbide mononitrate 10mg tablets (teva uk ltd)	1
34196	isosorbide mononitrate 10mg tablets (actavis uk ltd)	1
34318	isosorbide mononitrate 60mg modified-release tablet (lagap)	1
34342	doxazosin 1mg tablets (teva uk ltd)	1
34426	isosorbide mononitrate 20mg tablets (ivax pharmaceuticals uk ltd)	1
34547	isosorbide dinitrate 10mg tablets (actavis uk ltd)	1
34553	doxazosin 4mg tablets (mylan)	1
34558	isosorbide mononitrate 10mg tablets (a a h pharmaceuticals ltd)	1
34582	isosorbide mononitrate 20mg tablets (mylan)	1
34601	doxazosin 1mg tablets (mylan)	1
34625	doxazosin 2mg tablets (a a h pharmaceuticals ltd)	1
34715	doxazosin 1mg tablets (a a h pharmaceuticals ltd)	1

34835	isosorbide dinitrate 10mg/10ml solution for injection ampoules	1
34951	isosorbide mononitrate 20mg tablet (berk pharmaceuticals ltd)	1
35272	doxadura xl 4mg tablets (discovery pharmaceuticals)	1
35603	doxazosin 4mg/5ml oral suspension	1
36023	cardozin xl 4mg tablet (hillcross pharmaceuticals ltd)	1
36181	dynamin xl50 capsules (teva uk ltd)	1
36740	slocinx xl 4mg tablets (zentiva)	1
37028	isosorbide mononitrate starter pack tablet	1
37243	cardozin xl 4mg tablet (teva uk ltd)	1
38461	cardozin xl 4mg tablets (arrow generics ltd)	1
38883	elantan la25 capsules (aspire pharma ltd)	1
38946	elantan la50 capsules (aspire pharma ltd)	1
39035	elantan 20 tablets (ucb pharma ltd)	1
39052	cibral xl 60 tablets (ranbaxy (uk) ltd)	1
39130	ismo 20 tablets (intrapharm laboratories ltd)	1
39135	ismo 10 tablets (intrapharm laboratories ltd)	1
39552	elantan 40 tablets (ucb pharma ltd)	1
40310	moxonidine 200microgram tablets (teva uk ltd)	1
40678	doxazosin 4mg tablets (teva uk ltd)	1
40891	doxazosin 2mg tablets (ivax pharmaceuticals uk ltd)	1
41060	ismo retard 40mg tablets (intrapharm laboratories ltd)	1
41421	isosorbide mononitrate xl 40mg tablet (hillcross pharmaceuticals ltd)	1
41543	doxazosin 1mg tablets (ivax pharmaceuticals uk ltd)	1
41639	hydralazine 50mg tablets (actavis uk ltd)	1
41651	prazosin 500microgram tablet (approved prescription services ltd)	1
41652	prazosin 500microgram tablets (a a h pharmaceuticals ltd)	1
41661	methyldopa 250mg tablet (c p pharmaceuticals ltd)	1
41676	isosorbide mononitrate 20mg tablets (actavis uk ltd)	1
41687	isosorbide mononitrate 20mg tablets (teva uk ltd)	1
41688	isosorbide mononitrate 20mg tablets (a a h pharmaceuticals ltd)	1
41721	prazosin 1mg tablets (a a h pharmaceuticals ltd)	1
41737	isosorbide mononitrate 10mg tablets (ivax pharmaceuticals uk ltd)	1
41993	isosorbide dinitrate 40mg tablet	1
43421	isosorbide mononitrate 40mg tablets (ivax pharmaceuticals uk ltd)	1
43500	hydralazine 25mg tablets (actavis uk ltd)	1
43524	isosorbide dinitrate 10mg tablets (a a h pharmaceuticals ltd)	1
43531	moxonidine 400microgram tablets (sandoz ltd)	1
43547	prazosin 500microgram tablets (ivax pharmaceuticals uk ltd)	1
43615	tardisc xl 60 tablets (discovery pharmaceuticals)	1
43695	colixil xl 4mg tablets (sandoz ltd)	1
43988	aldomet 250mg tablets (aspen pharma trading ltd)	1
43989	aldomet 500mg tablets (aspen pharma trading ltd)	1

44179	imo la 50mg capsules (kent pharmaceuticals ltd)	1
44712	relosorb xl 60mg tablets (relonchem ltd)	1
45040	larbex xl 4mg tablets (teva uk ltd)	1
45265	doxazosin sr 4mg tablet (generics (uk) ltd)	1
45328	doxazosin 1mg tablets (sandoz ltd)	1
45342	doxazosin 4mg tablets (sandoz ltd)	1
45578	clonidine 25microgram tablets (a a h pharmaceuticals ltd)	1
45583	doxazosin 2mg tablets (dexcel-pharma ltd)	1
46066	cardozin xl 4mg tablets (almus pharmaceuticals ltd)	1
46526	raporsin xl 4mg tablets (actavis uk ltd)	1
46798	isosorbide mononitrate 60mg modified-release tablet (sovereign medical ltd)	1
46910	isosorbide mononitrate 10mg tablet (berk pharmaceuticals ltd)	1
46911	isosorbide mononitrate 10mg tablets (kent pharmaceuticals ltd)	1
46922	prazosin 1mg tablets (ivax pharmaceuticals uk ltd)	1
46949	isosorbide mononitrate 60mg modified-release tablet (kent pharmaceuticals ltd)	1
47722	isosorbide dinitrate 10mg/10ml concentrate for solution for injection ampoules (mercury pharma group ltd)	1
47803	isosorbide mononitrate 20mg tablets (sandoz ltd)	1
47807	doxazosin xl 4mg tablet (hillcross pharmaceuticals ltd)	1
47810	isosorbide mononitrate 40mg tablet (lagap)	1
47814	isosorbide mononitrate oral solution	1
47950	isosorbide mononitrate 50mg modified-release capsules (a a h pharmaceuticals ltd)	1
48150	doxazosin 1mg tablets (actavis uk ltd)	1
49684	clonidine 100micrograms/24hours transdermal patches	1
50467	doxazosin 2mg tablets (alliance healthcare (distribution) ltd)	1
51685	doxazosin 4mg tablets (actavis uk ltd)	1
52245	monosorb xl 60 tablets (kent pharmaceuticals ltd)	1
52555	clonidine 50micrograms/5ml oral solution	1
53033	doxzogen xl 4mg tablets (mylan)	1
53142	clonidine 50micrograms/5ml oral suspension	1
53322	doxazosin 4mg tablets (bristol laboratories ltd)	1
53687	isosorbide mononitrate 25mg modified-release capsules (alliance healthcare (distribution) ltd)	1
54467	clonidine 300micrograms/24hours transdermal patches	1
54757	eumon 40 xl tablets (tillomed laboratories ltd)	1
54785	doxazosin 4mg tablets (medreich plc)	1
54824	isosorbide mononitrate 10mg tablets (alliance healthcare (distribution) ltd)	1
55797	clonidine 25micrograms/5ml oral solution	1
55826	prazosin 5mg tablets (a a h pharmaceuticals ltd)	1
55906	doxazosin 1mg tablets (dexcel-pharma ltd)	1
55916	doxazosin 1mg tablets (alliance healthcare (distribution) ltd)	1
56145	doxazosin 2mg tablets (actavis uk ltd)	1
56416	imdur 60mg modified-release tablets (de pharmaceuticals)	1
56840	isoket 0.1% solution for injection 10ml ampoules (aspire pharma ltd)	1

56933	modisal xl 40mg tablets (ennogen pharma ltd)	1
57074	doxazosin 2mg tablets (sigma pharmaceuticals plc)	1
57448	doxazosin 4mg tablets (a a h pharmaceuticals ltd)	1
57784	doxazosin 2mg/5ml oral suspension	1
58079	isosorbide mononitrate 20mg/5ml oral solution	1
58090	clonidine 75micrograms/5ml oral solution	1
58133	isosorbide mononitrate 10mg tablets (sigma pharmaceuticals plc)	1
58276	doxazosin 2mg tablets (medreich plc)	1
58325	doxazosin 4mg tablets (phoenix healthcare distribution ltd)	1
58386	isosorbide mononitrate 20mg tablets (kent pharmaceuticals ltd)	1
58529	clonidine 200micrograms/24hours transdermal patches	1
59209	doxazosin 1mg tablets (kent pharmaceuticals ltd)	1
59512	hydralazine 50mg/5ml oral solution	1
59862	doxazosin 4mg tablets (dexcel-pharma ltd)	1
60055	isosorbide mononitrate 25mg modified-release capsules (waymade healthcare plc)	1
60089	clonidine 25microgram tablets (waymade healthcare plc)	1
60136	clonidine 100micrograms/5ml oral solution	1
60200	doxazosin 4mg tablets (de pharmaceuticals)	1
60316	prazosin 1mg tablet (approved prescription services ltd)	1
60319	doxazosin 1mg tablets (bristol laboratories ltd)	1
60336	isosorbide mononitrate 10mg tablets (waymade healthcare plc)	1
60826	isosorbide mononitrate 10mg/5ml oral solution	1
60898	moxonidine 200microgram tablets (mylan)	1
60941	ismo 20 tablets (waymade healthcare plc)	1
61036	physiotens 300microgram tablets (actavis uk ltd)	1
61066	doxazosin 2mg tablets (bristol laboratories ltd)	1
61116	hydralazine 50mg/5ml oral suspension	1
61123	doxazosin 4mg/5ml oral solution	1
61191	eumon 60 xl tablets (tillomed laboratories ltd)	1
61256	clonidine 5micrograms/5ml oral suspension	1
61283	doxazosin 4mg tablets (alliance healthcare (distribution) ltd)	1
61710	clonidine 25microgram tablets (teva uk ltd)	1
61998	isosorbide dinitrate 20mg tablets (waymade healthcare plc)	1
62019	doxazosin 1mg tablets (almus pharmaceuticals ltd)	1
62158	doxazosin 4mg tablets (almus pharmaceuticals ltd)	1
62351	doxazosin 2mg tablets (phoenix healthcare distribution ltd)	1
62404	isosorbide mononitrate 10mg tablets (de pharmaceuticals)	1
62513	methyldopa 250mg tablets (sovereign medical ltd)	1
62853	moxonidine 200microgram tablets (a a h pharmaceuticals ltd)	1
63158	doxazosin 2mg tablets (almus pharmaceuticals ltd)	1
63314	doxazosin 1mg tablets (sovereign medical ltd)	1
63652	hydralazine tablet	1

63938	moxonidine 300microgram tablets (sandoz ltd)	1
63971	clonidine 25microgram tablets (sigma pharmaceuticals plc)	1
64233	doxazosin 1mg tablets (waymade healthcare plc)	1
64253	hydralazine 5mg/5ml oral suspension	1
64284	dixarit 25microgram tablets (lexon (uk) ltd)	1
65159	doxazosin 4mg tablets (waymade healthcare plc)	1
65695	isosorbide mononitrate 25mg modified-release capsules (de pharmaceuticals)	1
65741	imdur 60mg modified-release tablets (lexon (uk) ltd)	1
65853	doxazosin 1mg tablets (mawdsley-brooks & company ltd)	1
66065	doxazosin 2mg tablets (kent pharmaceuticals ltd)	1
66790	isosorbide mononitrate 40mg modified-release capsules (cst pharma ltd)	1
67200	clonidine 10micrograms/5ml oral solution	1
67257	elantan la50 capsules (dowelhurst ltd)	1
67284	ismo retard 40mg tablets (dowelhurst ltd)	1
67321	elantan 10 tablets (waymade healthcare plc)	1
67335	elantan 20 tablets (waymade healthcare plc)	1
67486	isosorbide mononitrate 10mg/5ml oral suspension	1
67665	moxonidine 400microgram tablets (actavis uk ltd)	1
67808	physiotens 200microgram tablets (actavis uk ltd)	1
67810	imdur 60mg modified-release tablets (waymade healthcare plc)	1
67934	isosorbide mononitrate 20mg tablets (waymade healthcare plc)	1
68022	doxazosin 4mg tablets (sovereign medical ltd)	1
68161	doxazosin 4mg tablets (mawdsley-brooks & company ltd)	1
68384	elantan la50 capsules (mawdsley-brooks & company ltd)	1
69126	isosorbide mononitrate 20mg/5ml oral suspension	1
69127	isosorbide mononitrate 30mg/5ml oral suspension	1
69319	doxazosin 2mg tablets (de pharmaceuticals)	1
69521	isosorbide dinitrate 20mg tablets (actavis uk ltd)	1
69757	doxazosin 8mg/5ml oral suspension	1
69763	isosorbide dinitrate 50mg/50ml concentrate for solution for infusion vials (torbay pharmaceuticals)	1
70655	hydralazine 25mg/5ml oral suspension	1
70995	isosorbide mononitrate 10mg tablets (almus pharmaceuticals ltd)	1
71097	hydralazine 50mg tablets (almus pharmaceuticals ltd)	1
71110	aldomet 500mg tablets (sigma pharmaceuticals plc)	1
71256	hydralazine 20mg powder for concentrate for solution for injection ampoules (amco)	1
71385	aldomet 250mg tablets (sigma pharmaceuticals plc)	1
71405	cardura xl 4mg tablets (de pharmaceuticals)	1

Identification of AF

List of medical codes (medcode) and Read codes (readcode) used to identify AF and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of AF [21] and/or code lists from the Cambridge Code List Index [319]. Codes not identified as being QOF [21] or Cambridge [319] were additional codes added through searching the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify AF are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Old Codelist	Cambridge	Included
1664	G573000	Atrial fibrillation	384,648	52.4	1	1	1	1
2212	G573.00	Atrial fibrillation and flutter	150,695	20.5	1	1	1	1
1268	G573200	Paroxysmal atrial fibrillation	66,117	9.0	1	1	1	1
18746	662S.00	Atrial fibrillation monitoring	43,036	5.9				0
1757	G573100	Atrial flutter	19,466	2.7	1	1	1	1
45773	6A9..00	Atrial fibrillation annual review	18,459	2.5		1		1
6345	14AN.00	H/O: atrial fibrillation	16,684	2.3				0
90187	9Os0.00	Atrial fibrillation monitoring first letter	9,512	1.3				0
3757	3272.00	ECG: atrial fibrillation	7,712	1.1		1		1
57832	9Os..00	Atrial fibrillation monitoring administration	5,581	0.8				0
39114	9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent	3,435	0.5				0
90188	9Os1.00	Atrial fibrillation monitoring second letter	1,602	0.2				0
6771	3273.00	ECG: atrial flutter	1,496	0.2		1		0
23437	G573z00	Atrial fibrillation and flutter NOS	1,263	0.2	1	1	1	1
93460	14AR.00	History of atrial flutter	969	0.1				0
105554	8CMW200	Atrial fibrillation care pathway	604	0.1				0
90189	9Os2.00	Atrial fibrillation monitoring third letter	553	0.1				0
96076	G573500	Persistent atrial fibrillation	504	0.1	1	1	1	1
90191	9Os4.00	Atrial fibrillation monitoring telephone invite	351	0.0				0
90190	9Os3.00	Atrial fibrillation monitoring verbal invite	293	0.0				0
96277	G573400	Permanent atrial fibrillation	266	0.0	1	1	1	1
92361	793M000	Perc translum ablat pulmon vein to lft atrium conduct system	201	0.0		1		0
107472	G573600	Paroxysmal atrial flutter	177	0.0	1	1		1
63350	9hF..00	Exception reporting: atrial fibrillation quality indications	171	0.0				0
9479	7936A00	Implant intravenous pacemaker for atrial fibrillation	109	0.0		1		0
35127	G573300	Non-rheumatic atrial fibrillation	94	0.0	1	1	1	1
112181	G573800	Typical atrial flutter	3	0.0	1			0
111893	G573900	Atypical atrial flutter	2	0.0	1			0
111876	G573700	Chronic atrial fibrillation	1	0.0	1			0
			734,004	**100.0**				

Identification of CLD

List of medical codes (medcode) and Read codes (readcode) used to identify CLD and their descriptions are listed in the table below. Codes are identified as being used in the code lists from the Cambridge Code List Index [319]. Codes not identified as Cambridge [319] were additional codes added through searching the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. Identification of codes as pertaining to mild or moderate/severe CLD is provided. The final codes used to identify CLD are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	Mild	Moderate/Severe	Cambridge	Included
4743	J612.00	Alcoholic cirrhosis of liver	11,653	10.7		1	1	1
2860	A703.00	Viral (serum) hepatitis B	9,399	8.6	1		1	1
1638	J615z13	Cirrhosis of liver NOS	8,477	7.8		1	1	1
6863	J61..00	Cirrhosis and chronic liver disease	7,312	6.7		1	1	1
5638	J616000	Primary biliary cirrhosis	6,186	5.7		1	1	1
11431	ZV02B00	[V]Hepatitis B carrier	5,664	5.2	1		1	
1754	J614.00	Chronic hepatitis	5,410	5.0	1		1	1
5129	J623.00	Portal hypertension	4,492	4.1		1	1	1
10797	G858.00	Oesophageal varices NOS	4,299	3.9		1	1	1
30729	141E.00	History of hepatitis B	3,505	3.2	1		1	
1641	G85..11	Oesophageal varices	3,360	3.1		1	1	1
30586	A707200	Chronic viral hepatitis C	2,927	2.7	1		1	1
7943	J617.00	Alcoholic hepatitis	2,921	2.7	1		1	1
18652	J63B.00	Autoimmune hepatitis	2,679	2.5	1		1	1
9029	J614100	Chronic active hepatitis	2,434	2.2	1		1	1
9494	J616.00	Biliary cirrhosis	2,152	2.0		1	1	1
28703	ZV02C00	[V]Hepatitis C carrier	1,897	1.7	1		1	
16759	760C500	Fibreoptic endoscopic banding of oesophageal varices	1,886	1.7		1	1	1
24989	G850.00	Oesophageal varices with bleeding	1,791	1.6		1	1	1
10539	J61z.00	Chronic liver disease NOS	1,785	1.6	1		1	1
2834	A705000	Viral hepatitis C without mention of hepatic coma	1,623	1.5	1		1	1
6800	65Q7.00	Viral hepatitis carrier	1,415	1.3	1		1	1
7957	J614111	Autoimmune chronic active hepatitis	1,126	1.0	1		1	1
16725	J615.00	Cirrhosis - non alcoholic	1,107	1.0		1	1	1
30655	G851.00	Oesophageal varices without bleeding	1,066	1.0		1	1	1
98148	J61y800	Nonalcoholic steatohepatitis	902	0.8	1		1	1
16062	J62y.13	Hepatic failure	711	0.7				1
16455	J615z00	Non-alcoholic cirrhosis NOS	677	0.6		1	1	1
28929	G857.00	Gastric varices	609	0.6		1	1	1
15489	J614z00	Chronic hepatitis NOS	564	0.5	1		1	1

25383	J61y400	Hepatic fibrosis	483	0.4	1		1	1
18739	J615z12	Cryptogenic cirrhosis of liver	450	0.4		1	1	1
28798	J63y100	Nonspecific reactive hepatitis	443	0.4	1		1	1
10636	J624.00	Hepatorenal syndrome	421	0.4		1	1	1
17330	J613000	Alcoholic hepatic failure	414	0.4				1
8363	G852300	Oesophageal varices in alcoholic cirrhosis of the liver	411	0.4		1	1	1
96085	9kV..00	Hepatitis C screening positive - enhanced services admin	361	0.3	1		1	
24901	J625.00	[X] Hepatic failure	345	0.3				1
6015	Jyu7100	[X]Other and unspecified cirrhosis of liver	327	0.3		1	1	1
31897	J62..00	Liver abscess and sequelae of chronic liver disease	281	0.3		1	1	1
26037	C32y511	Hepatic familial steatosis	260	0.2	1		1	1
16766	ZV02600	[V]Viral hepatitis carrier	252	0.2	1		1	
11960	760C300	Fibreoptic endoscopic injection sclerotherapy oesoph varices	245	0.2		1	1	1
20912	7609400	Open injection sclerotherapy to oesophageal varices	228	0.2		1	1	1
104572	9NgR.00	On hepatitis C treatment plan	201	0.2	1		1	
26319	G852200	Oesophageal varices in cirrhosis of the liver	200	0.2		1	1	1
27663	J63X.00	Granulomatous hepatitis, not elsewhere classified	199	0.2	1		1	1
23578	J614000	Chronic persistent hepatitis	193	0.2	1		1	1
46647	760F400	Rigid oesophagoscopic banding of oesophageal varices	181	0.2		1	1	1
20233	7609z00	Open operation on oesophageal varices NOS	173	0.2		1	1	1
99898	9kR..00	Chronic hepatitis annual review - enhanced services admin	170	0.2	1		1	
25589	C376100	Alpha-1-antitrypsin hepatitis	169	0.2	1		1	1
26367	A707.00	Chronic viral hepatitis	166	0.2	1		1	1
24220	7609.00	Open operations on oesophageal varices	155	0.1		1	1	1
22841	J615z11	Macronodular cirrhosis of liver	138	0.1		1	1	1
41096	A707100	Chronic viral hepatitis B without delta-agent	133	0.1	1		1	1
41237	J631.00	Hepatitis in viral diseases EC	133	0.1	1		1	1
7602	J617000	Chronic alcoholic hepatitis	132	0.1	1		1	1
42843	J61y.00	Other non-alcoholic chronic liver disease	132	0.1	1		1	1
19512	C310400	Glycogenosis with hepatic cirrhosis	130	0.1		1	1	1
50245	Q409100	Congenital hepatitis B infection	124	0.1	1		1	1
3450	J615300	Diffuse nodular cirrhosis	122	0.1		1	1	1
21713	J612000	Alcoholic fibrosis and sclerosis of liver	121	0.1	1		1	1
26490	J601000	Subacute hepatic failure	99	0.1				1
48102	J62y.00	Other sequelae of chronic liver disease	71	0.1		1	1	1
33597	J61yz00	Other non-alcoholic chronic liver disease NOS	67	0.1	1		1	1
43404	7609300	Local ligation of oesophageal varices	61	0.1		1	1	1
24813	A707000	Chronic viral hepatitis B with delta-agent	60	0.1	1		1	1
53877	J614y00	Chronic hepatitis unspecified	60	0.1	1		1	1
58630	J616z00	Biliary cirrhosis NOS	50	0.0		1	1	1
32277	A707X00	Chronic viral hepatitis, unspecified	48	0.0	1		1	1
8206	C350012	Pigmentary cirrhosis of liver	44	0.0		1	1	1

1755	J614200	Chronic aggressive hepatitis	43	0.0		1	1	1
15424	J616100	Secondary biliary cirrhosis	42	0.0		1	1	1
34642	Q48yz11	Congenital hepatic fibrosis	41	0.0	1		1	1
40963	J61y300	Portal fibrosis without cirrhosis	37	0.0	1		1	1
27438	J615700	Cardiac portal cirrhosis	34	0.0		1	1	1
44424	G852.00	Oesophageal varices in diseases EC	31	0.0		1	1	1
60104	J61y500	Hepatic sclerosis	27	0.0	1		1	1
44120	J635600	Toxic liver disease with fibrosis and cirrhosis of liver	26	0.0		1	1	1
71453	J615z15	Hepatic fibrosis	26	0.0	1		1	1
53480	J614300	Recurrent hepatitis	25	0.0	1		1	1
62582	G852z00	Oesophageal varices in diseases EC NOS	22	0.0		1	1	1
31008	J630.00	Chronic passive liver congestion	20	0.0	1		1	1
36194	SP14200	Hepatic failure as a complication of care	20	0.0				
47214	760F300	Rigid oesophagoscopic injection sclerotherapy oesoph varices	20	0.0		1	1	1
66534	J614400	Chronic lobular hepatitis	20	0.0	1		1	1
39351	J635500	Toxic liver disease with chronic active hepatitis	19	0.0		1	1	1
55454	J615y00	Portal cirrhosis unspecified	18	0.0		1	1	1
48928	J615H00	Infectious cirrhosis NOS	15	0.0		1	1	1
17219	J635300	Toxic liver disease with chronic persistent hepatitis	14	0.0		1	1	1
47257	J615.11	Portal cirrhosis	14	0.0		1	1	1
56070	J62y.11	Hepatic failure NOS	11	0.0				1
40567	J615600	Capsular portal cirrhosis	9	0.0		1	1	1
69053	A702.00	Viral hepatitis B with coma	9	0.0		1	1	1
10721	SP14300	Hepatorenal syndrome as a complication of care	8	0.0				
64750	J635400	Toxic liver disease with chronic lobular hepatitis	8	0.0		1	1	1
65050	A704000	Viral hepatitis C with coma	8	0.0		1	1	1
44676	J615400	Fatty portal cirrhosis	4	0.0		1	1	1
68376	J612.11	Florid cirrhosis	4	0.0		1	1	1
92909	J615500	Hypertrophic portal cirrhosis	4	0.0		1	1	1
58184	J615812	Indian childhood cirrhosis	3	0.0		1	1	1
69204	J615100	Multilobular portal cirrhosis	3	0.0		1	1	1
96664	J615800	Juvenile portal cirrhosis	3	0.0		1	1	
100474	J612.12	Laennec's cirrhosis	3	0.0		1	1	
100592	J61y600	Hepatic fibrosis with hepatic sclerosis	3	0.0	1		1	1
102922	C370800	Cystic fibrosis related cirrhosis	3	0.0		1	1	
53704	J600200	Acute yellow atrophy	2	0.0	1		1	1
69313	J601200	Subacute yellow atrophy	2	0.0	1		1	
105611	Gyu9400	[X]Oesophageal varices in diseases classified elsewhere	2	0.0		1	1	
108800	J62z.00	Liver abscess and chronic liver disease causing sequelae NOS	2	0.0		1	1	
73139	G852100	Oesophageal varices without bleeding in diseases EC	1	0.0		1	1	1
73482	J615D00	Bacterial portal cirrhosis	1	0.0		1	1	1
91591	J616200	Biliary cirrhosis of children	1	0.0		1	1	

