AN EPIDEMIOLOGICAL APPROACH TO COMORBIDITIES IN PATIENTS WITH COPD

Rayan Abdulghafoor Siraj, MSc

Respiratory Medicine, School of Medicine

University of Nottingham

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

2020

Abstract

Chronic Obstructive Pulmonary Disease (COPD) is associated with comorbidities. Cardiovascular (CV) disease, cognitive impairment, dementia, and depression are common comorbidities in patients with COPD, leading to increased morbidity and mortality. However, there are considerable gaps in how these comorbidities are assessed, while the burden of others remains inadequately researched.

This PhD applied several methodologies and used different databases to 1) explore whether circulating biomarkers from the blood (soluble Receptor for Advanced Glycation End-products - sRAGE) and urine (microalbuminuria) might have a role in COPD related to prognostication of CV risk (assessed by aortic stiffness and carotid intima-media thickness), 2) evaluate the prevalence and incidence of cognitive impairment and dementia, 3) examine the incident risk of depression, and 4) assess the risks of respiratory-related morbidities associated with antidepressant use in patients with COPD.

Using data from a multisite UK study, sRAGE was not associated with aortic stiffness, carotid intima-media thickness, or CV disease in patients with COPD. However, there was a weak direct association between sRAGE and spirometric lung function measures. Data from the same cohort also showed that urinary albumin creatinine ratio (UACR) was not strongly associated with physiological CV risk measures. Nevertheless, patients with COPD and either diabetes, ischaemic heart disease, or cerebrovascular disease have increased UACR, compared to patients without these comorbidities. Microalbuminuria was also prevalent in all patients with COPD.

Using a large primary care database, this PhD demonstrates that patients with COPD have increased prevalence of cognitive impairment compared to subjects without

COPD, matched by age, gender and GP surgery. The incidence of cognitive impairment following COPD diagnosis was 23.1 per 1,000 person-years compared to 16.3 per 1,000 person-years in subjects without COPD. However, the prevalence and incidence of dementia were less frequently recorded in patients with COPD compared to individuals without COPD, indicating the possibility of underdiagnosis of dementia and highlighting the need for systematic assessment.

The incidence of depression was also greater following COPD diagnosis, compared to subjects without COPD, which indicates the need to stay alert and target accordingly. Antidepressant use was associated with increased risks of pneumonia and COPD exacerbations relative to periods of unexposed to antidepressants in patients with COPD, raising the concern of potential side-effects and adverse events.

This thesis addresses several aspects of COPD comorbidities and contributes new evidence for assessing, recognising, and managing comorbidities in patients with COPD.

Conference Presentation and personal awards

Abstracts presented at regional, national and international conferences

- **Siraj R**, McKeever TM, Buss L, Mohan D, Maki-Petaja K, Forman J, McEniery CM, Cheryian J, Gale N, Cockcroft JR, Calverley PM, MacNee W, Miller B, Tal-Singer R, Polkey M, Wilkinson IB, Bolton CE. ***Soluble Receptor for Advanced Glycation End-products (sRAGE) in Patients with COPD: The ERICA Study.*** Thorax 2017; 72(Suppl 3): A112.3-A113. [British Thoracic Society Winter Meeting 6th-8th December 2017 (POSTER DISCUSSION)].
- **Siraj R**, McKeever TM, Gordon AL, Bolton CE. ***Dementia in patients With Chronic Obstructive Pulmonary Disease (COPD): A UK Population-Based Study.*** Thorax 2018; 73(Suppl 4): A1–A282. [British Thoracic Society Winter Meeting 5th-7th December 2018 (POSTER DISCUSSION)].
- **Siraj R**, McKeever TM, Gordon AL, Bolton CE. ***Dementia in patients With Chronic Obstructive Pulmonary Disease (COPD): A UK Population-Based Stud*y**. East Midland Thoracic Society, October 11 2018.
- **Siraj R**, McKeever TM, Bolton CE on behalf of the ERICA Consortium co-investigators. ***Microalbuminuria Does not Relate to Cardiovascular Risk in Patients with Chronic Obstructive Pulmonary Disease (COPD): Cross-sectional Data from the ERICA Study.*** East Midland Thoracic Society, November 12 2019.
- **Siraj R**, McKeever T, Gibson J, Bolton CE. ***Incident Depression in Patients with Chronic Obstructive Pulmonary Disease: a UK Population based Study.*** European Respiratory Society, virtual meeting, 2020. Oral presentation.

Personal Awards

- An excellence award from the Royal Embassy of Saudi Arabia Cultural Bureau, 2018.
- An excellence award from the Royal Embassy of Saudi Arabia Cultural Bureau, 2019.
- 3rd prize winner on presenting some PhD work entitled "*Dementia and Cognitive Impairment in patients with chronic obstructive pulmonary disease*" at the School of Medicine Postgraduate Presentation Event on 24 May, 2019.

Published manuscript

1. Risk of Incident Dementia and Cognitive Impairment in Patients with Chronic Obstructive Pulmonary Disease (COPD): A Large UK Population-based Study. Siraj, R.A., et al., Risk of incident dementia and cognitive impairment in patients with chronic obstructive pulmonary disease (COPD): A large UK population-based study. Respir Med, 2020. 177: p. 106288.

Manuscript under preparation

1- Soluble Receptor for Advanced Glycation End-products (sRAGE) in Patients with COPD: The ERICA Study.
2- Incident Depression in Patients with COPD: A Large UK Population-based Cohort Study.

Acknowledgement

First and foremost, I thank Allah (God) for giving me the strength and patience to complete this thesis. I thank him for keeping me safe and alive to complete my studies in the UK and to pass through some hardships.

Second, I would like to thank several individuals who have been part of this PhD journey. I express my deepest respect and gratitude to my primary supervisor Professor Charlotte Bolton for convincing this project, and for the unlimited guidance and support throughout the past years. I thank her for taking me under her supervision and most importantly, for believing in me. I also would like to extend my gratitude to my second supervisor Professor Tricia McKeever for teaching me all the important statistical skills and believing in my abilities to make it to the finish line. I have learned a lot from them, and their comments and feedback have always been constructive and invaluable. I have been provided with the necessary skills to grow as a researcher, critical-thinker, and problem-solver. I also thank them for keeping their doors open and giving me the comfort to share and discuss my academic and personal issues. They encouraged and motivated me from the very beginning of my studies, and provided me with excellent support to submit papers, attend conferences, and complete my thesis. I am where I am because of them, and this thesis would not have been completed without their unlimited support and assistance.

I also would like to thank Dr Jack Gibson for his support with data management and helping me with the self-controlled case series analysis. I also would like to thank Mrs Tara Claringburn for her support and encouragement.

My thanks extend to my sponsor (King Faisal University) and the Saudi-Arabian Cultural Bureau in London for giving me this opportunity to pursue my higher education in the UK. I would not have made it to the UK without their support.

My sincerest gratitude also extends to my parents for their endless prayers for my success. I thank them for not giving up on me during my worst, weakest, and lowest. I thank my brothers and sister for looking after my parents for the past 12 years while I have been pursuing my education abroad.

My special thanks to my wife, Mariam, who has been supporting and encouraging me throughout this journey. I thank her for the sacrifices she has made, and for looking after me during my depression and anxiety.

Declaration

I, Rayan Siraj, hereby declare that this thesis is my own work, and neither the whole nor any part of this thesis has been submitted for a degree in any other university or institutions. Where information has been obtained from other sources, it has been indicated in this thesis.

Signature

Rayan Siraj

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AECOPD: Acute exacerbation of COPD

AGEs: Advanced Glycation End-products

aHR: Adjusted Hazard Ratio

ARIC: Atherosclerosis Risk in Communities

aOR: Adjusted Odds Ratio

BLF: British Thoracic Foundation

BMI: Body mass index

BP: Blood pressure

BTS: British Thoracic Society

CAT: COPD Assessment Test

CCI: Charlson Comorbidity Index

CHF: Chronic heart failure

CIMT: Carotid intima-media thickness

COPD: Chronic Obstructive Pulmonary Disease

COTE: COPD specific comorbidity test

CV: Cardiovascular

CT: Computed Tomography

CVD: Cerebrovascular disease

DLCO: Diffusion Capacity of Carbon Monoxide

eGFR: Estimated Glomerular Filtration Rate

ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints

ELISA: Enzyme-Linked Immunosorbent Assay

ERICA: Evaluating the Role of Inflammation in Chronic Airways disease

ERS: European Respiratory Society

FEV_1: Forced Expiratory Volume in 1 second

FVC: Forced Volume Capacity

GBD: Global Burden of Disease

GOLD: Global Initiative for Chronic Obstructive Lung Disease

GP: General Practice

HDL: High Density Lipoprotein

HR: Hazard Ratio

IHD: Ischemic heart disease

IQR: Interquartile Range

IRR: Incidence Relative Risk

LRTI: Lower Respiratory Tract Infection

MAB: Microalbuminuria

MAOI: Monoamine oxidase inhibitor

MAP: Mean Arterial Pressure

MI: Myocardial Infarction

MRC: Medical Research Council

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NIH: National Institutes of Health

OCS: Oral corticosteroid

OR: Odds Ratio

PR: Pulmonary rehabilitation

PVD: Peripheral vascular disease

PWV: pulse wave velocity

QOF: Quality and Outcomes Framework

RAGE: Receptor for Advanced Glycation End-products

RCT: Randomised controlled trial

SCCS: Self-controlled Case Series

SD: Standard Deviation

SES: Socioeconomic status

SNRI: Serotonin–norepinephrine reuptake inhibitor

sRAGE: soluble Receptor for Advanced Glycation End-products

SRC: Scientific Review Committee

SSRI: Selective serotonin reuptake inhibitor

TCA: Tricyclic

THIN: The Health Improvement Network

TORCH: Towards a Revolution in COPD Health

UACR: Urinary Albumin Creatinine Ratio

UK: United Kingdom

WHO: World Health Organization

Chapter 1 INTRODUCTION

1.1 **Definition of Chronic Obstructive Pulmonary Disease (COPD)**

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as "*a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases*" [1]. The key characteristic of COPD – that is persistent airflow limitation - is caused by a mixture of small airway disease and parenchymal destruction [1]. COPD is a disabling disease that usually occurs and worsens over time. COPD is also associated with comorbidities, which have a significant impact on morbidity and mortality [1].

The heterogeneity of COPD includes both chronic bronchitis and emphysema. Chronic bronchitis is defined clinically as the presence of cough and sputum for more than three months for two consecutive years, without any other condition causing sputum production [2]. Emphysema, meanwhile, is a pathological term refers to permanent enlargement of the airspace and destruction of the gas-exchanging surface (alveolar wall) distal to terminal bronchioles, leading to irreversible loss of elastic recoil [3].

1.2 **Risk factors for COPD**

Tobacco smoking is the primary environmental factor – especially in low and middle income class countries (LMICs) - which increases the risk of COPD [1]. Compared to non-smokers, smokers are associated with increased prevalence of lung function abnormalities and a higher rate of COPD mortality [4, 5]. Indeed, tobacco smoking induces inflammation in the lung and its airway by provoking inflammatory cytokines and macrophages. It is, however, important to mention that less than 50% of smokers develop COPD, irrespective of the scale of smoking [6]. This implies that other factors

are contributing to the development of COPD [7]. It is evident that non-smokers account for a considerable proportion of patients with COPD. The Burden of Obstructive Lung Disease (BOLD) study, which collected data from 14 countries, indicated that non-smokers (n= 4,291) comprise 28% of all COPD cases, 33% of mild COPD, and 23% of moderate COPD and worse [8].

Occupational exposures, which include fumes, chemicals, and organic/nonorganic dust, also contribute to the development of COPD [9, 10]. A recent UK population-based study (n= 94,551) identified several occupations (such as sculptors, gardeners, and warehouse workers) that were associated with amplified COPD risk among non-smokers and non-asthmatics [11]. According to US population-based data collected from 9,823 subjects, occupational exposures account for 19% of all COPD cases, and 31% of cases among lifelong non-smokers [12]. However, the risk from occupational exposures seems to be much more significant in LMICs. Therefore, it is important to take occupational history into account during respiratory assessment.

Air pollution, which occurs as a result of industrial operations, vehicular traffic, and biomass fuels, also increases the risk of developing COPD [13, 14]. A recent large population-based study within the UK, including 303,887 subjects aged 40-69, showed that higher exposures to ambient air pollution were associated with reduced lung function and increased prevalence of COPD [15]. Current literature also suggests that about 3 billion people, especially in LMICs, rely on solid fuels (coal and biomass) as an energy source (e.g. cooking and/or heating) [16, 17], contributing to higher exposure to household air pollution (HAP), and therefore to COPD. Indeed, in many countries, several studies have linked the exposure to solid fuel to increased risk of COPD [18-23]. A recent systematic review and meta-analysis involving 35 studies

(n=73,122) showed that exposure to HAP from biomass increases the risk of COPD by almost 3 times compared to non-biomass fuels [18]. A recent Chinese cohort study involving 277,838 people who never smoked demonstrated that solid fuel users were at increased risk of COPD compared to clean fuel users [24].

Women are more likely to be predisposed to COPD through HAP, resulting from solid fuels exposures, especially in LMICs [25, 26]. The association – that is the risk of COPD - is more significant in women living in rural areas (OR:1.95; CI: 1.54 to 2.37) compared to women in urban areas (OR: 1.61; CI: 1.20 to 2.02), given the higher exposure to solid fuels [25]. This may be attributed to the considerable exposure to smoke from biomass fuels to women living in rural areas [27].

The socioeconomic status (SES) has been considered as a strong determinant of health in a variety of diseases; one of which is COPD [28]. An analysis of three population-based studies involving 11,042 participants (aged 35–95 years) demonstrated that lower SES was associated with higher odds of having COPD, following adjustments for confounders [29]. In the UK, primary care data from The Health Improvement Network (THIN) has also shown that the prevalence of COPD was greater amongst individuals with lower SES, compared to subjects with a higher SES [30].

Genetic susceptibility to the development of COPD has been reported. Alpha-1 antitrypsin deficiency is recognised as a cause of COPD [1]. Previous studies indicated that a low concentration of alpha-1 antitrypsin, defined as < 11 micromol/L, is associated with early onset of emphysema [31]. However, deficiency in alpha-1 antitrypsin only accounts for a small proportion of COPD [32]; other genetic factors also contribute.

1.3 **COPD symptoms**

Patients with COPD often present with several symptoms, such as dyspnoea (breathlessness), cough, sputum production, wheezing, and chest tightness [1]. Dyspnoea, either chronic or progressive, is considered the hallmark of COPD, defined as "*a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*" [33]. Dyspnoea is common in all COPD stages [34], and has been associated with worse clinical outcomes, including a higher risk of COPD exacerbation [34], frequent visit to primary care practice [34], reduced physical activity [35], and depression [36].

A simple, validated method for the measurement of dyspnoea is by using the Medical Research Council (MRC) dyspnoea score (1 ─ 5;Table 1-1) [37, 38]. It is a unidimensional measure, where patients indicate how their breathlessness impacts on their everyday activity.

Table 1-1. Medical Research Council (MRC) dyspnoea grades [39]

Grade	Description
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 m or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

1.4 **COPD diagnosis**

According to the guideline produced by the National Institute for Health and Care Excellence (NICE), a diagnosis of COPD should be suspected in patients who have a risk factor (primarily a history of smoking in the high-income countries) and one or more of the aforementioned respiratory symptoms [40]. A COPD diagnosis is then confirmed by post-bronchodilator spirometry. The post-bronchodilator spirometric criterion of the airflow obstruction is defined as the ratio of forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) of less than 70% [1, 40]. Spirometry is the most reproducible, cost-effective, non-invasive measure for airflow limitation. It is noteworthy that good quality spirometry measurements are essential in making a diagnosis and assessing disease progression and severity.

1.4.1 COPD severity

NICE and GOLD guidelines grade COPD airflow obstruction severity based on the reduction in FEV_1 in those with the obstruction, and compare it to the individual's reference values: age, sex, and height and ethnicity [1, 40]. The GOLD and NICE classification of the severity of airflow limitation is presented in Table 1-2.

Table 1-2. GOLD and NICE classification of airflow limitation severity in COPD [1, 40].

GOLD stage	Severity	FEV_1% predicted
GOLD 1	Mild	• $FEV_1/FVC < 0.70$ • $FEV_1 \geq 80\%$
GOLD 2	Moderate	• $FEV_1/FVC < 0.70$ • $50\% \leq FEV_1 < 80\ \%$
GOLD 3	Severe	• $FEV_1/FVC < 0.70$ • $30\% \leq FEV_1 < 50\ \%$
GOLD 4	Very severe	• $FEV_1/FVC < 0.70$ • $FEV_1 < 30\%$

FEV_1: Forced expiratory volume in one second; FEV1/FVC: the ratio of forced expiratory volume in one second to forced vital capacity

1.5 **Epidemiology of COPD**

COPD presents a significant public health threat across the world. Its prevalence, incidence, as well as associated morbidity and mortality, have increased in recent years [41]. It is ranked as the 3rd leading cause of death worldwide [41]. The increased burden of COPD, especially in LMICs, is usually associated with the increased prevalence of smoking, whereas other factors (e.g. occupational and environmental) are common in LMICs [42].

1.5.1 Prevalence and Incidence of COPD

There has been an increasing trend in COPD prevalence over the past decades. Adeloye et al. reported that the global prevalence of COPD (defined based on spirometry) increased from 10.7% (95% CI: 7.3 to 14.0%) in 1990 to 11.7% (95% CI: 8.4% to 15%) [43]. The World Health Origination (WHO) reported that there were approximately 251 million cases of COPD globally in 2016 [44]. A recent geographical study, including population-based studies between 1995 and 2019, showed that western and central Europe had the highest mean prevalence of COPD

with approximately 14.2% (95% CI: 8.8% to 19.6%), followed by northern and southern Europe with 11.5% (95% CI: 8.8% to 14.1%) and 10.8% (95% CI: 7.8% to 13.8%), respectively [45].

In the UK, it is estimated that around 3 million people live with COPD; of whom, 2 million cases are undiagnosed. Statistics also suggest that 2% of the entire UK population, and 4-5% of people over the age of 40 in live with COPD [46]. Furthermore, the number of individuals who have received COPD diagnosis has increased in the last decade by 27%, from 1,600 to 2,000 per 1000,00. This may indicate that more people are getting diagnosed with COPD but could also mean that the prevalence of COPD is increasing. Indeed, between 2008 and 2012, the prevalence of COPD increased by 9%, and the proportion of males living with COPD is higher than that relating to females [46]. Data based on the Quality and Outcomes Framework (QOF) for general practices (GPs) indicates that the prevalence of COPD in England is estimated to be 1.9% [47].

1.5.2 Morbidity and economic burden of COPD

COPD imposes significant morbidities (e.g. emergency visits and hospitalisation) with a considerable economic burden. Indeed, it has become the 2nd largest cause of hospital admission in the UK, with 115,000 emergency admission and over a million bed days per year [48]. Available data also show that 43% of patients admitted with COPD were readmitted within 90 days after discharge in 2014, with a substantial increase from 33% in 2008 [49].

The cost of COPD to the National Health Service (NHS) is estimated to be £1.85 billion per year and is expected to increase to £2.32 billion by 2030 [50], with the most significant costs related to COPD exacerbation and hospitalisation. In addition, COPD

severity is directly related to healthcare cost – that is the direct cost per patient increases with the increased number of experienced COPD exacerbations [51]. As COPD is a disabling disease, 25% of patients with the condition are prevented from working, and the annual cost of lost productivity because of COPD is estimated to be £3.8 billion [52].

1.5.3 Mortality of COPD

COPD is a major cause of death, accounting for nearly 5% of all deaths worldwide [53]. The most significant proportion of COPD deaths occur in low-middle income – countries (about 90% of all COPD deaths) [44]. The Global Burden of Disease (GBD) study reported that there were more than 3 million deaths caused by COPD in 2015; an increase of 11.6% compared with the number of deaths recorded in 1990 [54]. By 2060, COPD and its related conditions are expected to cause more than 5.4 million deaths annually [55].

Statistics have shown that the UK is one of the top 20 countries in terms of COPD mortality, with an age-standardised mortality rate of 210.7 per 1000,000 of the population [46]. The British Lung Foundation (BLF) reported that there were 30,000 deaths from COPD in 2012, and this accounted for 5.3% of all mortality cases, making COPD the 5th largest cause of death in the country. The distribution of these deaths is slightly greater in men (51.2%; 15,254 deaths) compared to women (48.8%; 14,531 deaths) [46].

1.6 **Management and treatment of COPD**

As COPD is an irreversible condition, an effective COPD management plan such as assessing disease severity and progression, minimising risk factors, and managing stable COPD and exacerbations, should be employed. COPD management should, therefore, focus on improving patients' overall health by preserving lung function, and reducing symptoms, risk of exacerbation, and disease progression [1, 40].