96756	G852000	Oesophageal varices with bleeding in diseases EC	1	0.0		1	1	1
100253	J615C00	Xanthomatous portal cirrhosis	1	0.0		1	1	1
108819	J615711	Congestive cirrhosis	1	0.0				1
109540	J615G00	Zooparasitic portal cirrhosis	1	0.0				
			109,094	**100.0**				

Identification of diabetes

List of medical codes (medcode) and Read codes (readcode) used to identify diabetes and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of diabetes [21], code lists from the Cambridge Code List Index [319], and/or the diabetes type I and type II code lists from Wright et al. 2017 [320]. Codes not identified as being QOF [21], Cambridge [319], or Wright et al. [320] were additional codes added through searching the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. Identification of codes as pertaining to Type I or Type II diabetes is provided for codes obtained from Wright et al. [320]. The final codes to identify diabetes are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Type I [320]	Type II [320]	Cambridge	Included
9897	9OL..00	Diabetes monitoring admin.	2,289,982	11.3					
3550	66A..00	Diabetic monitoring	2,284,444	11.3					
6125	66AS.00	Diabetic annual review	1,977,518	9.8					1
2379	9N1Q.00	Seen in diabetic clinic	1,371,322	6.8					1
26666	2G5E.00	O/E - Right diabetic foot at low risk	989,739	4.9					
26667	2G5I.00	O/E - Left diabetic foot at low risk	980,543	4.9					
13194	9OL4.00	Diabetes monitoring 1st letter	980,465	4.9					
758	C10F.00	Type 2 diabetes mellitus	936,635	4.6	1		1	1	1
711	C10..00	Diabetes mellitus	824,543	4.1	1			1	1
608	66A2.00	Follow-up diabetic assessment	501,447	2.5					
12506	66AP.00	Diabetes: practice programme	400,485	2.0					
11094	9NND.00	Under care of diabetic foot screener	373,229	1.8					
11471	8B3I.00	Diabetes medication review	274,866	1.4					1
1684	66A4.00	Diabetic on oral treatment	236,521	1.2				1	1
13195	9OL5.00	Diabetes monitoring 2nd letter	228,847	1.1					
31157	2G5F.00	O/E - Right diabetic foot at moderate risk	212,714	1.1					
31156	2G5J.00	O/E - Left diabetic foot at moderate risk	209,771	1.0					
18311	68A7.00	Diabetic retinopathy screening	193,871	1.0					
13197	9OL1.00	Attends diabetes monitoring	182,738	0.9					
95994	66Aq.00	Diabetic foot screen	178,240	0.9					
10977	66Ac.00	Diabetic peripheral neuropathy screening	168,444	0.8					
8836	66AR.00	Diabetes management plan given	161,315	0.8					1
13067	66AZ.00	Diabetic monitoring NOS	159,665	0.8					
2378	66AJ.00	Diabetic - poor control	137,675	0.7				1	1
11348	9h42.00	Excepted from diabetes quality indicators: Informed dissent	125,011	0.6					
17478	8A17.00	Self monitoring of blood glucose	122,053	0.6					
7563	66A3.00	Diabetic on diet only	110,062	0.5				1	1
28873	66Ai.00	Diabetic 6 month review	109,314	0.5					1
12213	8BL2.00	Patient on maximal tolerated therapy for diabetes	109,116	0.5					1

12030	9OL6.00	Diabetes monitoring 3rd letter	108,215	0.5					
1323	F420.00	Diabetic retinopathy	100,745	0.5				1	1
506	C100112	Non-insulin dependent diabetes mellitus	96,166	0.5			1	1	1
1549	C10E.00	Type 1 diabetes mellitus	95,091	0.5	1	1		1	1
4513	C109.00	Non-insulin dependent diabetes mellitus	93,420	0.5			1	1	1
11433	2BBP.00	O/E - right eye background diabetic retinopathy	87,060	0.4					
11129	2BBQ.00	O/E - left eye background diabetic retinopathy	85,430	0.4					
11041	9h41.00	Excepted from diabetes qual indicators: Patient unsuitable	82,389	0.4					
13192	9OLA.00	Diabetes monitor. check done	81,372	0.4					
47032	8CS0.00	Diabetes care plan agreed	81,217	0.4					
9974	9N1v.00	Seen in diabetic eye clinic	81,011	0.4					
9145	9N4I.00	DNA - Did not attend diabetic clinic	79,089	0.4					
13074	13B1.00	Diabetic diet	78,628	0.4					
13057	679L.00	Health education - diabetes	76,313	0.4					
83532	66Ao.00	Diabetes type 2 review	76,198	0.4					1
8842	66A5.00	Diabetic on insulin	75,159	0.4				1	1
12675	66AQ.00	Diabetes: shared care programme	64,494	0.3					1
17817	7L19800	Subcutaneous injection of insulin	60,786	0.3					
13071	66AI.00	Diabetic - good control	60,108	0.3				1	1
31171	2G5G.00	O/E - Right diabetic foot at high risk	59,674	0.3					
31172	2G5K.00	O/E - Left diabetic foot at high risk	59,026	0.3					
13196	66AD.00	Fundoscopy - diabetic check	58,409	0.3					
8414	8CA4100	Pt advised re diabetic diet	53,772	0.3					
17859	C109.12	Type 2 diabetes mellitus	47,989	0.2			1	1	1
12483	8CAQ.00	Advice about blood glucose control	44,925	0.2					
6813	1434.00	H/O: diabetes mellitus	44,886	0.2				1	
31141	9OL8.00	Diabetes monitor.phone invite	43,583	0.2					
47144	2BBM.00	O/E - diabetic maculopathy absent both eyes	42,248	0.2					
22823	66Ab.00	Diabetic foot examination	41,605	0.2					
47011	8Hj0.00	Referral to diabetes structured education programme	39,063	0.2					
93854	9OLM.00	Diabetes structured education programme declined	38,235	0.2					
30648	9N4p.00	Did not attend diabetic retinopathy clinic	35,820	0.2					
1038	C100011	Insulin dependent diabetes mellitus	34,992	0.2		1		1	1
50175	66AW.00	Diabetic foot risk assessment	31,711	0.2					
31240	9OL7.00	Diabetes monitor.verbal invite	30,833	0.2					
11677	8H7r.00	Refer to diabetic foot screener	30,161	0.1					
12307	66AU.00	Diabetes care by hospital only	30,160	0.1					
38078	66A9.00	Understands diet - diabetes	29,689	0.1					
31241	9OLZ.00	Diabetes monitoring admin.NOS	28,045	0.1					
6430	9NM0.00	Attending diabetes clinic	26,206	0.1					
3837	F420400	Diabetic maculopathy	25,201	0.1				1	1
21689	13AB.00	Diabetic lipid lowering diet	25,028	0.1					

1647	C108.00	Insulin dependent diabetes mellitus	24,344	0.1		1		1	1
13070	66A1.00	Initial diabetic assessment	23,746	0.1					
12262	8I3X.00	Diabetic retinopathy screening refused	23,390	0.1					
18824	8I3W.00	Diabetic foot examination declined	22,870	0.1					
10642	ZC2C800	Dietary advice for diabetes mellitus	22,460	0.1					
10659	F464000	Diabetic cataract	22,460	0.1					
14889	C100111	Maturity onset diabetes	21,052	0.1				1	1
10824	9N1i.00	Seen in diabetic foot clinic	20,368	0.1					
93657	8Hj4.00	Referral to DESMOND diabetes structured education programme	20,151	0.1					
12247	8I6G.00	Diabetic foot examination not indicated	17,684	0.1					
22130	9OL3.00	Diabetes monitoring default	16,970	0.1					
93870	8Hj5.00	Referral to XPERT diabetes structured education programme	16,719	0.1					
13069	66A8.00	Has seen dietician - diabetes	16,376	0.1					
18167	66AT.00	Annual diabetic blood test	16,223	0.1					
28769	66AV.00	Diabetic on insulin and oral treatment	16,057	0.1				1	1
35383	9OLD.00	Diabetic patient unsuitable for digital retinal photography	15,971	0.1					
20900	9OLA.11	Diabetes monitored	15,755	0.1					
17236	14P3.00	H/O: insulin therapy	15,137	0.1					
14803	C100100	Diabetes mellitus, adult onset, no mention of complication	14,669	0.1				1	1
10755	F420600	Non proliferative diabetic retinopathy	14,083	0.1				1	1
1682	C101.00	Diabetes mellitus with ketoacidosis	13,759	0.1				1	1
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus	13,714	0.1	1		1	1	1
26604	66AY.00	Diabetic diet - good compliance	13,484	0.1					
16230	C106.00	Diabetes mellitus with neurological manifestation	13,147	0.1				1	1
13108	2BBX.00	O/E - left eye diabetic maculopathy	13,049	0.1					
20696	66AA.11	Injection sites - diabetic	12,909	0.1					
13102	2BBW.00	O/E - right eye diabetic maculopathy	12,868	0.1					
52237	9360	Patient held diabetic record issued	12,729	0.1					
19739	68A9.00	Diabetic retinopathy screening offered	12,343	0.1					
16490	66AH.00	Diabetic treatment changed	12,218	0.1					
12682	679R.00	Patient offered diabetes structured education programme	11,169	0.1					
18747	8I6F.00	Diabetic retinopathy screening not indicated	10,858	0.1					
32619	66Af.00	Patient diabetes education review	10,585	0.1					
64142	8Hl1.00	Referral for diabetic retinopathy screening	10,252	0.1					
3286	F420100	Proliferative diabetic retinopathy	9,793	0.0				1	1
7795	C106.12	Diabetes mellitus with neuropathy	9,448	0.0				1	1
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria	8,941	0.0	1		1	1	1
2342	F372.12	Diabetic neuropathy	8,715	0.0				1	1
7069	F420000	Background diabetic retinopathy	8,624	0.0					
13078	13AC.00	Diabetic weight reducing diet	8,546	0.0					
18505	C108.11	IDDM-Insulin dependent diabetes mellitus	8,528	0.0		1		1	1
61021	68AB.00	Diabetic digital retinopathy screening offered	8,012	0.0					

17886	66AM.00	Diabetic - follow-up default	8,000	0.0					
17846	8A18.00	Self monitoring of urine glucose	7,629	0.0					
17858	C108.12	Type 1 diabetes mellitus	6,571	0.0		1		1	1
63412	8CR2.00	Diabetes clinical management plan	6,434	0.0					
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus	6,411	0.0			1	1	1
28574	9h4..00	Exception reporting: diabetes quality indicators	6,226	0.0					
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis	6,081	0.0	1	1		1	1
35316	2G5H.00	O/E - Right diabetic foot - ulcerated	5,847	0.0					
17095	2G5A.00	O/E - Right diabetic foot at risk	5,781	0.0					
8618	ZLA2500	Seen by diabetic liaison nurse	5,686	0.0					
13099	2BBR.00	O/E - right eye preproliferative diabetic retinopathy	5,663	0.0					
35116	2G5L.00	O/E - Left diabetic foot - ulcerated	5,657	0.0					
13103	2BBS.00	O/E - left eye preproliferative diabetic retinopathy	5,471	0.0					
22884	C10F.11	Type II diabetes mellitus	5,404	0.0	1		1	1	1
18219	C109.13	Type II diabetes mellitus	5,262	0.0			1		1
11599	7276.00	Pan retinal photocoagulation for diabetes	5,212	0.0					
2986	F420200	Preproliferative diabetic retinopathy	5,100	0.0				1	1
26664	2G5B.00	O/E - Left diabetic foot at risk	5,097	0.0					
11018	8HBG.00	Diabetic retinopathy 12 month review	4,863	0.0					
28622	2126300	Diabetes resolved	4,846	0.0					
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria	4,703	0.0	1		1	1	1
85660	66An.00	Diabetes type 1 review	4,660	0.0					
68546	ZRB4.00	Diabetes clinic satisfaction questionnaire	4,520	0.0					
42217	8A19.00	Self monitoring of blood and urine glucose	4,349	0.0					
18278	C109J00	Insulin treated Type 2 diabetes mellitus	4,319	0.0	1		1	1	1
19381	8HTk.00	Referral to diabetic eye clinic	4,232	0.0					
83485	66Am.00	Insulin dose changed	4,018	0.0					
9835	2BBL.00	O/E - diabetic maculopathy present both eyes	3,953	0.0					
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder	3,917	0.0				1	1
22967	2BBF.00	Retinal abnormality - diabetes related	3,498	0.0					
2475	C104.11	Diabetic nephropathy	3,453	0.0				1	1
12507	9N2i.00	Seen by diabetic liaison nurse	3,400	0.0					
13097	2BBT.00	O/E - right eye proliferative diabetic retinopathy	3,270	0.0					
54601	9NN8.00	Under care of diabetologist	3,110	0.0					
13101	2BBV.00	O/E - left eye proliferative diabetic retinopathy	3,066	0.0					
25636	66Aa.00	Diabetic diet - poor compliance	3,007	0.0					
38986	C100.00	Diabetes mellitus with no mention of complication	2,910	0.0				1	1
18766	212H.00	Diabetes resolved	2,878	0.0					
96010	66Ap.00	Insulin treatment initiated	2,724	0.0					
38103	9N0m.00	Seen in diabetic nurse consultant clinic	2,708	0.0					
26605	9OLB.00	Attended diabetes structured education programme	2,684	0.0					
9881	M271200	Mixed diabetic ulcer - foot	2,640	0.0					

11930	9NN9.00	Under care of diabetes specialist nurse	2,603	0.0					
17067	F171100	Autonomic neuropathy due to diabetes	2,539	0.0					
46521	9N2d.00	Seen by diabetologist	2,455	0.0					
24327	M271000	Ischaemic ulcer diabetic foot	2,419	0.0					
32739	9N0n.00	Seen in community diabetes specialist clinic	2,333	0.0					
57389	93C4.00	Patient consent given for addition to diabetic register	2,256	0.0					
11626	F420z00	Diabetic retinopathy NOS	2,152	0.0				1	1
11663	M271100	Neuropathic diabetic ulcer - foot	2,071	0.0					
18496	C10F600	Type 2 diabetes mellitus with retinopathy	1,989	0.0	1		1	1	1
38129	9N0o.00	Seen in community diabetic specialist nurse clinic	1,920	0.0					
8403	C109700	Non-insulin dependant diabetes mellitus - poor control	1,886	0.0			1	1	1
93529	9OLK.00	DESMOND diabetes structured education programme completed	1,853	0.0					
26603	9OL2.00	Refuses diabetes monitoring	1,852	0.0					
95159	9NiD.00	Did not attend DESMOND diabetes structured education program	1,848	0.0					
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication	1,827	0.0				1	
97281	9NI4.00	Seen by general practitioner special interest in diabetes	1,807	0.0					
33254	C105.00	Diabetes mellitus with ophthalmic manifestation	1,800	0.0				1	
22023	66AJz00	Diabetic - poor control NOS	1,636	0.0				1	1
93631	9OLL.00	XPERT diabetes structured education programme completed	1,591	0.0					
31790	F372.00	Polyneuropathy in diabetes	1,562	0.0					
11551	C10B.00	Diabetes mellitus induced by steroids	1,482	0.0					
16502	C104.00	Diabetes mellitus with renal manifestation	1,471	0.0				1	1
25627	C10F700	Type 2 diabetes mellitus - poor control	1,357	0.0	1		1	1	1
51261	C10E.12	Insulin dependent diabetes mellitus	1,351	0.0	1	1		1	1
94955	9NiE.00	Did not attend XPERT diabetes structured education programme	1,346	0.0					
7059	8H2J.00	Admit diabetic emergency	1,343	0.0					
94186	9OLF.00	Diabetes structured education programme completed	1,221	0.0					
93704	8Hj3.00	Referral to DAFNE diabetes structured education programme	1,156	0.0					
2478	66AJ100	Brittle diabetes	1,100	0.0				1	
57723	8HHy.00	Referral to diabetic register	1,024	0.0					
24363	8A13.00	Diabetic stabilisation	1,021	0.0					
9013	66AJ.11	Unstable diabetes	969	0.0				1	1
27891	N030100	Diabetic Charcot arthropathy	932	0.0					
47954	C10F900	Type 2 diabetes mellitus without complication	903	0.0	1		1	1	1
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis	883	0.0	1		1	1	1
12703	3881.00	Education score - diabetes	869	0.0					
18056	2G5C.00	Foot abnormality - diabetes related	848	0.0					
24423	C108.13	Type I diabetes mellitus	837	0.0		1		1	1
10099	F420300	Advanced diabetic maculopathy	835	0.0				1	1
94011	9OLG.00	Attended XPERT diabetes structured education programme	814	0.0					
43951	66AK.00	Diabetic - cooperative patient	749	0.0				1	
7328	M037200	Cellulitis in diabetic foot	720	0.0					

94699	ZRB5.00	Diabetes treatment satisfaction questionnaire	714	0.0					
29041	66AN.00	Date diabetic treatment start	694	0.0					
101728	66As.00	Diabetic on subcutaneous treatment	650	0.0				1	
12455	C10E.11	Type I diabetes mellitus	638	0.0	1	1		1	1
2340	F381311	Diabetic amyotrophy	612	0.0				1	
50972	C100z00	Diabetes mellitus NOS with no mention of complication	607	0.0				1	1
16881	ZV65312	[V]Dietary counselling in diabetes mellitus	578	0.0					
25041	ZC2CA00	Dietary advice for type II diabetes	578	0.0					
68818	ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire	574	0.0					
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	570	0.0	1		1		1
31310	C108900	Insulin dependant diabetes maturity onset	565	0.0				1	1
66274	66Ah.00	Insulin needles changed for each injection	550	0.0					
18387	C10E700	Type 1 diabetes mellitus with retinopathy	547	0.0	1	1		1	1
38076	M21yC00	Insulin lipohypertrophy	544	0.0					
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria	534	0.0	1	1			1
10418	C10ED00	Type 1 diabetes mellitus with nephropathy	490	0.0	1	1		1	1
27921	2G51000	Foot abnormality - diabetes related	485	0.0					
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria	480	0.0	1	1		1	1
49884	6761.00	Diabetic pre-pregnancy counselling	455	0.0					
6791	C108800	Insulin dependant diabetes mellitus - poor control	437	0.0		1		1	1
35785	F372100	Chronic painful diabetic neuropathy	437	0.0					
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion	435	0.0					
46533	13Y1.00	Diabetic association member	434	0.0					
5002	F372.11	Diabetic polyneuropathy	393	0.0				1	
42505	C101z00	Diabetes mellitus NOS with ketoacidosis	388	0.0				1	1
51697	C10G.00	Secondary pancreatic diabetes mellitus	378	0.0	1			1	
15690	C103.00	Diabetes mellitus with ketoacidotic coma	358	0.0				1	1
35288	C10E800	Type 1 diabetes mellitus - poor control	354	0.0	1	1		1	1
36695	C10D.00	Diabetes mellitus autosomal dominant type 2	352	0.0	1			1	1
16946	13L4.11	Diabetic child	332	0.0				1	
107603	C10P.00	Diabetes mellitus in remission	331	0.0	1				
32193	C11y000	Steroid induced diabetes	326	0.0					
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis	323	0.0	1	1		1	1
38130	ZRB6.00	Diabetes wellbeing questionnaire	322	0.0					
37315	F3y0.00	Diabetic mononeuropathy	314	0.0				1	1
18142	N030000	Diabetic cheiroarthropathy	309	0.0					
35107	C104z00	Diabetes mellitis with nephropathy NOS	308	0.0				1	1
17869	66AL.00	Diabetic-uncooperative patient	307	0.0				1	
2471	K01x100	Nephrotic syndrome in diabetes mellitus	292	0.0					
36798	7L10000	Continuous subcutaneous infusion of insulin	290	0.0					
95553	9NiA.00	Did not attend diabetes structured education programme	289	0.0					
32403	C107.11	Diabetes mellitus with gangrene	278	0.0				1	1

47328	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy	275	0.0					
93390	9OLH.00	Attended DAFNE diabetes structured education programme	272	0.0					
29979	C109900	Non-insulin-dependent diabetes mellitus without complication	269	0.0			1	1	1
45250	ZL22500	Under care of diabetic liaison nurse	265	0.0					
32359	ZRbH.00	Perceived control of insulin-dependent diabetes	264	0.0					
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy	262	0.0	1		1	1	1
53392	C10F911	Type II diabetes mellitus without complication	261	0.0	1		1	1	1
22573	C106z00	Diabetes mellitus NOS with neurological manifestation	258	0.0				1	1
58159	8I3k.00	Insulin therapy declined	255	0.0					
6509	C108700	Insulin dependent diabetes mellitus with retinopathy	251	0.0		1		1	1
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma	249	0.0	1	1		1	1
93491	9OLJ.00	DAFNE diabetes structured education programme completed	245	0.0					
17247	F35z000	Diabetic mononeuritis NOS	243	0.0					
47341	8A12.00	Diabetic crisis monitoring	243	0.0					
18777	C10F000	Type 2 diabetes mellitus with renal complications	235	0.0	1		1	1	1
34152	G73y000	Diabetic peripheral angiopathy	233	0.0					
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer	229	0.0			1	1	1
46624	C10C.11	Maturity onset diabetes in youth	228	0.0	1			1	1
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy	226	0.0	1		1	1	1
43493	M21yC11	Insulin site lipohypertrophy	226	0.0					
21482	C102.00	Diabetes mellitus with hyperosmolar coma	225	0.0				1	1
47058	8Hg4.00	Discharged from care of diabetes specialist nurse	220	0.0					
50960	L180500	Pre-existing diabetes mellitus, insulin-dependent	219	0.0					
52041	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy	219	0.0					
44443	C108500	Insulin dependent diabetes mellitus with ulcer	215	0.0		1		1	1
18662	8HBH.00	Diabetic retinopathy 6 month review	213	0.0					
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion	208	0.0					
95636	C10ER00	Latent autoimmune diabetes mellitus in adult	204	0.0	1			1	
7045	14F4.00	H/O: Admission in last year for diabetes foot problem	202	0.0					
52212	Cyu2.00	[X]Diabetes mellitus	200	0.0				1	1
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation	199	0.0				1	1
95093	8I83.00	Did not complete DESMOND diabetes structured educat program	199	0.0					
35321	8H3O.00	Non-urgent diabetic admission	198	0.0					
47370	8HLE.00	Diabetology D.V. done	198	0.0					
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy	196	0.0	1		1	1	1
24571	F372200	Asymptomatic diabetic neuropathy	194	0.0					
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis	184	0.0	1		1	1	1
34268	C10F200	Type 2 diabetes mellitus with neurological complications	179	0.0	1		1	1	1
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation	165	0.0				1	1
22487	C10N.00	Secondary diabetes mellitus	160	0.0	1			1	1
53238	66AG.00	Diabetic drug side effects	160	0.0					
55431	L180X00	Pre-existing diabetes mellitus, unspecified	159	0.0				1	1

44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract	158	0.0	1		1	1	1
48078	F372000	Acute painful diabetic neuropathy	154	0.0					
58133	ZLD7500	Discharge by diabetic liaison nurse	152	0.0					
54846	9OL9.00	Diabetes monitoring deleted	136	0.0					
90301	66Ag.00	Insulin needles changed daily	133	0.0					
94956	8I84.00	Did not complete XPERT diabetes structured education program	130	0.0					
55123	66AO.00	Date diabetic treatment stopp.	128	0.0					
93380	C10N100	Cystic fibrosis related diabetes mellitus	124	0.0	1			1	
32556	C107.12	Diabetes with gangrene	123	0.0				1	
47584	F420500	Advanced diabetic retinal disease	123	0.0					
49074	C10F400	Type 2 diabetes mellitus with ulcer	121	0.0	1		1	1	1
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy	115	0.0			1	1	1
26108	C10B000	Steroid induced diabetes mellitus without complication	115	0.0					
64357	C10zz00	Diabetes mellitus NOS with unspecified complication	113	0.0				1	1
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis	110	0.0				1	
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis	108	0.0				1	1
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma	108	0.0	1		1	1	
95094	8I81.00	Did not complete diabetes structured education programme	108	0.0					1
64668	C10FJ11	Insulin treated Type II diabetes mellitus	107	0.0	1		1	1	1
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications	101	0.0	1		1	1	
28856	8CP2.00	Transition of diabetes care options discussed	100	0.0					
58639	8I57.00	Patient held diabetic record declined	99	0.0					
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation	98	0.0				1	1
53634	R054200	[D]Gangrene of toe in diabetic	95	0.0					
47315	C10F711	Type II diabetes mellitus - poor control	91	0.0	1		1	1	1
95813	9N1o.00	Seen in multidisciplinary diabetic clinic	90	0.0					
26855	C108400	Unstable insulin dependant diabetes mellitus	88	0.0				1	1
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation	88	0.0				1	1
45491	C10z.00	Diabetes mellitus with unspecified complication	85	0.0				1	1
30477	F420700	High risk proliferative diabetic retinopathy	84	0.0				1	
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy	84	0.0	1		1	1	1
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma	84	0.0	1	1		1	1
46577	66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet	77	0.0					
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder	77	0.0				1	1
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation	76	0.0				1	1
49640	2G5W.00	O/E - left chronic diabetic foot ulcer	74	0.0					
33343	C10y.00	Diabetes mellitus with other specified manifestation	72	0.0				1	1
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy	71	0.0	1		1	1	1
16491	C106.13	Diabetes mellitus with polyneuropathy	67	0.0				1	1
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy	67	0.0	1	1		1	1
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy	67	0.0			1	1	1
12640	C10FC00	Type 2 diabetes mellitus with nephropathy	65	0.0	1		1	1	1