Smoking cessation remains the most effective approach for people who smoke [1]. Indeed, it has been shown to alter the natural history of COPD and reduce the lung function decline [56]. Smoking cessation should be supported by pharmacological (e.g. nicotine replacement therapy) and non-pharmacological (e.g. counselling) therapies [1, 40].

Pharmacotherapy (e.g. inhaled medications), such as bronchodilators and corticosteroids, is mainly indicated to ameliorate symptoms, reduce the severity of COPD exacerbations, and improve exercise limitation and overall health status [1, 40]. The latest NICE COPD guidelines have published an algorithm for the selection of inhaled therapies based on clinical evidence. Short-acting bronchodilators are indicated (as necessary) to relieve shortness of breath and improve exercise limitation. Long-acting agents, such as long-acting anti-muscarinic (LAMA) and long-acting β_2 agonist (LABA), in addition to inhaled corticosteroids (ICS), are indicated if breathlessness persists, and to improve day to day symptoms and reduce exacerbations [1, 40]. Pneumococcal and influenza vaccinations are also recommended [1, 40]. They have been shown to reduce the risk of lower respiratory tract infection (LRTI)/pneumonia and mortality in patients with COPD [57].

An important non-pharmacological therapy is a pulmonary rehabilitation (PR), defined as "*an individually tailored, multidisciplinary care program for people with COPD, which aims to optimize physical and psychological condition through exercise training, education, and nutritional, psychological, and behavioural interventions*" [40]. PR should be considered in a wide range of respiratory diseases, one of which is COPD [58]. PR aims to improve symptoms, overall health, exercise limitation, and psychological well-being [1, 58].

1.7 **COPD exacerbation**

An acute exacerbation of COPD (AECOPD) is defined as "*a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations and is acute in onset*" [1] that requires a change in the treatment [59]. The GOLD report recommends managing COPD exacerbation based on the severity of the episode. The main goal of treating COPD exacerbation is to minimise the impact of the current episode as well as reduce the risk of subsequent/future ones. The majority of COPD exacerbation episodes (up to 80%) are managed in outpatient by pharmacotherapies such as bronchodilators, corticosteroids (oral), and antibiotics. In some cases, where COPD exacerbation cannot be managed by pharmacological therapies, hospital admission may be required [1].

COPD exacerbations are important events in the natural history of COPD and are associated with a significant impact on a patients' health [60]. Even a single exacerbation episode can significantly increase the lung function decline rate [61]. Also, COPD exacerbation is associated with increased readmission rates as well as in-hospital and post-discharge mortality [62-64]. Current evidence shows that exacerbations are associated with a more significant disease progression (e.g. faster

decline in FEV_1), and increased risk of a subsequent event [65, 66]. Indeed, 25% of COPD exacerbations are followed by a second recurrent episode within eight weeks [67].

1.8 **Comorbidities in COPD**

Although COPD mainly affects the lungs, it is commonly associated with other comorbid conditions. The term "comorbidity" is widely described as the co-existence of other medical conditions alongside the primary disease of interest (e.g. COPD). The co-existence of comorbidities does not necessarily imply that these comorbidities are directly related to COPD. Some comorbidities may arise independently, while others may occur due to common risk factors. Further, it is also possible that one condition could amplify the risk of the other. The underlying mechanisms linking COPD to its associated comorbidities remain for further investigation [68]. Comorbidities, either single or multiple, are common in patients with COPD, impacting on patients' health status, and increasing the risks of exacerbations, readmission, and mortality [69-74]. Nevertheless, current guidelines provide limited information on how to identify, assess, and manage these comorbidities in patients with COPD [1].

Current literature suggests that patients with COPD are more likely to suffer from a higher proportion of comorbidities, compared to subjects without COPD [75, 76]. Further, patients with COPD are more likely to die from non-pulmonary causes [73, 77]. In a cluster analysis of 213 well-characterised patients with COPD (defined based on FEV_1 % predicted), 98% had one or more comorbidities, and 53% had at least four comorbid conditions [78]. In a previous study, involving 1,969 patients with COPD and 316 subjects without COPD, Divo et al. reported that the median number of

comorbidities in patients with COPD is 4 (interquartile range; 2–7) compared to 2 (interquartile range; 0-3) in subjects without COPD [79].

The view that a considerable proportion of patients with COPD suffer from multiple comorbidities has a significant impact on survival. Almagro et al. demonstrated that comorbidities, quantified by Charlson comorbidity index score, was associated with 23% increased odds of mortality, following adjustment for confounders [80]. In the BODE COPD cohort, there was an amplified risk of death with higher values of COPD specific comorbidity test (COTE) index (Hazard Ratio (HR): 1.13; 95% CI: 1.08 – 1.18) [73]. Even the co-existence of a single comorbid condition in patients with COPD has a significant impact on survival. Data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study showed that the presence of 1 comorbidity was associated with 74% increased odds of mortality (compared to no comorbidity), while the co-existence of ≥ 4 comorbidities were associated with a 4-fold increase of death [81]. These observations - that is a significant proportion of patients with COPD have comorbidities (86% to 98%) - have led researchers to conclude that the co-existence of comorbidities (either single or multiple) in COPD is likely to be the rule as opposed to the exception [82].

Comorbidities are common at/in all COPD severities [83-85]. However, it appears that the impact of comorbidities is significantly greater on patients with advanced COPD severity [86]. Data from the Atherosclerosis Risk in Communities (ARIC) study of 20,296 patients showed that worse COPD severity (GOLD stage 3 or 4) was associated with increased odds of comorbidities, even after adjusting for common confounders. These comorbidities (e.g. diabetes, hypertension, and cardiovascular disease)

contributed to worse clinical outcomes such as an increased risk of hospitalisation and mortality [87].

The presence of comorbidities in patients with COPD makes the assessment and clinical management more challenging. To explain, some medications that are commonly prescribed for patients with COPD can potentially worsen or increase the risk of other medical conditions. For instance, bronchodilators may worsen the existing CV disease, or increase the risk of subsequent CV event [88]. Current evidence reports that more than 50% of patients with COPD take more than 4 medications [82]. This may add to the risk of drug interactions, resulting in potential adverse events [89]. In addition, clinical decision making is also complicated, as there are no sufficient recommendations regarding the management of patients with COPD who have comorbidities. The current COPD guidelines (e.g. GOLD and NICE) state that comorbidities should be managed according to usual care. However, identifying and diagnosing co-existing comorbidities is not always easy. Some comorbidities can be asymptomatic, whereas other symptoms (e.g. dyspnoea) may not be specific to COPD. Because of this, there needs to be a holistic approach when identifying and treating comorbidities in COPD.

Based on the preceding discussion, it is evident that comorbidities are a common issue in patients with COPD, with significant impacts on prognosis and management. However, it is noteworthy that studies on the burden of comorbidities (either single or multiple) in COPD are largely heterogeneous in data collection methods and in how patients with COPD were defined. There is a wide disparity with regards to the burden of comorbidities in COPD. This indicates that there is a need for more research to understand the broader spectrum of the disease and its associated comorbidities. There

have been many comorbidities recorded in patients with COPD [73, 79]. Nevertheless, there is a lack of understanding in some of these comorbidities, while others have not been adequately researched. In the following sections, specific comorbidities relevant to this thesis are discussed. These include cardiovascular disease, cognitive impairment, dementia, and depression.

1.8.1 Cardiovascular (CV) disease

1.8.1.1 Cardiovascular disease and lung function

A large body of evidence has demonstrated an association between impaired lung function and cardiovascular (CV) risk, even in the absence of established pulmonary disease [90]. Indeed, current evidence demonstrates that reduced lung function (FEV_1) is a marker of CV mortality, independent of common risk factors (e.g. age, sex, and history of smoking) [91]. Reduced lung function is also a predictor of all-cause mortality [92]. Even a small reduction in FEV_1 has shown to increase the risk of CV events. Recent longitudinal data on 4,761 subjects aged 18-30 years demonstrated that a reduction in FEV_1 (by 10% of FEV_1 percent predicted) and FVC (by 10% in FVC percent predicted) at a younger age, was associated with an 18% (adjusted HR: 1.18; 95% CI: 1.06 to 1.31) and 19% (adjusted HR: 1.19; 95% CI: 1.06 to 1.33) increased risk of CV events, respectively, in middle age, independent of traditional risk factors [93]. Agarwal et al. reported an inverse association between heart failure and FEV_1 – that is increased risk of heart failure with decreased FEV_1 even after adjustments for confounders [94].

There is also an association between CV risk and lung function decline. Analysis from the ARIC study on 10,351 subjects free of CV disease, showed that a fast decline in lung function (defined as a reduction in FEV_1 > 1.9% per year or FVC >2.1% per year)

over a 3-year follow-up period, was associated with a greater risk of CV disease, after accounting for smoking status and other confounders. The same study also showed that a rapid decline in FEV_1 in the first year of follow-up was the most prognostic (HR: 4.22) [95]. Collectively, these findings clearly show that there is an association between impaired lung function and CV risk.

1.8.1.2 Cardiovascular disease and COPD

Cardiovascular disease (CV) is a very common comorbidity in patients with COPD. Both conditions (e.g. COPD and CV disease) share similar risk factors, such as ageing, smoking, and unhealthy lifestyle (e.g. physical inactivity and unhealthy diet) [73]. Patients with COPD and CV disease, compared to subjects without COPD, are at increased risk of hospitalisation [87] and mortality [77, 96]. In addition, it is well-documented that the observed prevalence of CV disease in patients with COPD is independent of age, sex, smoking, and other risk factors [82, 87]. A recent meta-analysis, including 29 datasets, showed that patients with COPD were at 2 to 5 times greater risk of CV diseases (ischaemic heart disease, arrhythmias, heart failure, diseases of the pulmonary circulation, and diseases of arteries) [97]. It is clear that there is a significant CV risk in patients with COPD, which highlights the importance of increasing awareness, and emphases on routine screening/assessment to the CV state to increase detection.

A series of large-scale prospective, population-based studies demonstrated that patients with COPD are at increased risk of CV disease, both as a composite outcome and as a specific disease. It has been shown that patients with COPD are at increased risk of acute CV events, namely myocardial infarction (MI) and stroke [98-100]. In

addition, other studies have also reported increased CV disease other than MI and stroke (e.g. heart failure and arterial fibrillation) [96, 101, 102].

CV disease is also recognised as a significant determinant of survival in patients with COPD. Indeed, it has been shown that patients with COPD are more likely to die from CV disease than from respiratory causes [103]. Data from the Towards a Revolution in COPD Health (TORCH) study showed that CV deaths account for 27% of all deaths (n=911) in patients with moderate to severe COPD [77]. In addition, the Lung Health Study indicated that, even in patients with mild-moderate COPD, CV disease was also a significant cause of death, accounting for 22% of CV mortality [104].

The exact causes of the increased risk of CV disease in COPD remain poorly understood. This may be attributed to common risk factors, such as age, smoking, systematic inflammation, sedentary lifestyle, or conditions that can impair the heart from lung disease [73, 105]. However, what remains unclear is whether there are mechanistic pathways which contribute to the development of CV disease in COPD, or vice versa.

Given the greater burden of CV disease in COPD, healthcare professionals are encouraged to manage and treat comorbidities. This implies increasing the detection of CV disease in those patients. Thus, it is important to consider simple, easy-to-use, sub-clinical biomarkers over and beyond the guideline-recommended diagnostic procedures to assist in the detection and recognition of CV disease.

1.8.2 Cognitive impairment

Cognitive impairment refers to a condition in which individuals experience a decline in their cognitive function (e.g. memory), where deficits do not completely impair

independent functioning [106]. In the UK, the rate of cognitive impairment has been increasing. A recent report showed an increasing trend in the prevalence of cognitive impairment (without a diagnosis of dementia) in the general population (aged ≥ 65 years) over the past 2 decades, from 36.8% in 1991 to 40.4% in 2011 [107]. Several risk factors are associated with increased risk of cognitive impairment and dementia, including advanced ageing, hypoxia [108], systemic inflammation and oxidative stress [109], obesity [110], dietary insufficiencies [111] CV disease [112, 113], physical inactivity [114], smoking [115], and genetics predispositions [116]. Thus, interventions which could reduce the risk or even prevent dementia cases, such as childhood education, regular exercise, maintaining social engagement, and managing CV risk, and smoking cessation, have been suggested [117]. In addition, efforts have also been made to increase awareness and detection of dementia [118].

Cognitive impairment has a significant impact on health and is associated with worse clinical outcomes [119]. Indeed, the presence of cognitive impairment is recognised as a precursor to established dementia [120, 121], despite not all patients with cognitive impairment will eventually develop dementia [122]. A previous study showed that approximately 30% of patients with confirmed cognitive developed dementia over a median of 5-year follow up [122]. Therefore, important to understand the relationship between cognitive impairment and dementia and identify any modifiable risk factors. What remains unclear, however, is what clinical features might predict the progression to dementia.

Making a diagnosis of dementia is ideally made by a comprehensive cognitive test/assessment, which is not often performed in GP practices. Although GP doctors have been supported and encouraged to take an independent role in diagnosing

dementia, there is a hesitance in using the term “dementia” [123, 124]. Therefore, it is assumed that doctors may use the term “cognitive impairment” in place of the term “dementia” more often. This, in turn, may lead to under-or overestimation of the true prevalence of cognitive impairment and dementia. Furthermore, determining the severity of the cognitive impairment (e.g. mild, moderate, etc) can also be missed if no cognitive assessment being performed. This may limit timely appropriate interventions, as well as providing services that are structured to meet patients’ needs.

Although cognitive impairment and COPD have been studied as individual entities, current evidence suggests they often co-exist and may also be inter-related. Indeed, COPD is associated with hypoxemia, hypercapnia, smoking, and CV disease; all of which increase the risk of neuronal injury, and therefore, cognitive impairment and subsequent dementia [106]. Other risk factors have also been proposed, which include systematic inflammation and oxidative stress [106]. However, it is unlikely these factors to fully account for the presence of cognitive impairment and dementia in COPD.

Impaired cognitive function in people with COPD is an important determinant of clinical outcomes. A recent observational study, including 157 patients with COPD referred to a pulmonary rehabilitation program, showed that patients with COPD and co-existing cognitive impairment were less likely to adhere to pulmonary rehabilitation, compared to patients without cognitive impairment (23% vs 10%) [125]. However, PR was effective for patients who completed the program (even in those with cognitive impairment). This suggests that interventions should be taken to reduce the drop-out rates in those patients in order to bring greater benefits.

Cognitive impairment also has a significant impact on dependency and self-management in COPD. A systematic review including 13 studies demonstrated that patients with COPD and cognitive impairment need more assistance in many aspects of daily life activities, and also have improper inhaler technique [126]. Proper inhaler use is a major element for effective self-management, and also for optimising drug delivery [127]. However, there have been no specific recommendations on inhaler use for patients with COPD and co-existing cognitive impairment. Therefore, systematic assessment of the cognitive function in patients with COPD is of clinical importance, as it can make a clear distinction between patients with poor adherence due to cognitive impairment, and those with improper techniques [128].

Current estimates of cognitive impairment in patients with COPD are largely heterogeneous, depending on the study population and methods used to assess cognitive function [129]. Establishing accurate epidemiology of cognitive impairment in people with COPD has relevant clinical implications. This is because cognitive impairment increases the burden of COPD and raises the concern of the increased risk of subsequent dementia. A broader understanding of the association between COPD and cognitive impairment may; therefore, help identify any modifiable risk factors early in the course of the illness, allowing for timely interventions to avoid or at least minimise the risk of progressing to clinical dementia. Moreover, it may also help reduce the negative impact of cognitive impairment on COPD populations.

1.8.3 Dementia

Dementia is a devastating condition, defined as the development of multiple cognitive impairments that significantly interfere with social activities and occupational functioning. It is a progressive and irreversible disease, which contributes substantially

to the health and economic burdens [130]. Currently, there are more than 40 million people suffering from dementia around the world, but the prevalence is projected to increase to 135 million people by 2050 [131]. In the general population, 5-8% of people over 70 years old and 15-60% of people over 80 years old are more likely to develop dementia worldwide [132].

Whereas a growing body of literature has investigated the association between COPD and cognitive impairment, studies on dementia in patients with COPD are generally lacking. A recent systematic review, including 3 Taiwanese studies, reported that patients with COPD were at increased risk of dementia. However, the studies included in the latter systematic review are limited by some methodological flaws such as including patients with asthma [133], undefined follow-up period [134], and inadequate matching group [135]. In addition, another major limitation for the existing studies is the methodology used for COPD ascertainment [136-138]. Rusanen et al. showed that a diagnosis of COPD in midlife was associated with increased risk of mild cognitive impairment/dementia (HR: 1.85, 95% CI: 1.05 to 3.28) [136]. By contrast, a COPD diagnosed in later life (> 65 years) was inversely associated (although not significant) with dementia (HR: 0.30, 95% CI: 0.08 to 1.24). However, it is important to note that the latter study defined COPD based on self-reported history as opposed to a COPD diagnosis that is objectively confirmed, which further limit the applicability of the findings.

The findings of the existing studies regarding the association between COPD and dementia have also been inconsistent. A recent analysis from the ARIC study, including 14,184 subjects aged ≥ 45 years, with a median follow-up of 23 years, showed a nonsignificant risk of dementia in patients with COPD (n= 2,490) compared

to subjects without COPD (n=6,108) following adjustments for confounders (adjusted HR: 1.08; 95% CI: 0.92 to 1.27) [137]. In contrast, a Chinese study, with a short follow-up (3 years), showed that a self-reported COPD diagnosis in older subjects (mean age: 82.9 years) was associated with an increased risk of dementia (adjusted HR: 1.89; 95% CI: 1.07 to 3.33) [138]. Given the heterogeneity in the current literature, there is a need to further explore the relationship between COPD with cognitive impairment and dementia. Up to date, there are no previous population-based studies, which investigated the prevalence and incidence of cognitive impairment and dementia in patients with COPD in the UK.

1.8.4 Depression

The co-existence of poor mental health in COPD has a significant effect on health and prognosis. Depression is among the most common and modifiable comorbidities in COPD, contributing to impaired quality of life, poor adherence to medications and pulmonary rehabilitation [139, 140], and increased risk of death [141].

Depression is frequent, even in patients with mild COPD [142]. The reported prevalence varies across studies, as a result of differences in terms of the study's population and design. It is estimated that depression affects 27% [143] to 40% [144] of patients with stable COPD. The prevalence of depression also increases in line with the severity of COPD. Data from the ECLIPSE study showed that patients with more severe COPD (defined based on GOLD) had a higher prevalence of depression compared with lower COPD stage [145]. Furthermore, older studies indicated that patients with COPD are at increased risk of depression [146-148] and that patients with severe COPD (defined as oxygen use) are associated with a two-fold higher risk

of depression compared with mild COPD (defined as patients who received no drug treatment) [147].

Although the current guidelines recommend recognising depression in patients with COPD [40], there has been no evidence that depression is currently part of the standard assessment. Depressive symptoms may remain undiagnosed in patients with COPD; thus, undertreated [149], ultimately to the detriment of patients. Current evidence suggests that more than 60% of patients with COPD and depression receive no treatments [150]. Identifying depression as early as possible allows healthcare providers to develop appropriate strategies that meet patients' needs and guide the choice of pharmacological and non-pharmacological therapies. Therefore, it is important to recognise depression and be vigilant to symptoms to ensure that it is appropriately managed alongside COPD.

The current COPD guidelines (e.g. GOLD) indicate that the management of comorbidities in the presence of COPD should be done according to usual care [1]. This means that depression (when co-exists with COPD) should be managed using the existing guidelines for depression. However, it is important to be cautious when managing these patients, especially when prescribing antidepressants. As such, it is crucial to guide the choice of pharmacological treatment, as the risk of drug interactions may be increased, leading to adverse events. Recent evidence suggests that antidepressants are associated with an increased risk of respiratory-related morbidities (e.g. pneumonia, emergency visits, and hospitalisations) in patients with COPD compared to patients with COPD who do not use antidepressants [151]; however, this requires further investigation.

1.9 **Circulating Biomarkers**

There has been growing interest in identifying clinically relevant biomarkers in COPD. According to the National Institutes of Health, biomarkers are defined as "*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*" [152]. Unlike a physiological measure (FEV_1 and FVC), biological markers are considered to be substances. The clinical applications of biomarkers can include predicting the disease's course and severity, determining prognosis, categorising different clinical phenotypes, monitoring drug response, and assessing the pathophysiology of disease [153]. Potential characteristics of a clinically useful biomarker are to be safe, precise, reproducible, measurable, inexpensive, and easy to implement into clinical practice [152, 154, 155]. However, it is acknowledged that new biomarkers development is extremely challenging, as in many cases, biomarkers may fail because of poor reproducibility. For the selected biomarkers in this thesis, the purpose was not to reproduce previous findings; but rather, to increase understanding of the role of simple clinically relevant biomarkers.

Promoting CV disease prevention or at least minimising low CV risks have been of great interest [156]. Although, as previously discussed, there is an increased burden of CV disease in patients with COPD, there is inadequate information on how to assess the CV state in patients with COPD. There is also uncertainty regarding the optimal method for assessing CV risk in patients with COPD.

The clinical presentation of COPD is largely heterogeneous, making it unlikely for a single marker to capture the increased risk of CV abnormalities. Thus, changes in patient care are needed, so that the CV risk in patients with COPD are addressed. This

implies using a multi-dimensional approach, where other measures should be made available to address CV risk as opposed to merely assessing the lung function status in patients with COPD [157-159].

The field of biomarkers in COPD has received great interest. It is indeed of clinical importance to assess the CV abnormalities in patients with COPD. Several biomarkers have been investigated in the literature, including C-reactive protein (CRP), fibrinogen, surfactant protein [160-162]. Indeed, the role of CRP as a CV biomarker has been reported in the literature – that is increased CRP level is associated with increased risk of CV disease [163, 164]. In the setting of COPD, however, there seems to be inconsistency across studies. While some literature suggests that CRP relates to CV risk in patients with COPD [165, 166], another suggests otherwise. Findings from a recent multicentre study (n= 729) showed that neither CRP nor fibrinogen were associated with the non-invasive CV risk measure (as measured by aortic PWV) in patients with COPD [167]. It is worth noting that fibrinogen is the only biomarker with approval as a drug development tool for COPD [168]. Nevertheless, identifying inflammatory comorbidities, such CV disease, by fibrinogen remains not fully understood [169]. Therefore, there is a need to identify biomarkers that can help improve CV risk detection in patients with COPD.

Herein, two biological markers that have shown to have a predictive CV risk values in other disease groups and in the general population are explored in patients with COPD. These include soluble Receptor for Advanced Glycation End-products (sRAGE) and Microalbuminuria (MAB). In the following sections, the structure and clinical utility of these biomarkers will be briefly highlighted.

1.9.1 Advanced Glycation End-products (AGEs)

Advanced Glycation End-products (AGEs) are a heterogeneous group of compounds, which are irreversibly formed by a non-enzymatic glycation and oxidation reactions of lipids and proteins. Typically, AGEs are formed at a slow rate and accumulate in tissues with chronological ageing. The rate of this process accelerates under oxidative and inflammatory stress, leading to increased levels of AGEs; thereby contributing to age-related pathogenesis [170-172]. A previous prospective population-based study including subjects over the age of 65 years (n=1013) showed that increased AGEs was associated with increased risk of CV mortality (HR:1.84; 95% CI: 1.30 – 2.60) compared to subjects with lower AGEs [173].

1.9.2 Receptor for Advanced Glycation End-products (RAGE)

The receptor for advanced glycation end-products (RAGE) is a member of the immunoglobulin superfamily of cell-surface, and a pattern-recognition receptor that interacts with multiple ligands [174]; one of which is AGEs. RAGE is at highest baseline level in the lungs, including proximal and distal airways [175, 176]. However, it is expressed at a very low or undetectable level in most other body tissues [175]. Wheresoever its ligands accumulate, RAGE is overexpressed. This can be seen in conditions associated with inflammation, such as CV disease and COPD.

1.9.3 Soluble Receptor for Advanced Glycation End-products (sRAGE)

RAGE exists in two isoforms, namely membrane (mRAGE) and soluble (sRAGE). The physiological function of sRAGE is not yet fully understood. However, it has been suggested that sRAGE can act as a decoy receptor for RAGE ligands by blocking the binding of AGEs to RAGE.

1.9.3.1 Soluble RAGE and COPD

The role of AGE and RAGE in both the airways and circulation has been studied in COPD. AGEs levels have shown to be significantly elevated in patients with COPD. [177]. Ferhani et al. also reported that smokers with COPD have significantly increased levels of RAGE, especially in their proximal and distal airways, compared to non-smokers and smokers without COPD. In contrast, studies have consistently shown that sRAGE levels are reduced in patients with COPD, in comparison to subjects without COPD [178-181]. Besides, reduced sRAGE levels are directly associated with FEV_1 [179, 182-184], and inversely associated with GOLD severity [181]. A weak association between lower sRAGE levels and FEV_1/FVC decline over 4 years has also been reported [178].

1.9.3.2 Soluble RAGE and CV disease

Studies on the associations between sRAGE and CV events are largely heterogeneous, with some studies showing inverse associations between sRAGE with CV disease [172, 185, 186], while others are showing positive associations [187, 188]. The discrepancies across studies are attributed to different study designs and populations. A recent 3-year longitudinal study, involving 933 patients with CV disease demonstrated that increased sRAGE was associated with a new CV event [189]. Furthermore, Nin et al. indicated that elevated sRAGE at baseline in subjects with type 1 diabetes (n= 339) free of CV disease was associated with increased risk of incident CV disease and all-cause mortality [170]. It is worth noting, though, that this association has also been shown in subjects without diabetes [190, 191]. Whether sRAGE is related to the CV status in patients with COPD remains unknown.

1.9.4 Microalbuminuria (MAB)

Microalbuminuria (MAB) is defined as a moderate increase in urinary albumin (protein) above the normoalbuminuria range. The clinical threshold, which defines MAB, is based on increased urinary albumin creatinine ratio (UACR) of 2.5 mg/mmol in males and 3.5 mg/mmol in females. Increased UACR above the level of MAB is termed "macroalbuminuria (UACR > 30 mg/mmol)", and it is likely to be associated with both significant kidney damage and CV disease.

1.9.4.1 Microalbuminuria and CV disease

Microalbuminuria is considered the hallmark of early kidney damage in individuals with diabetes [192], independent of the overall measure of kidney function the estimated glomerular filtration rate (eGFR) [193]. In addition, MAB is is an indicator of increased CV risk and a predictor for mortality in the general population [194-197]. MAB has also been related to arterial stiffness – a non-invasive physiological CV measure and a predictor of CV events (assessed by pulse wave velocity) – in individuals with diabetes, hypertension, and in subjects from the general population [198-200]. Furthermore, even a small increase in UACR within the normal limits is still associated with an increased risk of renal and CV disease [201]. A collaborative meta-analysis, involving 105,872 participants from the general population indicated that an albumin creatinine ratio (ACR) of 1.1 mg/mmol (which is below the threshold of microalbuminuria) was associated with a 20% amplified risk of all-cause mortality [202]. These findings highlight that MAB can be used in other disease groups associated with increased CV risk; one of which is COPD.

1.9.4.2 Microalbuminuria and COPD

The limited number of studies which investigated the prevalence of MAB in patients with COPD have shown that MAB is frequent in patients at times of exacerbations [203, 204] and at clinical stability; although the prevalence varies across studies [205-207]. John et al. demonstrated that patients with COPD (n=52) at clinical stability had glomerular damage evidenced by increased UACR, and associated with aortic stiffness in patients with COPD, compared to smokers without COPD (n=34) [208]. Findings from the Nord-Trøndelag Health Study involving 3,129 participants also reported that patients with COPD and confirmed MAB (n=136) were at 54% increased risk of all-cause mortality, compared to patients with COPD without MAB (n=495)[209]. Of importance though, these results remained the same even after excluding CV disease at baseline. Microalbuminuria may be a potential marker to detect patients with COPD at increased CV risk and mortality; nevertheless, further investigations are needed.

1.10 **Summary and aims of the studies in this thesis**

COPD presents a significant public health issue, with increased prevalence, morbidity, and mortality globally. COPD is associated with a number of comorbidities, including CV disease, cognitive impairment, dementia, and depression. These comorbidities have a considerable impact on disease management and are associated with increased morbidity and mortality. Increase the understanding of these comorbidities has important management implications for the multidisciplinary team who manage COPD across primary and secondary care.

Although a significant proportion of patients with COPD suffer and die from CV disease, assessment of CV status is neither performed at diagnosis nor during follow-up. Simple, clinically relevant biomarkers may help identify patients at increased CV risk and assist in assessing and diagnosing patients in clinical settings. Two possible biomarkers are investigated in this thesis, which might have a role in COPD related to prognostication/presence of CV comorbidities: 1) soluble Receptor for Advanced Glycation End-products (sRAGE) and 2) Microalbuminuria (MAB).

Cognitive impairment and dementia are common in COPD, yet there are considerable disparities in the report of their prevalence and incidence within the general COPD population. Further, the awareness of the increased burden of cognitive impairment and dementia in patients with COPD emphasises the need for more research. Also, depression is amongst the understudied key comorbidities in COPD, with serious impacts on health and prognosis.

This introduction underlines important gaps in our understanding of COPD comorbidities and circulating biomarkers. Reviewing the existing literature has

enabled me to address these gaps by applying different methodologies from clinical and epidemiological perspectives. Thus, the specific aims of this thesis are:

1- To explore the potential role of sRAGE as a cardiovascular (CV) biomarker, in patients with COPD from the ERICA multicentre cohort of stable patients Chapter 2).
2- To determine the prevalence of microalbuminuria (MAB) and explore the role of MAB as a CV biomarker in patients with COPD at clinical stability, using data from the ERICA cohort (Chapter 3).
3- To report the prevalence of cognitive impairment and dementia at the time of COPD diagnosis, compared to subjects without COPD, using primary care data within The Health Improvement Network (THIN) (Chapter 4).
4- To determine the incidence of cognitive impairment and dementia in patients with COPD, compared to subjects without COPD, using the THIN database (Chapter 4)
5- To determine the incidence of newly diagnosed depression or antidepressant prescription following a diagnosis of COPD and compare this to subjects without COPD using the THIN database (Chapter 5).
6- To evaluate the association between antidepressant prescription and respiratory-related morbidity (pneumonia and COPD exacerbations) in patients with COPD, using the THIN database (Chapter 6).

Chapter 2 Soluble Receptor for Advanced Glycation End Products (sRAGE) and Cardiorespiratory Physiology in COPD: the ERICA Study

2.1 INTRODUCTION

It is well-established that patients with COPD are at increased risk of cardiovascular (CV) disease independent of age, gender, smoking and other common risk factors [87, 97]. Whilst CV disease is a known cause of morbidity [87] and mortality [73] in COPD, there is no systematic assessment of CV status in routine practice. Thus, a shift in patient care is needed to actively assess and screen CV risk in patients with COPD.

Given the impact of CV disease on COPD, early detection is important. Although CV risk scores (which use algorithms to predict CV risk) have been developed to identify those at increased CV risk and to guide treatment [210, 211], they do not include COPD, which gives a cause for concern that CV risk estimation may not be optimal in COPD [212]. Other methods for assessing the CV risk have been suggested. Aortic stiffness, determined by aortic pulse wave velocity (PWV), is a non-invasive measure of vascular function and an independent marker for increased CV risk in both the general population and in patients with COPD [213-215]; however, it is not part of routine clinical practice. Carotid intima-media thickness (CIMT), a surrogate for subclinical atherosclerosis, is another subclinical marker that has been associated with increased CV risk and mortality in COPD patients [216, 217]. However, the use of CIMT in clinical settings is limited, owing to its high cost and technical nature. The identification of CV biomarkers using a fresh approach to aid the assessment of patients with increased CV risk is therefore of interest.

Advanced Glycation End-products (AGEs), its receptor (RAGE) and soluble receptor (sRAGE) have been implicated in CV disease [218]. AGEs are markers of inflammatory and oxidative stress which can damage tissues (e.g. collagen and elastin) by modifying protein function and structure through cross-linking between molecules

or by binding with it receptor - RAGE [219]. sRAGE, which can be detected in blood samples, has predictive value for CV risk in other disease groups [170, 188, 189] and may, therefore, be applicable as a CV biomarker in COPD.

The role of AGEs, RAGE (in the airways), and sRAGE (in the circulating) in COPD has been considered [177, 179, 220]. Current evidence shows associations of COPD with sRAGE [179, 181]. RAGE appears to have a pathogenic role in COPD whilst sRAGE appears to be protective. In a case-control study, Ferhani et al. demonstrated that patients with COPD (n = 30) have increased levels of RAGE, especially in their proximal and distal airways (bronchial tissues), compared to never smokers (n = 20) and smokers without COPD (n = 20) [220]. On the other hand, sRAGE is found at lower levels in patients with COPD compared to those without COPD [178-180]. Smith et al. reported that the reduction in sRAGE levels in patients with COPD was independently associated with the degree of airflow obstruction, as defined by FEV_1 [179]. John et al. also reported direct associations between sRAGE and spirometric measures but not with aortic stiffness [221]; however, the role of sRAGE as a CV biomarker in COPD has not been fully explored.

Given the existing literature, it is hypothesised that sRAGE is independently related to measures of CV risk and lung function. The aim of this chapter is to evaluate whether sRAGE is associated with measures of both CV and lung functional status in patients with COPD in the 'Evaluating the Role of Inflammation in Chronic Airway disease' (ERICA) cohort.

2.2 METHODS

2.2.1 Design

The ERICA study is an observational, longitudinal study that was conducted at five centres across the UK (Nottingham, Cambridge, London, Liverpool and Cardiff) and supported by Innovate UK (formerly the Technology Strategy Board). This chapter provides an analysis of the baseline, cross-sectional data of one aspect of the ERICA study. The patient recruitment and data collection were conducted by research personnel at the five universities prior to the commencement of my PhD.

2.2.2 Subjects

The ERICA study has been described in detail in the literature [222]. Briefly, the study included 729 patients with confirmed COPD (GOLD II–IV). All subjects provided written informed consent. The study was approved by the Cambridge South East Research Ethics Committee (REC: 11/EE/0357), and the research and development departments at each participating site [222]. The ERICA study was registered with the UK Clinical Research Network Study Portfolio.

The original ERICA study was powered based on tertiary analysis of two key variables: aortic pulse wave velocity and quadriceps maximal volitional contraction, with an estimated sample of 800 patients. Additional information can be found in the original protocol [222].

2.2.3 Inclusion and exclusion criteria

Patients were included if they were clinically diagnosed with COPD, had a post-bronchodilator forced expiratory volume in the first second (FEV_1) of ≤80% of predicted values, had a baseline FEV_1/forced vital capacity (FVC) ratio of <0.7, were

40 years of age or older, had a smoking history of ≥ 10 pack years, and were clinically stable (no hospitalisation or exacerbation) for at least four weeks prior to the study commencement. Participants were excluded if they were unable to provide written consent, were deficient in alpha-1 antitrypsin, had neurological or muscular disorders, were pregnant or were participating in a trial of an experimental drug. Patients with other self-reported comorbidities, such as diabetes, cerebrovascular disease or ischaemic heart disease (IHD) were deliberately not excluded to be representative of clinical practice.

2.2.4 Measurements

All study measurements were conducted at baseline over two visits. Details of the standardised procedures and outcome measures that were used in all participating centres are described elsewhere [222]. Measurements of interest that are relevant to this study are described in this chapter.

Cardiovascular measurements

- Blood Pressure

Blood pressure (BP) was measured in the non-dominant arm in the supine position after 10 minutes of rest, and an average of the final two out of three measurements (separated by a 1-minute interval) was recorded. A further recording was considered if the difference between the second and third readings was greater than 5mm Hg. Mean arterial pressure (MAP) and pulse pressure (PP) were calculated. Heart rate (HR) was also measured. The calculations of MAP and PP were conducted as follows:

- MAP = ((2 x diastolic blood pressure) + systolic blood pressure) ÷ 3
- PP= systolic blood pressure – diastolic blood pressure

- Aortic pulse wave velocity

Aortic (carotid-femoral) pulse wave velocity (PWV) was calculated via the SphygmoCor® system (AtCor,West Ryde, Australia), using a piezoelectric tonometer placed over the artery and Electrocardiogram (ECG) gating as described previously [222]. Patients fasted for at least 4 hours and refrained from bronchodilators for at least 6 hours before the aortic PWV measurement.

- Carotid intima-media thickness

High-resolution B-mode ultrasound imaging using a 7–12 MHz linear probe [222] was applied to determine the carotid intimal medial thickness (CIMT) of the right and left common carotid arteries, measured at 1 cm from the carotid bulb. Measurements were obtained following 10 minutes of supine rest. Each artery had three 10-second loops recordings. The highest values for the right and left CIMT were recorded, and the mean was used in the analysis. Image analysis was conducted using Vascular Tools 5 software (Medical Imaging Application LLC, Coralville, USA).

Anthropometry and lung function

Height and weight were measured, and body mass index (BMI) was calculated. Fat-free mass (FFM) was determined using bioelectric impedance (Tanita Corporation, Tokyo, Japan). A height squared fat-free mass index (FFMI) was calculated.

Post-bronchodilator spirometry was performed within 1 hour of administration of the patient's bronchodilator to determine the post-bronchodilator FEV_1, FVC and FEV_1/FVC ratio.

Blood parameters, biochemistry and other measurements

Venous blood samples were drawn from a peripheral vein by venepuncture after four hours of fasting and six hours of refraining from medications [222]. Plasma sRAGE

levels in the venous blood samples were determined using an enzyme-linked immunosorbent assay (ELISA) method in batched samples following storage at -80 degrees celsius. Cholesterol profiles were also obtained. The estimated glomerular filtration rate (eGFR) was calculated [223].

Detailed histories, including comorbidities, medication and smoking, were recorded. Participants completed the COPD assessment tool (CAT) questionnaire [224].

2.2.5 Statistics

Data were analysed using Stata (version 15) statistical software. The results are presented as number (%) or arithmetic mean (SD) for categorical and continuous variables, respectively. The normality of the data was graphically assessed. Within group differences (e.g. smokers vs ex-smokers) in the mean (SD) sRAGE levels were analysed using parametric tests (independent sample t-test and one-way analysis of variance (ANOVA)).

The primary analyses tested the associations between sRAGE and CV measures (aortic PWV and CIMT), and lung function measures. Correlation of sRAGE with aortic PWV, CIMT, lung function measures and other factors was determined using Pearson's correlation coefficient. Multiple linear regression was performed to assess whether sRAGE was independently associated with aortic PWV, CIMT, and lung function measures, with adjustment for potential confounders. Confounders were considered as such if they changed the regression coefficient by 10%. Known CV risk factors (e.g. smoking) have also been considered for their confounding effects. All potential covariates were assessed in separate regression models. A P value of <0.05 was considered significant. For assessing the association with aortic PWV and CIMT, adjustments were made for BMI, FEV_1% predicted, smoking status, smoking history, pulse pressure and self-reported comorbidities (diabetes, cerebrovascular disease or

IHD). For assessing the association of sRAGE with FEV_1% predicted, adjustments were made for BMI, smoking status, smoking history and the presence of self-reported comorbidities. *A priori* confounders such as age and gender were considered regardless of their confounding effects. These associations were assessed in all patients with COPD and then in those without self-reported comorbidities (diabetes, cerebrovascular disease or IHD).

2.3 **RESULTS**

Out of a total of 746 patients screened, 729 met the inclusion criteria. Of those, 677 subjects were included in this analysis, representing those with a sRAGE result (Figure 2-1). The mean (SD) age of the study population was 67 (8) years, and there were more males (62%) than females. A third of the cohort were current smokers and the mean (SD) FEV_1% predicted was 52.4% (16%). The population had mean (SD) levels of sRAGE of 1056 (543.2) pg/ml, aortic PWV of 10.2 (3) m/sec and CIMT of 0.78 (0.2) mm. The baseline characteristics for the patients included in the ERICA study, and those included in this analysis are presented in Table 2-1.