18264	C109J12	Insulin treated Type II diabetes mellitus	64	0.0	1		1	1	1
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy	62	0.0	1	1		1	1
17313	F440700	Diabetic iritis	60	0.0					
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria	60	0.0	1		1	1	1
52630	2BBo.00	O/E - sight threatening diabetic retinopathy	59	0.0					
61523	C106y00	Other specified diabetes mellitus with neurological comps	59	0.0				1	1
93727	C10FE11	Type II diabetes mellitus with diabetic cataract	58	0.0	1		1	1	1
12736	C10F500	Type 2 diabetes mellitus with gangrene	57	0.0	1		1	1	1
69043	ZC2C900	Dietary advice for type I diabetes	57	0.0					
108005	C109312	Type 2 diabetes mellitus with multiple complications	57	0.0			1	1	1
62384	2G5V.00	O/E - right chronic diabetic foot ulcer	56	0.0					
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder	56	0.0				1	1
50937	8HTe.00	Referral to diabetes preconception counselling clinic	55	0.0					
40682	C10E900	Type 1 diabetes mellitus maturity onset	54	0.0	1			1	1
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication	54	0.0				1	1
31053	R054300	[D]Widespread diabetic foot gangrene	53	0.0					
69676	C10EA00	Type 1 diabetes mellitus without complication	53	0.0	1	1		1	1
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma	52	0.0		1		1	1
47582	C10E000	Type 1 diabetes mellitus with renal complications	52	0.0	1	1		1	1
59253	C10FG00	Type 2 diabetes mellitus with arthropathy	52	0.0	1			1	1
52236	C10A.00	Malnutrition-related diabetes mellitus	51	0.0				1	
61210	TJ23z00	Adverse reaction to insulins and antidiabetic agents NOS	51	0.0					
24458	C109711	Type II diabetes mellitus - poor control	49	0.0			1	1	1
43921	C10E400	Unstable type 1 diabetes mellitus	49	0.0	1	1		1	1
45913	C109712	Type 2 diabetes mellitus - poor control	49	0.0			1	1	1
62209	C10EM11	Type I diabetes mellitus with ketoacidosis	48	0.0	1	1		1	1
18683	C10E500	Type 1 diabetes mellitus with ulcer	47	0.0	1	1		1	1
44033	F345000	Diabetic mononeuritis multiplex	47	0.0					
69152	66Aj.00	Insulin needles changed less than once a day	46	0.0					
107824	C10P100	Type II diabetes mellitus in remission	45	0.0	1				
33807	C107200	Diabetes mellitus, adult with gangrene	44	0.0				1	1
50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent	44	0.0				1	1
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis	43	0.0				1	1
39420	F381300	Myasthenic syndrome due to diabetic amyotrophy	41	0.0				1	
56803	C107400	NIDDM with peripheral circulatory disorder	41	0.0				1	1
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	40	0.0	1		1		1
102201	C10FC11	Type II diabetes mellitus with nephropathy	40	0.0	1		1	1	1
49655	C10F611	Type II diabetes mellitus with retinopathy	39	0.0	1		1	1	1
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs	39	0.0	1				
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications	39	0.0			1	1	1
65267	C10F300	Type 2 diabetes mellitus with multiple complications	38	0.0	1		1	1	1
43857	C10M.00	Lipoatrophic diabetes mellitus	37	0.0	1			1	

47650	C10E300	Type 1 diabetes mellitus with multiple complications	37	0.0	1	1		1	1
65463	F420800	High risk non proliferative diabetic retinopathy	37	0.0				1	1
43453	C10C.00	Diabetes mellitus autosomal dominant	36	0.0	1			1	1
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy	36	0.0	1	1		1	1
21472	Q441.00	Neonatal diabetes mellitus	35	0.0					
38617	C101y00	Other specified diabetes mellitus with ketoacidosis	35	0.0				1	1
59903	C106.11	Diabetic amyotrophy	35	0.0				1	1
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma	34	0.0	1		1	1	1
11848	C314.11	Renal diabetes	32	0.0					
34528	3882.00	Diabetes well being questionnaire	31	0.0					
59991	C10D.11	Maturity onset diabetes in youth type 2	31	0.0	1			1	1
46963	C108000	Insulin-dependent diabetes mellitus with renal complications	30	0.0		1		1	1
57333	N030011	Diabetic cheiropathy	30	0.0					
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy	28	0.0		1			1
104639	C10FF11	Type II diabetes mellitus with peripheral angiopathy	27	0.0	1		1	1	1
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus	25	0.0	1		1	1	1
42762	C109612	Type 2 diabetes mellitus with retinopathy	24	0.0			1	1	1
42831	C10E200	Type 1 diabetes mellitus with neurological complications	24	0.0	1	1		1	1
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma	24	0.0				1	1
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma	23	0.0	1		1	1	1
18209	C109012	Type 2 diabetes mellitus with renal complications	21	0.0			1	1	1
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications	21	0.0	1	1		1	1
56448	C108A00	Insulin-dependent diabetes without complication	21	0.0		1		1	1
58604	C109611	Type II diabetes mellitus with retinopathy	21	0.0			1	1	1
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract	20	0.0	1	1		1	1
50527	C10FB11	Type II diabetes mellitus with polyneuropathy	20	0.0	1		1	1	1
68928	TJ23.00	Adverse reaction to insulins and antidiabetic agents	20	0.0					
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps	19	0.0			1	1	
55075	C109411	Type II diabetes mellitus with ulcer	19	0.0			1	1	1
67664	ZRBa.00	Education score - diabetes	19	0.0					
46850	C108811	Type I diabetes mellitus - poor control	18	0.0		1		1	1
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps	18	0.0		1		1	1
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy	18	0.0		1		1	1
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract	18	0.0			1	1	1
103902	C10FG11	Type II diabetes mellitus with arthropathy	18	0.0	1		1	1	1
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps	17	0.0			1	1	1
95343	C10E711	Type I diabetes mellitus with retinopathy	17	0.0	1	1		1	1
45276	C10E312	Insulin dependent diabetes mellitus with multiple complications	16	0.0	1	1		1	1
45919	C109212	Type 2 diabetes mellitus with neurological complications	16	0.0			1	1	1
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps	16	0.0			1	1	1
72702	C10E812	Insulin dependent diabetes mellitus - poor control	16	0.0	1	1		1	1
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy	15	0.0			1	1	1

46290	C108y00	Other specified diabetes mellitus with multiple comps	15	0.0				1	
65684	U602311	[X] Adverse reaction to insulins and antidiabetic agents	15	0.0					
68390	C108512	Type 1 diabetes mellitus with ulcer	15	0.0		1		1	1
69124	C107300	IDDM with peripheral circulatory disorder	15	0.0				1	1
70821	C10yz00	Diabetes mellitus NOS with other specified manifestation	15	0.0				1	1
13279	C104y00	Other specified diabetes mellitus with renal complications	14	0.0				1	1
38161	C108711	Type I diabetes mellitus with retinopathy	14	0.0		1		1	1
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene	14	0.0			1	1	1
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma	14	0.0		1		1	1
48192	C109E11	Type II diabetes mellitus with diabetic cataract	14	0.0			1	1	1
65704	C109412	Type 2 diabetes mellitus with ulcer	14	0.0			1	1	1
96235	C10E911	Type I diabetes mellitus maturity onset	14	0.0	1			1	1
97849	C10E912	Insulin dependent diabetes mellitus maturity onset	14	0.0	1			1	1
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma	13	0.0				1	1
64283	C10zy00	Other specified diabetes mellitus with unspecified comps	12	0.0				1	1
69993	C10E600	Type 1 diabetes mellitus with gangrene	12	0.0	1	1		1	1
18642	C10EH00	Type 1 diabetes mellitus with arthropathy	11	0.0	1	1		1	1
23479	C350011	Bronzed diabetes	11	0.0					
40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy	11	0.0				1	1
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy	11	0.0		1		1	1
52104	C108300	Insulin dependent diabetes mellitus with multiple complicatn	11	0.0		1		1	1
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy	11	0.0	1	1		1	1
95351	C10FA11	Type II diabetes mellitus with mononeuropathy	11	0.0	1		1	1	1
24836	C109C12	Type 2 diabetes mellitus with nephropathy	10	0.0			1	1	1
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma	10	0.0			1	1	1
46150	C109512	Type 2 diabetes mellitus with gangrene	10	0.0			1	1	1
51957	C108511	Type I diabetes mellitus with ulcer	10	0.0		1		1	1
60499	C108600	Insulin dependent diabetes mellitus with gangrene	10	0.0		1		1	1
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct	10	0.0					
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma	9	0.0				1	1
41049	C108712	Type 1 diabetes mellitus with retinopathy	9	0.0		1		1	1
43227	C10F311	Type II diabetes mellitus with multiple complications	9	0.0	1		1	1	1
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract	9	0.0			1	1	1
45914	C108812	Type 1 diabetes mellitus - poor control	9	0.0		1		1	1
49949	C10E411	Unstable type I diabetes mellitus	9	0.0	1	1		1	1
50225	C109011	Type II diabetes mellitus with renal complications	9	0.0			1	1	1
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps	9	0.0		1		1	1
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath	9	0.0					1
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps	9	0.0			1	1	1
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy	9	0.0			1	1	1
10098	C10yy00	Other specified diabetes mellitus with other spec comps	8	0.0				1	1
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract	8	0.0		1		1	1

45499	K01x111	Kimmelstiel - Wilson disease	8	0.0				1	
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy	8	0.0			1	1	1
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma	8	0.0			1	1	1
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation	8	0.0				1	1
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy	8	0.0	1	1		1	1
94383	C10N000	Secondary diabetes mellitus without complication	8	0.0	1			1	1
102112	C10E611	Type I diabetes mellitus with gangrene	8	0.0	1	1		1	1
105337	C10E811	Type I diabetes mellitus - poor control	8	0.0	1	1		1	1
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma	9	0.0				1	1
41049	C108712	Type 1 diabetes mellitus with retinopathy	9	0.0		1		1	1
43227	C10F311	Type II diabetes mellitus with multiple complications	9	0.0	1		1	1	1
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract	9	0.0			1	1	1
45914	C108812	Type 1 diabetes mellitus - poor control	9	0.0		1		1	1
49949	C10E411	Unstable type I diabetes mellitus	9	0.0	1	1		1	1
50225	C109011	Type II diabetes mellitus with renal complications	9	0.0			1	1	1
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps	9	0.0		1		1	1
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath	9	0.0					1
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps	9	0.0			1	1	1
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy	9	0.0			1	1	1
10098	C10yy00	Other specified diabetes mellitus with other spec comps	8	0.0				1	1
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract	8	0.0		1		1	1
45499	K01x111	Kimmelstiel - Wilson disease	8	0.0				1	
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy	8	0.0			1	1	1
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma	8	0.0			1	1	1
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation	8	0.0				1	1
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy	8	0.0	1	1		1	1
94383	C10N000	Secondary diabetes mellitus without complication	8	0.0	1			1	1
102112	C10E611	Type I diabetes mellitus with gangrene	8	0.0	1	1		1	1
105337	C10E811	Type I diabetes mellitus - poor control	8	0.0	1	1		1	1
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma	7	0.0				1	1
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn	7	0.0				1	1
55140	8A1A.00	Self monitoring urine ketones	7	0.0					
62107	C109511	Type II diabetes mellitus with gangrene	7	0.0			1	1	1
66872	C108D11	Type I diabetes mellitus with nephropathy	7	0.0		1		1	1
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication	7	0.0				1	1
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma	7	0.0				1	1
95539	C10FS00	Maternally inherited diabetes mellitus	7	0.0	1			1	1
97809	8I82.00	Did not complete DAFNE diabetes structured education program	7	0.0					
98392	C10C.12	Maturity onset diabetes in youth type 1	7	0.0	1			1	1
106926	PKyP.11	Wolfram syndrome	7	0.0	1				
54600	C10E412	Unstable insulin dependent diabetes mellitus	6	0.0	1	1		1	1
61344	C108011	Type I diabetes mellitus with renal complications	6	0.0		1		1	1

61829	C108212	Type 1 diabetes mellitus with neurological complications	6	0.0		1		1	1
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation	6	0.0				1	1
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy	6	0.0	1	1		1	1
93878	C10E511	Type I diabetes mellitus with ulcer	6	0.0	1	1		1	1
17545	C108F11	Type I diabetes mellitus with diabetic cataract	5	0.0		1		1	1
21983	C108012	Type 1 diabetes mellitus with renal complications	5	0.0		1		1	1
41686	Cyu2000	[X]Other specified diabetes mellitus	5	0.0				1	1
57278	C10F011	Type II diabetes mellitus with renal complications	5	0.0	1		1	1	1
64571	C109C11	Type II diabetes mellitus with nephropathy	5	0.0			1	1	1
67905	C109211	Type II diabetes mellitus with neurological complications	5	0.0			1	1	1
91164	ZRB4.11	CSQ - Diabetes clinic satisfaction questionnaire	5	0.0					
91646	C10F411	Type II diabetes mellitus with ulcer	5	0.0	1		1	1	1
91942	C10E311	Type I diabetes mellitus with multiple complications	5	0.0	1	1		1	1
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation	5	0.0				1	1
100964	C10F111	Type II diabetes mellitus with ophthalmic complications	5	0.0	1		1	1	1
106528	C10FN11	Type II diabetes mellitus with ketoacidosis	5	0.0	1		1	1	1
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy	4	0.0			1	1	1
47409	C109B11	Type II diabetes mellitus with polyneuropathy	4	0.0			1	1	1
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy	4	0.0			1	1	1
60107	C108411	Unstable type I diabetes mellitus	4	0.0		1		1	1
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy	4	0.0			1	1	1
62613	C10EA11	Type I diabetes mellitus without complication	4	0.0	1	1		1	1
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy	4	0.0		1		1	1
67212	C10H000	Diabetes mellitus induced by non-steroid drugs without complication	4	0.0	1				
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma	4	0.0				1	1
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria	4	0.0	1		1	1	1
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications	4	0.0	1	1		1	1
109197	C10FH11	Type II diabetes mellitus with neuropathic arthropathy	4	0.0	1		1	1	1
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy	3	0.0		1			1
59288	C103y00	Other specified diabetes mellitus with coma	3	0.0			1	1	1
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy	3	0.0		1		1	1
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy	3	0.0		1			1
64449	C108z00	Unspecified diabetes mellitus with multiple complications	3	0.0				1	1
66675	C10A000	Malnutrition-related diabetes mellitus with coma	3	0.0				1	1
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma	3	0.0		1		1	1
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy	3	0.0			1	1	1
97474	C108412	Unstable type 1 diabetes mellitus	3	0.0		1		1	1
98704	C10E512	Insulin dependent diabetes mellitus with ulcer	3	0.0	1	1		1	1
104323	C10F511	Type II diabetes mellitus with gangrene	3	0.0	1		1	1	1
105784	C109912	Type 2 diabetes mellitus without complication	3	0.0			1	1	1
109865	C109B12	Type 2 diabetes mellitus with polyneuropathy	3	0.0			1		1
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy	4	0.0			1	1	1

47409	C109B11	Type II diabetes mellitus with polyneuropathy	4	0.0			1	1	1
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy	4	0.0			1	1	1
60107	C108411	Unstable type I diabetes mellitus	4	0.0		1		1	1
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy	4	0.0			1	1	1
62613	C10EA11	Type I diabetes mellitus without complication	4	0.0	1	1		1	1
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy	4	0.0		1		1	1
67212	C10H000	Diabetes mellitus induced by non-steroid drugs without complication	4	0.0	1				
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma	4	0.0				1	1
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria	4	0.0	1		1	1	1
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications	4	0.0	1	1		1	1
109197	C10FH11	Type II diabetes mellitus with neuropathic arthropathy	4	0.0	1		1	1	1
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy	3	0.0		1			1
59288	C103y00	Other specified diabetes mellitus with coma	3	0.0			1	1	1
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy	2	0.0		1		1	1
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma	2	0.0			1	1	1
59725	C109111	Type II diabetes mellitus with ophthalmic complications	2	0.0			1	1	1
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder	2	0.0				1	1
96506	C10G000	Secondary pancreatic diabetes mellitus without complication	2	0.0	1			1	1
97446	C108912	Type 1 diabetes mellitus maturity onset	2	0.0				1	1
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy	2	0.0	1	1		1	1
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic complications	2	0.0	1	1		1	1
98616	C10F211	Type II diabetes mellitus with neurological complications	2	0.0	1		1	1	1
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma	2	0.0	1	1		1	1
99719	C10EA12	Insulin-dependent diabetes mellitus without complication	2	0.0	1	1		1	1
100292	Cyu2300	[X]Unspecified diabetes mellitus with renal complications	2	0.0				1	1
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy	2	0.0	1	1		1	1
106927	PKyP.00	Diabetes insipidus, diabetes mellitus, optic atrophy and deafness	2	0.0	1				1
107701	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus	2	0.0	1		1		1
108360	C10P000	Type I diabetes mellitus in remission	2	0.0	1				
18143	C109G11	Type II diabetes mellitus with arthropathy	1	0.0			1	1	1
49146	C108211	Type I diabetes mellitus with neurological complications	1	0.0		1		1	1
49869	C109G12	Type 2 diabetes mellitus with arthropathy	1	0.0			1	1	1
50813	C109A11	Type II diabetes mellitus with mononeuropathy	1	0.0			1	1	1
62352	C108H11	Type I diabetes mellitus with arthropathy	1	0.0		1		1	1
63017	C108911	Type I diabetes mellitus maturity onset	1	0.0		1		1	1
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma	1	0.0	1	1		1	1
70073	ZRq2.11	SDMT - Symbol digit modalities test	1	0.0					
91943	C10EC11	Type I diabetes mellitus with polyneuropathy	1	0.0	1	1		1	1
95992	C108A11	Type I diabetes mellitus without complication	1	0.0		1		1	1
97824	ZRB6.11	DWBQ - Diabetes wellbeing questionnaire	1	0.0					
99231	C108B11	Type I diabetes mellitus with mononeuropathy	1	0.0		1		1	1
99311	C10E111	Type I diabetes mellitus with ophthalmic complications	1	0.0	1	1		1	1

100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn	1	0.0				1	1
100770	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract	1	0.0	1	1		1	1
101735	C10E212	Insulin-depended diabetes mellitus with neurological comps	1	0.0	1	1		1	1
102163	C10ED12	Insulin dependent diabetes mellitus with nephropathy	1	0.0	1	1		1	1
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria	1	0.0	1	1		1	1
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications	1	0.0		1		1	1
106061	C10FP11	Type II diabetes mellitus with ketoacidotic coma	1	0.0	1			1	1
108007	C108311	Type I diabetes mellitus with multiple complications	1	0.0		1		1	1
108724	C10EQ11	Type I diabetes mellitus with gastroparesis	1	0.0	1	1		1	1
109051	C10E612	Insulin dependent diabetes mellitus with gangrene	1	0.0	1	1		1	1
109133	L180700	Pre-existing malnutrition-related diabetes mellitus	1	0.0				1	1
109837	C10E011	Type I diabetes mellitus with renal complications	1	0.0	1	1			1
110400	C108F12	Type 1 diabetes mellitus with diabetic cataract	1	0.0		1			1
111798	C10FQ11	Type II diabetes mellitus with exudative maculopathy	1	0.0	1				1
109103	C109911	Type II diabetes mellitus without complication	-	0.0			1	1	1
			20,210,190	**100.0**					
	C10M000	*Lipoatrophic diabetes mellitus without complication*	*no medcode*		*1*				
	C10Q.00	*Maturity onset diabetes of the young type 5*	*no medcode*		*1*				

Identification of IHD

List of medical codes (medcode) and Read codes (readcode) used to identify IHD and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of IHD [21], code lists from the Cambridge Code List Index [319], and/or the IHD code list from Reeves et al. [321]. Codes not identified as being QOF [21], Cambridge [319], or Reeves et al. [321] were additional codes added through searching the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. Identification of codes as pertaining to MI, angina, and ACS are identified where appropriate. The final codes to identify IHD are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	IHD	MI	Angina	ACS	Cambridge	Reeves	Included
1430	G33..00	angina pectoris	804,843	19.5	1	1		1		1	1	1
240	G3...00	Ischaemic heart disease	606,186	14.7	1	1				1	1	1
25814	9Ob3.00	Coronary heart disease monitoring 1st letter	480,223	11.6		1						
18135	6A2..00	Coronary heart disease annual review	402,795	9.7		1						
241	G30..00	acute myocardial infarction	225,466	5.5	1	1	1		1	1	1	1
1792	G3...13	IHD - Ischaemic heart disease	138,682	3.4	1	1				1	1	1
34207	9Ob4.00	Coronary heart disease monitoring 2nd letter	109,562	2.6		1						
1677	G30..15	MI - acute myocardial infarction	86,861	2.1	1	1	1	1	1	1	1	1
14658	G30z.00	Acute myocardial infarction NOS	79,825	1.9	1	1	1		1	1	1	1
11648	8B3k.00	Coronary heart disease medication review	74,026	1.8		1						
68357	G31y100	Microinfarction of heart	68,357	1.7	1	1	1			1	1	1
66388	G33z000	Status anginosus	66,388	1.6	1	1		1		1	1	1
19542	662K000	angina control - good	61,341	1.5		1		1				1
10562	G307100	acute non-st segment elevation myocardial infarction	56,673	1.4	1	1	1		1	1	1	1
737	792..11	Coronary artery bypass graft operations	55,140	1.3		1		1		1		1
34329	9Ob5.00	Coronary heart disease monitoring 3rd letter	48,669	1.2		1						
10260	6A4..00	Coronary heart disease review	48,432	1.2		1						
18150	9Ob..00	Coronary heart disease monitoring administration	46,517	1.1		1						
13185	662K.00	angina control	45,781	1.1		1		1				
1344	G340.12	Coronary artery disease	40,384	1.0	1	1				1	1	1
1431	G311.13	unstable angina	34,892	0.8	1	1		1	1	1	1	1
1676	G3z..00	Ischaemic heart disease NOS	33,508	0.8	1	1				1	1	1
2901	7928.00	Transluminal balloon angioplasty of coronary artery	29,330	0.7		1				1		1
11983	G311500	acute coronary syndrome	28,706	0.7	1	1		1	1	1	1	1
7347	G311100	Unstable angina	25,805	0.6	1	1		1	1	1	1	1
6336	14A5.00	H/O: angina pectoris	24,927	0.6				1		1		
8942	7929400	Insertion of coronary artery stent	23,109	0.6		1				1		1
57962	388F.00	cardiovascular limitations and symptoms profile angina score	20,275	0.5		1		1				
12229	G30X000	Acute ST segment elevation myocardial infarction	20,234	0.5	1	1	1		1	1	1	1
5904	792..00	Coronary artery operations	16,719	0.4		1				1		1

28554	G33zz00	angina pectoris nos	12,585	0.3	1	1		1		1	1	1
1678	G308.00	Inferior myocardial infarction NOS	12,525	0.3	1	1	1		1	1	1	1
7137	7920y00	Saphenous vein graft replacement of coronary artery OS	12,124	0.3		1				1		1
43939	793G.00	Perc translumin balloon angioplasty stenting coronary artery	10,822	0.3		1				1		1
4017	G32..00	Old myocardial infarction	10,752	0.3	1	1				1	1	1
733	7A54000	Percutaneous transluminal angioplasty of artery NEC	9,949	0.2		1						
39500	9Ob8.00	Coronary heart disease monitoring check done	9,640	0.2		1						
1655	G340.11	Triple vessel disease of the heart	9,583	0.2	1	1				1	1	1
5413	G340.00	Coronary atherosclerosis	9,062	0.2	1	1				1	1	1
18134	182A.00	chest pain on exertion	8,890	0.2		1		1				
1021	5543.00	Coronary arteriograph.abnormal	8,655	0.2		1		1				
17464	G32..12	personal history of myocardial infarction	8,477	0.2		1				1	1	
37908	9Ob9.00	Coronary heart disease monitoring verbal invitation	8,248	0.2		1						
70160	9Ob9.00	Coronary heart disease monitoring telephone invite	7,875	0.2		1						
105184	792E.00	Percutaneous coronary intervention	7,471	0.2		1						1
1414	G33z300	angina on effort	7,385	0.2	1	1		1		1	1	1
25842	G33z.00	angina pectoris nos	7,284	0.2	1	1		1		1	1	1
12804	G33z700	stable angina	6,802	0.2	1	1		1		1	1	1
3999	G340000	Single coronary vessel disease	5,603	0.1	1	1				1	1	1
4656	G311.11	crescendo angina	5,126	0.1	1	1		1		1	1	1
35373	9Ob0.00	Attends coronary heart disease monitoring	4,908	0.1		1						
1204	G30..14	Heart attack	4,903	0.1	1	1	1		1	1	1	1
5674	ZV45K11	[V]Presence of coronary artery bypass graft - CABG	4,815	0.1		1				1		1
5744	7927500	Open angioplasty of coronary artery	4,442	0.1		1				1		1
29300	662K300	angina control - worsening	4,194	0.1		1		1				
732	7928z00	Transluminal balloon angioplasty of coronary artery NOS	3,861	0.1		1				1		1
103932	8CMP.00	Coronary heart disease care plan	3,855	0.1		1						
5254	G340100	Double coronary vessel disease	3,704	0.1	1	1				1	1	1
2491	G30..12	Coronary thrombosis	3,455	0.1	1	1	1		1	1	1	1
3704	G307.00	acute subendocardial infarction	3,416	0.1	1	1	1		1	1	1	1
12734	SP07600	Coronary artery bypass graft occlusion	3,384	0.1		1				1		1
36523	G311.00	preinfarction syndrome	3,232	0.1	1	1		1		1	1	1
14897	G301z00	Anterior myocardial infarction NOS	3,164	0.1	1	1	1		1	1	1	1
47798	9Ob2.00	Coronary heart disease monitoring default	3,161	0.1		1						
7442	7920200	Saphenous vein graft replacement of three coronary arteries	3,111	0.1		1				1		1
18118	G311400	worsening angina	3,092	0.1	1	1		1		1	1	1
15373	662K100	angina control - poor	2,911	0.1		1	1	1				1
52637	388E.00	Canadian Cardiovascular Society classification of angina	2,865	0.1		1		1				
5703	7928.11	Percutaneous balloon coronary angioplasty	2,836	0.1		1				1		
9276	G31y000	Acute coronary insufficiency	2,561	0.1	1	1		1	1	1	1	1
35674	14A3.00	H/O: myocardial infarct <60	2,552	0.1						1		1
18249	7920.00	Saphenous vein graft replacement of coronary artery	2,522	0.1		1				1		1