Figure 2-1. Flow chart of the study

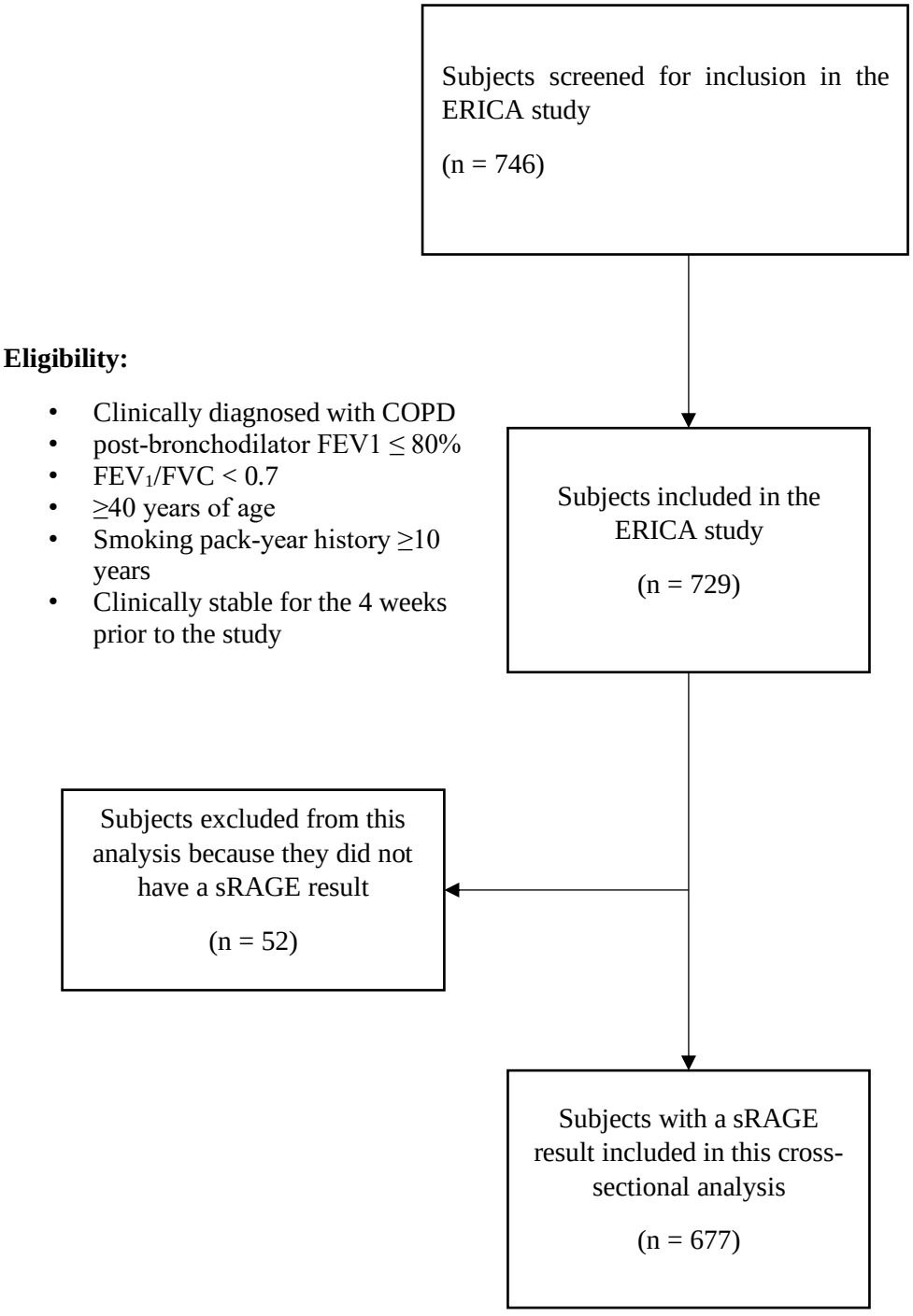


Table 2-1. Characteristics of patients included in the ERICA study

Variable/ (No. missing observations*)	Subjects in ERICA study (n = 729)	Subjects with sRAGE result (n = 677)
Age (years)	67 (8)	67 (8)
Gender (male %)	441 (61%)	417 (62%)
Clinical parameters		
BMI (kg/m^2)/(n = 11)	27.3 (5.8)	27.3 (5.7)
Fat-free mass index (FFM kg/m^2)/(n = 37)	18.2 (2.7)	18.2 (2.6)
CAT score/(n=16)	19.7 (8.4)	19.6 (8.4)
Smoking history (pack-years)/(n = 10)	47.6 (27.7)	47.6 (27.2)
Current smokers (%)	220 (30%)	208 (31%)
Ex-smokers (%)	503 (69%)	466 (69%)
Unknown/missing (%)	6 (1%)	3 (0.4%)
Lung function parameters		
FEV_1 (L)/(n = 3)	1.34 (0.53)	1.34 (0.52)
FVC (L)/ (n=3)	2.8 (0.87)	2.8 (0.86)
FEV_1% predicted /(n = 3)	52.2 (16.1)	52.4 (16.1)
FEV_1/FVC ratio/(n = 3)	0.48 (0.13)	0.48 (0.12)
Haemodynamic parameters		
Aortic PWV (m/s)/(n = 67)	10.3 (2.6)	10.2 (2.6)
Mean CIMT (mm)/(n = 71)	0.78 (0.16)	0.78 (0.16)
Supine systolic BP (mm Hg)/(n = 16)	138 (17)	138 (17)
Supine diastolic BP (mm Hg)/(n = 16)	77(10)	77 (10)
Supine MAP (mm Hg)/(n = 16)	97 (11)	97 (11)
Supine PP (mm Hg)/(n = 16)	61 (13.7)	61 (15.2)
HR (bpm)/(n = 58)	70 (12)	70 (12)
Blood biochemistry		
sRAGE (pg/ml)/(n = 52)	—	1056 (543.2)
eGFR (ml/min)/(n = 41)	88 (18.3)	88. (18.4)
Total cholesterol (mmol/L)/(n = 15)	5.1 (1.2)	5.1 (1.1)
LDL cholesterol (mmol/L)/(n = 38)	2.9 (0.9)	2.9 (0.9)
HDL cholesterol (mmol/L)/(n = 14)	1.5 (0.5)	1.5 (0.5)
Self-reported comorbidities		
Diabetes (%)/(n = 8)	82 (11%)	79 (12%)
IHD (%)/(n = 10)	57 (8%)	54 (8%)
Cerebrovascular disease (%)/(n = 10)	57 (%)	54 (8%)
Medications		
High blood pressure [a] (%)/(n = 418)	248 (34%)	228 (33.8%)

Values are presented as mean (SD) unless otherwise stated.
Abbreviations: BMI: body mass index; BP: blood pressure; CAT: COPD assessment test; CIMT: carotid intima-media thickness; eGFR: estimated glomerular filtration; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; distance; FM: fat-free mass; HR: heart rate; IHD: ischaemic heart disease; MAP: mean arterial pressure; PP: pulse pressure; PWV: pulse wave velocity; sRAGE: soluble receptor for advanced glycation end products.
* Number of missing observations per variable from subjects in ERICA study (n = 729).
[a] list of high blood pressure medications is provided in the appendices (Appendix 9-1).

Associations of sRAGE levels with vascular measures

The results of the associations of sRAGE (as the dependent variable) with aortic PWV and CIMT are presented in Table 2-2. sRAGE was not found to be associated with either aortic PWV ($p = 0.312$; $n = 619$) or CIMT ($p = 0.413$; $n = 615$) overall or in the subgroup without self-reported comorbidities.

In all patients, there was a positive weak correlation between sRAGE and pulse pressure ($r = 0.13$; $p < 0.001$), and inverse correlations with heart rate ($r = -0.11$; $p = 0.002$) and diastolic blood pressure ($r = -0.09$; $p = 0.022$). Similar correlations were also observed in the subset without comorbidities, as shown in Table 2-3.

Table 2-2. Analysis of the associations of sRAGE with aortic PWV, and CIMT in 1) all subjects with COPD and 2) subjects without comorbidities

Dependent variable: sRAGE (pg/mL)			
All patients with COPD			
	β (95% CI)	**Adjusted β (95% CI)**	**P-value**
Aortic PWV – per 1 m/sec change	-14.1 (-31.2 to 3.1) (n = 619)	-9.4 (-23.7 to 11.7)[1] (n = 606)	0.503
CIMT – per 1 mm change	-59.6 (-327.1 to 207.8) (n = 615)	-111.9 (-383.2 to 159.3)[1] (n = 602)	0.413
Patients without comorbidities			
	β (95% CI)	**Adjusted β (95% CI)**	**P-value**
Aortic PWV – per 1 m/sec change	-6.7 (-27.3 to 13.8) (n = 473)	-2.10 (-23.7 to 19.5)[2] (n = 464)	0.848
CIMT – per 1 mm change	-22.7 (-313.6 to 268.3) (n = 461)	-88.9 (-396.7 to 218.8)[2] (n = 451)	0.146

[1] Adjusted for age, sex, BMI, smoking status, smoking history, PP, self-reported comorbidities and study site.
[2] Adjusted for age, sex, BMI, smoking status, smoking history, PP and study site.
Abbreviations: BMI: body mass index; CI: confidence interval; CIMT: carotid intima-media thickness; FEV_1: forced expiratory volume in 1 second; PP: pulse pressure; PWV: pulse wave velocity.
Self-reported comorbidities: diabetes, ischaemic heart disease and cerebrovascular disease.

Table 2-3. Correlations between sRAGE and vascular measures in 1) all patients with COPD and 2) patients without self-reported comorbidities

Variable	All patients with COPD		Patients without comorbidities	
	sRAGE		sRAGE	
	r	P-value	r	P-value
Age	0.15 (n= 677)	<0.001	0.12 (n= 514)	0.004
Supine PP	0.13 (n= 670)	<0.001	0.10 (n= 508)	0.017
Supine DBP	-0.09 (n= 670)	0.002	-0.08 (n= 508)	0.048
HR	-0.11 (n= 628)	0.002	0.09 (n= 479)	0.032

Abbreviations: DBP: diastolic blood pressure; HR: heart rate; PP: pulse pressure.
Patients without comorbidities: excluding patients with diabetes, ischaemic heart disease, and cerebrovascular disease

sRAGE levels in relation to self-reported comorbidities and smoking status

Analysis of sRAGE levels in the subgroup of patients with self-reported IHD (n = 54) compared to those without (n = 616) showed no statistical difference (1123 [555.5] vs. 1051 [544.5] pg/mL; p = 0.353). Similarly, there was no statistical significant difference in sRAGE levels in those with diabetes (n = 79) and those without (n = 593; 1006 [475.7] vs. 1064 [553.2] pg/mL; p = 0.375).

sRAGE levels were also compared in current (n = 208) and former smokers (n = 466). There was no statistical difference in the mean (SD) sRAGE levels in current 1081 (574.6) pg/mL and ex-smokers 1045 (529.9) pg/mL (p = 0.428) and the history of smoking was not associated with sRAGE (r= -0.05; p = 0.195).

Association of sRAGE with lung function measures

The mean sRAGE levels for each of the GOLD stages of COPD (II, III, IV) are presented in Table 2-4. As seen, there was a progressive decrease in the sRAGE level as the GOLD severity increased (p = 0.001). Even after adjusting for confounders, a more advanced COPD stage was associated with reduced sRAGE compared to less severe COPD, Table 2-5.

Table 2-4. sRAGE according to stages of COPD based on GOLD classification

GOLD stage	n	sRAGE (pg/ml)
GOLD II	335 (49%)	1146.9 (626.6)
GOLD III	279 (41%)	978.6 (430.2)
GOLD IV	61 (9%)	920.9 (427.9)

Results are presented as mean (SD)
Abbreviation: GOLD: Global Initiative for Chronic Obstructive Lung Disease

Pearson correlation analysis showed that there was a positive weak correlation between sRAGE and FEV_1% predicted (r = 0.12; p = 0.001; n = 675) and FEV_1/FVC (r = 0.15, p < 0.001, n = 675) in all patients with COPD. This was also seen in patients without self-reported comorbidities for FEV_1% predicted (r = 0.11; p = 0.14; n = 512) and FEV_1/FVC (r = 0.14; p = 0.001; n = 512).

A multiple linear regression model showed that FEV_1% predicted was associated with sRAGE levels following adjustment for age, sex, BMI, smoking status, smoking history self-reported comorbidities, and study site (adjusted β: 3.5 pg/mL; 95% CI: 1.16–6.52; p = 0.001; n = 664; Table 2-5). In the subset of patients without either diabetes, cerebrovascular disease or ischaemic heart disease (n = 514), sRAGE remained independently associated with FEV_1% predicted (adjusted β: 3.4 pg/mL; 95% CI: 0.40–6.5; p = 0.026; n = 503; Table 2-5).

Table 2-5. Analysis of the associations of sRAGE with lung function measures

Dependent variable: sRAGE (pg/mL)			
All patients with COPD			
	β (95% CI)	**Adjusted β (95% CI)**	**P-value**
FEV_1 – per 1% predicted change	4.2 (1.6 to 6.8) (n = 675)	3.5 (1.2 to 6.5)[1] (n = 664)	0.005
GOLD stage			
GOLD II	Reference	Reference	
GOLD III	-168.5 (-253.9 to -83.1)	-183.8 (-269.6 to -98.1)[1]	<0.001
GOLD IV	-225.9 (-372.6 to -79.2)	-202.7 (-351.2 to -54.3)[1]	0.008
Patients without comorbidities			
	β (95% CI)	**Adjusted β (95% CI)**	**P-value**
FEV_1 – per 1% predicted change	3.6 (0.7 to 6.5) (n=512)	3.4 (0.4 to 6.5)[2] (n=503)	0.026
GOLD stage			
GOLD II	Reference	Reference	
GOLD III	-153.3 (-253.9 to -52.7)	-209.7 (-313.5 to -105.9)[2]	0.001
GOLD IV	-182.9 (-347.6 to -18.2)	-233.1 (-406.6 to -59.5)[2]	0.009

[1] Adjusted for age, sex, BMI, smoking status, smoking history, self-reported comorbidities and study site.
[2] Adjusted for age, sex, BMI, smoking status, smoking history and study site.
Abbreviations: BMI: body mass index; CI: confidence interval; FEV_1: Forced expiratory volume in 1 second.
Self-reported comorbidities: either diabetes, ischaemic heart disease or cerebrovascular disease.

2.4 **DISCUSSION**

In this well-defined group of patients with COPD, a direct, independent association was found between sRAGE, and FEV_1 % predicted, albeit weak. However, neither aortic stiffness nor carotid intima-media thickness were associated with sRAGE, despite separate reports in the literature supporting the role of sRAGE in both COPD and CVD [172, 179]. Therefore, this study does not support the application of sRAGE as a clinical CV biomarker in patients with COPD.

sRAGE and CV risk in COPD

sRAGE has been studied in several other chronic inflammatory conditions, including CV disease, a common COPD comorbidity. However, the literature on the associations of sRAGE with CV events is inconsistent with studies showing both direct and inverse associations [186, 225]. These discrepancies are attributed to study designs (e.g., cross-sectional and longitudinal), study populations, and ethnic groups. However, increased sRAGE levels have been associated with CV events in some disease groups [188-190, 226]. Nin et al. demonstrated that elevated sRAGE at baseline in subjects with type 1 diabetes (n = 339) free of CV disease, followed for 12 years, was associated with an increased risk of CV disease and mortality [170]. Recently, a 3-year longitudinal study of patients with proven CV disease (n = 933) demonstrated that elevated sRAGE was associated with new CV events [189], highlighting the possibility that sRAGE may have different relationships in different disease states.

It is well-established that patients with COPD are at increased CV risk. Current evidence shows that patients with COPD have increased aortic stiffness and CIMT relative to subjects without COPD. Contrary to expectations, the present study found no associations between sRAGE and subclinical vascular measures (aortic PWV or

CIMT), or with CV disease or diabetes. This suggests that sRAGE is unlikely to be a useful clinical marker to address the CV status in COPD, adding further evidence to the existing literature [221]. Although a study by John and colleagues [221] demonstrated a weak association between aortic stiffness (PWV) and skin AGEs (which are increased in COPD), they failed to find an association with sRAGE. Whereas some literature shows reduced sRAGE levels in patients with COPD [178, 179, 181], the opposite appears to be true in CV disease [189], which may explain the lack of association here. Furthermore, the finding that there was no difference in sRAGE levels in patients with and without IHD suggests that the reduced sRAGE consistently reported in COPD is unlikely to be attributed to the presence of CV disease, in line with the existing literature [179]. However, it is still important to consider the likelihood of the presence of subclinical CV disease in patients with COPD, which emphasises the need for a new approach for CV disease prognostication.

sRAGE in patients with COPD and lung function

There has been recent interest in the possible role of sRAGE in predicting disease progression and assisting in phenotyping in subjects with COPD [227]. Current research shows that sRAGE levels are lower in patients with stable COPD compared to subjects without COPD [179, 181]. Smith et al. reported that patients with COPD (GOLD II or worse) have reduced sRAGE levels compared to healthy controls [179]. The mechanisms behind the reduced sRAGE levels that are consistently found in patients with COPD are currently unknown. Although this study did not have a comparator group (e.g., control), the mean (SD) sRAGE levels presented in this study are comparable to those reported from previous studies in patients with stable COPD [184, 221]. Gopal et al. reported a mean (SD) sRAGE of 1042.41 (928.81) pg/mL in

patients with stable COPD (GOLD I-IV; n = 146) compared to 1477.66 (668.68) pg/mL in healthy controls (n=81) [184].

The finding that lower sRAGE is independently associated with lung function (FEV_1) is concordant with the current literature [179, 181]. This study also found an inverse association between sRAGE and COPD severity, extending the findings from a previous study [181]. Gopal et al. demonstrated that reduced sRAGE level in patients with COPD is related to lung function, and patients with COPD receiving long-term oxygen therapy have lower levels of sRAGE than patients not receiving oxygen [184].

The longitudinal association of sRAGE and lung function has also been studied. Iwamoto et al. reported that reduced sRAGE was correlated with a greater lung function decline (FEV_1/FVC), particularly in smokers with COPD (n = 51) [178]. However, the correlations were mainly weak, with a marked variation in the sRAGE levels of patients with COPD and significant overlap between patients with COPD and non-COPD subjects. In contrast, recent data from the SUMMIT trial, including 1,673 subjects, showed no association between sRAGE at baseline and lung function decline over 3 months [228], thus raising questions over the clinical utility of sRAGE in predicting the decline in lung function in patients with COPD. Although statistically significant associations are important for research, they do not necessarily mean that they are of clinical importance. For a single biomarker (e.g. sRAGE) to be used in clinical practice, it must provide important information beyond that obtained using everyday practice procedures. Therefore, a realistic interpretation of the role of sRAGE as a biomarker in COPD should be considered.

This study found no difference in the sRAGE levels in current and ex-smokers; although the impact of smoking on sRAGE levels is not fully understood. However, it

is important to note that this study does not have a control group to determine whether smoking is the exact cause of reduced sRAGE commonly seen in patients with COPD. Nevertheless, in a study conducted by Smith and colleagues, sRAGE levels were similar in healthy subjects who ever smoked and in those who never smoked, and significantly greater than those in patients with COPD [179]. In the latter study, multiple linear regression analysis did not show that a previous smoking history was associated with sRAGE, suggesting other mechanisms to the reduced sRAGE in patients with COPD. Even in the studies that have shown reduced sRAGE among smokers (young control subjects, old control subjects, and patients with COPD), it is likely that the reduction is a consequence of recent smoking (within 2 hours of a blood sample) instead of chronic exposure, as suggested by Pouwels and colleges [229]. The latter study also showed that there was no difference in sRAGE levels between active and never smokers [229]. While some literature shows no difference in sRAGE levels between smokers and non-smokers [179, 230], others showed lower sRAGE among smokers [178, 231], which could, again, be attributed to recent smoking effect within the smoking groups. Thus, whether the reduced sRAGE commonly seen in patients with COPD is caused by smoking – per se, is to be determined.

2.4.1 Strengths and limitations of the study

This study is one of a few to have examined the relationship between sRAGE and CV measures in COPD. The strengths of this study are its well-defined inclusion criteria and analyses with adjustments for relevant physiological confounders and CV risk factors. In addition, this study included patients with co-existing comorbidities, making it representative of typical patients with COPD. However, the main limitation of this analysis is its cross-sectional nature with regards to the physiological markers; thus, it does not allow the determination of causality, despite follow-up being ongoing.

Another limitation is that some data for key measures were missing for some of the patients. However, these patients had similar characteristics to the rest of the patients who were included in the analyses, and the number of patients included in each analysis was also reported. It is worth mentioning that participants in the ERICA were allowed to perform some of the study measurements over either a single or two visits (within three months), meaning that some markers (including sRAGE) may have been measured on a separate day to aortic PWV and CIMT.

2.5 **CONCLUSION**

In conclusion, this study has shown that sRAGE is associated with simple spirometric lung function but not with physiological CV measures, CV disease or diabetes in the ERICA cohort. This study does not support sRAGE being a clinical CV biomarker in patients with COPD.

Chapter 3 Microalbuminuria in Patients with COPD: A Cross-sectional Analysis from the ERICA Study

3.1 **INTRODUCTION**

Although the current COPD guidelines recommend recognising CV disease in patients with COPD [1], there is no detailed information on when and how to screen/assess for CV risk in patients with COPD. This considerable gap has been highlighted in the literature [157, 158], reinforcing that CV risk should be assessed in COPD. The identification of easy-to-use CV markers in COPD is the subject of increased research interest. Such markers could, therefore, help identify patients at increased CV risk, understand CV disease pathophysiology, offer targets for intervention and personalise therapy for that particular phenotype [232].

Microalbuminuria (MAB), which is assessed via the urinary albumin creatinine ratio (UACR), is regarded as an early index for microvascular impairment, reflecting vascular abnormalities of the glomeruli [233]. In other words, the kidneys act as a window to the vasculature. The presence of MAB is not only considered the hallmark of renal damage in patients with diabetes [234] but has also been associated with CV events and mortality in subjects from the general population [195, 235]. Therefore, it is proposed as a potential biomarker, which could identify patients with COPD at increased CV risk and may also be a target for CV risk reduction.

Only a few studies in the literature have evaluated the prevalence of MAB in patients with COPD at clinical stability [205-209, 236]. These studies reported that MAB is common in patients with COPD, but the prevalence varies, depending on the study design, sample size [207] and study population age, which may affect UACR [206], and whether the co-existence of COPD associated comorbidities (which are likely to affect the prevalence) was considered [209]. The presence of MAB has been associated with all-cause mortality in patients with COPD, compared to patients without MAB,

even after excluding patients with CV comorbidities [209]; highlighting the significant impact of MAB on patients with COPD.

The associations of MAB with indices of macrovascular complications, such as aortic pulse wave velocity (PWV) and CIMT, have been reported in several conditions (e.g., diabetes and hypertension) and in the general population [198-200]. However, very few investigations have evaluated these relationships in patients with COPD. In a small cross-sectional study, John et al. showed that, compared with non-COPD subjects (n = 34), patients with COPD (n = 52) had increased UACR, being related to increased arterial stiffness, suggesting potential subclinical renal damage [208]. Nevertheless, the full extent of the relationship requires further investigation.

Based on the existing literature, it is hypothesised that MAB, as measured by increased UACR, is prevalent in patients with COPD and is related to macrovascular indices (aortic PWV and CIMT), indicating subclinical glomerular damage and potential CV events.

The objectives of this chapter are:

1- To determine and compare the prevalence of MAB in patients with COPD with and without co-existing COPD comorbidities (diabetes, cerebrovascular disease and ischaemic heart disease).
2- To assess the relationship of aortic stiffness and carotid intima-media thickness with urinary albumin creatinine ratio (UACR) as an indicator for the presence of subclinical glomerular injury and CV events in all patients and then in those without comorbidities.

3.2 **METHODS**

3.2.1 Study design and participants

This study used data obtained from the previously described ERICA cohort [222] (Chapter 2). The cross-sectional baseline data from four of the five participating centres were analysed. Data from patients with confirmed COPD recruited from the Nottingham, Cambridge, London and Liverpool study sites were included. Data from the Cardiff site was not available. All data collection was performed by research personnel at the participating universities prior to my commencing this PhD.

3.2.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria are described in Chapter 2 (subsection 2.2.3.). Briefly, patients with COPD (GOLD II–IV) confirmed by post-bronchodilator spirometry were included. Patients had to be clinically stable, which means that they experienced no exacerbation in the four weeks prior to recruitment. Patients with co-existing comorbidities were not excluded.

3.2.3 Measurements

Details of all procedures and measurements are described elsewhere [222]. Variables related to this analysis are described below.

Anthropometry measures and lung function

The anthropometry and lung function measures are described in detail in Chapter 2. In brief, BMI was calculated from height and weight. FFMI was calculated from a height squared. Post-bronchodilator spirometry was performed to determine FEV_1, FVC, and the FEV_1/FVC ratio. In addition, resting oxygen saturation was also measured.

Detailed biochemistry

Spot urine samples were collected after 4 hours of fasting and stored for later determination of urinary albumin, protein and creatinine. All samples were analysed by Nottingham University Hospitals Trust clinical laboratories. From this, the urinary albumin creatinine ratio (UACR) and protein to creatinine ratio (UPCR) were obtained. Clinical microalbuminuria (MAB) thresholds of 2.5 mg/mmol for males and 3.5 mg/mmol for females were used. Macroalbuminuria was defined as UACR >30 mg/mmol.

Venous blood samples were drawn after four hours of fasting and six hours of refraining from medications and analysed for urea, electrolytes, creatinine, total cholesterol, HDL cholesterol and triglycerides. The estimated glomerular filtration rate (eGFR) was calculated [223].

Cardiovascular measurements

Cardiovascular measurements were described in Chapter 2.

- Blood pressure was measured in the supine position after 10 minutes of rest. From this, MAP and PP were calculated.

- Aortic pulse wave velocity

Aortic stiffness was assessed based on the aortic (carotid-femoral) pulse wave velocity (aortic PWV) as described previously [237].

- Carotid intima medic thickness

CIMT was measured using B-mode ultrasound with a 7–12 MHz linear probe [222]. The largest values for the right and left bilateral CIMT were obtained, and the mean of the left and right values was used in the analysis.

Self-reported comorbidity

Self-reported history of comorbidities, such as ischaemic heart disease, diabetes and cerebrovascular disease, was recorded.

Other measurements

Medication and smoking history were recorded.

3.2.4 Statistics

The data are summarised as relative frequencies for categorical data and arithmetic mean (SD) for normally distributed continuous variables where appropriate. The normality of the data was assessed graphically. Non-normally distributed (e.g. positively skewed) continuous data (UACR, urine albumin, urine creatinine, urine protein and UPCR) were $\log_{10}$ transformed in order to perform parametric analysis. The results of these variables were back-transformed to obtain the geometric mean (SD).

In this study, the COPD patients were divided into two groups: those with and without comorbidities. Independent sample t-tests were performed to compare the mean differences between groups for continuous variables, and the chi-squared test was used for categorical variables.

The prevalence of MAB in patients with and without comorbidities was calculated. Multivariable logistic regression analysis was performed to estimate the odds ratio (OR) for MAB in patients with COPD with and without comorbidities, with adjustments for confounders. Confounders were considered as such if they changed the OR by 10%. The model was adjusted for age, sex, BMI, smoking and MAP. A P value of <0.05 was considered significant.

Multiple linear regression models were then applied to estimate the dependence of $\log_{10}$ UACR on aortic PWV and CIMT, with adjustments for potential confounders. All known and expected confounders were assessed in separate regression models and then included in the final models if they altered the regression coefficient by ≥10%. Known risk factors for increased CV risk have also been considered as potential confounders. For determining the association with aortic PWV, adjustments were made for age, sex, BMI, oxygen saturation, eGFR, MAP, smoking status and comorbidities. For the association with CIMT, adjustments were made for age, sex, BMI, MAP, smoking status, and comorbidities. These analyses were done in 1) all subjects (excluding those with macroalbuminuria), and then 2) in patients without any co-existing comorbidities (in order to minimise the residual confounding of underlying disease). *A priori* confounders such as age and gender were considered regardless of their confounding effects. only complete cases were considered, and the number of observations included in each analysis was reported. Data management and analyses were done using Stata (version 15) statistical software.

3.2.4.1 Sensitivity analyses

In the sensitivity analyses, clinical characteristics and haemodynamic and vascular measures (aortic PWV and CIMT) were compared in patients with clinical macroalbuminuria versus patients without macroalbuminuria. The sensitivity analyses were conducted as the clinical threshold of MAB is defined as UACR of 2.5 mg/mmol for males and 3.5 mg/mmol for females, although a small increase in UACR within the normal limit is still associated with CV risk.

3.3 **RESULTS**

Of the 729 patients in the ERICA cohort, 335 patients were included in the current study, representing those with urine samples and hence UACR data (Figure 3-1). For information, patients studied at Cardiff did not have available urine. Three further patients were excluded because they had macroalbuminuria. Of the 332 remaining, 68 patients had at least one comorbidity (diabetes, cerebrovascular disease or IHD). There were a total of 56 (17%) patients with a clinical threshold of MAB. Baseline characteristics for the whole study population are presented in Table 3-1.

The baseline characteristics for the sample included in this analysis (n = 332) are similar to those for the subjects included in the ERICA cohort (n = 729) in terms of age, gender, BMI, lung function and haemodynamic measures.

Figure 3-1. Flow chart of the included study population

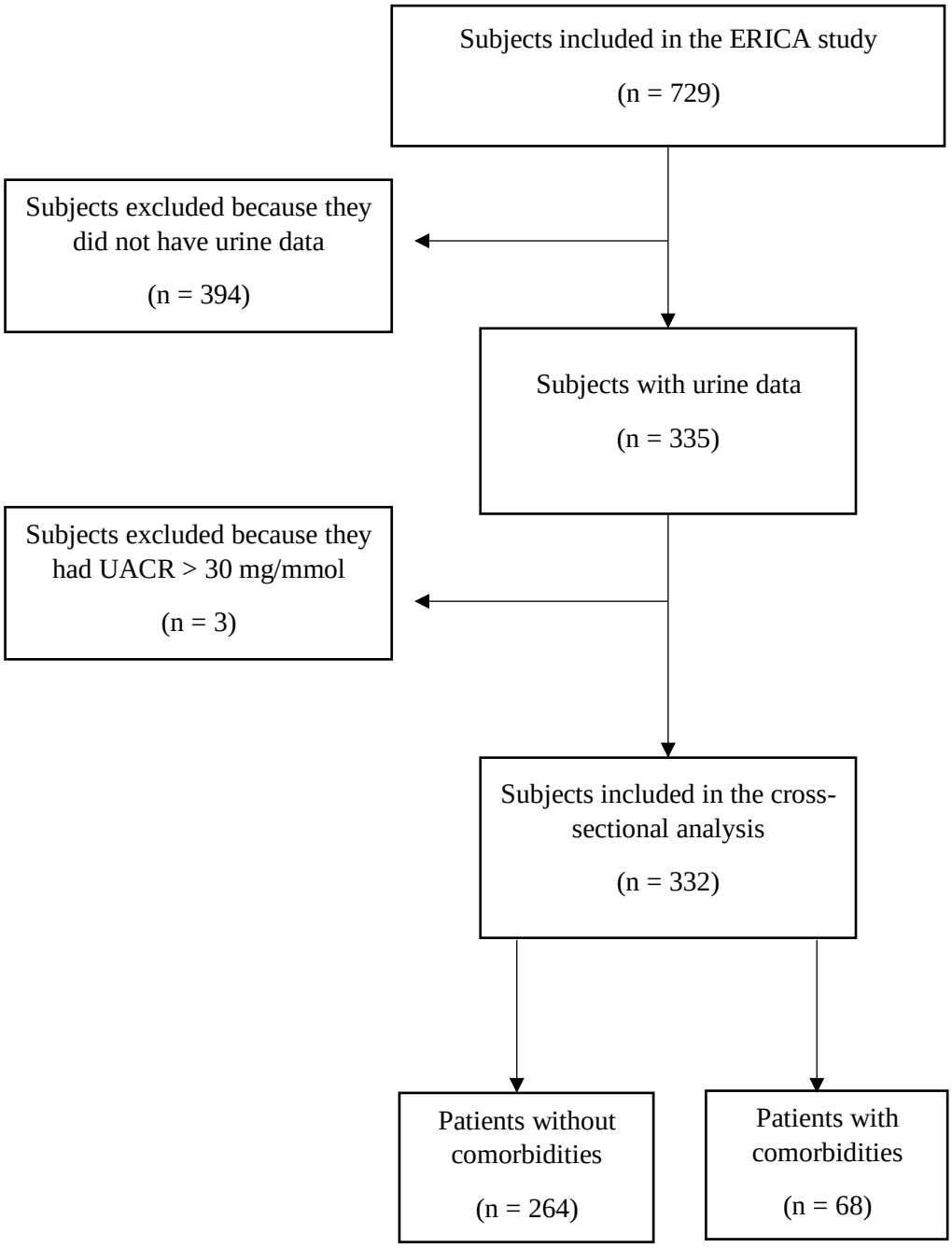


Table 3-1. Baseline characteristics for subjects included in the study (n = 332)

Variable/ No. missing observations	Mean (SD unless stated otherwise)
Age	67.9 (8)
Male, n (%)	225 (67%)
Clinical parameters	
BMI (kg/m^2)/(n = 6)	26.4 (5.9)
FFMI (FFM kg/m^2)/(n = 27)	18.1 (2.8)
Smoking history (pack-years)/(n = 7)	47.8 (28.8)
Smoking status, n (%)	
Current smokers	80 (24%)
Ex-smokers	249 (75%)
Not recorded	3 (1%)
Urine biochemistry	
UACR (mg/mmol)[a]	0.83 (3.2)
Urine albumin (mg/l)[a]	7.3 (4.1)
Urine creatinine (mmol/l)[a]	8.7 (1.9)
Urine protein (mg/l)[a]	83.9 (2.1)
UPCR (mg/mmol)[a]	9.7 (1.7)
Clinical MAB, n (%)	56 (17%)
Haemodynamic status	
Aortic PWV (m/s)/(n = 50)	10.2 (2.8)
Mean CIMT (mm)/(n = 117)	0.78 (0.15)
Supine MAP (mm Hg)/(n = 8)	102 (12.6)
Supine PP (mm Hg)/(n = 5)	59 (13.8)
Supine heart rate (beats/min)/(n = 45)	75 (0.78)
Lung function parameters	
FEV_1 (L)/(n = 2)	1.34 (0.52)
FEV_1% predicted (%)/(n = 2)	50.4 (16.4)
FVC (L)/(n = 2)	3 (0.8)
Oxygen saturations (%)/ (n= 13)	95 (2)
Blood biochemistry	
eGFR (ml/min)/(n = 19)	85 (18.6)
Total cholesterol (mmol/L)/(n = 3)	5.1 (1.1)
LDL cholesterol (mmol/L)/(n = 3)	2.9 (0.8)
HDL cholesterol (mmol/L)/(n = 3)	1.6 (0.5)
Triglycerides (mg/dL)/(n = 6)	1.29 (0.6)
Medical therapy	
High blood pressure medication[b]/(n = 198)	106 (32%)

[a] Geometric mean.
[b] A list of high blood pressure medications is described in the appendices.
Abbreviations: BMI: body mass index; CIMT: carotid intima-media thickness; eGFR: estimated glomerular filtration rate; FFMI: fat-free mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced volume capacity; MAB: microalbuminuria; MAP: mean arterial pressure; PP: pulse pressure; PWV: pulse wave velocity; UACR: urinary albumin creatinine ratio; UPCR: urinary protein creatinine ratio.

Clinical characteristics, renal, haemodynamic and vascular markers in patients with and without self-reported comorbidities

Patients with COPD and comorbidities were older and had a higher BMI, but the gender proportion was not different (Table 3-2). Of all patients, there were 30 patients with eGFR < 60 ml/min. Of those, there were 12 patients with comorbidities and 18 patients without comorbidities.

The geometric mean (SD) for UACR was significantly greater for patients with COPD and comorbidities (1.17 [3.5] mg/mmol) compared to those without comorbidities (0.76 [3.1] mg/mmol; p = 0.008). The difference remained significant following adjustment for age, sex, BMI, smoking and MAP (adjusted β [95% CI] of 1.49 [1.09 – 2.06]; n = 320; p = 0.013; Table 3-3). The proportion of patients with clinical MAB was greater for those with COPD and comorbidities (n = 15/68; 22%) than for those without comorbidities (n = 41/264; 15.5%) but the difference did not reach statistical significance (p = 0.200). Furthermore, the odds of having clinical MAB were not significantly different between patients with and without comorbidities (adjusted odds ratio (aOR) 1.89; 95% CI 0.91–3.89; n = 320; p = 0.083; Table 3-3).

Haemodynamic measures were mostly similar between patients with and without comorbidities. The mean (SD) aortic PWV was greater in patients with comorbidities (10.94 [2.9] m/s) than in those without comorbidities (10.05 [2.8] ms/s; p = 0.037). However, adjustments for confounders diminished the difference (adjusted β: 0.63 ms/s; 95% CI -0.14 to 1.40; n = 279; p = 0.109; Table 3-3). Further, CIMT was not significantly different in patients with and without comorbidities (n = 211; p = 0.833).

Table 3-2. Baseline characteristics for patients with comorbidities (n = 68) vs. patients without comorbidities (n = 264)

Variable	Without comorbidities (n = 264)	With comorbidities [a] (n = 68)	P-value
Age	67.3 (7.7)	70.6 (7.9)	0.002
Male, n (%)	175 (66.3%)	50 (73.5%)	0.255
Clinical parameters			
BMI (kg/m^2)	25.9 (5.8)	28.3 (5.9)	0.003
FFMI (FFM kg/m^2)	17.9 (2.8)	19.10 (2.6)	0.004
Smoking history (pack-years)	47.5 (28.7)	48.8 (29.3)	0.730
Smoking status, n (%)			
Current smokers	66 (25%)	14 (21%)	
Ex-smokers	195 (74%)	54 (79%)	0.512
Urine biochemistry			
UACR (mg/mmol)[b]	0.76 (3.1)	1.17 (3.5)	0.008
Urine albumin (mg/l)[b]	6.8 (3.9)	9.1 (4.3)	0.131
Urine creatinine (mmol/l)[b]	8.9 (2.1)	7.7 (1.9)	0.126
Urine Protein (mg/l)[b]	82.2 (2.1)	90.9 (2.3)	0.340
UPCR (mg/mmol)[b]	9.2 (1.6)	11.7 (1.8)	0.001
Clinical MAB, n (%)	41 (15.5%)	15 (22%)	0.200
Haemodynamic status			
Aortic PWV (m/s)	10.1 (2.8)	10.9 (2.9)	0.037
Mean CIMT (mm)	0.75 (0.15)	0.79 (0.14)	0.153
Supine MAP (mm Hg)	103 (13)	101 (12)	0.252
Supine PP (mm Hg)	57 (14)	64 (15)	0.001
Heart rate (beat/min)	76.49 (12.5)	73 (48)	0.095
Lung function parameters			
FEV_1 (L)	1.3 (0.5)	1.4 (0.5)	0.417
FEV_1% predicted (%)	49.7 (17)	53 (15)	0.141
FVC (L)	3 (0.8)	3 (0.8)	0.681
Oxygen saturations (%)	95 (2)	95 (2)	0.174
Blood biochemistry			
eGFR (ml/min)	86.3 (18.1)	78.1 (19.4)	0.002
Total cholesterol (mmol/L)	5.2 (1)	4.6 (1.2)	0.001
LDL cholesterol (mmol/L)	3.01 (0.8)	2.43 (0.9)	0.001
HDL cholesterol (mmol/L)	1.61 (0.5)	1.52 (0.5)	0.182
Triglycerides (mg/dL)	1.26 (0.6)	1.39 (0.6)	0.940
Medical therapy			
High blood pressure medication [c]	70 (27%)	36 (53%)	0.100

[a] COPD with comorbidities: diabetes, cerebrovascular disease or ischaemic heart disease.
[b] Geometric mean.
[c] A list of high blood pressure medications is described in the appendices.
Abbreviations: BMI: body mass index; CIMT: carotid intima-media thickness; eGFR: estimated glomerular filtration rate; FFMI: fat-free mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced volume capacity; MAB: microalbuminuria; MAP: mean arterial pressure; PP: pulse pressure; PWV: pulse wave velocity; UACR: urinary albumin creatinine ratio; UPCR: urinary protein creatinine ratio.

Table 3-3. Comparison of renal markers and vascular measures in patients with and without comorbidities

	Patients without comorbidities	Patients with comorbidities	P-value
Renal markers			
UACR (mg/mmol), β (95% CI)			
Unadjusted (95% CI)	Reference	1.53 (1.12 to 2.1)	0.008
Adjusted (95% CI)	Reference	1.49 (1.09 to 2.06)[1]	0.013
Clinical MAB, OR (95% CI)			
Unadjusted (95% CI)	Reference	1.54 (0.79-2.98)	0.202
Adjusted (95% CI)	Reference	1.89 (0.91-3.89)[1]	0.083
Vascular markers			
PWV (m/s), β (95% CI)			
Unadjusted (95% CI)	Reference	0.88 (0.05 to 1.71)	0.037
Adjusted (95% CI)	Reference	0.63 (-0.14 to 1.40)[2]	0.109
CIMT (mm), β (95% CI)			
Unadjusted (95% CI)	Reference	0.04 (-0.013 to 0.086)	0.153
Adjusted (95% CI)	Reference	0.006 (-0.043 to 0.055)[2]	0.833

[1] Adjusted for age, sex, BMI, smoking and MAP.
[2] Adjusted for age, sex, BMI, smoking, FEV_1% predicted and MAP.
Abbreviations: BMI: body mass index; CI: confidence interval; CIMT: carotid intimal medial thickness; FEV_1: forced expiratory volume in 1 second; MAB: microalbuminuria; MAP: Mean arterial pressure; OR: odds ratio; UACR: urine albumin creatinine ratio.

Association of log_{10} UACR with vascular markers and other variables

The results from multivariable linear regression models with log_{10} UACR as the dependent variable and its associations with aortic PWV and CIMT adjusted for confounders are presented in Table 3-4. Log_{10} UACR was associated with both aortic PWV and CIMT following adjusting for age and sex in all subjects or in patients without comorbidities. However, in the fully adjusted models, neither aortic PWV nor CIMT were associated with log_{10} UACR in all subjects or in patients without comorbidities (Table 3-4).