5030	ZV45K00	[V]Presence of coronary artery bypass graft	2,496	0.1		1				1		1
20095	G330.00	angina decubitus	2,465	0.1	1	1		1		1	1	1
8568	G37..00	Cardiac syndrome X	2,321	0.1						1		
20416	G3...12	Atherosclerotic heart disease	2,290	0.1	1	1					1	1
14782	662K200	angina control - improving	2,286	0.1		1		1				
7320	G343.00	Ischaemic cardiomyopathy	2,180	0.1	1	1				1	1	1
5387	G301.00	other specified anterior myocardial infarction	2,098	0.1	1	1	1		1	1	1	1
42304	7929500	Insertion of drug-eluting coronary artery stent	1,889	0.0		1				1		1
40399	14A4.00	H/O: myocardial infarct > 60	1,726	0.0						1		1
12139	G300.00	acute anterolateral infarction	1,692	0.0	1	1	1		1	1	1	1
15349	662Kz00	Angina control NOS	1,689	0.0		1		1				1
17307	G311200	angina at rest	1,638	0.0	1	1		1		1	1	1
52517	Gyu3.00	[X]Ischaemic heart diseases	1,638	0.0	1	1						
11610	7920300	Saphenous vein graft replacement of four+ coronary arteries	1,559	0.0						1		1
8935	G302.00	acute inferolateral infarction	1,542	0.0	1	1	1		1	1	1	1
18670	7928000	Percut transluminal balloon angioplasty one coronary artery	1,412	0.0		1				1		1
19046	7929300	Rotary blade coronary angioplasty	1,369	0.0		1				1		
7634	7920100	Saphenous vein graft replacement of two coronary arteries	1,351	0.0		1				1		1
8312	7920.11	Saphenous vein graft bypass of coronary artery	1,330	0.0		1				1		1
36854	G332.00	coronary artery spasm	1,264	0.0		1		1		1	1	1
23078	G34y100	Chronic myocardial ischaemia	1,236	0.0	1	1				1	1	1
10603	792z.00	Coronary artery operations NOS	1,231	0.0		1				1		1
32450	G33z400	ischaemic chest pain	1,187	0.0	1	1		1		1	1	1
17872	G301100	acute anteroseptal infarction	1,126	0.0	1	1	1		1	1	1	1
18889	G34z000	Asymptomatic coronary heart disease	1,052	0.0	1	1				1	1	1
2155	G341000	Ventricular cardiac aneurysm	1,007	0.0		1				1		
22828	7929000	Percutaneous transluminal laser coronary angioplasty	995	0.0		1				1		1
9507	G307000	acute non-q wave infarction	926	0.0	1	1	1		1	1	1	1
60067	793G000	Perc translum ball angio insert 1-2 drug elut stents cor art	879	0.0		1				1		1
12986	G331.00	prinzmetal's angina	834	0.0	1	1		1		1	1	1
33471	792Dz00	Other bypass of coronary artery NOS	831	0.0		1				1		1
24783	G3...11	Arteriosclerotic heart disease	820	0.0	1	1					1	1
34963	792D.00	Other bypass of coronary artery	814	0.0		1				1		1
6980	ZV45L00	[V]Status following coronary angioplasty NOS	780	0.0						1		
22383	G3y..00	Other specified ischaemic heart disease	754	0.0	1	1				1	1	1
23892	G304.00	posterior myocardial infarction nos	731	0.0	1	1	1		1	1	1	1
28138	G34..00	Other chronic ischaemic heart disease	716	0.0	1	1				1	1	1
22020	792B000	Endarterectomy of coronary artery NEC	693	0.0		1				1		
19655	G311.14	angina at rest	636	0.0	1	1		1		1	1	1
18643	ZV45800	[V]Presence of coronary angioplasty implant and graft	625	0.0		1				1		
35277	9Ob1.00	Refuses coronary heart disease monitoring	614	0.0		1						
86773	8A56400	Percutaneous transluminal balloon angioplasty of artery	604	0.0		1						

17133	G30A.00	mural thrombosis	588	0.0		1				1	1	1
29421	G344.00	Silent myocardial ischaemia	580	0.0	1	1				1	1	1
15661	G310.11	Dressler's syndrome	543	0.0						1	1	1
14898	G305.00	Lateral myocardial infarction NOS	539	0.0	1	1	1		1	1	1	1
26863	G33z600	new onset angina	507	0.0	1	1		1		1	1	1
8679	7920000	Saphenous vein graft replacement of one coronary artery	506	0.0		1				1		1
20903	7A6G100	Peroperative angioplasty	484	0.0		1				1		
29643	G303.00	Acute inferoposterior infarction	483	0.0	1	1	1		1	1	1	1
7134	7921.11	Other autograft bypass of coronary artery	456	0.0		1				1		
100139	14AT.00	history of myocardial infarction	453	0.0		1						
101121	8L40.00	Coronary artery bypass graft operation planned	443	0.0		1						
17689	G30..17	silent myocardial infarction	442	0.0	1	1	1			1	1	1
13571	G30..16	Thrombosis - coronary	433	0.0	1	1	1		1	1	1	1
13566	G30..11	Attack - heart	423	0.0	1	1	1		1	1	1	1
33461	7924.00	Revision of bypass for coronary artery	401	0.0		1				1		1
103655	187..00	frequency of angina	398	0.0		1		1				
33735	7928100	Percut translum balloon angioplasty mult coronary arteries	394	0.0		1				1		1
15754	G34z.00	Other chronic ischaemic heart disease NOS	366	0.0	1	1				1	1	1
6331	G341.00	Aneurysm of heart	362	0.0						1		
16408	G32..11	healed myocardial infarction	353	0.0	1	1				1	1	1
24888	7929.00	Other therapeutic transluminal operations on coronary artery	341	0.0		1				1		
18842	G35..00	subsequent myocardial infarction	324	0.0	1	1	1		1	1	1	1
21844	G31y300	Transient myocardial ischaemia	324	0.0	1	1				1	1	1
46017	G30yz00	other acute myocardial infarction nos	323	0.0	1	1	1		1	1	1	1
57910	ZR3P.11	clasp angina score	315	0.0		1		1				
9414	7921.00	Other autograft replacement of coronary artery	311	0.0		1				1		1
47788	7927.00	Other open operations on coronary artery	306	0.0		1				1		
51515	7920z00	Saphenous vein graft replacement coronary artery NOS	298	0.0		1				1		1
26318	G563.00	Left main stem bundle branch block	288	0.0		1						
36609	G342.00	Atherosclerotic cardiovascular disease	288	0.0	1	1				1	1	1
41547	7928y00	Transluminal balloon angioplasty of coronary artery OS	282	0.0		1				1		
34803	G30y.00	other acute myocardial infarction	271	0.0	1	1	1		1	1	1	1
18125	G330000	nocturnal angina	262	0.0	1	1		1		1	1	1
33650	7929100	percut transluminal coronary thrombolysis with streptokinase	247	0.0		1	1			1		1
9555	G33z500	Post infarct angina	237	0.0	1	1				1	1	1
85947	793G200	Perc translum balloon angioplasty insert 1-2 stents cor art	227	0.0		1				1		1
32272	G38..00	postoperative myocardial infarction	214	0.0	1	1	1			1	1	1
3159	792Dy00	Other specified other bypass of coronary artery	213	0.0		1				1		1
31571	792y.00	Other specified operations on coronary artery	203	0.0		1				1		1
61208	793Gz00	Perc translum balloon angioplasty stenting coronary art NOS	200	0.0		1				1		1
55673	ZR3P.00	clasp angina score	190	0.0		1		1				
30421	G30..13	Cardiac rupture following myocardial infarction (MI)	184	0.0	1	1	1		1	1	1	1

27951	G31..00	Other acute and subacute ischaemic heart disease	174	0.0	1	1				1	1	1
2975l	G30X.00	acute transmural myocardial infarction of unspecif site	172	0.0	1	1	1		1	1	1	1
41221	G30y200	Acute septal infarction	168	0.0	1	1	1		1	1	1	1
10209	7921200	Autograft replacement of three coronary arteries NEC	166	0.0		1				1		1
32651	7922.11	Allograft bypass of coronary artery	163	0.0		1				1		1
27484	G341.11	Cardiac aneurysm	161	0.0		1				1		
34328	G311300	refractory angina	158	0.0	1	1		1		1	1	1
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct	157	0.0		1				1	1	
59350	ZR37.00	Canadian Cardiovascular Society classification of angina	150	0.0		1		1				
38813	7A54500	Rotary blade angioplasty	145	0.0		1				1		
11048	G331.11	variant angina pectoris	144	0.0		1		1		1	1	1
57062	14AJ.00	H/O: Angina in last year	138	0.0				1		1		1
87849	793G100	Perc tran ball angio ins 3 or more drug elut stents cor art	137	0.0		1				1		1
24540	G34y000	Chronic coronary insufficiency	135	0.0	1	1				1	1	1
44723	7925200	Single anast mammary art to left ant descend coronary art	122	0.0		1				1		
36011	7923.11	Prosthetic bypass of coronary artery	112	0.0		1				1		
50372	14AH.00	H/O: Myocardial infarction in last year	110	0.0		1				1		1
34965	792A.00	Diagnostic transluminal operations on coronary artery	106	0.0						1		
37682	7925.00	Connection of mammary artery to coronary artery	104	0.0		1				1		
40429	G301000	acute anteroapical infarction	104	0.0	1	1	1		1	1	1	1
9413	G31y.00	Other acute and subacute ischaemic heart disease	102	0.0	1	1				1	1	1
45960	8B27.00	antianginal therapy	101	0.0		1		1				
30330	G309.00	acute q-wave infarct	99	0.0	1	1	1		1	1	1	1
23579	G310.00	Postmyocardial infarction syndrome	96	0.0		1				1	1	1
39693	G31y200	Subendocardial ischaemia	95	0.0	1	1				1	1	1
28736	G30y000	acute atrial infarction	92	0.0	1	1	1			1	1	1
19413	7921100	Autograft replacement of two coronary arteries NEC	90	0.0		1				1		
39449	G312.00	Coronary thrombosis not resulting in myocardial infarction	89	0.0	1	1		1		1	1	
48206	7927300	Transposition of coronary artery NEC	83	0.0						1		
44561	7921000	Autograft replacement of one coronary artery NEC	82	0.0		1				1		
42708	7921300	Autograft replacement of four of more coronary arteries NEC	80	0.0		1				1		
53546	P6y4z00	Coronary artery anomaly NOS	79	0.0		1						
56990	7925z00	Connection of mammary artery to coronary artery NOS	79	0.0		1				1		
27977	G31yz00	Other acute and subacute ischaemic heart disease NOS	74	0.0	1	1				1	1	1
59193	G341200	Aneurysm of coronary vessels	67	0.0						1		
34633	G34y.00	Other specified chronic ischaemic heart disease	66	0.0	1	1				1	1	1
100437	9hM..00	exception reporting: myocardial infarction quality indicator	66	0.0		1						
54251	G311z00	preinfarction syndrome nos	61	0.0	1	1		1		1	1	
105479	G39..00	Coronary microvascular disease	60	0.0	1	1				1		
31679	7929z00	Other therapeutic transluminal op on coronary artery NOS	59	0.0		1				1		
32854	G30B.00	acute posterolateral myocardial infarction	59	0.0	1	1	1		1	1	1	1
61072	G311000	Myocardial infarction aborted	56	0.0	1	1					1	

42462	7928200	Percut translum balloon angioplasty bypass graft coronary a	55	0.0		1				1		1
45809	G350.00	Subsequent myocardial infarction of anterior wall	55	0.0	1	1	1		1	1	1	1
100496	8CEJ.00	Coronary heart disease leaflet given	54	0.0		1						
31556	7922.00	Allograft replacement of coronary artery	53	0.0		1				1		
35119	G501.00	Post infection pericarditis	53	0.0						1		
37657	G362.00	Ventric septal defect/curr comp fol acut myocardial infarctn	53	0.0		1				1	1	1
38609	G351.00	subsequent myocardial infarction of inferior wall	52	0.0	1	1	1		1	1	1	1
44585	792Bz00	Repair of coronary artery NOS	52	0.0		1				1		1
63467	G306.00	true posterior myocardial infarction	52	0.0	1	1	1		1	1	1	1
7696	G33z200	Syncope anginosa	51	0.0	1	1		1		1	1	1
35713	G34yz00	Other specified chronic ischaemic heart disease NOS	51	0.0	1	1				1	1	1
33620	792B.00	Repair of coronary artery NEC	50	0.0		1				1		
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	49	0.0		1				1	1	1
55137	G311011	MI - myocardial infarction aborted	48	0.0	1	1				1	1	
18913	ZV45700	[V]Presence of aortocoronary bypass graft	47	0.0		1				1		1
29902	G330z00	angina decubitus nos	46	0.0	1	1		1		1	1	
41677	G341z00	Aneurysm of heart NOS	46	0.0		1				1		
19402	7923.00	Prosthetic replacement of coronary artery	45	0.0		1				1		
48822	7925011	LIMA sequential anastomosis	45	0.0		1				1		
92927	793G300	Percutaneous cor balloon angiop 3 more stents cor art NEC	44	0.0		1				1		
107406	7.92E+02	Emergency percutaneous coronary intervention	43	0.0		1						
6182	7929y00	Other therapeutic transluminal op on coronary artery OS	38	0.0		1				1		
22647	7925311	LIMA single anastomosis	38	0.0		1				1		
23708	G361.00	Atrial septal defect/curr comp folow acut myocardial infarct	35	0.0						1	1	1
28837	7925.11	Creation of bypass from mammary artery to coronary artery	35	0.0		1				1		
55598	792C.00	Other replacement of coronary artery	35	0.0		1				1		
39584	3889.00	euroscore for angina	34	0.0		1		1				
70755	792Cz00	Replacement of coronary artery NOS	34	0.0		1				1		
66236	7923200	Prosthetic replacement of three coronary arteries	33	0.0		1				1		
95550	8H2V.00	Admit ischaemic heart disease emergency	33	0.0		1						
36423	G36..00	Certain current complication follow acute myocardial infarct	32	0.0		1			1	1	1	1
41835	G384.00	postoperative subendocardial myocardial infarction	32	0.0	1	1	1			1	1	1
51702	7927400	Exploration of coronary artery	30	0.0						1		
45886	7922200	Allograft replacement of three coronary arteries	29	0.0		1				1		
86071	7928300	Percut translum cutting balloon angioplasty coronary artery	29	0.0		1				1		
93706	793H000	Percutaneous transluminal balloon dilation cardiac conduit	29	0.0						1		
70185	7A54800	Percutaneous transluminal atherectomy	28	0.0		1						
31540	7924200	Revision of bypass for three coronary arteries	27	0.0		1				1		
33718	7925000	Double anastomosis of mammary arteries to coronary arteries	26	0.0		1				1		
51507	7925300	Single anastomosis of mammary artery to coronary artery NEC	25	0.0		1				1		
93618	7929600	Percutaneous transluminal atherectomy of coronary artery	23	0.0		1				1		
46276	G381.00	postoperative transmural myocardial infarction inferior wall	22	0.0	1	1	1			1	1	

96804	7926.00	Connection of other thoracic artery to coronary artery	22	0.0		1				1		
39546	Gyu3000	[x]other forms of angina pectoris	21	0.0	1	1		1		1		
45370	7922300	Allograft replacement of four or more coronary arteries	21	0.0		1				1		
91774	G341300	Acquired atrioventricular fistula of heart	20	0.0						1		
67087	G341100	Other cardiac wall aneurysm	19	0.0						1		
67761	7923300	Prosthetic replacement of four or more coronary arteries	19	0.0		1				1		
7609	7921z00	Other autograft replacement of coronary artery NOS	18	0.0		1				1		
41757	7927z00	Other open operation on coronary artery NOS	18	0.0		1				1		
68139	7925400	Single implantation of mammary artery into coronary artery	18	0.0		1				1		
52938	7924000	Revision of bypass for one coronary artery	17	0.0		1				1		
66921	7A6H400	Percutaneous transluminal angioplasty of vascular graft	17	0.0						1		
47637	Gyu3300	Other forms of chronic ischaemic heart disease	14	0.0	1	1						
67554	7924100	Revision of bypass for two coronary arteries	14	0.0		1				1		
57241	7922100	Allograft replacement of two coronary arteries	13	0.0		1				1		
61248	792Az00	Diagnostic transluminal operation on coronary artery NOS	13	0.0						1		
68748	G38z.00	postoperative myocardial infarction, unspecified	13	0.0	1	1	1			1	1	
56905	792Ay00	Diagnostic transluminal operations on coronary artery OS	12	0.0						1		
69247	792By00	Other specified repair of coronary artery	12	0.0		1				1		
69776	SP00300	Mechanical complication of coronary bypass	12	0.0		1						
37719	7925y00	Connection of mammary artery to coronary artery OS	11	0.0		1				1		
40996	7929111	Percut translum coronary thrombolytic therapy- streptokinase	11	0.0		1				1		
46166	G35X.00	subsequent myocardial infarction of unspecified site	11	0.0	1	1	1			1	1	
55092	792C000	Replacement of coronary arteries using multiple methods	11	0.0		1				1		
107967	661M000	angina self-management plan agreed	11	0.0		1		1				
48767	7922z00	Allograft replacement of coronary artery NOS	10	0.0		1				1		
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct	10	0.0		1			1			
64923	7A6H300	Prosthetic graft patch angioplasty	10	0.0						1		
68401	Gyu3200	Other forms of acute ischaemic heart disease	10	0.0	1	1						
31519	7925100	Double implant of mammary arteries into coronary arteries	9	0.0		1				1		
35287	322Z.00	ECG: myocardial ischaemia NOS	9	0.0		1		1				
49735	G5y6.00	Rupture of papillary muscle	9	0.0		1						
54535	G33z100	Stenocardia	9	0.0	1	1		1		1	1	
66664	7923100	Prosthetic replacement of two coronary arteries	9	0.0		1				1		
72562	G353.00	subsequent myocardial infarction of other sites	9	0.0	1	1	1		1	1	1	1
61310	7921y00	Other autograft replacement of coronary artery OS	8	0.0		1				1		
96537	793Gy00	OS perc translumina balloon angioplast stenting coronary art	8	0.0		1						
19193	7923z00	Prosthetic replacement of coronary artery NOS	7	0.0		1				1		
26966	32E3.00	ECG: S-T elevation	7	0.0		1						
42104	32E4.00	ECG: S-T depression	7	0.0		1		1				
57634	7924z00	Revision of bypass for coronary artery NOS	7	0.0		1				1		
95382	7927y00	Other specified other open operation on coronary artery	7	0.0		1				1		
46112	G380.00	postoperative transmural myocardial infarction anterior wall	6	0.0	1	1	1			1	1	

59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	6	0.0		1				1	1	1
66583	7929200	Percut translum inject therap subst to coronary artery NEC	6	0.0		1				1		
58135	5C11.00	Radionuclide heart study abnormal	5	0.0		1		1				
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	5	0.0		1			1	1	1	
93828	792Cy00	Other specified replacement of coronary artery	5	0.0		1				1		
39655	G311.12	impending infarction	4	0.0	1	1		1		1	1	
70111	7922000	Allograft replacement of one coronary artery	4	0.0		1				1		
92419	7923000	Prosthetic replacement of one coronary artery	4	0.0		1				1		
99991	Gyu3600	[x]subsequent myocardial infarction of unspecified site	4	0.0	1	1	1		1	1		
60753	7926300	Single implantation thoracic artery into coronary artery NEC	3	0.0		1				1		
62608	7926000	Double anastom thoracic arteries to coronary arteries NEC	3	0.0		1				1		
62626	G30y100	acute papillary muscle infarction	3	0.0	1	1	1			1	1	
67591	7926200	Single anastomosis of thoracic artery to coronary artery NEC	3	0.0		1				1		
92233	7925012	RIMA sequential anastomosis	3	0.0		1				1		
92267	G5yy200	Papillary muscle dysfunction	3	0.0		1						
98295	ZRB1.00	euroscore for angina	3	0.0		1		1				
109391	661N000	angina self-management plan review	3	0.0		1		1				
59423	7922y00	Other specified allograft replacement of coronary artery	2	0.0		1				1		
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	2	0.0		1			1	1	1	
96838	Gyu3400	[x]acute transmural myocardial infarction of unspecif site	2	0.0	1	1	1		1	1		
97953	7924y00	Other specified revision of bypass for coronary artery	2	0.0		1				1		
63153	7924500	Revision of implantation of thoracic artery into heart	1	0.0		1				1		
68123	7925312	RIMA single anastomosis	1	0.0		1				1		
72780	7926z00	Connection of other thoracic artery to coronary artery NOS	1	0.0		1				1		
101569	7924300	Revision of bypass for four or more coronary arteries	1	0.0		1				1		
105250	G341111	Mural cardiac aneurysm	1	0.0								
106812	G383.00	postoperative transmural myocardial infarction unspec site	1	0.0	1	1				1		
109035	Gyu3500	[x]subsequent myocardial infarction of other sites	1	0.0	1	1			1	1		
			4,136,639	**100.0**								

Identification of PAD

List of medical codes (medcode) and Read codes (readcode) used to identify PAD and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of PAD [21] and/or code lists from the Cambridge Code List Index [319]. Codes not identified as being QOF [21] or Cambridge [319] were additional codes added through searching the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify PAD are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Cambridge	Included
1517	G73z000	intermittent claudication	115,800	22.2	1	1	1
3530	G73z.00	peripheral vascular disease nos	49,363	9.5	1	1	1
2760	G73zz00	peripheral vascular disease nos	46,783	9.0	1	1	1
1735	G71..00	Aortic aneurysm	41,885	8.0			
5943	G73..00	other peripheral vascular disease	22,987	4.4	1	1	1
1002	G730000	Raynaud's disease	17,169	3.3			1
8801	M271400	Mixed venous and arterial leg ulcer	14,085	2.7			1
6853	G73z011	claudication	13,127	2.5	1		1
18499	662U.00	peripheral vascular disease monitoring	12,482	2.4		1	1
2652	G634.00	Carotid artery stenosis	12,203	2.3			
5595	G730100	Raynaud's phenomenon	11,685	2.2			1
4325	G73yz00	other specified peripheral vascular disease nos	9,243	1.8			
1867	G714.00	Abdominal aortic aneurysm without mention of rupture	8,731	1.7			
2654	7A20400	Endarterectomy of carotid artery NEC	7,618	1.5			
1736	7A14.11	Aortic aneurysm repair	7,567	1.5			
7975	16I..00	Claudication distance	7,208	1.4			
11624	M271300	Arterial leg ulcer	7,019	1.3			
106260	9m10.00	Peripheral vascular disease monitoring first letter	6,611	1.3			
6356	7A4B100	Percutaneous transluminal angioplasty of femoral artery	6,186	1.2			
4970	R054.00	[D]Gangrene	5,858	1.1			1
17345	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture	5,513	1.1			
14797	G702.00	Extremity artery atheroma	4,887	0.9			1
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder	3,917	0.8			
10827	7A44000	Percutaneous transluminal angioplasty of iliac artery	3,808	0.7			1
5702	G73..11	peripheral ischaemic vascular disease	3,217	0.6	1		1
8511	P769000	Renal artery stenosis	3,084	0.6			
2066	7A4A400	Other bypass of femoral artery or popliteal artery NOS	3,071	0.6			1
6827	G73..13	peripheral ischaemia	2,627	0.5	1		1
6308	M271.12	Ischaemic leg ulcer	2,506	0.5			1
24327	M271000	Ischaemic ulcer diabetic foot	2,419	0.5			
11680	2I16.00	O/E - gangrene	2,392	0.5			1
9561	2G63.00	Ischaemic toe	2,321	0.4			1