Table 3-4. Associations of log_{10} UACR with aortic PWV and CIMT in 1) all subjects with COPD and 2) subjects without comorbidities

Dependent variable: log_{10} UACR			
All subjects with COPD			
	β (95% CI)	**Adjusted β (95% CI)**	**P-value**
Aortic PWV – per 1 m/sec change	0.033 (0.013 to 0.054) (n = 282)	0.012 (-0.010 to 0.036)[1] (n = 269)	0.278
CIMT – per 1 mm change	0.51 (0.047 to 0.92) (n = 215)	0.37 (-0.12 to 0.87)[2] (n = 209)	0.140
Subjects without comorbidities			
	β (95% CI)	**Adjusted β (95% CI)**	**P-value**
Aortic PWV – per 1 m/sec change	0.025 (0.002 to 0.049) (n = 227)	0.011 (-0.014 to 0.037)[3] (n=217)	0.386
CIMT – per 1 mm change	0.60 (0.077 to 1.12) (n = 166)	0.44 (-0.12 to 1.01)[4] (n = 161)	0.122

[1] Adjusted for age, sex, BMI, oxygen saturation, eGFR, MAP, smoking status, comorbidities and study site.
[2] Adjusted for age, sex, BMI, MAP, smoking status, comorbidities and study site
[3] Adjusted for age, sex, BMI, oxygen saturation, eGFR, MAP, comorbidities and study site
[4] Adjusted for age, sex, BMI, MAP, smoking status, comorbidities and study site
Abbreviations: BMI: body mass index; CI: confidence interval; CIMT: carotid intimal medial thickness; eGFR: estimated glomerular filtration rate; MAP: mean arterial pressure; PWV: pulse wave velocity; UACR: urine albumin creatinine ratio.
Comorbidities: diabetes, ischaemic heart disease and cerebrovascular disease.

In the whole study population, log_{10} UACR was also positively correlated with age (r = 0.15; p < 0.005; n = 332), MAP (r = 0.17; p = 0.002; n = 324) and PP (r = 0.12; p = 0.020; n = 327) and inversely correlated with eGFR (r = -0.11; p = 0.047; n = 313) and resting oxygen saturation (r = -0.11; p = 0.035; n = 320), but no associations were observed with FEV_1% predicted or BMI. In the subgroup without comorbidities, these associations remained largely similar, except for supine PP and eGFR (Table 3-4).

Table 3-5. Correlations between log_{10} UACR and vascular measures (aortic PWV and CIMT) and other factors in all patients with COPD and 2) patients without comorbidities

Variable	All patients with COPD		Patients without comorbidities	
	Log_{10} UACR		Log_{10} UACR	
	r	P-value	r	P-value
Age	0.15 (n= 332)	0.006	0.12 (n= 264)	0.005
BMI	0.04 (n= 326)	0.437	0.02 (n= 259)	0.713
FEV_1 % predicted	-0.06 (n= 330)	0.248	-0.08 (n= 262)	0.195
Supine MAP	0.17 (n= 324)	0.002	0.19 (n= 256)	0.003
Supine PP	0.12 (n= 327)	0.020	0.10 (n= 260)	0.096
eGFR	-0.11 (n= 313)	0.048	-0.08 (n= 249)	0.215
Oxygen saturation	-0.11 (n= 320)	0.035	-0.15 (n= 256)	0.018

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; FEV_1: forced expiratory volume in 1 second; MAP: mean arterial pressure; PP: pulse pressure; PWV: pulse wave velocity; UACR: urine albumin creatinine ratio.
Self-reported comorbidities: diabetes, ischaemic heart disease and cerebrovascular disease.

Sensitivity analysis: Clinical characteristics and vascular measures in patients with and without microalbuminuria

The patients included in this study (n = 332) were divided into two groups based on the presence or absence of microalbuminuria. The demographics and clinical characteristics were largely similar between the two groups (Table 3-6).

The mean aortic PWV was significantly greater for patients with MAB (11.51 [2.8] m/s) compared to patients without MAB (10.03 [2.8] m/s; p = 0.019). Even following adjustment for confounders, the aortic PWV was 1.03 m/s higher in patients with MAB than patients without MAB (adjusted β: 1.03 m/s; 95% CI: 0.12 to 1.96; n = 263; p = 0.038; Table 3-7). However, there was no difference in CIMT in patients with and without MAB.

Table 3-6. Baseline characteristics of COPD patients with and without clinical microalbuminuria

Variable	COPD without MAB (n = 276)	COPD with MAB (n = 56)	P-value
Age	67.7 (7.8)	69.4 (7.9)	0.131
Male, n (%)	191 (66%)	34 (61%)	0.215
Clinical parameters			
BMI (kg/m^2)	26.5 (5.9)	25.9 (5.9)	0.522
FFMI (FFM kg/m^2)	18.1 (2.8)	18 (3.1)	0.932
Smoking history (pack-years)	48 (28.9)	46.6 (28.1)	0.759
Smoking status, n (%)			
Current smokers	67 (24%)	13 (25%)	0.523
Ex-smokers	211 (75%)	38 (75%)	
Haemodynamic status			
Aortic PWV (m/s)	10.03 (2.8)	11.51 (2.8)	0.002
Mean CIMT (mm)	0.76 (0.15)	0.78 (0.14)	0.445
Supine MAP (mm Hg)	101 (12.1)	106 (14.3)	0.017
Supine PP (mm Hg)	58.02 (13.4)	63.44 (16.7)	0.014
Lung function parameters			
FEV_1 (L)	1.36 (0.52)	1.23 (0.48)	0.088
FEV_1% predicted (%)	51 (16.6)	47 (14.9)	0.118
FVC (L)	3.1 (0.8)	2.8 (0.7)	0.068
Oxygen saturations (%)	95 (2)	95 (2)	0.175
Blood biochemistry			
eGFR (ml/min)	85.84 (17.8)	78.19 (21.5)	0.008
Total cholesterol (mmol/L)	5.08 (1.1)	5.02 (1.1)	0.746
LDL cholesterol (mmol/L)	2.92 (0.9)	2.72 (0.9)	0.145
HDL cholesterol (mmol/L)	1.57 (0.5)	1.69 (0.6)	0.155

Abbreviations: BMI: body mass index; CIMT: carotid intima-media thickness; eGFR: estimated glomerular filtration rate; FEV_1: forced expiratory volume in 1 second; FFMI: fat-free mass index; FVC: forced volume capacity; MAB: microalbuminuria; MAP: mean arterial pressure; PP: pulse pressure; PWV: pulse wave velocity.

Table 3-7. Vascular measures (aortic PWV and CIMT) in patients with and without microalbuminuria

	Patients without MAB	Patients with MAB	P-value
PWV (m/sec), β (95% CI)			
Unadjusted (95% CI)	Reference	1.48 (0.52 to 2.44) (n = 282)	0.002
Adjusted (95% CI)	Reference	1.03 (0.12 to 1.96)[1] (n = 263)	0.038
CIMT (mm), β (95% CI)			
Unadjusted (95% CI)	Reference	0.02 (0.03 to 0.08) (n = 215)	0.446
Adjusted (95% CI)	Reference	0.01 (0.05 to 0.07)[1] (n = 202)	0.729

[1] Adjusted for age, sex, BMI, smoking status, eGFR, MAP, and comorbidities.
Abbreviations: BMI: body mass index; CI: confidence interval; CIMT: carotid intimal medial thickness; eGFR: estimated glomerular filtration rate; FEV_1: forced expiratory volume in 1 second; MAB: microalbuminuria; MAP: mean arterial pressure; PWV: pulse wave velocity; UACR: urine albumin creatinine ratio.
Comorbidities: diabetes, ischaemic heart disease and cerebrovascular disease.

3.4 DISCUSSION

In this group of stable patients with COPD, patients with co-existing comorbidities exhibited significantly greater UACR than patients without comorbidities. The prevalence of microalbuminuria was also greater in patients with comorbidities, although this did not reach statistical significance. However, the associations of $\log_{10}$ UACR with aortic PWV and CIMT were nullified, becoming non-statistically significant, after adjustments for known confounders.

Only a few studies in the literature have reported the prevalence of MAB in COPD at clinical stability [205-207, 209, 236]. Current estimates of the prevalence of MAB in patients with COPD vary across studies, depending on sample size, population age, COPD severity and whether co-existing comorbidities were considered. For instance, Casanova et al. showed that the prevalence of MAB in patients with COPD was 24% compared with 6% in smokers without COPD [206]. However, age was markedly different between groups, which is likely to affect UACR and, consequently, the prevalence of MAB. The overall prevalence of MAB reported in this study at 17% (22% in patients with comorbidities) is slightly higher than the prevalence reported by Johan and colleagues at 13%, using similar inclusion criteria [208]. However, Johan's study included patients with GOLD I (unlike this study where patients with GOLD II and worse were included). This suggests that MAB is common in patients with COPD regardless of the co-existing comorbidities and level of severity.

It was a little unexpected not to find an independent association for $\log_{10}$ UACR with aortic PWV and CIMT, following adjustments for confounders. Both aortic PWV and CIMT are well-recognised markers for increased CV risk in people with COPD [214-217] and have also been associated with MAB in a number of conditions as well as in

the general population [198-200]. However, there is a lack of studies investigating the association between UACR and aortic PWV or CIMT in patients with COPD. In a previous study, John et al. reported an association between aortic PWV and UACR in patients with COPD, independent of common risk factors [208]. In their study, 29% (15/52) of patients with COPD had an eGFR < 60 ml/min (mean eGFR = 67 ml/min; mean age = 68 years), demonstrating that a large proportion of patients have renal dysfunction, and highlighting the increased risk of CV events [238]. In contrast, only 9% (30/332) of patients included in this study had an eGFR < 60 ml/min (mean = 84.7 ml/min; mean age = 68 years). In fact, there is no apparent reason that the eGFR noted by John et al. should be different from the eGFR reported in this study, as the age and clinical characteristics were largely similar, except that patients in the ERICA cohort were recruited across five centres (four included in this analysis), and that the cross-sectional measurements were performed over either one or two visits.

Another point to consider for the lack of associations between UACR and aortic PWV is that the aortic PWV reported in this study was generally lower than in previous literature [208]. John and colleagues reported a higher aortic PWV in patients with confirmed microalbuminuria (mean = 12.3 m/sec) compared to the aortic PWV of 11.5 m/sec found in this study [208]. Indeed, current evidence demonstrates that an increase of 1 m/sec in aortic PWV is associated with a 14% increase in total CV events and a 15% increase in CV mortality [239]. The differences in the patient characteristics across studies are likely to produce different results. It is also possible that the lack of associations reported here is because patients had a low UACR, and their haemodynamic measures were generally within the normal range (including aortic PWV and CIMT). In addition, given that a third of the study population were on blood

pressure medications, which are known to reduce aortic stiffness and microalbuminuria [240], may also explain the lack of associations.

Despite the lack of associations between UACR and aortic PWV or CIMT, it is important to emphasise that the existence of MAB, by itself, is an indicator of increased CV risk and a predictor for mortality in the general population [194-197]. This study showed that MAB was prevalent even in patients with COPD without known comorbidities. Romundstad et al. demonstrated that patients with COPD and MAB were at 54% increased risk of all-cause mortality (but not CV mortality) compared to patients without MAB [209]. Interestingly, the risk also remains (49% increased risk) even after excluding patients with self-reported CV disease [209]. Therefore, periodic MAB monitoring for potential renal impairment, CV events and mortality should be considered for patients with COPD.

Current evidence suggests that albuminuria is a continuum and that kidney injury and CV disease can still occur even below the clinical threshold for microalbuminuria [241-243]. A collaborative meta-analysis showed that a urine albumin creatinine ratio of 1.1 mg/mmol (which is below the clinical threshold of MAB) was associated with a 20% increased risk of all-cause mortality in the general population, compared with a urine albumin creatinine ratio of 0.6 mg/mmol [202]. It has also been suggested that an increase in UACR of 3.5 mg/g (≈ 0.4 mg/mmol) is associated with a 6% increase in CV risk [197]. In this context, it is important to consider the minimal increase in UACR in patients with COPD. Indeed, this study showed that patients with self-reported comorbidities have a significantly higher UACR compared to those without (although both were within the normal range), highlighting the potential increased risk of subsequent CV events and mortality.

In addition to the macrovascular abnormalities associated with increased arterial stiffness, it has also been linked to microvascular damage (e.g. renal dysfunction) [244, 245]. Studies have shown that elevated arterial stiffness is an independent risk factor for a renal function decline in patients with kidney disease [246, 247]. The present study demonstrated that patients with COPD and MAB (which is a marker of renal impairment) had significantly higher aortic PWV compared to patients without MAB. Indeed, increased aortic stiffness contributes to greater pressure and oscillation exposure in the renal system [248] and, since the kidneys are very sensitive, they are more likely to be affected by the excessive blood pressure [249], potentially leading to injured glomerular capillaries. Further investigation is needed to determine whether the increase in aortic stiffness mechanistically leads to the development of MAB. Nevertheless, the clinical prognostic implications of the microvascular state should be considered in COPD management.

The prevalence of patients with COPD having renal impairment has been highlighted in the literature [250-254]. Incalzi et al. showed that patients with COPD have increased prevalence of chronic renal failure (both overt and concealed), defined as (GFR < 60 mL/min/1.73 m^2) compared to age-matched subjects without COPD [250]. However, identifying renal impairment based on eGFR alone is likely to underestimate the true prevalence as its role in the elderly is still under debate [255]. This does not imply that eGFR should not be taken into consideration when assessing renal function, but rather it should be interpreted with caution. Microalbuminuria usually occurs before any loss of GFR. In addition, it is considered the most important indicator for renal impairment and has also been associated with worse clinical outcomes, independent of eGFR [193, 195, 235, 256].

3.4.1 Clinical implications

Increasing evidence suggests that COPD and CV disease often co-exist [97]. Current COPD guidelines recognise CV disease as one of the most common comorbidities in patients with COPD and suggest that it should be routinely assessed and managed [1]. Although no specific recommendations have been made on how to do so, healthcare professionals are encouraged to manage comorbidities (CV disease in this instance) as if the patients do not have COPD. This, however, implies recognising, diagnosing and assessing the co-existing comorbidity in the first place. For instance, if kidney function is influenced by changes in the haemodynamic status or vice versa, it is therefore important to assess the interplay between micro- and macro-vascular states in patients with COPD.

The utilisation of biological markers not only helps identify patients at increased CV risk but also provides a route for targeted therapy for that particular phenotype. Indeed, MAB is considered as a therapeutic target in the clinical management of patients with diabetes and hypertension [257, 258]. Thus, MAB could provide an opportunity for early and appropriate interventions before the development of a major CV disease in patients with COPD.

3.4.2 Strengths and limitations

The main strengths of this study are its well-defined inclusion criteria and adjustments for known physiological confounders. Additionally, this study included patients with confirmed COPD with co-existing comorbidities, such as diabetes, cerebrovascular disease and ischaemic heart disease, a different approach that has not been widely used in previous studies. It is thus representative of typical patients with COPD seen in clinical settings. However, the current study has some limitations. First, the cross-

sectional nature of the study did not allow assessment for any causality. Second, the patients with COPD and comorbidities were significantly older than the patients without comorbidities, which could explain the higher UACR observed in patients with comorbidities. However, age and gender were adjusted for in the multivariable analysis and UACR was still higher. Another limitation is that some key measures were missing for some of the patients, which may lead to potential bias, loss of power and therefore an underestimation to the examined associations. It is acknowledged that missing data is a common issue in epidemiological research and should therefore be dealt with appropriately. It is nevertheless important to mention that the complete case analysis approach used in this chapter was appropriate, as the complete cases (patients included in these analyses) have similar characteristics to those who were missing (patients included in the ERICA cohort). In addition, only data (urine samples) from 4 of the 5 recruiting centres for ERICA were available for this analysis and thus included in this chapter. This study has also reported the number of observations included in each analysis and carried a number of sensitivity analyses to test the robustness of the main findings.

3.5 **CONCLUSION**

Although there is evidence of increased UACR in patients with co-existing comorbidities, UACR was not found to be strongly associated with aortic stiffness or carotid intima-media thickness in the ERICA cohort. However, microalbuminuria was still prevalent in all patients with COPD, highlighting a potential risk of sub-glomerular damage and subsequent CV events. Therefore, screening for MAB and early intervention to optimise the CV status should be considered.

Chapter 4 Dementia and Cognitive Impairment in Patients with COPD: A UK Population-based Study

4.1 INTRODUCTION

Cognitive impairment contributes to greater functional disability [259, 260], increased need for care services [119], lower adherence to complex medication regimens [261], difficulties in managing chronic diseases [262], worse clinical outcomes [263] and predicts mortality in certain COPD populations [264]. Potential causes contributing to impaired cognitive state in patients with COPD are likely multiple and include ageing, co-existent cardiovascular (CV) disease, smoking, hypoxemia and hypercapnia [106].

Despite an association between cognitive impairment and COPD [129, 265, 266], the prevalence of cognitive impairment in COPD remains uncertain. Cognitive impairment is estimated to affect between 4% to 61% of patients with COPD [262, 267], depending on the study populations and assessment methods [129, 268]. However, it remains less clear how this compares to age- and sex-matched subjects without COPD. Current literature also suggests that the prevalence increase in line with severity of COPD, although severity measures have not been consistent across studies [129, 268]. The existing studies investigating the prevalence of cognitive impairment in COPD are limited by methodological differences, such as study design, population age, inadequate matching group, and short follow-up [269-272]. Thus, the estimated prevalence is caveated.

Cognitive impairment represents a spectrum leading to dementia in a proportion of patients [122]; however, not all patients with confirmed cognitive impairment will eventually progress to dementia. Current literature on the association between COPD and dementia are generally scarce. However, it is suggested that COPD increases the risk of cognitive impairment and subsequent dementia [136, 138]. Although these prior studies provide some information on the relationship between COPD and dementia, they utilised a self-reported history of COPD or had a short follow-up time. Current

evidence suggests that patients with COPD and cognitive impairment are at increased risk of developing dementia [271]. Identifying the proportion of patients with COPD at increased risk of cognitive impairment and dementia is important in understanding the broader clinical spectrum of COPD and in providing services that are structured to meet patient needs.

The association between COPD and either cognitive impairment or dementia remains less clear. The hypothesises of this chapter are 1) patients with COPD would have a greater proportion of coded cognitive impairment and dementia at the time of COPD diagnosis/index date compared to subjects without COPD, and 2) they are at increased risk of incident cognitive impairment and dementia following COPD diagnosis/index date.

The aims of this chapter are twofold:

1- To report the prevalence of cognitive impairment and dementia at the time of COPD diagnosis in patients with COPD and matched subjects without COPD.
2- To determine the incidence of cognitive impairment and dementia following a diagnosis of COPD in patients with COPD and matched subjects without COPD.

4.2 **METHODS**

4.2.1 Study design

Aim 1: A case-control study was used to describe and report the prevalence of cognitive impairment at the time of COPD diagnosis. A similar study design was also conducted to report the prevalence of dementia.

Aim 2: A matched cohort study was conducted to determine the incidence of cognitive impairment following COPD diagnosis/index date in patients with COPD and subjects without COPD. The incidence of dementia was also determined using the same study design.

4.2.2 Data source

The cohort information was obtained using The Health Improvement Network (THIN). See subsection 4.2.2.1.

4.2.2.1 Description of The Health Improvement Network (THIN)

The THIN is a large, representative UK database, which contains longitudinal fully anonymised patients' electronic health records (>12 million people) from over 550 general practices (GPs) and covering more than 6% of the UK population, using Vision computer software [273]. The data collection in THIN started in January 2003. This was after the partnership between the Epidemiology and Pharmacology Information Core (EPIC) (which provides the primary care data) and In Practice Systems (which developed the software used in GP practices). A significant proportion of people whose records are recorded within THIN are still actively contributing data. Historical data may also be present for those who have died or left the GP practice.

All information obtained from primary care visits to a GP, or any other healthcare professionals at practices participating in THIN is recorded in the database. Data are stored in several files (patient, medical, therapy, additional health details, and postcode variable indicator), created by individual practice, and linked to each other by a unique identifier (patient, consultation, or staff). Patients' data within THIN include demographics, medications, past medical history, diagnostic results, and lifestyle characteristics [274]. Clinical Information within THIN is recorded using hierarchical READ codes, and medication information is recorded using drug codes.

The recruitment of practices in THIN is done through the partnership between the two companies (EPIC and In practice Systems). Participating practices in THIN are paid for the utilisation of their data. It is important to note that practices must meet minimum quality standards for data recording, suggested by EPIC, in order to join THIN. Such standards are subject to routine adjustments to meet the changes in NHS requirement for data collection and storage. Failure to meet the required quality of recordings can result in a suspension of that practice until problems are resolved. If problems persist, that practice may be excluded from THIN.

The version of the THIN data used in this thesis was provided by the University of Nottingham, Division Respiratory medicine and Division of epidemiology and public health. The initial data preparation - pulling the raw data from THIN - which contains records of all patients with COPD and subjects without COPD, was organised by Dr. Gibson prior to commencing this PhD. The candidate performed subsequent data extractions and performed all data analyses.

4.2.3 Ethical approval

Ethical approval for this study was provided by an independent Scientific Review Committee (SRC), reference number - 17THIN095.

4.2.4 Study population

The index population comprised individuals aged ≥40 years with a first-time COPD diagnosis (defined based READ codes; appendix 9-2) from 1st April 2006 to 31st December 2015, with ≥ 1 year of record prior to the diagnosis of COPD. Up to four comparison subjects without a diagnosis of COPD were matched for each patient with COPD by age, gender and GP practice. The beginning of the study period (01-04-2006) was chosen based on the initial introduction of dementia coding to the quality and outcomes framework (QOF) [275].

4.2.5 Outcome definitions

1- Cognitive impairment was defined based on READ codes. In this study, the term cognitive impairment does not include a diagnosis of dementia (READ coded), as cognitive impairment does not necessarily lead to a diagnosis of dementia.

2- A diagnosis of dementia was defined based on READ codes. An expert geriatrician (Prof. Adam Gordon) was consulted to help identify all available Read codes related to dementia. An inclusive approach was taken where any potentially relevant diagnosis was considered. (Read codes are available in appendices 9-3 & 9-4).

3- Either cognitive impairment or dementia was also considered as a separate outcome (see subsection 4.2.7.1). In the absence of the systematic assessment in GP practice, these terms may have been used synonymously. It is also

important to note that anyone with a diagnosis of dementia is, by definition, cognitively impaired. Therefore, it was important to consider such an outcome.

4.2.6 Outcome measures and follow-up

Prevalence

The prevalence of cognitive impairment was defined as the first of any READ code recorded prior to, at, or 6 months after the index date. This was determined in patients with COPD and subjects without COPD. The prevalence of coded dementia was similarly determined.

Incidence

1- **Cognitive impairment:** subjects with a code of cognitive impairment and dementia recorded prior to, at, or 6 months after the index date were excluded. Subjects were then followed-up from 6 months after the index date until either they received a cognitive impairment Read code (first READ code), left the GP practice, died or reached the end of the follow-up (31/12/2015), whichever came first.
2- **Dementia:** subjects with a former diagnosis of dementia recorded prior to, at, or 6 months after the index were excluded from analyses related to dementia incidence. Incident dementia was defined as the first READ coded recorded from 6 months after the index date.

Explanatory variables and potential confounders

A number of explanatory variables were identified at baseline.

Definition of variables

- Age at diagnosis was determined and categorised as follows: < 60, 60-69, 70-79, and 80 years and older.
- Body mass index (BMI) was determined within 2 years (before and after) of index date. BMI consisted of documented and computed values. Where there was no documented BMI, where possible, BMI was calculated from the height and weight records. The BMI was then categorised as follows: (underweight - <18.5 kg/m^2, normal – 18.5-<25 kg/m^2, overweight – 25-<30 kg/m^2, obese - >30 kg/m^2). Subjects with no available BMI data were categorised under "no records".
- The closest record of MRC dyspnoea score [37], 1 year either side of the index date, was obtained. The MRC score was categorized as follows: 1, 2, 3 or 4-5. A further category of "no records" was then added for any subject without available data.
- For smoking, the most recent record to COPD diagnosis, whether prior or after the index date, was used. The smoking status was categorized into 3 main categories: never smoked, ex-smoker, and current smoker. A 4^{th} category "unknown" was then added for subjects without available smoking data. Individuals who were initially recorded as "current smoker" then "never smoked" were recorded as "ex-smoker."
- A modified Charlson Comorbidity Index (CCI) [276, 277], excluding dementia and cardiovascular (CV) disease (congestive heart failure, ischemic heart

disease, and peripheral vascular disease), was determined before or at the index date. A modified CCI was categorised as follows: 0-1, 2, 3, and ≥ 4. CCI is an approach to classify comorbid conditions, where each comorbidity is assigned to score (from 1 to 6). (Appendix 9-7).

- For alcohol, the most recent record to COPD diagnosis was determined, whether prior to or at the index date. Alcohol status was categorised into three main groups as follows: lifelong teetotaller, ex-drinker, and current drinker. Subjects with no available data were categorised under "no records".
- Townsend score (a measurement of social class) [278] was determined before or at the index date. It was classified as follows: 1 (least deprived), 2, 3, 4, and 5 (most deprived). The Townsend score combines information from different categories, such as unemployment, car ownership, homeownership, and overcrowding.
- Having been prescribed at least one prescription of corticosteroids within one year (prior and after) of the index date was considered as a risk factor.
- Individual comorbidities such as diabetes, cardiovascular disease, and cerebrovascular disease were determined prior to, at, or 6 months after the index date. (Appendices 9-9 & 9-10).

4.2.7 Statistical analysis

Aim 1: The prevalence of cognitive impairment was obtained by calculating the proportion of individuals who had coded cognitive impairment within the COPD and without COPD population before, at, or 6 months within the index date. McNemar test was used to compare categorical data, including the prevalence of cognitive impairment between groups. A $p<0.05$ was considered significant.

Multivariable conditional logistic regression analysis was performed to estimate the odds ratio (OR) for the prevalence of cognitive impairment for both groups (patients with COPD and subjects without COPD). The OR of the prevalence of cognitive impairment was assessed in a multiple conditional logistic regression to adjust for accepted confounders. Confounders were considered in the final model if they independently changed the OR for cognitive impairment by ≥ 5%. All covariates were assessed in separate regression models.

Aim 2: Those with a coded cognitive impairment and/or coded dementia at baseline (prior, at, or within 6 months after the index date) were excluded from analysis related to cognitive impairment incidence. The incidence of cognitive impairment was defined as the time from 6 months after the index date to the diagnosis of cognitive impairment, leaving the GP clinic, death, or end of the follow up (31/12/2015), whichever comes first.

Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) for cognitive impairment in patients with COPD and matched subjects. Survival analysis and Kaplan-Meier plots were performed to compare the incidence of cognitive impairment between patients with COPD and subjects without COPD. Potential confounders as above were considered in the final model (for each outcome) if they changed the HR by 5% or more. Each confounder was assessed in a sperate model

(one at a time), with removing the existing potential confounder before adding the next one. Potential confounders include BMI, MRC dyspnoea score, smoking status, modified CCI, Townsend score, corticosteroid prescription, and CV disease. The assumption of cox regression model was checked using Schoenfeld residuals.

The same analyses were then conducted for dementia in place of cognitive impairment in subjects without a former code of dementia. Data management and statistical analyses were conducted using STATA version 15.0 software.

4.2.7.1 Sensitivity analyses

Several sensitivity analyses were carried.

1- The prevalence and incidence of cognitive impairment were compared within patients with COPD based on MRC dyspnoea score (1-3 vs 4-5). Similarly, analysis for dementia was conducted in place of cognitive impairment.
2- The prevalence and incidence of coded vascular dementia were determined in patients with COPD and subjects without COPD.
3- A sensitivity analysis was conducted to examine the difference in the prevalence and incidence of dementia in patients with COPD and their matched subjects without COPD at two different incident COPD diagnosis timeframes: 1) 01-01-2004 (the National Institute for Health and Care Excellence (NICE) [279] COPD guideline published in 2004) to 31-12-2015 and 2) 01-04-2012 (the enhancement of dementia coding in QOF [280]) to 31-12-2015 in individuals who are 65 years and older.
4- The cumulative prevalence of either cognitive impairment/dementia or both were determined in patients with COPD and subjects without COPD from 01-04-2006 onwards to 31-12-2015.

5- The incidence of either cognitive impairment or dementia was also determined in patients with COPD and subjects without COPD, excluding subjects with a former code of cognitive impairment and dementia.

4.3 **RESULTS**

A total of 65,068 patients with COPD and 249,166 subjects without COPD were included in the analyses (Figure 4-1). The baseline characteristics of the study population are presented in Table 4-1. There were more males than females (53% vs 47%). The mean (SD) at diagnosis was 65 (10.9) years. The median follow-up period was 4.3 years across both groups. Co-morbidities were greater in patients with COPD compared to subjects without COPD.

Figure 4-1. Flow chart to the study

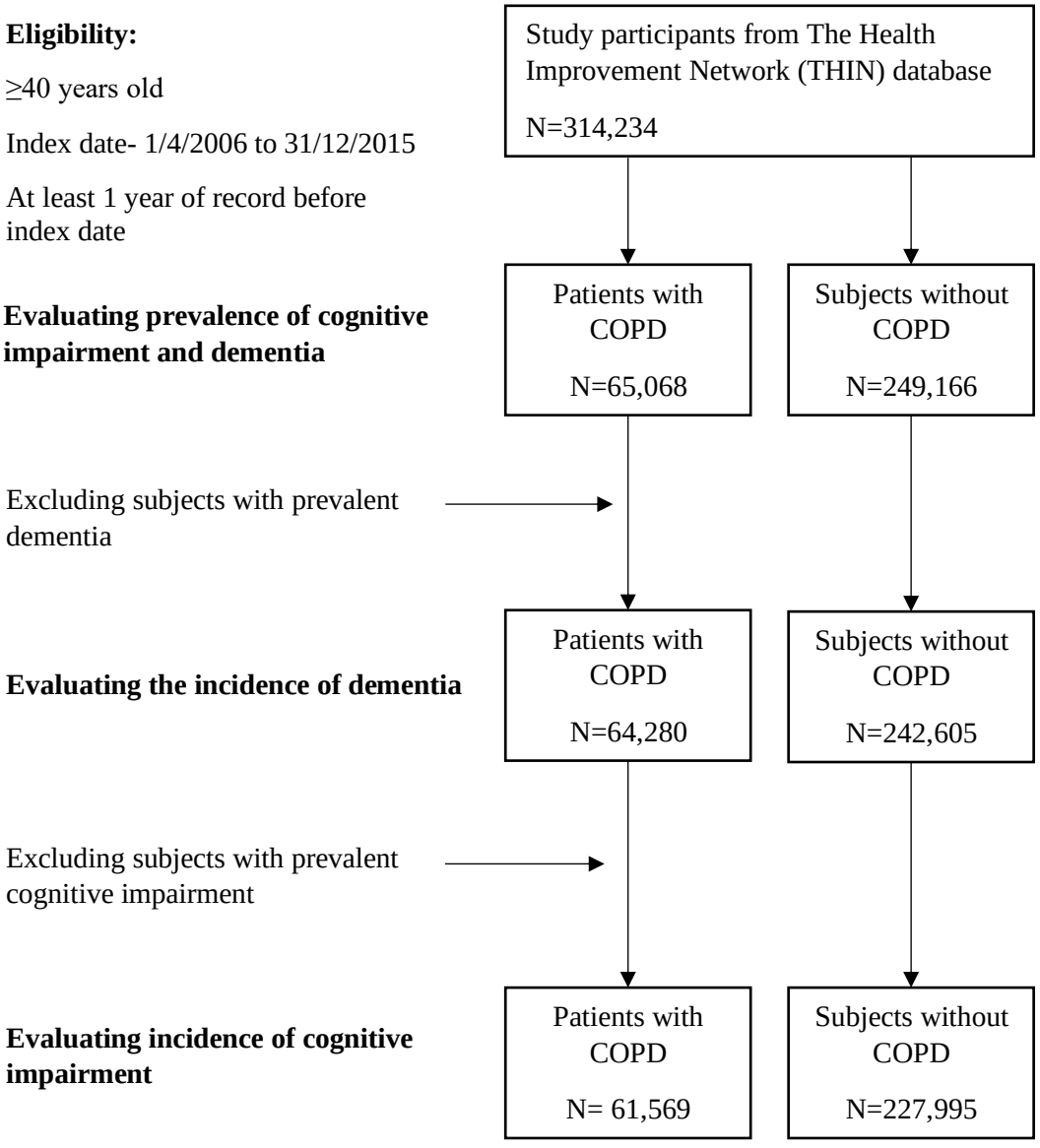


Table 4-1. Baseline characteristics for patients with COPD and up to four subjects without COPD matched by age, gender and GP

Characteristics	Patients with COPD		Subjects without COPD		
	n = 65,068	%	n = 249,166	%	P-value
Age at diagnosis (years)					
<60	17,957	27.60	71,181	28.57	
60–69	21,269	32.69	83,070	33.34	
70–79	17,716	27.23	66,504	26.69	
≥80	8,126	12.49	28,411	11.40	
Gender					
Male	34,404	52.87	130,292	52.29	
Female	30,664	47.13	118,874	47.71	
Townsend score					
1 least deprived	10,563	16.23	60,373	24.23	
2	11,518	17.70	55,552	22.30	
3	13,171	20.24	49,063	19.69	<0.001
4	14,837	22.80	43,390	17.41	
5 most deprived	12,490	19.20	30,452	12.22	
No records	2,489	3.83	10,336	4.15	
BMI (kg/m^2)					
Underweight (<18)	3,898	5.99	4,421	1.77	
Normal (18-24.9)	21,923	33.69	72,544	29.11	
Overweight (25-29.9)	20,296	31.19	87,720	35.21	<0.001
Obese (≥30)	17,645	27.12	61,860	24.83	
No records	1,306	2.01	22,621	9.08	
MRC dyspnoea score					
1	9,197	14.13	1,151	0.46	
2	18,928	29.1	1,066	0.43	
3	10,126	15.56	433	0.17	<0.001
4–5	5,032	7.73	173	0.07	
No records	21,785	33.47	246,343	98.87	
Smoking status					
Never smoked	5,466	8.40	117,190	47.03	
Ex-smoker	35,400	54.40	89,839	36.06	<0.001
Current smoker	24,127	37.08	34,307	13.77	
Unknown	75	0.12	7,830	3.14	
Modified CCI					
0–1	33,851	52.02	178,172	71.51	
2	10,119	15.55	35,175	14.12	
3	10,389	15.97	19,609	7.87	<0.001
≥ 4	10,709	16.46	16,210	6.51	
Medications					
Corticosteroids	27,471	42.22	16,203	6.50	<0.001

Table 4-1. (continued)

Characteristics	Patients with COPD		Subjects without COPD		
	n = 65,068	%	n = 249,166	%	P-value
Comorbidities					
Diabetes mellitus	9,047	13.90	32,271	12.95	<0.001
CV disease (CHF, IHD, PVD)	17,400	26.74	41,848	16.80	0.001
Cerebrovascular disease	5,489	8.44	14,721	5.91	<0.001
Alcohol status					
Lifelong teetotaler	13,114	20.15	44,753	17.96	<0.001
Ex-drinker	4,606	7.08	9,206	3.69	
Current drinker	44,046	67.69	171,476	68.82	
No records	3,302	5.07	23,731	9.52	

Abbreviations: BMI: body mass index; CCI, Charlson comorbidity index; CHF: chronic heart failure; CV: cardiovascular; IHD: Ischemic heart disease; MRC: Medical Research Council; PVD: peripheral vascular disease.

Prevalence around index date

Prevalence of cognitive impairment

A total of 10,517 subjects (patients with COPD and subjects without COPD) had a doctor recode of cognitive impairment at index date. The proportion of cognitive impairment without a diagnosis of dementia was significantly greater for patients with COPD (n=2,629; 4.1%) than for subjects without COPD (n=7,883; 3.2%), p<0.001.

Cognitive impairment remained more prevalent in patients with COPD after adjustment for age, gender, and GP practice (OR: 1.32 (95% CI: 1.26 to 1.39, p<0.001); Table 4-2). This association was then diminished by the effect of smoking, CV disease, and modified CCI in the fully adjusted model (adjusted OR [aOR]: 0.97 (95% CI 0.87 to 1.09, p=0.629), Table 4-2).

Table 4-2. Univariate and multivariate conditional logistic regression models of the prevalence of cognitive impairment for patients with COPD (n= 65,068) and subjects without COPD (n= 249,166), matched by age, gender, and GP practice

Descriptor	OR (95% CI)	Fully adjusted OR (95% CI)
Subjects		
Subjects without COPD	**1**	**1**
Patients with COPD	1.32 (1.26 to 1.39)	0.97 (0.87 to 1.09)
Modified CCI		
Score 0-1	**1**	**1**
Score 2	1.57 (1.53 to 1.30)	1.62 (1.53 to 1.70)
Score 3	2.97 (2.87 to 3.05)	2.48 (1.35 to 2.64)
Score 4 and more	3.84 (3.73 to 3.95)	2.93 (2.75 to 3.13)
Smoking Status		
Never	**1**	**1**
Former	9.79 (9.47 to 10.1)	7.24 (6.68 to 7.65)
Current	18.79 (18.14 to 19.47)	14.81 (13.96 to 15.79)
Unknown	0.20 (0.16 to 0.26)	0.49 (0.35 to 0.70)
Townsend score		
1 least deprived	**1**	**1**
2	1.25 (1.21 to 1.29)	1.16 (1.09 to 1.24)
3	1.71 (1.66 to 1.76)	1.35 (1.27 to 1.45)
4	2.32 (2.25 to 2.39)	1.66 (1.55 to 1.78)
5 most deprived	3.01 (2.91 to 3.11)	1.80 (1.17 to 1.53)
No records	1.60 (1.51 to 1.70)	1.36 (1.20 to 1.53)
CV disease		
No	**1**	1
Yes	1.87 (1.83 to 1.91)	1.08 (1.02 to 1.12)
Corticosteroids		
No	**1**	1
Yes	11.08 (10.8 to 11.37)	7.37 (7.37 to 8.10)

The fully adjusted Odds Ratio (aOR) was 0.97, 95% CI 0.87 to 1.09, p=0.629 – the multivariable conditional logistic regression model derived aOR was adjusted for age, gender, GP practice, modified Charlson comorbidity index, smoking status, socioeconomic class, Cardiovascular disease, and oral corticosteroid use.

Abbreviations: CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; GP: general practice; OR: odds ratio.

Prevalence of Dementia

At index date, there were less patients with COPD with coded dementia (705; 1.1%) than subjects without COPD (4,209; 1.7%), p<0.001. The prevalence of dementia was less frequently recorded in patients with COPD, compared to subjects without COPD, after adjusting for confounders (aOR: 0.86; 95% CI: 0.74 to 0.98; p=0.049; Table 4-3).

A sensitivity analysis was performed to estimate the prevalence of vascular dementia at index date in patients with COPD and subjects without COPD. There were less patients with COPD with vascular dementia compared to subjects without COPD (n=1,132 (0.45%) vs n=214 (0.33%); p<0.001). After adjusting for confounders, the prevalence of vascular dementia was not different between patients with COPD and subjects without COPD (aOR: 0.90; 95% CI, 0.67-1.20; p=0.663; Table 4-4).

The difference in the prevalence of dementia was assessed at two incident COPD diagnosis timeframes: 1) 01-01-2004 to 31-12-2015, and 2) 01-04-2012 to 31-12-2015. In the first timeframe (2004-2015), the prevalence of coded dementia was lower in patients with COPD (n=80,874) compared to subjects without COPD (n=308,999) (aOR, 0.69; 95% CI, 0.59 to 0.80; P<0.001). In older subjects (≥ 65 years old) included from 2012 onwards to 2015, the prevalence of coded dementia was not statistically different between patients with COPD patients (n=12,932) and subjects without COPD (n=48,559), (aOR, 0.84; 95% CI, 0.65 to 1.09; p=209).

Table 4-3. Univariate and multivariate conditional logistic regression models of the prevalence of dementia for patients with COPD (n= 65,068) and subjects without COPD (n= 249,166), matched by age, gender, and GP practice

Descriptor	OR (95% CI)	Fully adjusted OR (95% CI)
Subjects		
Subjects without COPD	**1**	**1**
Patients with COPD	0.57 (0.52 to 0.62)	0.86 (0.74 to 0.98)
Modified CCI		
Score 0-1	**1**	**1**
Score 2	1.57 (1.53 to 1.61)	1.49 (1.41 to 1.57)
Score 3	2.96 (2.88 to 3.05)	2.47 (2.36 to 2.63)
Score 4 and more	3.38 (3.72 to 3.94)	2.89 (2.75 to 3.09)
Smoking Status		
Never	**1**	**1**
Former	9.78 (9.46 to 10.1)	7.20 (6.78 to 7.64)
Current	18.78 (18.12 to 19.45)	14.84 (13.95 to 15.78)
Unknown	0.20 (0.16 to 0.26)	0.50 (0.35 to 0.71)
Townsend score		
1 least deprived	**1**	**1**
2	1.25 (1.21 to 1.29)	1.23 (1.16 to 1.31)
3	1.71 (1.66 to 1.76)	1.61 (1.52 to 1.72)
4	2.32 (2.25 to 2.39)	2.09 (1.52 to 1.72)
5 most deprived	3.01 (2.91 to 3.11)	1.62 (1.44 to 1.82)
No records	1.60 (1.51 to 1.70)	1.36 (1.21 to 1.54)
CV disease		
No	**1**	**1**
Yes	1.88 (1.84 to 1.92)	1.07 (1.02 to 1.12)
Corticosteroids		
No	**1**	**1**
Yes	11.07 (10.80 to 11.35)	7.71 (7.34 to 8.09)

The fully adjusted Odds Ratio (aOR) was 0.86, 95% CI 0.74 to 0.98, p=0.049 – the multivariable conditional logistic regression model derived aOR was adjusted for age, gender, GP practice, modified Charlson comorbidity index, smoking status, socioeconomic class, CV disease, and oral corticosteroid use.