4240	G631.00	Carotid artery occlusion	2,152	0.4			
16993	14AE.00	H/O: aortic aneurysm	2,144	0.4			
1318	G700.00	Aortic atherosclerosis	2,125	0.4			
1826	G73..12	ischaemia of legs	2,094	0.4	1		1
106224	9m1..00	Peripheral vascular disease monitoring invitation	2,032	0.4			
2065	G742400	Embolism and thrombosis of the femoral artery	1,791	0.3			1
7694	G76z100	Femoral artery occlusion	1,777	0.3			
5414	G732000	Gangrene of toe	1,590	0.3			1
29112	G711.00	Percutaneous transluminal angioplasty of popliteal artery	1,399	0.3			1
98174	G733.00	ischaemic foot	1,395	0.3			
13572	G713000	Ruptured abdominal aortic aneurysm	1,379	0.3			
6872	G71z.00	Aortic aneurysm NOS	1,325	0.3			
105317	G734.00	peripheral arterial disease	1,315	0.3	1		1
106660	9m11.00	Peripheral vascular disease monitoring second letter	1,303	0.3			
10500	G73y800	Erythromelalgia	1,245	0.2			
16521	G710.00	Dissecting aortic aneurysm	1,157	0.2			
16366	G723200	Aneurysm of popliteal artery	1,154	0.2			
9204	G732.00	Peripheral gangrene	1,090	0.2			1
23532	G713.00	Thoracic aortic aneurysm without mention of rupture	1,059	0.2			
17767	G713.11	Abdominal aortic aneurysm which has ruptured	1,048	0.2			
2761	7A12100	Bypass bifurc aorta by anastom aorta to femoral artery NEC	1,023	0.2			
12413	5C10.00	Carotid artery doppler abnormal	1,005	0.2			
15304	G715000	Ruptured aortic aneurysm NOS	968	0.2			
3005	G761.00	Stricture of artery	929	0.2			
22677	G70y011	Carotid artery disease	776	0.1			
17220	7A13.11	Emergency repair of aortic aneurysm	770	0.1			
17560	G722000	Aneurysm of iliac artery	700	0.1			
106855	9m12.00	Peripheral vascular disease monitoing third letter	696	0.1			
23497	G731000	Buerger's disease	660	0.1			
39097	G730z00	Raynaud's syndrome NOS	624	0.1			1
98356	N14A.00	Neurogenic claudication	618	0.1			
19155	G700.11	Aorto-iliac disease	593	0.1			
37806	C10FF00	type 2 diabetes mellitus with peripheral angiopathy	593	0.1			
6684	G723100	Aneurysm of femoral artery	579	0.1			
12735	G732100	Gangrene of foot	557	0.1			1
9554	G76z200	Popliteal artery occlusion	550	0.1			1
15863	G73z100	Spasm of peripheral artery	548	0.1			
12888	G703.00	Acquired renal artery stenosis	538	0.1			
101698	68B5100	Aortic aneurysm screening abnormal	538	0.1			
12634	G673200	Carotid artery dissection	514	0.1			
27580	7A48200	Bypass femoral artery by fem/pop art anast c prosthesis NEC	472	0.1			1
25844	7A32000	Percutaneous transluminal angioplasty of renal artery	451	0.1			

15302	G742z00	Peripheral arterial embolism and thrombosis NOS	421	0.1			1
28030	7A48400	Bypass femoral artery by fem/pop art anast c vein graft NEC	413	0.1			1
101379	G714200	Intrarenal abdominal aortic aneurysm	395	0.1			
29973	7A22000	Percutaneous transluminal angioplasty of carotid artery	382	0.1			
16284	G701.00	Renal artery atherosclerosis	370	0.1			
28840	7A4B000	Operation on aneurysm of femoral artery NEC	335	0.1			
16034	G716.00	Aortic aneurysm without mention of rupture NOS	319	0.1			
37199	G70y000	Carotid artery atherosclerosis	303	0.1			
32403	C107.11	diabetes mellitus with gangrene	278	0.1			
9759	G720.00	Leaking abdominal aortic aneurysm	271	0.1			
43001	9N4h.00	DNA - did not attend peripheral vascular disease clinic	265	0.1			
5650	G740.12	Aortoiliac obstruction	244	0.0			
4539	G742500	Embolism and thrombosis of the popliteal artery	237	0.0			1
16800	G712.00	Ruptured thoracic aortic aneurysm	235	0.0			
34152	G73y000	diabetic peripheral angiopathy	233	0.0			
38732	G72y500	Aneurysm of splenic artery	228	0.0			
14796	R055000	[D]Failure of peripheral ciculation	226	0.0			
16395	G722100	Aneurysm of common iliac artery	210	0.0			
30484	R055011	[D]Peripheral circulatory failure	210	0.0			
83577	7A1C000	Endovas ins stent graft for intrarenal abdom aortic aneurysm	207	0.0			
103613	66f3.00	Aortic aneurysm monitoring	190	0.0			
11766	7A47.16	Other emergency bypass of femoral artery	182	0.0			
97122	G673300	Vertebral artery dissection	179	0.0			
29276	J42..00	Vascular insufficiency of the intestine	178	0.0			
35752	J420z00	Acute intestinal vascular insufficiency NOS	167	0.0			
37935	J420.00	Acute intestinal vascular insufficiency	159	0.0			
27494	G74y300	Embolism and thrombosis of the iliac artery unspecified	154	0.0			1
15532	7A12300	Bypass bifurcation aorta by anastom aorta to iliac artery	146	0.0			
42640	7A48.12	Other bypass of femoral artery or popliteal artery OS	144	0.0			1
38907	G73y.00	other specified peripheral vascular disease	136	0.0	1		1
31723	7A28000	Percutaneous transluminal angioplasty of subclavian artery	133	0.0			
37750	R054z00	[D]Gangrene NOS	133	0.0			
32556	C107.12	diabetes with gangrene	123	0.0			
97217	7A1B800	Endovascul insert stent infrarenal abdominal aortic aneurysm	123	0.0			
27563	G711.11	Thoracic aortic aneurysm which has ruptured	122	0.0			
44835	G742900	Embolism and thrombosis of a leg artery NOS	120	0.0			1
40787	G716000	Thoracoabdominal aortic aneurysm, without mention of rupture	109	0.0			
23352	7A10100	Bypass aorta by anastomosis axillary to femoral artery NEC	106	0.0			1
39749	7A43200	Operation on aneurysm of iliac artery NEC	104	0.0			
28616	7A41100	Bypass iliac artery by iliac/femoral artery anastomosis NEC	103	0.0			
53634	R054200	[D]Gangrene of toe in diabetic	95	0.0			
9099	7A47.00	Other emergency bypass of femoral artery or popliteal artery	92	0.0			1

34638	G731.00	Thromboangiitis obliterans	92	0.0			
70446	7A1B000	Endovascular stenting infrarenal abdominal aortic aneurysm	89	0.0			
22018	G673000	Dissection of cerebral arteries, nonruptured	85	0.0			
44439	7A46.14	Other replacement of aneurysmal popliteal artery	84	0.0			
16260	G702z00	Extremity artery atheroma NOS	83	0.0			
45521	G715.00	Juxtarenal aortic aneurysm	83	0.0			
19996	7A14400	Replace aneurysm abdominal aorta by anast aorta to aorta NEC	79	0.0			
19825	5593.00	Femoral arteriogram abnormal	78	0.0			
35529	G72y500	Aneurysm of subclavian artery	77	0.0			
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder	77	0.0			
39949	G732200	Gangrene of finger	74	0.0			
44030	J421.00	Chronic intestinal vascular insufficiency	74	0.0			
51124	7A4A500	Ligation of aneurysm of popliteal artery	71	0.0			
104467	585I000	Abdominal aortic aneurysm screen ultrasound scan abnormal	70	0.0			
20811	7A20200	Bypass to carotid arery NEC	66	0.0			
54865	G74y000	Embolism and/or thrombosis of the common iliac artery	62	0.0			1
41823	7A48800	Bypass femoral artery by fem/tib art anast c vein graft NEC	60	0.0			1
45428	7A48y00	Bypass femoral artery by femoral/femoral art anastomosis NEC	59	0.0			1
12736	C10F500	type 2 diabetes mellitus with gangrene	57	0.0			
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder	56	0.0			
31053	R054300	[D]Widespread diabetic foot gangrene	53	0.0			
11430	G715000	Thoracoabdominal aortic aneurysm, ruptured	52	0.0			
33807	C107200	diabetes mellitus, adult with gangrene	44	0.0			
37465	7A28100	Percutaneous transluminal angioplasty of brachial artery	42	0.0			
56803	C107400	NIDDM with peripheral circulatory disorder	41	0.0			
26232	7A14411	Tube graft of Abdominal aortic aneurysm	38	0.0			
59534	14NB.00	H/O: Peripheral vascular disease procedure	37	0.0			
52358	7A11.00	Replacement of aneurysmal bifurcation of aorta	36	0.0			
58794	G722z00	Aneurysm of internal iliac artery	35	0.0			
101866	G73z012	vascular claudication	35	0.0	1		
98556	38DJ.00	Edinburgh claudication questionnaire	34	0.0			
46125	7A45.14	Emergency replacement of aneurysmal popliteal artery	33	0.0			
51166	7A11311	Y graft abdominal Aortic aneurysm	33	0.0			
36443	7A41300	Bypass iliac artery by femoral/femoral art anastomosis NEC	30	0.0			
69346	7A46.00	Other replacement of aneurysmal artery	28	0.0			
46164	7A35000	Percutaneous transluminal angioplasty of coeliac artery NEC	27	0.0			
64368	J42z.00	Intestinal vascular insufficiency NOS	27	0.0			
99787	7A1BB00	Endovascular ins stent for aortic dissection in any position	27	0.0			
104639	C10FF11	type ii diabetes mellitus with peripheral angiopathy	27	0.0			
41825	55A2.00	Lower limb arteriogram abnorm.	26	0.0			
73961	Gyu7400	[x]other specified peripheral vascular diseases	25	0.0	1		
39877	7A48600	Bypass femoral artery by fem/tib art anast c prosthesis NEC	24	0.0			1

40732	7A48000	Other bypass of superficial femoral artery	24	0.0			
38921	7A41z00	Other bypass of iliac artery NOS	23	0.0			
51061	7A1B200	Endovascular stenting of thoracic aortic aneurysm	23	0.0			
28109	G714100	Inflammatory abdominal aortic aneurysm	22	0.0			
32634	G74y100	Embolism and/or thrombosis of the internal iliac artery	22	0.0			1
53675	7A48C00	Bypass femoral artery by fem/peron a anast c vein graft NEC	22	0.0			1
37787	7A48.13	Other bypass of common femoral artery	21	0.0			
89714	7A1C300	Endov ins stent graft for aortic dissection in any position	20	0.0			
45308	7A27C00	Operation on aneurysm of subclavian artery	19	0.0			
63408	7A13411	Tube graft abdominal Aortic aneurysm (emergency)	19	0.0			
31055	G723600	Ruptured popliteal artery aneurysm	18	0.0			
52357	7A41.00	Other specified other bypass of iliac artery	17	0.0			
59756	7A40.00	Replacement of aneurysmal iliac artery	17	0.0			
56919	G74y200	Embolism and/or thrombosis of the external iliac artery	16	0.0			1
98542	7A1BA00	Endovascular insertion of stent for thoracic aortic aneurysm	16	0.0			
42444	7A14100	Replace aneurysm thoracic aorta by anast of aorta/aorta NEC	15	0.0			
61666	7A45.00	Emergency replacement of aneurysmal femoral/popliteal artery	15	0.0			
69124	C107300	IDDM with peripheral circulatory disorder	15	0.0			
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene	14	0.0			
54192	7A13400	Emerg replace aneurysm abdom aorta by anast aorta/aorta NEC	14	0.0			
61393	J421z00	Chronic intestinal vascular insufficiency NOS	14	0.0			
48939	7A47C00	Emerg bypass femoral artery by fem/fem art anastomosis NEC	13	0.0			
51634	R054000	[D]Gangrene, spreading cutaneous	13	0.0			
59538	G72y900	Aneurysm of superior mesenteric artery	13	0.0			
41703	7A22z00	Transluminal operation on carotid artery NOS	12	0.0			
69993	C10E600	type 1 diabetes mellitus with gangrene	12	0.0			
23672	G732400	Gangrene of hand	11	0.0			
23871	G73y100	peripheral angiopathic disease ec nos	11	0.0			
56510	7A11300	Replace aneurysm bifurc aorta by anast aorta to iliac artery	11	0.0			
60879	G722200	Aneurysm of external iliac artery	11	0.0			
15007	7A20000	Replacement of carotid artery using graft	10	0.0			
46150	C109512	type 2 diabetes mellitus with gangrene	10	0.0			
60499	C108600	insulin dependent diabetes mellitus with gangrene	10	0.0			
67026	G723300	Aneurysm of anterior tibial artery	10	0.0			
32492	7A41900	Bypass common iliac artery by aorta/com iliac art anast NEC	9	0.0			
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath	9	0.0			
63059	G723000	Aneurysm of leg artery NOS	9	0.0			
66232	7A13300	Emerg replace aneurysm infrarenal aorta by anast aorta/aorta	9	0.0			
73022	7A21000	Repair of carotid artery NEC	8	0.0			
102112	C10E611	type i diabetes mellitus with gangrene	8	0.0			
55074	7A28200	Percutaneous transluminal angioplasty of vertebral artery	7	0.0			
62107	C109511	type ii diabetes mellitus with gangrene	7	0.0			

63920	G714.00	Ruptured suprarenal aortic aneurysm	7	0.0			
66633	7A34K00	Operation on aneurysm visceral branch of abdominal aorta NEC	7	0.0			
69847	G723400	Aneurysm of dorsalis pedis artery	7	0.0			
92925	7A11211	Y graft abdominal Aortic aneurysm (emergency)	7	0.0			
97030	7A1B000	Endovascular stenting of suprarenal aortic aneurysm	7	0.0			
41220	7A35300	Percutaneous transluminal angioplasty suprarenal NEC	6	0.0			
48755	7A12000	Emerg bypass bifurc aorta by anast aorta to femoral artery	6	0.0			
51057	G732300	Gangrene of thumb	6	0.0			
69922	7A11200	Emerg repl aneurysm bifurc aorta by anast aorta to iliac a	6	0.0			
83527	7A1B300	Endovascular stenting of aortic dissection in any position	6	0.0			
93468	C10EG00	type 1 diabetes mellitus with peripheral angiopathy	6	0.0			
99859	7A1BC00	Endovas insert stent for aortic aneurysm of bifurcation NEC	6	0.0			
105917	G727.00	Dissection of iliac artery	6	0.0			
57135	G72yA00	Aneurysm of inferior mesenteric artery	5	0.0			
66761	7A11z00	Replacement of aneurysmal bifurcaiton of aorta NOS	5	0.0			
69232	G742600	Embolism and thrombosis of the anterior tibial artery	5	0.0			1
70235	7A21z00	Other open operaiton on carotid artery NOS	5	0.0			
72448	7A41200	Emerg bypass iliac artery by femoral/femoral art anast NEC	5	0.0			
94784	7A45.15	Emergency replacement aneurysmal superficial femoral artery	5	0.0			
100579	Gyu7000	[X]Atherosclerosis of other arteries	5	0.0			
54899	C109F11	type ii diabetes mellitus with peripheral angiopathy	4	0.0			
60699	C109F12	type 2 diabetes mellitus with peripheral angiopathy	4	0.0			
72062	G723500	Aneurysm of posterior tibial artery	4	0.0			
94682	7A1C100	Endovas insert of stent graft for suprarenal aortic aneurysm	4	0.0			
97661	7A46C00	Replace aneurysm fem artery by fem/fem art anastomosis NEC	4	0.0			
105117	G728.00	Dissection of artery of lower extremity	4	0.0			
107998	G726.00	Dissection of renal artery	4	0.0			
59536	G72yB00	Aneurysm of other visceral artery	3	0.0			
61042	7A34E00	Operation on aneurysm of inferior mesenteric artery NEC	3	0.0			
62025	7A45200	Emerg replace aneurysm fem art by fem/pop anast c vein graft	3	0.0			
64446	C108G00	insulin dependent diab mell with peripheral angiopathy	3	0.0			
67982	7A48A00	Bypass femoral artery by fem/peron a anast c prosthesis NEC	3	0.0			1
71141	7A46300	Replace aneurysm pop art by pop/pop a anast c vein graft NEC	3	0.0			
71860	G742700	Embolism and thrombosis of the dorsalis pedis artery	3	0.0			1
94556	7A46y00	Other replacement of aneurysmal femoral/popliteal artery OS	3	0.0			
102725	Gyu7100	[X]Aortic aneurysm of unspecified site, ruptured	3	0.0			
104323	C10F511	type ii diabetes mellitus with gangrene	3	0.0			
106488	7A40y00	Other specified replacement of aneurysmal iliac artery	3	0.0			
106780	7A1B900	Endovascular insertion of stent for suprarenal aortic aneurysm	3	0.0			
55394	7A45D00	Emerg replace aneurysm pop artery by pop/fem art anastomosis	2	0.0			
67401	G731z00	Thromboangiitis obliterans NOS	2	0.0			
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder	2	0.0			

91084	7A34D00	Operation on aneurysm of superior mesenteric artery NEC	2	0.0			
95503	7A40z00	Replacement of aneurysmal iliac artery NOS	2	0.0			
96656	7A46z00	Other replacement of aneurysmal femoral/popliteal artery NOS	2	0.0			
96699	7A40000	Emerg replace aneurysm iliac art by iliac/femoral art anast	2	0.0			
96744	SP01200	Mechanial complication of carotid artery bypass	2	0.0			
99727	7A40A00	Replace aneurysm iliac art by aorta/ext iliac art anast NEC	2	0.0			
101910	7A41.11	Other bypass of iliac artery by anastomosis	2	0.0			
103988	7A45.12	Emergency replacement of aneurysmal common femoral artery	2	0.0			
55476	7A45000	Emerg replace aneurysm fem art by fem/pop art anast c prosth	1	0.0			
58092	7A46100	Replace aneurysm pop art by pop/pop art anastom c prosth NEC	1	0.0			
62301	7A11y00	Replacement of aneurysmal bifurcation of aorta OS	1	0.0			
63238	7A47.13	Other emergency bypass of deep femoral artery	1	0.0			
68385	7A46.11	Other replacement aneurysmal femoral artery by anastomosis	1	0.0			
93060	7A13100	Emerg replace aneurysm thor aorta by anastom aorta to aorta	1	0.0			
95416	7A46D00	Replace aneurysm popliteal artery by pop/fem anastomosis NEC	1	0.0			
96472	7A46000	Replace aneurysm fem art by fem/pop art anastom c prosth NEC	1	0.0			
96654	7A11000	Emerg repl aneurysm bifurc aorta by anast aorta to fem art	1	0.0			
97606	7A47.15	Other emergency bypass of superficial femoral artery	1	0.0			
100036	7A41D00	Bypass iliac artery by iliac/iliac artery anastomosis NEC	1	0.0			
100113	7A47.12	Other emergency bypass of common femoral artery	1	0.0			
102719	Gyu7200	[X]Aortic aneurysm of unspecified site, nonruptured	1	0.0			
103044	7A45y00	Emergency replacement aneurysmal femoral/popliteal artery NOS	1	0.0			
103347	7A40.11	Replacement of aneurysmal iliac artery by anastomsosis	1	0.0			
103731	7A46.15	Other replacement of aneurysmal superficial femoral artery	1	0.0			
107071	G701011	ARAS - Atherosclerotic renal arery stenosis	1	0.0			
109431	7A40200	Emerg replace aneurysmal iliac artery by fem/fem art anast	1	0.0			
110372	G725.00	Dissection of artery of upper extremity	1	0.0			
110617	7A45C00	Emerg replace aneurysm fem artery by fem/fem art anastomosis	1	0.0			
89470	7A45700	Emerg replace aneurym pop art by pop/tib anast c vein graft	-	0.0			
			520,512	**100.0**			

Identification of stroke

List of medical codes (medcode) and Read codes (readcode) used to identify stroke and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of stoke [21], the code list currently undergoing validation by our group, the code lists from the Cambridge Code List Index [319], the code list from Kontopanelis et al. 2012 [322], and/or having been found during a search of the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify stroke are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Cambridge	Kontopantelis	Undergoing Validation	Included
1469	G66..00	Stroke and cerebrovascular accident unspecified	224,698	22.1	1	1	1	1	1
2418	G6...00	Cerebrovascular disease	185,313	18.3		1		1	1
1298	G66..11	cva unspecified	117,132	11.5	1	1	1	1	1
18686	662e.00	Stroke/CVA annual review	101,259	10.0			1	1	1
10792	662M.00	Stroke monitoring	91,610	9.0			1	1	1
1786	G60..00	subarachnoid haemorrhage	28,143	2.8				1	1
3149	G64z.00	Cerebral infarction NOS	27,257	2.7	1	1	1	1	1
5363	G64..11	CVA - cerebral artery occlusion	26,837	2.6	1	1	1	1	1
8837	G64..00	Cerebral arterial occlusion	20,849	2.1	1	1	1	1	1
32959	9N0p.00	Seen in stroke clinic	20,017	2.0			1		
6116	G66..13	cva - cerebrovascular accident unspecified	17,141	1.7	1	1	1	1	1
18804	8HTQ.00	Referral to stroke clinic	15,908	1.6			1		
5051	G61..00	Intracerebral haemorrhage	14,983	1.5	1	1	1	1	1
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage	11,474	1.1	1	1	1	1	1
5871	14A7.12	H/O: stroke	10,162	1.0			1	1	1
34135	14A7.00	H/O: CVA/stroke	9,503	0.9			1	1	1
5602	G64z.12	Cerebellar infarction	6,837	0.7	1	1	1	1	1
98188	G679.00	small vessel cerebrovascular disease	6,189	0.6				1	1
6253	G66..12	stroke unspecified	5,918	0.6	1	1	1	1	1
7780	G667.00	Left sided CVA	5,297	0.5	1	1	1	1	1
6155	G64..13	stroke due to cerebral arterial occlusion	4,755	0.5	1	1	1	1	1
12833	G668.00	Right sided CVA	4,655	0.5	1	1	1	1	1
569	G64..12	infarction - cerebral	4,103	0.4	1	1	1	1	1
18912	G623.00	subdural haematoma nos	3,827	0.4				1	1
16517	G640.00	Cerebral thrombosis	3,433	0.3	1	1	1	1	1
17734	G622.00	subdural haematoma - nontraumatic	3,352	0.3				1	1
10062	G6z..00	cerebrovascular disease nos	2,817	0.3				1	1
4273	G621.00	subdural haemorrhage - nontraumatic	2,314	0.2				1	1
4240	G631.00	carotid artery occlusion	2,152	0.2				1	1

33543	G6X..00	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	2,112	0.2	1	1	1	1	1
18604	G61..12	Stroke due to intracerebral haemorrhage	2,098	0.2	1	1	1	1	1
9985	G64z200	Left sided cerebral infarction	2,097	0.2	1	1	1	1	1
10504	G64z300	Right sided cerebral infarction	1,977	0.2	1	1	1	1	1
3535	G61z.00	Intracerebral haemorrhage NOS	1,898	0.2	1	1	1	1	1
13564	G613.00	Cerebellar haemorrhage	1,570	0.2	1	1	1	1	1
17322	G664.00	Cerebellar stroke syndrome	1,550	0.2	1	1	1	1	1
23671	G63y000	Cerebral infarct due to thrombosis of precerebral arteries	1,383	0.1	1	1	1	1	1
8443	G663.00	Brain stem stroke syndrome	1,302	0.1	1	1	1	1	1
15019	G641.00	Cerebral embolism	1,275	0.1	1	1	1	1	1
16554	14AF.00	h/o sub-arachnoid haemorrhage	1,216	0.1				1	1
26424	G64z400	Infarction of basal ganglia	1,188	0.1	1	1	1	1	1
36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries	835	0.1	1	1	1	1	1
23580	G60z.00	subarachnoid haemorrhage nos	814	0.1				1	1
20284	G62z.00	intracranial haemorrhage nos	713	0.1				1	1
30202	G617.00	Intracerebral haemorrhage, intraventricular	706	0.1		1		1	1
25615	G64z000	Brainstem infarction	703	0.1	1	1	1	1	1
18689	G660.00	Middle cerebral artery syndrome	639	0.1	1	1	1	1	1
19348	ZV12511	[V]Personal history of stroke	639	0.1			1		
7138	ZV12512	[V]Personal history of cerebrovascular accident (CVA)	577	0.1			1		
16956	G669.00	Cerebral palsy, not congenital or infantile, acute	532	0.1		1			
53745	Gyu6400	[X]Other cerebral infarction	500	0.0	1	1	1	1	1
33499	G665.00	Pure motor lacunar syndrome	468	0.0	1	1	1	1	1
19260	G662.00	Posterior cerebral artery syndrome	428	0.0	1	1	1	1	1
6228	G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction	426	0.0			1	1	1
37493	G67z.00	other cerebrovascular disease nos	419	0.0				1	1
40758	G6W..00	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	403	0.0	1	1	1	1	1
15252	G64z.11	Brainstem infarction NOS	381	0.0	1	1	1	1	1
45781	G63..00	precerebral arterial occlusion	353	0.0					
24446	G63y100	Cerebral infarction due to embolism of precerebral arteries	346	0.0	1	1	1	1	1
7912	G614.00	Pontine haemorrhage	343	0.0	1	1	1	1	1
19412	G602.00	subarachnoid haemorrhage from middle cerebral artery	340	0.0				1	1
19280	G661.00	Anterior cerebral artery syndrome	329	0.0	1	1	1	1	1
5185	G64z111	Lateral medullary syndrome	272	0.0		1	1	1	1
39344	G676000	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	251	0.0	1	1		1	1
17326	G60X.00	subarachnoid haemorrh from intracranial artery, unspecif	229	0.0				1	1
40338	G611.00	Internal capsule haemorrhage	220	0.0	1	1	1	1	1
40847	G632.00	vertebral artery occlusion	218	0.0				1	1
28314	G61X000	Left sided intracerebral haemorrhage, unspecified	216	0.0	1	1	1	1	1
40053	G671.00	generalised ischaemic cerebrovascular disease nos	206	0.0				1	1
36178	G620.00	extradural haemorrhage - nontraumatic	200	0.0				1	1
19201	G61X100	Right sided intracerebral haemorrhage, unspecified	199	0.0	1	1	1	1	1

28914	662o.00	Haemorrhagic stroke monitoring	196	0.0			1	1	1
27975	G641000	Cerebral infarction due to embolism of cerebral arteries	194	0.0	1	1	1	1	1
31805	G62..00	other and unspecified intracranial haemorrhage	194	0.0				1	1
43451	G682.00	sequelae of other nontraumatic intracranial haemorrhage	180	0.0				1	1
4152	G631.12	thrombosis, carotid artery	167	0.0					
55351	7P24200	Delivery of rehabiliation for stroke	156	0.0			1	1	1
32447	G630.00	basilar artery occlusion	150	0.0				1	1
12555	G671z00	generalised ischaemic cerebrovascular disease nos	147	0.0				1	1
42331	G603.00	subarachnoid haemorrhage from anterior communicating artery	144	0.0				1	1
51767	G666.00	Pure sensory lacunar syndrome	139	0.0	1	1	1	1	1
29939	G600.00	ruptured berry aneurysm	124	0.0				1	1
31595	G610.00	Cortical haemorrhage	124	0.0	1	1	1	1	1
39403	G683.00	sequelae of cerebral infarction	121	0.0				1	1
46316	G612.00	Basal nucleus haemorrhage	118	0.0	1	1	1	1	1
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified	117	0.0	1	1	1	1	1
34117	G67y.00	other cerebrovascular disease os	107	0.0				1	1
51311	G6y.00	other specified cerebrovascular disease	107	0.0					
51759	G677000	occlusion and stenosis of middle cerebral artery	97	0.0				1	1
66873	14AK.00	H/O: Stroke in last year	86	0.0			1	1	1
91627	Gyu6300	[X]Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	86	0.0	1	1	1	1	1
107440	G619.00	Lobar cerebral haemorrhage	84	0.0	1			1	1
47607	L440.11	cva - cerebrovascular accident in the puerperium	82	0.0			1	1	1
9696	G604.00	subarachnoid haemorrhage from posterior communicating artery	80	0.0				1	1
34758	G641.11	Cerebral embolus	75	0.0	1	1	1	1	1
56458	8HHM.00	Ref to multidisciplinary stroke function improvement service	73	0.0			1	1	1
100639	1M4..00	Central post-stroke pain	70	0.0				1	1
93459	Fyu5600	[x]other lacunar syndromes	63	0.0				1	1
41910	G605.00	subarachnoid haemorrhage from basilar artery	60	0.0				1	1
73901	Gyu6.00	[x]cerebrovascular diseases	45	0.0				1	1
55602	G677300	occlusion and stenosis of cerebellar arteries	42	0.0				1	1
71585	G63z.00	precerebral artery occlusion nos	42	0.0				1	1
105100	662M100	stroke 6 month review	40	0.0				1	1
57495	G63..11	infarction - precerebral	39	0.0				1	1
94482	Gyu6G00	[X]Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	39	0.0	1	1	1	1	1
47642	G64z100	Wallenberg syndrome	38	0.0	1	1	1	1	1
30045	G616.00	External capsule haemorrhage	36	0.0	1	1	1	1	1
44740	G680.00	sequelae of subarachnoid haemorrhage	36	0.0				1	1
51326	G63y.00	other precerebral artery occlusion	35	0.0				1	1
53810	Gyu6200	[X]Other intracerebral haemorrhage	35	0.0	1		1	1	1
57315	G618.00	Intracerebral haemorrhage, multiple localized	35	0.0	1	1	1	1	1
92036	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries	35	0.0	1	1	1	1	1
48149	G681.00	sequelae of intracerebral haemorrhage	34	0.0				1	1

107886	662e.11	stroke annual review	22	0.0				1	1
104505	662M200	stroke initial post discharge review	20	0.0				1	1
57527	G677100	occlusion and stenosis of anterior cerebral artery	16	0.0				1	1
90572	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries	16	0.0	1	1	1	1	1
62342	G615.00	Bulbar haemorrhage	14	0.0	1	1	1	1	1
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified	13	0.0	1	1		1	1
60692	G606.00	subarachnoid haemorrhage from vertebral artery	12	0.0				1	1
65745	Gyu6100	[x]other subarachnoid haemorrhage	12	0.0				1	1
65770	G677200	occlusion and stenosis of posterior cerebral artery	12	0.0				1	1
56279	L440.12	stroke in the puerperium	11	0.0			1	1	1
70536	G671000	acute cerebrovascular insufficiency nos	11	0.0				1	1
56007	G601.00	subarachnoid haemorrhage from carotid siphon and bifurcation	9	0.0				1	1
107195	661M700	stroke self-management plan agreed	6	0.0				1	1
98642	G633.00	multiple and bilateral precerebral arterial occlusion	5	0.0				1	1
110337	Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction	4	0.0			1	1	1
71274	G677400	occlusion+stenosis of multiple and bilat cerebral arteries	3	0.0				1	1
104638	8IEC.00	ref multidisciplinary stroke function improvement declined	2	0.0				1	1
108630	Gyu6E00	[x]subarachnoid haemorrh from intracranial artery, unspecif	2	0.0				1	1
108668	Gyu6000	[x]subarachnoid haemorrhage from other intracranial arteries	2	0.0				1	1
109743	661N700	stroke self-management plan review	1	0.0				1	1
111096	Gyu6700	[x]other specified cerebrovascular diseases	1	0.0				1	1
			1,014,572	**100.0**					

Identification of HTN

List of medical codes (medcode) and Read codes (readcode) used to identify HTN and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of HTN [21], the code lists from the Cambridge Code List Index [319], the code list from Reeves et al. 2014 [321], the code list from Sinnott et al. 2017 [323], and/or having been found during a search of the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. The final codes to identify HTN are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Cambridge	Reeves	Sinnott	Included
4444	662..12	Hypertension monitoring	2,881,785	23.9				1	
799	G20..00	Essential hypertension	2,840,569	23.5	1	1	1	1	1
204	G2...00	Hypertensive disease	1,531,807	12.7	1	1	1	1	1
13186	662P.00	Hypertension monitoring	1,065,426	8.8				1	
31117	9OI4.00	Hypertens.monitor.1st letter	890,850	7.4				1	
19070	662d.00	Hypertension annual review	475,666	3.9				1	
351	G20..11	High blood pressure	225,911	1.9		1	1		1
31127	9OI5.00	Hypertens.monitor 2nd letter	223,815	1.9				1	
10818	G20z.00	Essential hypertension NOS	157,395	1.3	1	1	1	1	1
2666	14A2.00	H/O: hypertension	154,056	1.3				1	
18482	662c.00	Hypertension six month review	137,271	1.1				1	
4344	9N03.00	Seen in hypertension clinic	133,256	1.1				1	
10976	9h32.00	Excepted from hypertension qual indicators: Informed dissent	132,279	1.1				1	
11056	8BL0.00	Patient on maximal tolerated antihypertensive therapy	131,580	1.1				1	1
5215	9OI..00	Hypertension monitoring admin.	118,403	1.0				1	
31175	9OI6.00	Hypertens.monitor 3rd letter	99,395	0.8				1	
3712	G20z.11	Hypertension NOS	86,061	0.7	1	1	1	1	1
10961	9h31.00	Excepted from hypertension qual indicators: Patient unsuit	77,970	0.6				1	
16565	6627.00	Good hypertension control	67,064	0.6				1	
36305	9OIA.00	Hypertension monitor.chck done	64,561	0.5				1	
3425	662O.00	On treatment for hypertension	48,820	0.4				1	1
27511	6628.00	Poor hypertension control	43,608	0.4				1	1
7057	G2z..00	Hypertensive disease NOS	41,855	0.3	1	1	1	1	1
28874	9OI8.00	Hypertens.monitor phone invite	38,581	0.3				1	
45149	9OI1.00	Attends hypertension monitor.	38,059	0.3				1	
27634	9N1y200	Seen in hypertension clinic	36,054	0.3				1	
1894	G201.00	Benign essential hypertension	34,277	0.3	1	1	1	1	1
34281	9N4L.00	DNA - Did not attend hypertension clinic	28,222	0.2				1	
13188	662G.00	Hypertensive treatm.changed	27,164	0.2				1	1
10632	246M.00	White coat hypertension	25,185	0.2					
41634	9OI7.00	Hypertens.monitor verbal inv.	24,340	0.2				1	
8732	G2...11	BP - hypertensive disease	21,813	0.2	1			1	1

3269	2126100	Hypertension resolved	21,166	0.2			1		
4372	G202.00	Systolic hypertension	16,916	0.1	1	1	1	1	1
22356	1JD..00	Suspected hypertension	14,512	0.1					
28828	9OI3.00	Hyperten.monitor offer default	9,308	0.1				1	
19342	212K.00	Hypertension resolved	8,836	0.1					
24127	9OIA.11	Hypertension monitored	8,258	0.1				1	
27525	9OI..11	Hypertension clinic admin.	7,491	0.1				1	
34192	9OIZ.00	Hypertens.monitoring admin.NOS	6,734	0.1				1	
18057	8B26.00	Antihypertensive therapy	6,679	0.1				1	1
21826	662F.00	Hypertension treatm. started	6,225	0.1				1	1
8296	6624.00	Borderline hyperten:yearly obs	5,673	0.0				1	
34108	9h3..00	Exception reporting: hypertension quality indicators	5,131	0.0				1	
6702	F421300	Hypertensive retinopathy	5,042	0.0				1	
30776	6629.00	Hypertension:follow-up default	4,436	0.0				1	
18590	662b.00	Moderate hypertension control	3,979	0.0				1	1
16292	G21..00	Hypertensive heart disease	3,542	0.0				1	1
15377	G200.00	Malignant essential hypertension	3,324	0.0	1	1	1	1	1
7329	G24..00	Secondary hypertension	2,820	0.0	1	1	1	1	1
12948	662H.00	Hypertension treatm.stopped	2,693	0.0				1	
12680	8CR4.00	Hypertension clinical management plan	2,562	0.0				1	
105316	G25..11	Stage 1 hypertension	2,181	0.0	1				1
4668	G22..00	Hypertensive heart disease	1,902	0.0				1	1
105274	G28..00	Stage 2 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	1,655	0.0	1				1
18765	G2y..00	Other specified hypertensive disease	1,502	0.0	1	1	1	1	
8857	G21z011	Cardiomegaly - hypertensive	1,498	0.0				1	1
105371	G25..00	Stage 1 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	1,404	0.0	1				1
43220	9OI2.00	Refuses hypertension monitor.	652	0.0				1	
83473	G203.00	Diastolic hypertension	614	0.0	1	1	1	1	1
20497	TJC7z00	Adverse reaction to antihypertensives NOS	594	0.0				1	
29310	G22z.11	Renal hypertension	573	0.0				1	
3979	G672.00	Hypertensive encephalopathy	526	0.0				1	
21660	TJC7.00	Adverse reaction to other antihypertensives	525	0.0				1	
16059	G24z.00	Secondary hypertension NOS	470	0.0	1	1	1	1	1
16173	G21zz00	Hypertensive heart disease NOS	416	0.0				1	1
22333	8I3N.00	Hypertension treatment refused	393	0.0				1	
31341	G24z100	Hypertension secondary to drug	290	0.0		1	1	1	1
32976	6146200	Hypertension induced by oral contraceptive pill	274	0.0				1	
66645	9OI9.00	Hypertens.monitor deleted	270	0.0					
15106	G22z.00	Hypertensive renal disease NOS	266	0.0				1	
31387	G24z000	Secondary renovascular hypertension NOS	185	0.0	1	1	1	1	
34744	G244.00	Hypertension secondary to endocrine disorders	182	0.0	1	1	1	1	
105487	G26..11	Severe hypertension	174	0.0	1				1

42229	G24zz00	Secondary hypertension NOS	165	0.0	1	1	1	1	1
31816	G672.11	Hypertensive crisis	128	0.0				1	
39649	G220.00	Malignant hypertensive renal disease	123	0.0				1	
31464	G21z.00	Hypertensive heart disease NOS	121	0.0				1	1
69753	Gyu2.00	[X]Hypertensive diseases	114	0.0	1	1		1	1
108136	G250.00	Stage 1 hypertension (NICE 2011) without evidence of end organ damage	105	0.0	1				1
25371	G241000	Secondary benign renovascular hypertension	97	0.0		1	1	1	
31755	G240.00	Secondary malignant hypertension	82	0.0	1	1	1	1	1
32423	G222.00	Hypertensive renal disease with renal failure	82	0.0				1	
57288	G241.00	Secondary benign hypertension	77	0.0	1	1	1	1	1
61166	G21z000	Hypertensive heart disease NOS without CCF	73	0.0				1	1
62718	G21z100	Hypertensive heart disease NOS with CCF	72	0.0				1	1
63164	U60C500	[X]Oth antihyperten drug caus advers eff in therap use, NEC	57	0.0				1	
43664	L127.00	Pre-eclampsia or eclampsia with pre-existing hypertension	56	0.0				1	
44350	U60C51A	[X] Adverse reaction to antihypertensives NOS	52	0.0				1	
30770	U60C511	[X] Adverse reaction to other antihypertensives	50	0.0				1	
37086	F404200	Blind hypertensive eye	50	0.0				1	
51635	G241z00	Secondary benign hypertension NOS	50	0.0	1	1	1	1	1
28684	G233.00	Hypertensive heart and renal disease with renal failure	48	0.0				1	
43935	G221.00	Benign hypertensive renal disease	46	0.0				1	
105989	G26..00	Severe hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	45	0.0	1				1
63466	G23..00	Hypertensive heart and renal disease	39	0.0				1	
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure	31	0.0				1	
52427	G211.00	Benign hypertensive heart disease	31	0.0				1	
52621	L128200	Pre-exist 2ndry hypertens comp preg childbth and puerperium	31	0.0				1	
50157	G210.00	Malignant hypertensive heart disease	28	0.0				1	
52127	G211100	Benign hypertensive heart disease with CCF	24	0.0				1	
44549	L128.00	Pre-exist hypertension compl preg childbirth and puerperium	19	0.0				1	
59383	G240000	Secondary benign renovascular hypertension	12	0.0		1	1	1	
61660	G211000	Benign hypertensive heart disease without CCF	12	0.0				1	
66567	L122.00	Other pre-existing hypertension in preg/childbirth/puerp	12	0.0				1	
109797	G251.00	Stage 1 hypertension (NICE 2011) with evidence of end organ damage	11	0.0	1				1
67232	G230.00	Malignant hypertensive heart and renal disease	9	0.0				1	
57987	G234.00	Hyperten heart&renal dis +both(congestv)heart and fail	8	0.0				1	
68659	G23z.00	Hypertensive heart and renal disease NOS	8	0.0				1	
62432	L122z00	Other pre-existing hypertension in preg/childb/puerp NOS	7	0.0				1	
73293	G240z00	Secondary malignant hypertension NOS	7	0.0	1	1	1	1	1
73586	L122000	Other pre-existing hypertension in preg/childb/puerp unspec	7	0.0				1	
95359	662r.00	Trial withdrawal of antihypertensive therapy	7	0.0				1	
97533	Gyu2100	[X]Hypertension secondary to other renal disorders	6	0.0				1	
72668	G210100	Malignant hypertensive heart disease with CCF	5	0.0				1	
63000	G231.00	Benign hypertensive heart and renal disease	4	0.0				1	

85944	7Q01.00	High cost hypertension drugs	4	0.0				1	
93055	L127z00	Pre-eclampsia or eclampsia + pre-existing hypertension NOS	4	0.0				1	
102458	Gyu2000	[X]Other secondary hypertension	4	0.0	1	1			1
72030	L122100	Other pre-existing hypertension in preg/childb/puerp - deliv	3	0.0				1	
95334	G210000	Malignant hypertensive heart disease without CCF	2	0.0				1	
60655	L128000	Pre-exist hyperten heart dis compl preg childbth+puerperium	1	0.0				1	
96743	L122300	Other pre-exist hypertension in preg/childb/puerp-not deliv	1	0.0				1	
			12,067,001	**100**					

Identification of CKD

List of medical codes (medcode) and Read codes (readcode) used to identify CKD and their descriptions are listed in the table below. Codes are identified as being used in the QOF definition of CKD [21], the code lists from the Cambridge Code List Index [319], the code list from Kontopanelis et al. 2012 [322], and/or having been found during a search of the CPRD Code Browser at the time of cohort definition in 2018. The number of clinical events recording the code within the CPRD database in February 2018 are listed along with the percentage of clinical events represented by each code. Codes identifying nephrotic syndrome, CKD stage 1-2, and CKD stage 3-4 are identified. The final codes to identify CKD are identified in the far right column by a '1'.

medcode	readcode	description	clinical events	% clinical events	QOF	Nephrotic	Stage 3-4	Stage 1-2	Kontopantelis	Included
12566	1Z12.00	Chronic kidney disease stage 3	457,678	41.4	1		1		1	1
30739	9Ot0.00	Chronic kidney disease monitoring first letter	116,932	10.6						
95394	1Z11.00	Chronic kidney disease stage 2	95,394	8.6	1			1		1
512	K05..00	Chronic renal failure	63,175	5.7					1	1
30735	6AA..00	Chronic kidney disease annual review	62,090	5.6						
12479	1Z13.00	Chronic kidney disease stage 4	50,972	4.6	1		1		1	1
350	K06..00	Renal failure unspecified	39,293	3.6						
72962	9Ot1.00	Chronic kidney disease monitoring second letter	23,083	2.1						
29013	1Z10.00	Chronic kidney disease stage 1	22,857	2.1	1			1		1
94965	1Z15.00	Chronic kidney disease stage 3A	20,683	1.9	1		1			1
104619	K01..00	Nephrotic syndrome	15,773	1.4		1				1
95175	K053.00	Chronic kidney disease stage 3	14,189	1.3	1		1			1
95123	1Z1E.00	Chronic kidney disease stage 3A without proteinuria	12,378	1.1	1		1			1
12585	1Z1C.00	Chronic kidney disease stage 3 without proteinuria	11,196	1.0	1		1			1
72964	1Z14.00	Chronic kidney disease stage 5	10,148	0.9	1		1		1	1
95179	9Ot2.00	Chronic kidney disease monitoring third letter	8,437	0.8						
4503	1Z16.00	Chronic kidney disease stage 3B	7,843	0.7	1		1			1
2996	PD11.00	Polycystic kidney disease	7,086	0.6						
71271	7L1A200	Haemodialysis NEC	6,143	0.6						1
95177	9Ot..00	Chronic kidney disease monitoring administration	5,798	0.5						
6712	1Z1G.00	Chronic kidney disease stage 3B without proteinuria	4,654	0.4	1		1			1
69679	K050.00	End stage renal failure	4,119	0.4						1
11773	9Ot4.00	Chronic kidney disease monitoring telephone invite	3,706	0.3						
2994	7L1A.11	Dialysis for renal failure	3,194	0.3						1
94793	K0z..00	Nephritis, nephrosis and nephrotic syndrome NOS	3,057	0.3		1				1
95121	7L1A100	Peritoneal dialysis	2,989	0.3						1
20196	1Z1B.00	Chronic kidney disease stage 3 with proteinuria	2,911	0.3	1		1			1
95408	1Z1A.00	Chronic kidney disease stage 2 without proteinuria	2,466	0.2	1			1		1
88494	14V2.00	h/o: renal dialysis	2,090	0.2						
20073	1Z1D.00	Chronic kidney disease stage 3A with proteinuria	1,762	0.2	1		1			1

95406	9Ot3.00	Chronic kidney disease monitoring verbal invite	1,637	0.1						
95178	7L1A000	Renal dialysis	1,632	0.1						1
95122	1Z1J.00	Chronic kidney disease stage 4 without proteinuria	1,617	0.1	1		1			1
104963	K0...00	Nephritis, nephrosis and nephrotic syndrome	1,440	0.1		1				1
15917	1Z1F.00	Chronic kidney disease stage 3B with proteinuria	1,364	0.1	1		1			1
3927	1Z1H.00	Chronic kidney disease stage 4 with proteinuria	1,321	0.1	1		1			1
8037	K054.00	Chronic kidney disease stage 4	1,256	0.1	1		1			1
25394	PD1..00	Congenital cystic kidney disease	777	0.1						
20629	7L1B000	Insertion of ambulatory peritoneal dialysis catheter	698	0.1						
109804	D215000	Anaemia secondary to chronic renal failure	677	0.1					1	
8330	1Z19.00	Chronic kidney disease stage 2 with proteinuria	537	0.0	1			1		1
105383	K011.00	Nephrotic syndrome with membranous glomerulonephritis	537	0.0		1				1
60302	PD1..11	Congenital cystic renal disease	496	0.0						
61930	1Z1T.00	CKD G3aA1 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A1	494	0.0	1		1			1
95508	K0D..00	End-stage renal disease	452	0.0						1
105151	K052.00	Chronic kidney disease stage 2	428	0.0	1			1		1
22252	7A60600	Creation of graft fistual for dialysis	409	0.0						
95572	Kyu2.00	[X]Renal failure	386	0.0						
56852	1Z1K.00	Chronic kidney disease stage 5 with proteinuria	374	0.0	1		1			1
109963	K055.00	Chronic kidney disease stage 5	344	0.0	1		1			1
95188	ZV45100	[V]Renal dialysis status	337	0.0						
13736	K01z.00	Nephrotic syndrome NOS	309	0.0		1				1
53852	K01x100	Nephrotic syndrome in diabetes mellitus	292	0.0		1				1
5475	1Z18.00	Chronic kidney disease stage 1 without proteinuria	263	0.0	1			1		1
64828	PD11z00	Polycystic kidney disease NOS	228	0.0						
95405	K015.00	Nephrotic syndrome, focal and segmental glomerular lesions	218	0.0		1				1
109805	1Z1X.00	CKD G3bA1 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A1	197	0.0	1		1			1
95176	1z1C.11	CKD stage 3 without proteinuria	188	0.0	1		1			1
109657	K013.00	Nephrotic syndrome with minimal change glomerulonephritis	184	0.0		1				1
46438	K05..12	End stage renal failure	183	0.0						1
99312	7261011	Cyclodialysis	169	0.0						
110269	7L1A600	Peritoneal dialysis NEC	168	0.0						1
95145	K016.00	Nephrotic syndrome, diffuse membranous glomerulonephritis	155	0.0		1				1
31277	1Z1L.00	Chronic kidney disease stage 5 without proteinuria	152	0.0	1		1			1
105143	1Z1V.00	CKD G3aA2 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A2	150	0.0	1		1			1
59315	1Z1E.11	CKD stage 3A without proteinuria	139	0.0	1		1			1
44422	1Z17.00	Chronic kidney disease stage 1 with proteinuria	138	0.0	1			1		1
97587	K017.00	Nephrotic syn difus mesangial prolifertiv glomerulonephritis	130	0.0		1				1

110108	1Z1Y.00	CKD G3bA2 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A2	110	0.0	1		1			1
109980	SP05613	[X] Peritoneal diaysis associated peritonitis	108	0.0						
100633	1Z1H.11	CKD stage 4 with proteinuria	92	0.0	1		1			1
95180	K013.12	Steroid sensitive nephrotic syndrome	88	0.0		1				1
97978	1Z1Q.00	CKD G2A1 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A1	87	0.0	1			1		1
109904	K01x000	Nephrotic syndrome in amyloidosis	82	0.0		1				
36442	1z1B.11	CKD stage 3 with proteinuria	75	0.0	1		1			1
95422	K019.00	Nephrotic syn,diffuse mesangiocapillary glomerulonephritis	73	0.0		1				1
109990	K014.00	Nephrotic syndrome, minor glomerular abnormality	68	0.0		1				1
95571	PD11111	Autosomal dominant polycystic kidney disease	66	0.0						
69760	SP07G00	Stenosis of arteriovenous dialysis fistula	63	0.0						
105392	K01x400	Nephrotic syndrome in systemic lupus erythematosus	59	0.0		1				
88597	14V2.11	h/o: kidney dialysis	56	0.0						
26903	1Z1J.11	CKD stage 4 without proteinuria	54	0.0	1		1			1
97979	K01B.00	Nephrotic syndrome, diffuse crescentic glomerulonephritis	52	0.0		1				1
99160	1Z1R.00	CKD G2A2 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A2	44	0.0	1			1		1
60446	1Z1a.00	CKD G4A1 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A1	43	0.0	1		1			1
110626	1Z1G.11	CKD stage 3B without proteinuria	43	0.0	1		1			1
46145	K0y..00	Other specified nephritis, nephrosis or nephrotic syndrome	39	0.0		1				1
96347	1Z1F.11	CKD stage 3B with proteinuria	36	0.0	1		1			1
53940	1Z1A.11	CKD stage 2 without proteinuria	36	0.0	1			1		1
97683	1Z1b.00	CKD G4A2 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A2	35	0.0	1		1			1
106720	7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail	35	0.0						
60743	9Ni9.00	Did not attend chronic kidney disease monitoring clinic	33	0.0						
110467	1Z1W.00	CKD G3aA3 - chronic kidney disease with glomerular filtration rate category G3a and albuminuria category A3	30	0.0	1		1			1
105919	1Z1Z.00	CKD G3bA3 - chronic kidney disease with glomerular filtration rate category G3b and albuminuria category A3	29	0.0	1		1			1
110033	1Z1D.11	CKD stage 3A with proteinuria	26	0.0	1		1			1
72336	ZVu3G00	[X]Other dialysis	26	0.0						
63502	K051.00	Chronic kidney disease stage 1	24	0.0	1			1		1
59031	7L1A400	Automated peritoneal dialysis	24	0.0						
110003	K01w.00	Congenital nephrotic syndrome	24	0.0		1				
110251	1Z19.11	CKD stage 2 with proteinuria	22	0.0	1			1		1
107188	1Z1K.11	CKD stage 5 with proteinuria	19	0.0	1		1			1
66714	Z919.00	Care of haemodialysis equipment	19	0.0						
97980	K010.00	Nephrotic syndrome with proliferative glomerulonephritis	18	0.0		1				1

104719	1Z1c.00	CKD G4A3 - chronic kidney disease with glomerular filtration rate category G4 and albuminuria category A3	17	0.0	1		1			1
60498	ZV56011	[V]Aftercare involving renal dialysis NOS	17	0.0						
45160	7A61900	Ligation of arteriovenous dialysis fistula	16	0.0						
106860	Kyu2100	[X]Other chronic renal failure	16	0.0					1	
107082	1Z1L.11	CKD stage 5 without proteinuria	14	0.0	1		1			1
106975	Gy21.00	Thrombosis of dialysis arteriovenous fistula	13	0.0						
59018	ZV56.00	[V]Aftercare involving intermittent dialysis	13	0.0						
109884	K01A.00	Nephrotic syndrome, dense deposit disease	11	0.0		1				1
101912	1Z1f.00	CKD G5A3 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A3	10	0.0	1		1			1
110133	PD11011	Autosomal recessive polycystic kidney disease	10	0.0						
101756	1Z1M.00	CKD G1A1 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A1	9	0.0	1			1		1
109809	Z919100	Priming haemodialysis lines	9	0.0						
107260	Z91A.00	Peritoneal dialysis bag procedure	9	0.0						
107900	K0A0700	Acute nephrotic syndrm diffuse crescentic glomerulonephritis	9	0.0		1				
108785	PD1yz00	Other congenital cystic kidney disease NOS	8	0.0						
69266	1Z1N.00	CKD G1A2 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A2	7	0.0	1			1		
109981	SP06B00	Continuous ambulatory peritoneal dialysis associated perit	7	0.0						
110484	K01x300	Nephrotic syndrome in polyarteritis nodosa	7	0.0		1				
62062	1Z1S.00	CKD G2A3 - chronic kidney disease with glomerular filtration rate category G2 and albuminuria category A3	6	0.0	1			1		
104586	G72D.00	Aneurysm of dialysis arteriovenous fistula	6	0.0						
107746	TB11.11	Renal dialysis with complication, without blame	6	0.0						
108699	1Z17.11	CKD stage 1 with proteinuria	5	0.0	1			1		1
108116	Z1A1.00	Peritoneal dialysis training	5	0.0						
108213	Z919300	Reversing haemodialysis lines	5	0.0						
111103	ZV56y11	[V]Aftercare involving peritoneal dialysis	5	0.0						
110072	K018.00	Nephrotic syn,difus endocapilary proliftv glomerulonephritis	5	0.0		1				
63038	C353600	Renal failure-associated hyperphosphataemia	4	0.0						
111022	Gy31.00	Occlusion of dialysis arteriovenous fistula	4	0.0						
35545	Gy51.00	Haemorrhage of dialysis arteriovenous fistula	4	0.0						
42345	PD1y.00	Other specified congenital cystic kidney disease	4	0.0						
107719	SP0H.00	Disorder associated with dialysis	4	0.0						
110095	Z1A..00	Dialysis training	4	0.0						
109135	K01y.00	Nephrotic syndrome with other pathological kidney lesions	4	0.0		1				
110051	K012.00	Nephrotic syndrome + membranoproliferative glomerulonephritis	4	0.0		1				
108759	1Z1d.00	CKD G5A1 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A1	3	0.0	1		1			
108423	7L1A011	Thomas intravascular shunt for dialysis	3	0.0						

109945	Gy2..00	Thrombosis of dialysis vascular access	3	0.0						
110976	Gy41.00	Infection of dialysis arteriovenous fistula	3	0.0						
45096	SP0E.00	Disorders associated with peritoneal dialysis	3	0.0						
98888	SP0F.00	Haemodialysis first use syndrome	3	0.0						
101736	TA22000	Failure of sterile precautions during kidney dialysis	3	0.0						
2999	1Z1e.00	CKD G5A2 - chronic kidney disease with glomerular filtration rate category G5 and albuminuria category A2	2	0.0	1		1			
15780	1Z1P.00	CKD G1A3 - chronic kidney disease with glomerular filtration rate category G1 and albuminuria category A3	2	0.0	1			1		
1803	7L1B200	Flushing of peritoneal dialysis catheter	2	0.0						
27427	Gy1..00	Stenosis of dialysis vascular access	2	0.0						
2471	Gy10.00	Stenosis of dialysis arteriovenous graft	2	0.0						
22852	Gy3..00	Occlusion of dialysis vascular access	2	0.0						
29634	Gy40.00	Infection of dialysis arteriovenous graft	2	0.0						
19316	SP0E100	Thrombus in peritoneal dialysis catheter	2	0.0						
21947	Z919200	Washing back through haemodialysis lines	2	0.0						
57926	ZV56z00	[V]Unspecified aftercare involving intermittent dialysis	2	0.0						
47922	K01x.00	Nephrotic syndrome in diseases EC	2	0.0		1				
21989	K01w200	Congenital nephrotic syndrome with focal glomerulosclerosis	2	0.0		1				
23913	1Z18.11	CKD stage 1 without proteinuria	1	0.0	1			1		
49150	7A61A00	Ligation of arteriovenous dialysis graft	1	0.0						
63786	G72D000	Aneurysm of superficialised artery of dialysis AV fistula	1	0.0						
9840	Gy30.00	Occlusion of dialysis arteriovenous graft	1	0.0						
56987	Gy4..00	Infection of dialysis vascular access	1	0.0						
61814	Gy5..00	Haemorrhage of dialysis vascular access	1	0.0						
58750	Gy60.00	Rupture of dialysis arteriovenous graft	1	0.0						
50472	K0A1400	Rapid progres neph syn df endocapilary prolifv glomnephritis	1	0.0						
94373	Z1A1.11	PD - Peritoneal dialysis training	1	0.0						
99644	K01x200	Nephrotic syndrome in malaria	1	0.0		1				
108816	K01w112	Wilms' tumour + nephrotic syndrome + pseudohermaphroditism	1	0.0		1				
110749	K01wz00	Congenital nephrotic syndrome NOS	1	0.0		1				
108922	4I29.00	peritoneal dialysis sample	-	0.0						
111370	4N0.00	Dialysis fluid urea level	-	0.0						
			1,104,644	**100.0**						

Appendix IV: Supplementary material to Chapter IV

	All HF Types	Left-Sided HF	Right-Sided HF	Biventricular HF	Unspecified HF
Number of Patients (N)	8,935	3,598	867	128	4,342
% of COPD patients (N = 181,519)	4.9	2.0	0.48	0.07	2.4
Female	3,480 (39.0)	1,231 (34.2)	401 (46.3)	39 (30.5)	1,809 (41.7)
Age at COPD Diagnosis, years Median (interquartile range)	69.4 (61.5, 76.4)	68.4 (61.1, 75.4)	63.9 (57.2, 72.5)	67.7 (58.5, 74.7)	71.2 (63.1, 77.7)
Age at HF Diagnosis, years Median (interquartile range)	76.1 (69.0, 82.2)	74.9 (68.0, 81.1)	72.9 (65.6, 80.0)	73.6 (67.1, 81.5)	77.9 (70.9, 83.6)
Smoking Status					
Current Smoker	3,007 (33.7)	1,227 (34.1)	389 (44.9)	48 (37.5)	1,343 (30.9)
Former Smoker	5,928 (66.4)	2,371 (65.9)	478 (55.1)	80 (62.5)	2,999 (69.1)
Body Mass Index					
Underweight (< 18.5)	290 (3.3)	103 (2.9)	56 (6.5)	< 5	128 (3.0)
Healthy Weight (18.5-24.9)	2,403 (26.9)	994 (27.6)	266 (30.7)	26 (20.3)	1,117 (25.7)
Overweight (25.0-29.9)	2,869 (32.1)	1,224 (34.0)	226 (26.1)	42 (32.8)	1,377 (31.7)
Obese (>= 30)	3,131 (35.0)	1,210 (33.6)	289 (33.3)	53 (41.4)	1,579 (36.4)
Missing Data	242 (2.71)	67 (1.9)	30 (3.46)	< 5	141 (3.25)
GOLD Stage					
1: Mild	3,172 (35.5)	1,316 (36.6)	252 (29.1)	37 (28.9)	1,567 (36.1)
2: Moderate	1,819 (21.0)	816 (22.7)	141 (16.3)	25 (19.5)	837 (19.3)
3: Severe	1,231 (13.8)	449 (12.5)	172 (19.8)	26 (20.3)	584 (13.5)
4: Very Severe	285 (3.2)	82 (2.3)	80 (9.2)	8 (6.3)	115 (2.7)
Missing	2,428 (27.2)	935 (26.0)	222 (25.6)	32 (25.0)	1,239 (28.5)
HF Risk Factors‡					
Atrial Fibrillation	1,218 (13.6)	420 (11.7)	75 (8.7)	23 (18.0)	700 (16.1)
Diabetes	1,653 (18.5)	621 (17.3)	112 (12.9)	23 (18.0)	897 (20.7)
Hypertension	4,461 (49.9)	1,714 (47.6)	343 (39.6)	61 (47.7)	2,343 (54.0)
Ischaemic Heart Disease	27,241 (15.8)	1,293 (35.9)	161 (18.6)	39 (30.5)	1,443 (33.2)
Peripheral Artery Disease	909 (10.2)	395 (11.0)	53 (6.1)	6 (4.7)	455 (10.5)
Stroke	805 (9.01)	310 (8.6)	43 (5.0)	11 (8.6)	441 (10.2)

Supplementary Table 4.1. Descriptive statistics for the chronic obstructive pulmonary disease (COPD) cohort by type of heart failure (HF). Interquartile range (IQR). Not significant (NS). Global Initiative for Chronic Obstructive Lung Diseases (GOLD) staging of COPD severity [1]. ‡Recorded at start of follow-up; patients could have multiple risk factors.

	Incident HF in 2006 n (%)	No Incident HF in 2006 n (%)
Number of Patients (N)	418	40,057
% of COPD patients	1.03	99.0
Female	177 (42.3)	18,191 (45.4)
Age at COPD Diagnosis, years Median (interquartile range)	69.4 (62.0-77.0)	64.6 (57.0-72.6)
Age at HF Diagnosis, years Median (interquartile range)	75.4 (68.0-81.6)	~
Number of Deaths*	354 (84.7)	22,860 (57.1)
Age at Death, years* Median (interquartile range)	80.4 (72.8-85.6)	79.5 (72.6-85.4)
Smoking Status		
Current Smoker	107 (25.6)	15,252 (38.1)
Former Smoker	311 (74.4)	24,805 (61.9)
Body Mass Index		
Underweight (< 18.5)	22 (5.60)	2,246 (5.61)
Healthy Weight (18.5-24.9)	137 (32.8)	14,061 (35.1)
Overweight (25.0-29.9)	104 (24.9)	12,539 (31.3)
Obese (>= 30)	133 (31.8)	9,729 (24.3)
Missing Data	22 (5.26)	1,482 (3.70)
GOLD Stage		
1-2: Mild-Moderate	194 (46.4)	22,667 (56.6)
3-4: Severe-Very Severe	101 (24.2)	7,659 (19.2)
Missing Data	123 (29.4)	9,731 (24.3)
HF Risk Factors‡		
Atrial Fibrillation	57 (13.6)	2,191 (5.47)
Diabetes	81 (19.4)	4,124 (10.3)
Hypertension	200 (47.9)	20,343 (50.8)
Ischaemic Heart Disease	151 (36.1)	7,167 (17.9)
Peripheral Artery Disease	40 (9.57)	2,743 (6.85)
Stroke	38 (9.09)	2,777 (6.93)

Supplementary Table 4.2. Descriptive statistics for the chronic obstructive pulmonary disease (COPD) cohort with and without incident heart failure (HF) in 2006. Presented for the chronic obstructive pulmonary disease (COPD) with incident heart failure (HF) during 2006 and those without incident HF during 2006. Interquartile range (IQR). Not significant (NS). Global Initiative for Chronic Obstructive Lung Diseases (GOLD) staging of COPD severity [1]. *Number and age at death for those patients who died at any time during the study period from 01/01/2006 to 31/12/2016. ‡Recorded at start of follow-up; patients could have multiple risk factors.

	Incident HF in 2011 n (%)	No Incident HF in 2011 n (%)
Number of Patients (N)	494	51,528
% of COPD patients	0.95	99.1
Female	188 (38.1)	24,199 (47.0)
Age at COPD Diagnosis, years Median (interquartile range)	68.9 (61.2-76.6)	63.9 (56.3-71.8)
Age at HF Diagnosis, years Median (interquartile range)	76.1 (68.8-82.0)	~
Number of Deaths*	317 (64.2)	16,847 (32.7)
Age at Death, years* Median (interquartile range)	79.9 (72.9-85.6)	79.5 (72.1-85.8)
Smoking Status		
Current Smoker	151 (30.6)	22,083 (42.9)
Former Smoker	343 (69.4)	29,445 (57.1)
Body Mass Index		
Underweight (< 18.5)	13 (2.63)	1,937 (3.76)
Healthy Weight (18.5-24.9)	115 (23.3)	16,917 (32.8)
Overweight (25.0-29.9)	165 (33.4)	16,933 (32.9)
Obese (>= 30)	191 (38.7)	14,868 (28.9)
Missing Data	10 (2.02)	873 (1.69)
GOLD Stage		
1-2: Mild-Moderate	307 (62.2)	33,710 (65.4)
3-4: Severe-Very Severe	87 (17.6)	7,032 (13.7)
Missing Data	100 (20.9)	10,786 (20.9)
HF Risk Factors‡		
Atrial Fibrillation	54 (10.9)	2,188 (4.25)
Diabetes	94 (19.0)	5,388 (10.5)
Hypertension	264 (53.4)	26,064 (50.6)
Ischaemic Heart Disease	147 (29.8)	7,695 (14.9)
Peripheral Artery Disease	47 (9.51)	2,658 (5.16)
Stroke	40 (8.10)	2,840 (5.51)

Supplementary Table 4.3. Descriptive statistics for the chronic obstructive pulmonary disease (COPD) cohort with and without incident heart failure (HF) in 2011. Presented for the chronic obstructive pulmonary disease (COPD) with incident heart failure (HF) during 2011 and those without incident HF during 2011. Interquartile range (IQR). Not significant (NS). Global Initiative for Chronic Obstructive Lung Diseases (GOLD) staging of COPD severity [1]. *Number and age at death for those patients who died at any time during the study period from 01/01/2011 to 31/12/2016. ‡Recorded at start of follow-up; patients could have multiple risk factors.

	Incident HF in 2015 n (%)	No Incident HF in 2015 n (%)
Number of Patients (N)	347	37,105
% of COPD patients	0.93	99.1
Female	126 (36.3)	17,616 (47.5)
Age at COPD Diagnosis, years Median (interquartile range)	70.0 (61.5-76.4)	63.4 (55.5-71.0)
Age at HF Diagnosis, years Median (interquartile range)	76.7 (69.5-83.1)	~
Number of Deaths**	94 (27.1)	4,186 (11.3)
Age at Death, years Median (interquartile range)**	80.4 (73.1-85.0)	79.1 (71.6-85.8)
Smoking Status		
Current Smoker	121 (34.9)	16,658 (44.9)
Former Smoker	226 (65.1)	20,447 (55.1)
Body Mass Index		
Underweight (< 18.5)	6 (1.73)	1,311 (3.53)
Healthy Weight (18.5-24.9)	88 (25.4)	11,708 (31.6)
Overweight (25.0-29.9)	111 (32.0)	12,294 (33.1)
Obese (>= 30)	134 (38.6)	11,232 (30.3)
Missing Data	8 (2.31)	560 (1.51)
GOLD Stage		
1-2: Mild-Moderate	216 (62.3)	25,122 (67.7)
3-4: Severe-Very Severe	43 (12.4)	3,485 (9.39)
Missing Data	88 (25.4)	8,498 (22.9)
HF Risk Factors‡		
Atrial Fibrillation	43 (12.4)	1,460 (3.93)
Diabetes	71 (20.5)	4,225 (11.4)
Hypertension	179 (51.6)	17,910 (48.3)
Ischaemic Heart Disease	110 (31.7)	4,721 (12.7)
Peripheral Artery Disease	31 (8.93)	1,642 (4.43)
Stroke	26 (7.49)	1,900 (5.12)

Supplementary Table 4.4. Descriptive statistics for the chronic obstructive pulmonary disease (COPD) cohort with and without incident heart failure (HF) in 2015. Presented for the chronic obstructive pulmonary disease (COPD) with incident heart failure (HF) during 2015 and those without incident HF during 2015. Interquartile range (IQR). Not significant (NS). Global Initiative for Chronic Obstructive Lung Diseases (GOLD) staging of COPD severity [1]. *Number and age at death for those patients who died at any time during the study period from 01/01/2015 to 31/12/2016. ‡Recorded at start of follow-up; patients could have multiple risk factors.

Appendix V: Supplementary material to Chapter V

	COPD patients without evidence of HF	COPD patients with diagnosed HF
Number of Patients (N)	4,132	2,066
Female	1,486 (36.0)	743 (36.0)
Age, years (IQR)	71 (64, 78)	74 (67, 81)
Smoking Status		
Current Smoker	1,411 (34.2)	497 (24.1)
Former Smoker	2,721 (65.9)	1,569 (75.9)
Body Mass Index		
Underweight (< 18.5)	200 (4.84)	113 (5.47)
Healthy Weight (18.5-24.9)	1,521 (36.8)	640 (31.0)
Overweight (25.0-29.9)	1,415 (34.2)	595 (28.8)
Obese (>= 30)	910 (22.0)	667 (32.3)
Missing Data	86 (2.08)	51 (2.47)
Index of Multiple Deprivation		
1 – Most deprived	695 (16.8)	268 (13.0)
2	856 (20.7)	403 (19.5)
3	826 (20.0)	406 (19.7)
4	909 (22.0)	473 (22.9)
5 – Least deprived	846 (20.5)	516 (25.0)
GOLD Stage		
1: Mild	1,577 (38.2)	703 (34.0)
2: Moderate	1,122 (27.2)	486 (23.5)
3: Severe	605 (14.6)	426 (20.6)
4: Very Severe	112 (2.71)	166 (8.03)
Missing	716 (17.3)	285 (13.8)

	COPD patients without evidence of HF	COPD patients with diagnosed HF
Exacerbation History*	1 (0, 2)	2 (1, 4)
COPD medications†		
SABA/SAMA	2,600 (62.9)	1,489 (72.1)
LABA alone	106 (2.57)	31 (1.50)
LAMA alone	256 (6.20)	163 (7.89)
ICS alone	532 (12.9)	92 (4.45)
LABA+LAMA	35 (0.85)	29 (1.40)
LABA+ICS	1,077 (26.1)	476 (23.0)
LAMA+ICS	78 (1.89)	27 (1.31)
Triple	578 (14.0)	823 (39.8)
No long-acting inhaler	1,470 (35.6)	425 (20.6)
History of Cardiovascular Disease‡	2,288 (55.4)	1,687 (81.7)
Atrial fibrillation	172 (4.16)	671 (32.5)
Hypertension	1,935 (46.8)	1,033 (50.0)
Ischaemic heart disease	610 (14.8)	838 (40.6)
Peripheral artery disease	210 (5.08)	222 (10.8)
Stroke	229 (5.54)	231 (11.2)
CVD medications†		
ACEi	697 (16.9)	1,230 (59.5)
ARB	262 (6.34)	332 (16.1)
Beta-blockers	293 (7.09)	737 (35.7)
Calcium channel blockers	397 (9.61)	329 (15.9)
MRA	10 (0.24)	479 (23.2)
Statins	1,215 (29.4)	1,152 (55.8)
Vasodilators	254 (6.15)	320 (15.5)

Supplementary Table 5.1. Descriptive statistics for the matched cohort of chronic obstructive pulmonary disease (COPD) patients without evidence of heart failure (HF) and COPD patients with diagnosed HF. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). *Average number of exacerbations per patient (range) in the year prior to the start of follow-up. †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	COPD patients without evidence of HF	COPD patients with possible HF	p-value*
Number of Patients (N)	16,792	8,423	
Female	8,365 (49.8)	4,206 (49.9)	NS
Age, years (IQR)	73 (65, 80)	73 (66, 80)	NS
Smoking Status			
Current Smoker	5,872 (35.0)	2,561 (30.4)	< 0.0001
Former Smoker	10,920 (65.0)	5,862 (69.6)	
Body Mass Index			
Underweight (< 18.5)	1,005 (5.98)	351 (4.17)	
Healthy Weight (18.5-24.9)	6,448 (38.4)	2,231 (26.5)	
Overweight (25.0-29.9)	5,458 (32.5)	2,323 (27.6)	< 0.0001
Obese (>= 30)	3,353 (20.0)	3,180 (37.8)	
Missing Data	528 (3.14)	338 (4.01)	
Index of Multiple Deprivation			
1 – Most deprived	2,699 (16.1)	1,123 (13.4)	
2	3,491 (20.8)	1,707 (20.3)	
3	3,310 (19.7)	1,602 (19.0)	< 0.0001
4	3,759 (22.4)	1,964 (23.3)	
5 – Least deprived	3,533 (21.0)	2,021 (24.0)	
GOLD Stage			
1: Mild	6,208 (37.0)	2,985 (35.4)	
2: Moderate	4,347 (25.9)	1,753 (20.8)	
3: Severe	2,383 (14.2)	1,447 (17.2)	< 0.0001
4: Very Severe	503 (3.00)	401 (4.76)	
Missing	3,351 (20.0)	1,837 (21.8)	

	COPD patients without evidence of HF	COPD patients with possible HF	p-value*
Exacerbation History**	1 (0, 2)	2 (0, 3)	< 0.0001
COPD medications†			
SABA/SAMA	10,834 (64.5)	6,194 (73.5)	< 0.0001
LABA alone	454 (2.70)	250 (2.97)	NS
LAMA alone	1,068 (6.36)	535 (6.35)	NS
ICS alone	2,115 (12.6)	939 (11.2)	0.001
LABA+LAMA	129 (0.77)	80 (0.95)	NS
LABA+ICS	4,421 (26.3)	2,423 (28.8)	< 0.0001
LAMA+ICS	373 (2.22)	205 (2.43)	NS
Triple	2,414 (14.4)	1,915 (22.7)	< 0.0001
No long-acting inhaler	5,818 (34.7)	2,076 (24.7)	< 0.0001
History of Cardiovascular Disease‡	9,353 (55.7)	6,485 (77.0)	< 0.0001
Atrial fibrillation	716 (4.26)	987 (11.7)	< 0.0001
Hypertension	7,818 (46.6)	5,444 (64.6)	< 0.0001
Ischaemic heart disease	2,381 (14.2)	2,218 (26.3)	< 0.0001
Peripheral artery disease	1,004 (5.98)	652 (7.74)	< 0.0001
Stroke	1,018 (6.06)	786 (9.33)	< 0.0001
CVD medications†			
ACEi	2,721 (16.2)	2,436 (28.9)	< 0.0001
ARB	1,053 (6.27)	896 (10.6)	< 0.0001
Beta-blockers	1,062 (6.32)	1,002 (11.9)	< 0.0001
Calcium channel blockers	1,770 (10.5)	1,462 (17.4)	< 0.0001
MRA	62 (0.37)	276 (3.28)	< 0.0001
Statins	4,611 (27.5)	3,490 (41.4)	< 0.0001
Vasodilators	1,142 (6.80)	1,250 (14.8)	< 0.0001

Supplementary Table 5.2. Descriptive statistics for the matched cohort of chronic obstructive pulmonary disease (COPD) patients without evidence of heart failure (HF) and COPD patients with possible HF. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). *p-values from Chi-squared test for categorical variables and test of medians for continuous variables. **Average number of exacerbations per patient (range) in the year prior to the start of follow-up. †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

Appendix VI: Supplementary material to Chapter VI

	Non-Users of ACEi	Incident Users of ACEi (<6 months)	Prevalent Users of ACEi (≥6 months)
Number of Patients (N)	4,136	1,237	5,055
Female	1,707 (41.3)	455 (36.8)	1,698 (33.6)
Age, years (IQR)	78.5 (72.0, 84.2)	77.2 (70.4, 83.0)	76.5 (69.5, 82.5)
Smoking Status			
Current Smoker	776 (18.8)	281 (22.7)	1,131 (22.4)
Former Smoker	3,360 (81.2)	956 (77.3)	3,924 (77.6)
Body Mass Index			
Underweight (< 18.5)	158 (3.82)	41 (3.31)	156 (3.09)
Healthy Weight (18.5-24.9)	1,167 (28.2)	386 (31.2)	1,403 (27.8)
Overweight (25.0-29.9)	1,260 (30.5)	367 (29.7)	1,592 (31.5)
Obese (>= 30)	1,340 (32.4)	414 (33.5)	1,766 (34.9)
Missing Data	211 (5.10)	29 (2.34)	138 (2.73)
Index of Multiple Deprivation			
1 – Most deprived	572 (13.8)	155 (12.5)	696 (13.8)
2	823 (19.9)	242 (19.6)	1,006 (19.9)
3	840 (20.3)	233 (18.8)	978 (19.4)
4	961 (23.2)	306 (24.7)	1,156 (22.9)
5 – Least deprived	940 (22.7)	301 (24.3)	1,219 (24.1)
GOLD Stage			
1: Mild	1,511 (36.5)	429 (34.7)	1,826 (36.1)
2: Moderate	850 (20.6)	279 (22.6)	1,156 (22.9)
3: Severe	569 (13.8)	213 (17.2)	819 (16.2)
4: Very Severe	149 (3.60)	72 (5.82)	223 (4.41)
Missing	1,057 (25.6)	244 (19.7)	1,031 (20.4)

	Non-Users of ACEi	Incident Users of ACEi (<6 months)	Prevalent Users of ACEi (≥6 months)
Exacerbation History (IQR)	2 (1, 4)	3 (1, 4)	2 (1, 4)
COPD medications†			
SABA/SAMA	4,136 (100)	1,237 (100)	5,055 (100)
LABA alone	81 (1.96)	30 (2.43)	111 (2.20)
LAMA alone	331 (8.00)	92 (7.44)	395 (7.81)
ICS alone	356 (8.61)	97 (7.84)	422 (8.35)
LABA+LAMA	45 (1.09)	16 (1.29)	73 (1.44)
LABA+ICS	1,055 (25.5)	321 (26.0)	1,221 (24.2)
LAMA+ICS	58 (1.40)	19 (2.34)	94 (1.86)
Triple	1,016 (24.6)	313 (25.3)	1,253 (24.8)
No long-acting inhaler	0	0	0
History of Cardiovascular Disease‡	3,604 (87.1)	1,119 (90.5)	4,583 (90.7)
Atrial fibrillation	1,461 (35.3)	450 (36.4)	1,803 (35.7)
Hypertension	2,265 (54.8)	707 (57.2)	2,940 (58.2)
Ischaemic heart disease	2,105 (50.9)	699 (56.5)	2,916 (57.7)
Peripheral artery disease	548 (13.3)	140 (11.3)	693 (13.7)
Stroke	603 (14.6)	181 (14.6)	719 (14.2)
CVD medications†			
ARB	1,648 (39.9)	106 (8.57)	147 (2.91)
Beta-blockers	1,140 (27.6)	331 (26.8)	1,780 (35.2)
Calcium channel blockers	687 (16.6)	221 (17.9)	775 (15.3)
Loop diuretics	2,760 (66.7)	801 (64.8)	3,523 (69.7)
MRA	858 (20.7)	226 (18.3)	1,130 (22.4)
Statins	2,180 (52.7)	713 (57.6)	3,294 (65.2)
Vasodilators	907 (21.9)	287 (23.2)	1,162 (23.0)

Supplementary Table 6.1. Descriptive statistics for non-users, incident users, and prevalent users of angiotensin converting enzyme inhibitors (ACEi) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of ARB	Incident Users of ARB (<6 months)	Prevalent Users of ARB (≥6 months)
Number of Patients (N)	7,253	668	1,914
Female	2,645 (36.5)	257 (38.5)	723 (37.8)
Age, years (IQR)	77.5 (70.5, 83.5)	76.9 (69.6, 82.4)	76.6 (70.1, 82.2)
Smoking Status			
Current Smoker	1,606 (22.1)	110 (16.5)	277 (14.5)
Former Smoker	5,647 (77.9)	558 (83.5)	1,637 (85.5)
Body Mass Index			
Underweight (< 18.5)	280 (3.86)	14 (2.10)	29 (1.52)
Healthy Weight (18.5-24.9)	2,092 (28.8)	177 (26.5)	445 (23.3)
Overweight (25.0-29.9)	2,242 (30.9)	205 (30.7)	611 (31.9)
Obese (>= 30)	2,328 (32.1)	263 (39.4)	796 (41.6)
Missing Data	311 (4.29)	9 (1.35)	33 (1.72)
Index of Multiple Deprivation			
1 – Most deprived	988 (13.6)	108 (16.2)	287 (15.0)
2	1,428 (19.7)	136 (20.4)	403 (21.1)
3	1,383 (19.1)	144 (21.6)	430 (22.5)
4	1,690 (23.3)	143 (21.4)	408 (21.3)
5 – Least deprived	1,764 (24.3)	137 (20.5)	386 (20.2)
GOLD Stage			
1: Mild	2,545 (35.1)	284 (42.5)	798 (41.7)
2: Moderate	1,528 (21.1)	169 (25.3)	463 (24.2)
3: Severe	1,114 (15.4)	101 (15.1)	271 (14.2)
4: Very Severe	305 (4.21)	26 (3.89)	60 (3.13)
Missing	1,761 (24.3)	88 (13.2)	322 (16.8)

	Non-Users of ARB	Incident Users of ARB (<6 months)	Prevalent Users of ARB (≥6 months)
Exacerbation History (IQR)	2 (0, 3)	2 (1, 4)	2 (1, 4)
COPD medications†			
SABA/SAMA	7,253 (100)	668 (100)	1,914 (100)
LABA alone	156 (2.15)	10 (1.50)	45 (2.35)
LAMA alone	554 (7.64)	60 (8.98)	166 (8.67)
ICS alone	648 (8.93)	54 (8.08)	143 (7.47)
LABA+LAMA	90 (8.93)	6 (0.90)	21 (1.10)
LABA+ICS	1,776 (24.5)	162 (24.3)	494 (25.8)
LAMA+ICS	121 (1.67)	15 (2.25)	33 (1.72)
Triple	1,759 (24.3)	206 (30.8)	519 (27.1)
No long-acting inhaler	0	0	0
History of Cardiovascular Disease‡	6,369 (87.8)	616 (92.2)	1,803 (94.2)
Atrial fibrillation	2,548 (35.1)	242 (36.2)	697 (36.4)
Hypertension	3,927 (54.1)	435 (65.1)	1,269 (66.3)
Ischaemic heart disease	3,886 (53.6)	394 (59.0)	1,149 (60.0)
Peripheral artery disease	968 (13.4)	102 (15.3)	283 (14.8)
Stroke	1,055 (14.6)	66 (9.88)	246 (12.9)
CVD medications†			
ACEi	4,918 (67.8)	380 (56.9)	425 (22.2)
Beta-blockers	2,234 (30.8)	233 (34.9)	669 (35.0)
Calcium channel blockers	1,117 (15.4)	127 (19.0)	330 (17.2)
Loop diuretics	4,967 (68.5)	449 (67.2)	1,288 (67.3)
MRA	1,536 (21.2)	163 (24.4)	453 (23.7)
Statins	4,205 (58.0)	434 (65.0)	1,298 (67.8)
Vasodilators	1,592 (22.0)	179 (26.8)	498 (26.0)

Supplementary Table 6.2. Descriptive statistics for non-users, incident users, and prevalent users of angiotensin receptor blockers (ARB) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of BB	Incident Users of BB (<6 months)	Prevalent Users of BB (≥6 months)
Number of Patients (N)	6,161	1,163	3,259
Female	2,457 (40.0)	356 (30.6)	985 (30.2)
Age, years (IQR)	78.4 (71.5, 83.8)	76.9 (70.1, 82.7)	75.7 (68.5, 81.8)
Smoking Status			
Current Smoker	1,199 (19.5)	202 (17.4)	723 (22.2)
Former Smoker	4,962 (80.5)	961 (82.6)	2,536 (77.8)
Body Mass Index			
Underweight (< 18.5)	239 (3.88)	31 (2.67)	77 (2.36)
Healthy Weight (18.5-24.9)	1,783 (28.9)	335 (28.8)	849 (26.1)
Overweight (25.0-29.9)	1,849 (30.0)	351 (30.2)	1,052 (32.3)
Obese (>= 30)	1,991 (32.3)	432 (37.2)	1,230 (37.7)
Missing Data	299 (4.85)	14 (1.20)	51 (1.56)
Index of Multiple Deprivation			
1 – Most deprived	831 (13.5)	173 (14.9)	480 (14.7)
2	1,240 (20.1)	220 (18.9)	637 (19.6)
3	1,228 (19.9)	216 (18.6)	619 (19.0)
4	1,397 (22.7)	272 (23.4)	768 (23.6)
5 – Least deprived	1,465 (23.8)	282 (24.3)	755 (23.2)
GOLD Stage			
1: Mild	2,108 (34.2)	462 (39.7)	1,341 (41.2)
2: Moderate	1,263 (20.5)	314 (27.0)	806 (24.7)
3: Severe	970 (15.7)	179 (15.4)	460 (14.1)
4: Very Severe	288 (4.67)	36 (3.10)	79 (2.42)
Missing	1,532 (24.9)	172 (14.8)	573 (17.6)

	Non-Users of BB	Incident Users of BB (<6 months)	Prevalent Users of BB (≥6 months)
Exacerbation History (IQR)	2 (1, 3)	2 (1, 4)	2 (1, 4)
COPD medications†			
SABA/SAMA	6,161 (100)	1,163 (100)	3,259 (100)
LABA alone	139 (2.26)	25 (2.15)	62 (1.90)
LAMA alone	389 (6.31)	77 (6.62)	345 (10.6)
ICS alone	620 (10.1)	50 (4.30)	189 (5.80)
LABA+LAMA	75 (1.22)	9 (0.77)	40 (1.23)
LABA+ICS	1,706 (27.7)	268 (23.0)	627 (19.2)
LAMA+ICS	106 (1.72)	20 (1.72)	56 (1.72)
Triple	1,519 (24.7)	345 (29.7)	826 (25.4)
No long-acting inhaler	0	0	0
History of Cardiovascular Disease‡	5,367 (87.1)	1,095 (94.2)	3,048 (93.5)
Atrial fibrillation	2,029 (32.9)	535 (46.0)	1,355 (41.6)
Hypertension	3,371 (54.7)	705 (60.6)	1,978 (60.7)
Ischaemic heart disease	3,115 (50.6)	760 (65.4)	2,090 (64.1)
Peripheral artery disease	803 (13.0)	183 (15.7)	490 (15.0)
Stroke	891 (14.5)	186 (16.0)	473 (14.5)
CVD medications†			
ACEi	3,406 (55.3)	700 (60.2)	2,100 (64.4)
ARB	1,144 (18.6)	249 (21.4)	721 (22.1)
Calcium channel blockers	1,155 (18.8)	201 (17.3)	320 (9.82)
Loop diuretics	4,178 (67.8)	811 (69.7)	2,295 (70.4)
MRA	1,095 (17.8)	282 (24.3)	994 (30.5)
Statins	3,322 (53.9)	785 (67.5)	2,346 (72.0)
Vasodilators	1,378 (22.4)	319 (27.4)	803 (24.6)

Supplementary Table 6.3. Descriptive statistics for non-users, incident users, and prevalent users of beta-blockers (BB) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of LD	Incident Users of LD (<6 months)	Prevalent Users of LD (≥6 months)
Number of Patients (N)	3,037	2,105	6,334
Female	1,025 (33.8)	746 (35.4)	2,428 (38.3)
Age, years (IQR)	76.2 (69.1, 82.3)	78.1 (71.4, 83.6)	78.2 (71.4, 83.7)
Smoking Status			
Current Smoker	747 (24.6)	402 (19.1)	1,186 (18.7)
Former Smoker	2,290 (75.4)	1,703 (80.9)	5,148 (81.3)
Body Mass Index			
Underweight (< 18.5)	135 (4.45)	83 (3.94)	186 (2.94)
Healthy Weight (18.5-24.9)	935 (30.8)	592 (28.1)	1,703 (26.9)
Overweight (25.0-29.9)	964 (31.7)	647 (30.7)	1,935 (30.6)
Obese (>= 30)	891 (29.3)	717 (34.1)	2,271 (35.9)
Missing Data	112 (3.69)	66 (3.14)	239 (3.77)
Index of Multiple Deprivation			
1 – Most deprived	450 (14.8)	308 (14.6)	842 (13.3)
2	576 (19.0)	430 (20.4)	1,283 (20.3)
3	610 (20.1)	424 (20.1)	1,256 (19.8)
4	709 (23.4)	286 (23.1)	1,444 (22.8)
5 – Least deprived	692 (22.8)	457 (21.7)	1,509 (23.8)
GOLD Stage			
1: Mild	1,146 (37.7)	785 (37.3)	2,272 (35.9)
2: Moderate	664 (21.9)	481 (22.9)	1,397 (22.1)
3: Severe	439 (14.5)	341 (16.2)	1,005 (15.9)
4: Very Severe	110 (3.62)	92 (4.37)	260 (4.10)
Missing	678 (22.3)	406 (19.3)	1,400 (22.1)

	Non-Users of LD	Incident Users of LD (<6 months)	Prevalent Users of LD (≥6 months)
Exacerbation History (IQR)	1 (0, 3)	2 (1, 4)	2 (1, 4)
COPD medications†			
SABA/SAMA	3,037 (100)	2,105 (100)	6,334 (100)
LABA alone	67 (2.21)	34 (1.63)	136 (2.15)
LAMA alone	262 (8.63)	153 (7.27)	474 (7.48)
ICS alone	248 (8.17)	166 (7.89)	544 (8.59)
LABA+LAMA	35 (1.15)	30 (1.43)	76 (1.20)
LABA+ICS	695 (22.9)	525 (24.9)	1,606 (25.4)
LAMA+ICS	52 (1.71)	45 (2.14)	105 (1.66)
Triple	688 (22.7)	579 (27.5)	1,678 (26.5)
No long-acting inhaler	0	0	0
History of Cardiovascular Disease‡	2,649 (87.2)	1,908 (90.6)	5,702 (90.0)
Atrial fibrillation	875 (28.8)	827 (39.3)	2,468 (39.0)
Hypertension	1,624 (53.5)	1,225 (58.2)	3,696 (58.4)
Ischaemic heart disease	1,625 (53.5)	1,167 (55.4)	3,524 (55.6)
Peripheral artery disease	413 (13.6)	292 (13.9)	873 (13.8)
Stroke	414 (13.6)	322 (15.3)	938 (14.8)
CVD medications†			
ACEi	1,684 (55.5)	1,159 (55.1)	3,728 (58.9)
ARB	566 (18.6)	466 (22.1)	1,295 (20.5)
Beta-blockers	941 (31.0)	616 (29.3)	2,054 (32.4)
Calcium channel blockers	501 (16.5)	353 (16.8)	983 (15.5)
MRA	367 (12.1)	402 (19.1)	1,643 (25.9)
Statins	1,781 (58.6)	1,227 (58.3)	3,810 (60.2)
Vasodilators	591 (19.5)	507 (24.1)	1,553 (24.5)

Supplementary Table 6.4. Descriptive statistics for non-users, incident users, and prevalent users of loop diuretics (LD) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of MRA	Incident Users of MRA (<6 months)	Prevalent Users of MRA (≥6 months)
Number of Patients (N)	7,146	1,335	2,244
Female	2,674 (37.4)	428 (32.1)	731 (32.6)
Age, years (IQR)	77.6 (71.1, 83.5)	77.3 (70.8, 83.4)	75.9 (68.6, 81.9)
Smoking Status			
Current Smoker	1,468 (20.5)	239 (17.9)	460 (20.5)
Former Smoker	5,678 (79.5)	1,096 (82.1)	1,784 (79.5)
Body Mass Index			
Underweight (< 18.5)	265 (3.71)	32 (2.40)	53 (2.36)
Healthy Weight (18.5-24.9)	2,048 (28.7)	354 (26.5)	554 (24.7)
Overweight (25.0-29.9)	2,234 (31.3)	409 (30.6)	702 (31.3)
Obese (>= 30)	2,316 (32.4)	491 (36.8)	863 (38.5)
Missing Data	283 (3.96)	49 (3.67)	71 (3.21)
Index of Multiple Deprivation			
1 – Most deprived	998 (14.0)	179 (13.4)	301 (13.4)
2	1,425 (19.9)	285 (21.4)	436 (19.4)
3	1,416 (19.8)	278 (20.8)	453 (20.2)
4	1,635 (22.9)	319 (23.9)	531 (23.7)
5 – Least deprived	1,672 (23.4)	274 (20.5)	523 (23.3)
GOLD Stage			
1: Mild	2,591 (36.3)	469 (35.1)	820 (36.5)
2: Moderate	1,531 (21.4)	321 (24.0)	524 (23.4)
3: Severe	1,061 (14.9)	261 (19.6)	385 (17.2)
4: Very Severe	276 (3.86)	64 (4.79)	103 (4.59)
Missing	1,687 (23.6)	220 (16.5)	412 (18.4)

	Non-Users of MRA	Incident Users of MRA (<6 months)	Prevalent Users of MRA (≥6 months)
Exacerbation History (IQR)	2 (0, 3)	3 (1, 5)	2 (1, 4)
COPD medications†			
SABA/SAMA	7,146 (100)	1,335 (100)	2,244 (100)
LABA alone	155 (2.17)	27 (2.02)	46 (2.05)
LAMA alone	561 (7.85)	80 (5.99)	169 (7.53)
ICS alone	629 (8.80)	78 (5.84)	158 (7.04)
LABA+LAMA	89 (1.25)	17 (1.27)	24 (1.07)
LABA+ICS	1,764 (24.7)	325 (24.3)	558 (24.9)
LAMA+ICS	119 (1.67)	26 (1.95)	39 (1.74)
Triple	1,698 (23.8)	458 (34.3)	683 (30.4)
No long-acting inhaler	0	0	0
History of Cardiovascular Disease‡	6,355 (88.9)	1,230 (92.1)	2,028 (90.4)
Atrial fibrillation	2,458 (34.4)	615 (46.1)	942 (42.0)
Hypertension	4,064 (56.9)	780 (58.4)	1,275 (56.8)
Ischaemic heart disease	3,861 (54.0)	813 (60.9)	1,333 (59.4)
Peripheral artery disease	983 (13.8)	196 (14.7)	298 (13.3)
Stroke	1,052 (14.7)	200 (15.0)	302 (13.5)
CVD medications†			
ACEi	4,104 (57.4)	773 (57.9)	1,354 (60.3)
ARB	1,349 (18.9)	342 (25.6)	537 (23.9)
Beta-blockers	2,030 (28.4)	475 (35.6)	989 (44.1)
Calcium channel blockers	1,217 (17.0)	200 (15.0)	263 (11.7)
Loop diuretics	4,657 (65.2)	1,076 (80.6)	1,818 (81.0)
Statins	4,186 (58.6)	833 (62.4)	1,433 (63.9)
Vasodilators	1,589 (22.2)	369 (27.6)	584 (26.0)

Supplementary Table 6.5. Descriptive statistics for non-users, incident users, and prevalent users of mineralocorticoid receptor antagonists (MRA) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

Exposure	Adjusted Hazard Ratio (95% confidence interval)
ACEi	
Incident use vs non-use	5.38 (4.79, 6.05)
Prevalent use vs non-use	1.11 (1.03, 1.19)
Prevalent use vs incident use	0.24 (0.22, 0.27)
ARB	
Incident use vs non-use	5.99 (5.08, 7.07)
Prevalent use vs non-use	1.22 (1.12, 1.32)
Prevalent use vs incident use	0.23 (0.20, 0.26)
BB	
Incident use vs non-use	5.65 (4.92, 6.49)
Prevalent use vs non-use	1.41 (1.32, 1.51)
Prevalent use vs incident use	0.27 (0.25, 0.30)
LD	
Incident use vs non-use	4.76 (4.31, 5.25)
Prevalent use vs non-use	1.12 (1.05, 1.20)
Prevalent use vs incident use	0.25 (0.23, 0.27)
MRA	
Incident use vs non-use	6.01 (5.31, 6.80)
Prevalent use vs non-use	1.61 (1.48, 1.74)
Prevalent use vs incident use	0.32 (0.28, 0.35)

Supplementary Table 6.6. Adjusted hazard ratios comparing incident use, prevalent use, and non-use of heart failure medications. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Loop diuretics (LD). Mineralocorticoid receptor antagonists (MRA).

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Axson EL, Sundaram V, Bloom CI, Bottle A, Cowie MR, and Quint JK. 2018. Hospitalisation and mortality outcomes of patients with comorbid COPD and heart failure: a systematic review protocol. *BMJ Open*. 8:e023058. doi.org/10.1136/bmjopen-2018-023058	The Authors	CC BY-NC 4.0
Axson EL, Ragutheeswaran K, Sundaram V, Bloom CI, Bottle A, Cowie MR, and Quint JK. 2020. Hospitalisation and mortality in patients with comorbid COPD and heart failure: a systematic review and meta-analysis. *Respiratory Research*. 21:54. doi.org/10.1186/s12931-020-1312-7	The Authors	CC BY 4.0
Axson EL, Sundaram V, Bloom CI, Bottle A, Cowie MR, Quint JK. 2020. Temporal trends in the incidence of heart failure among patients with COPD and its association with mortality. Annals of the American Thoracic Society. 17(8). doi.org/10.1513/AnnalsATS.201911-820OC.	American Thoracic Society	See permissions

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Figure 1.2	Morgan AD, Zakeri R, and Quint JK. 2018. Defining the relationship between COPD and CVD: what are the implications for clinical practice? *Ther Adv Respir Dis*. 12, 1753465817750524. doi.org/10.1177/1753465817750524	The Authors	CC BY-NC 4.0

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Best,

Eleanor L Axson MPH AFHEA
Research Assistant in Statistics and Epidemiology
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Diane Gern, Publisher
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27 July 2020

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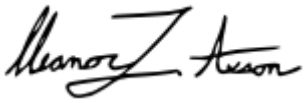

Eleanor L. Axson MPH AFHEA

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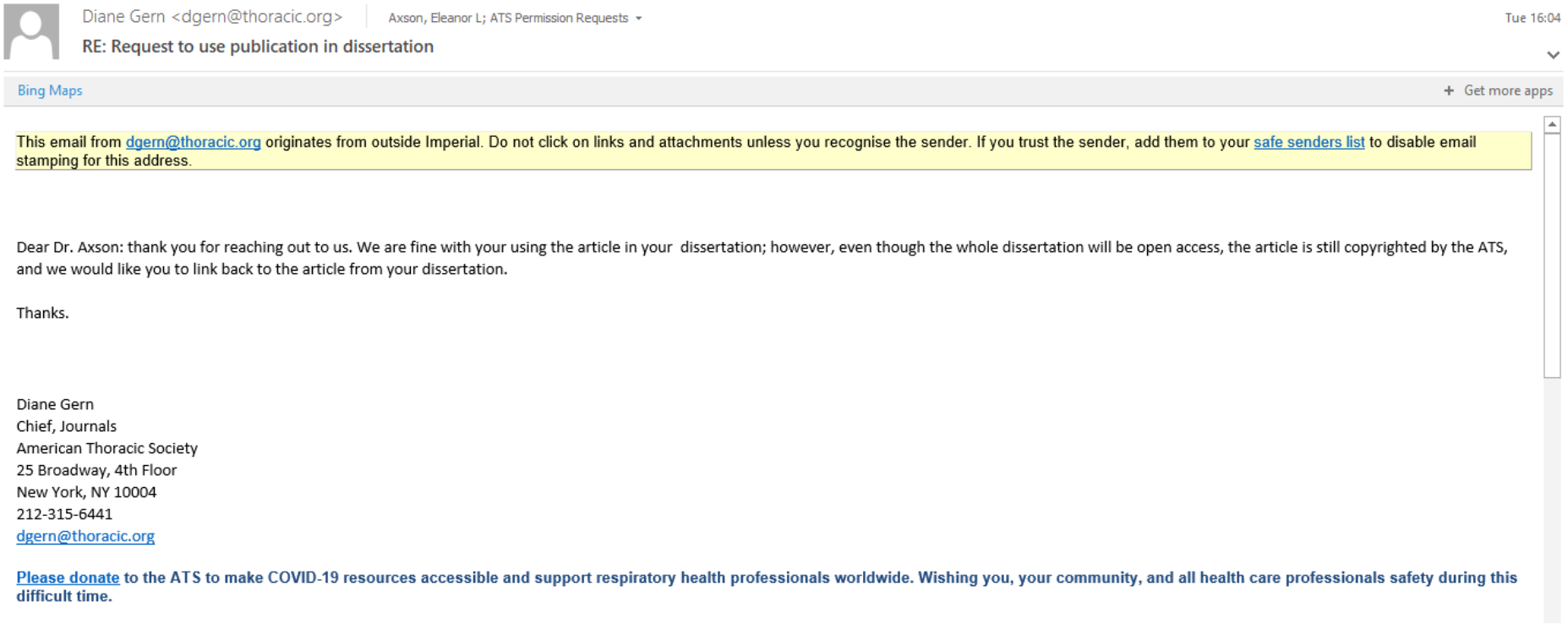

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Eleanor L Axson MPH AFHEA
Research Assistant in Statistics and Epidemiology
PhD Student in Clinical Medicine Research (Respiratory Epidemiology)

27 July 2020

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Name: Ann D Morgan

Organisation: National Heart and Lung Institute, Imperial College London

Job title: Research Associate

Appendix VIII: Publications Associated with this Thesis

Peer-Reviewed Articles

Axson EL, Bottle A, Cowie MC, Quint JK. The relationship between heart failure, and heart failure medication use, and the risk of acute exacerbation of COPD. [Under Review]. [**Chapters V and VI**].

Axson EL, Sundaram V, Bloom CI, Bottle A, Cowie MR, Quint JK. 2020. Temporal trends in the incidence of heart failure among patients with COPD and its association with mortality. *Annals of the American Thoracic Society.* 17(8). https://doi.org/10.1513/AnnalsATS.201911-820OC. [**Chapter IV].**

Axson EL, Ragutheeswaran K, Sundaram V, Bloom CI, Bottle A, Cowie MR, Quint JK. 2020. Hospitalisation and mortality in patients with comorbid COPD and heart failure: a systematic review and meta-analysis. *Respiratory Research.* 21(1):54. https://doi.org/10.1186/s12931-020-1312-7. [**Chapter II**].

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