Abbreviations: CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; OR: odds ratio.

Table 4-4. Univariate and multivariate conditional logistic regression models of the prevalence of vascular dementia for patients with COPD (n= 65,068) and subjects without COPD (n= 249,166), matched by age, gender, and GP practice

Descriptor	OR (95% CI)	Fully adjusted OR (95% CI)
Subjects		
Subjects without COPD	**1**	**1**
Patients with COPD	0.66 (0.57 to 0.76)	0.90 (0.67 to 1.20)
Modified CCI		
Score 0-1	**1**	**1**
Score 2	1.57 (1.53 to 1.61)	1.62 (1.53 to 1.71)
Score 3	2.97 (2.89 to 3.05)	2.51(1.37 to 2.66)
Score 4 and more	3.38 (3.72 to 3.95)	2.97 (2.78 to 3.17)
Smoking Status		
Never	**1**	**1**
Former	9.77 (9.46 to 10.11)	7.22 (6.78 to 7.64)
Current	18.80 (18.15 to 19.47)	17.56 (16.37 to 18.83)
Unknown	0.20 (0.16 to 0.26)	0.57 (0.40 to 0.81)
BMI (kg/m^2)		
Underweight (<18)	2.95 (2.82 to 3.09)	2.68 (2.44 to 2.94)
Normal (18-24.9)	1	
Overweight (25-29.9)	0.76 (0.74 to 0.77)	0.76 (0.72 to 0.79)
Obese (≥30)	0.95 (0.93 to 0.97)	0.82 (0.78 to 0.86)
No records	0.17 (0.16 to 0.19)	0.51 (0.46 to 0.56)
Townsend score		
1 least deprived	**1**	**1**
2	1.25 (1.21 to 1.29)	1.15 (1.07 to 1.23)
3	1.71 (1.66 to 1.76)	1.33 (1.24 to 1.43)
4	2.32 (2.25 to 2.39)	1.61 (1.50 to 1.73)
5 most deprived	3.01 (2.91 to 3.11)	1.29 (1.12 to 1.48)
No records	1.60 (1.51 to 1.70)	1.34)1.19 to 1.52)
CV disease		
No	**1**	**1**
Yes	1.88 (1.84 to 1.92)	1.12 (1.05 to 1.17)
Corticosteroids		
No	**1**	**1**
Yes	11.08 (10.81 to 11.37)	7.72 (7.36 to 8.10)

The fully adjusted Odds Ratio (aOR) was 0.90, 95% CI 0.76 to 1.20, p=0.503 – the multivariable conditional logistic regression model derived aOR was adjusted for age, gender, GP practice, modified Charlson comorbidity index, smoking status, BMI; socioeconomic class, CV disease, and oral corticosteroid use.
Abbreviations: BMI: body mass index; CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; OR: odds ratio.

Prevalence of either cognitive impairment or dementia

The prevalence of either coded cognitive impairment and/or dementia at index date was calculated for patients with COPD and subjects without COPD. There were 3,334 (5.1%) patients with COPD with either cognitive impairment or dementia, compared with 12,092 (4.9%) subjects without COPD, $p<0.004$.

There was no significant difference in the prevalence of either cognitive impairment and/or dementia between patients with COPD and subjects without COPD following adjustment for confounders ((aOR): 0.96 (95% CI 0.86 to 1.06); p=0.435; Table 4-5).

Table 4-5. Univariate and multivariate conditional logistic regression models of the prevalence of either cognitive impairment or dementia for patients with COPD (n= 65,068) and subjects without COPD (n= 249,166), matched by age, gender, and GP practice

Descriptor	OR (95%CI)	Fully adjusted OR (95% CI)
Subjects		
Subjects without COPD	1	1
Patients with COPD	1.02 (0.98 to 1.07)	0.96 (0.86 to 1.06)
Modified CCI		
Score 0-1	1	1
Score 2	1.57 (1.53 to 1.62)	1.62 (1.53 to 1.70)
Score 3	2.98 (2.90 to 3.06)	2.49 (1.35 to 2.64)
Score 4 and more	3.86 (3.75 to 3.97)	2.93 (2.75 to 3.13)
Smoking Status		
Never	1	1
Former	9.79 (9.48 to 10.11)	7.25 (6.83 to 7.71)
Current	18.80 (18.14 to 19.47)	14.84 (13.95 to 15.79)
Unknown	0.21 (0.16 to 0.26)	0.56 (0.40 to 0.79)
Townsend score		
1 least deprived	1	1
2	1.25 (1.21 to 1.29)	1.15 (1.07 to 1.23)
3	1.71 (1.66 to 1.76)	1.34 (1.25 to 1.43)
4	2.32 (2.25 to 2.39)	1.62 (1.51 to 1.74)
5 most deprived	3.01 (2.91 to 3.11)	1.77 (1.64 to 1.92)
No records	1.60 (1.51 to 1.70)	1.36 (1.21 to 1.54)
CV disease		
No	1	1
Yes	1.87 (1.84 to 1.92)	1.07 (1.02 to 1.13)
Corticosteroids		
No	1	1
Yes	11.09 (10.81 to 11.37)	7.72 (7.37 to 8.10)

The fully adjusted Odds Ratio (aOR) was 0.96, 95% CI 0.86 to 1.06, p=0.435– the multivariable conditional logistic regression model derived aOR was adjusted for age, gender, GP practice, modified Charlson comorbidity index, smoking status, socioeconomic class, CV disease, and oral corticosteroid use.

Abbreviations: CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; OR: odds ratio.

Table 4-6. Summary of the prevalence of cognitive impairment, dementia, and either cognitive impairment or dementia for patients with COPD (n= 65,068) and subjects without COPD (n= 249,166), matched by age, gender, and GP practice

	Subjects without COPD	Patients with COPD	P-value
Cognitive impairment, n (%)	2,629 (4.1%)	7,883 (3.2%)	<0.001
OR (95% CI)	1	1.32 (1.26 to 1.39)	<0.001
Fully adjusted (95% CI)	1	0.97 (0.87 to 1.09) [a]	0.629
Dementia, n (%)	705 (1.1%)	4,209 (1.7%)	<0.001
OR (95% CI)	1	0.57 (0.52 to 0.62)	<0.001
Fully adjusted (95% CI)	1	0.86 (0.74 to 0.98) [a]	0.049
Either cognitive impairment or dementia, n (%)	3,334 (5.1%)	12,092 (4.9%)	0.004
OR (95% CI)	1	1.02 (0.98 to 1.07)	0.203
Fully adjusted (95% CI)	1	0.96 (0.86 to 1.06) [a]	0.435

[a] The multivariable conditional logistic regression model derived aOR was adjusted for age, gender, GP practice, modified CCI, smoking status, socioeconomic class, CV disease, and oral corticosteroid use.

Abbreviations: CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; GP: general practice; OR: odds ratio.

Association of MRC dyspnoea score with prevalence of cognitive impairment, dementia, and either

A sensitivity analysis was conducted to estimate the prevalence of cognitive impairment in patients with COPD based on MRC dyspnoea score (1-3 vs 4-5) at time of COPD diagnosis. A total of 43,283 patients with COPD were identified with coded MRC dyspnoea score. Of those, 38,251 patients had an MRC dyspnoea score 1-3, and 5,032 patients with MRC score 4-5.

Patients with COPD with MRC dyspnoea score 4-5 had a greater prevalence of cognitive impairment (n=317; 6.3%) than patients with MRC score 1-3 (n=1,643; 4.3%), Table 4-7. The prevalence of cognitive impairment at COPD diagnosis in patients with MRC score 4-5 remained significantly greater, even after adjustment for confounders (aOR, 1.14; 95% CI, 1.01 to 1.28; p=0.034).

In the fully adjusted models, there was a significantly greater prevalence of dementia (aOR, 1.36; 95% CI, 1.05 to 1.75; p=0.018), and either cognitive impairment or dementia (aOR, 1.17; 95% CI, 1.04 to 1.31; p=0.008) in patients with an MRC score of 4–5 compared with those with an MRC score 1–3 (Table 4-7).

Table 4-7. Comparison of prevalence of cognitive impairment, dementia, or either cognitive impairment or dementia in patients with COPD according to MRC dyspnoea score (1–3 vs 4–5)

	MRC dyspnea score 1-3 (n = 38,251)	MRC dyspnea score 4-5 (n = 5,032)	P-value
Cognitive impairment, n (%)	1,643 (4.3%)	317 (6.3%)	<0.001
OR (95% CI)	1	1.29 (1.15 to 1.45)	<0.001
Fully adjusted (95% CI)	1	1.14 (1.01 to 1.28) [a]	0.034
Dementia, n (%)	267 (0.7%)	89 (1.8%)	<0.001
OR (95% CI)	1	1.52 (1.18 to 1.95)	<0.001
Fully adjusted (95% CI)	1	1.36 (1.05 to 1.75) [a]	0.018
Either cognitive impairment or dementia, n (%)	1,910 (5%)	406 (8.1%)	<0.001
OR (95% CI)	1	1.32 (1.18 to 1.48)	<0.001
Fully adjusted (95% CI)	1	1.17 (1.04 to 1.31) [a]	0.008

[a] Adjusted for age, gender, modified Charlson comorbidity index, smoking status, socioeconomic class, CV disease, and oral corticosteroid use.

Abbreviations: CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; MRC: Medical Research Council; OR: odds ratio.

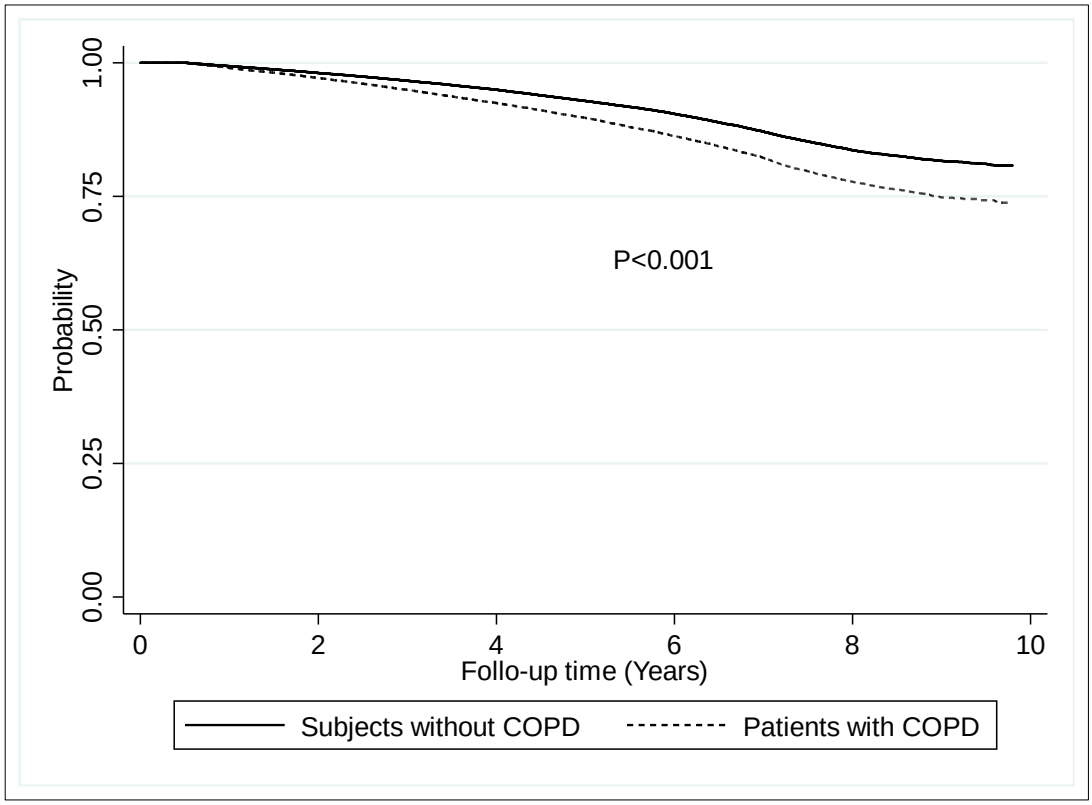
Incidence

Incidence of Cognitive Impairment

After excluding subjects with former coded cognitive impairment and/or dementia, there were 61,569 patients with COPD and 227,995 subjects without COPD; and demographics remained similar. Of patients with COPD, 5,059 (8.3%) had a recorded incidence of cognitive impairment (without a diagnosis of dementia) compared to 14,514 (6.4%) subjects without COPD, $p<0.001$.

The incidence rate of cognitive impairment in patients with COPD was 23.1 per 1,000 person-years (95% CI: 22.4 to 23.4) compared to 16.3 per 1,000 person-years (95% CI: 16.1 to 16.4) in subjects without COPD. The time to first recorded incidence of cognitive impairment was significantly shorter in patients with COPD compared to non-COPD subjects, $P<0.001$, Figure 4-2. In the fully adjusted model, patients with COPD, compared with subjects without COPD, were significantly more likely to have an incident diagnosis of cognitive impairment (adjusted HR [aHR]: 1.17 (95% CI 1.12 to 1.23); $p<0.001$; Table 4-8).

Figure 4-2. Kaplan-Meier analysis of the incidence of cognitive impairment for patients with COPD and subjects without COPD



Kaplan-Meier plots comparing the incidence of cognitive impairment for patients with COPD and subjects without COPD. The Y-axis represents the probability of patients free of cognitive impairment. The X-axis represents the follow-up time in years (2006 to 2015). The solid line represents subjects without COPD. The dashed line represents patients with COPD.

Table 4-8. Univariate and multivariate Cox regression models of the incidence of cognitive impairment for patients with COPD (n=61,569) and subjects without COPD (n=227,995) matched by age, gender, and GP practice

Descriptor	HR (95% CI)	Adjusted HR (95% CI)
Subjects		
Subjects without COPD	**1**	**1**
Patients with COPD	1.48 (1.43 to 1.53)	1.17 (1.12 to 1.23)
Modified CCI		
Score 0-1	**1**	**1**
Score 2	1.52 (1.44 to 1.59)	1.23 (1.17 to 1.29)
Score 3	2.28 (2.17 to 2.41)	1.87 (1.77 to 1.97)
Score 4 and more	2.84 (2.68 to 3.01)	1.92 (1.81 to 2.04)
Smoking Status		
Never	**1**	**1**
Former	1.30 (1.25 to 1.36)	1.17 (1.13 to 1.22)
Current	1.17 (1.10 to 1.24)	1.09 (1.30 to 1.16)
Unknown	0.18 (0.01 to 0.04)	0.24 (0.01 to 0.05)
Townsend score		
1 least deprived	**1**	**1**
2	0.99 (0.95 to 1.04)	0.99 (0.94 to 1.04)
3	1.04 (0.99 to 1.10)	0.95 (0.96 to 1.07)
4	1.10 (1.04 to 1.17)	1.05 (0.99 to 1.12)
5 most deprived	1.20 (1.12 to 1.18)	1.12 (1.04 to 1.20)
No records	1.06 (0.93 to 1.20)	1.14 (0.87 to 1.08)
CV disease		
No	**1**	**1**
Yes	3.15 (3.03 to 3.28)	2.27 (2.17 to 2.37)
Corticosteroids		
No	**1**	**1**
Yes	1.18 (1.12 to 1.24)	1.09 (1.03 to 1.14)

The fully adjusted Hazard Ratio (aHR) was 1.17, 95% CI 1.12 to 1.23, $p<0.001$ – the cox regression model was adjusted for age, gender, modified Charlson comorbidity index, smoking status, socioeconomic class, CV disease, and oral corticosteroid use.

Abbreviations: CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; HR: Hazard ratio.

Incidence of Dementia

After excluding subjects with former codes of dementia (but not those with cognitive impairment codes), there were 64,280 patients with COPD and 242,605 subjects without COPD, and demographics remained similar.

Of patients with COPD, 1,041 (1.6%) were recorded with incident dementia compared to 4,158 (1.7%) subjects without COPD, p=0.099. The incidence rate was 4.4 per 1,000 person-years for patients with COPD and subjects without COPD. The incidence of dementia was not statistically different between patients with COPD and subjects without COPD following adjustments for age, gender, and GP practice (HR: 1.01; 95% CI: 0.94 to 1.09; p=0.665). Following adjustments for confounders, the incidence of coded dementia in patients with COPD was less than in non-COPD subjects (aHR: 0.87, 95% CI: 0.77 to 0.96; p=0.019; Table 4-9).

Similar proportions of patients in both groups with cognitive impairment developed dementia (around 7.8%). In patients with COPD, those with diagnosed cognitive impairment were nearly nine times more likely to develop dementia than those without cognitive impairment (aHR: 8.85; 95% CI: 7.42–10.54). A similar finding was also observed in subjects without COPD.

There were more patients with COPD with coded vascular dementia (n=386; 0.6%) compared to subjects without COPD (n=1,263; 0.5%), p=0.014. The incidence rate of vascular dementia in patients with COPD was 1.6 per 1,000 person-years (95% CI: 1.5 to 1.8) compared to 1.3 per 1,000 person-years (95% CI: 1.2 to 1.4) in subjects without COPD. The incidence of vascular dementia was greater in patients with COPD than non-COPD subjects matched for age, gender and GP (HR: 1.29; 95% CI: 1.14–1.46).

In the fully adjusted model, this association was diminished (aHR: 1.09; 95% CI: 0.89–1.33; p = 0.388; Table 4-10).

A sensitivity analysis was conducted in subjects who were identified from 2004 until 2015. The incidence of dementia was less frequently coded in patients with COPD compared to subjects without COPD (aHR 0.76; 95% CI: 0.72 to 0.81; p<0.001). In contrast, subjects who were older than 65 years with an incident diagnosis of COPD from 01-04-2012 to 31-12-2015 did not show any differences even after adjusting for the same confounders (aHR 1.11; 95% CI: 0.65 to 1.87; p=692).

Table 4-9. Univariate and multivariate Cox regression models of the incidence of dementia for patients with COPD (n=64,280) and subjects without COPD (n=242,605) matched by age, gender, and GP practice

Descriptor	HR (95% CI)	Adjusted HR (95% CI)
Subjects		
Subjects without COPD	**1**	**1**
Patients with COPD	1.01 (0.94 to 1.09)	0.87 (0.77 to 0.96)
Modified CCI		
Score 0-1	**1**	**1**
Score 2	1.11 (1.01 to 1.21)	1.05 (0.96 to 1.15)
Score 3	1.14 (1.01 to 1.28)	1.06 (0.94 to 1.96)
Score 4 and more	1.37 (1.20 to 1.55)	1.24 (1.09 to 1.42)
Smoking Status		
Never	**1**	**1**
Former	1.06 (0.89 to 1.04)	1.05 (0.97 to 1.14)
Current	0.97 (0.86 to 1.10)	0.84 (0.74 to 0.95)
Unknown	0.03 (0.01 to 0.07)	0.04 (0.02 to 0.09)
BMI (kg/m^2)		
Underweight (<18)	1.79 (1.55 to 2.07)	1.82 (1.57 to 2.11)
Normal (18-24.9)	1	
Overweight (25-29.9)	0.69 (0.64 to 0.75)	0.67 (0.62 to 0.73)
Obese (≥30)	0.65 (0.59 to 0.72)	0.62 (0.56 to 0.69)
No records	0.44 (0.38 to 0.52)	0.70 (0.59 to 0.83)
Townsend score		
1 least deprived	**1**	**1**
2	1.08 (0.97 to 1.19)	1.09 (0.98 to 1.21)
3	1.07 (0.96 to 1.19)	1.09 (0.98 to 1.22)
4	1.15 (1.03 to 1.28)	1.16 (1.04 to 1.31)
5 most deprived	1.23 (1.08 to 1.40)	1.27 (1.12 to 1.45)
No records	1.09 (0.89 to 1.34)	1.16 (0.94 to 1.44)
CV disease		
No	1	1
Yes	1.33 (1.23 to 1.43)	1.24 (1.16 to 1.36)
Corticosteroids		
No	1	1
Yes	1.05 (0.94 to 1.16)	1.02 (0.92 to 1.13)

The fully adjusted Hazard Ratio (aHR) was 0.87, 95% CI 0.77 to 0.96, p=0.019– the cox regression model was adjusted for age, gender, GP practice, modified Charlson comorbidity index, smoking status, BMI, socioeconomic class, cardiovascular disease, and oral corticosteroid use.

Abbreviations: BMI: body mass index; CCI: Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; HR: Hazard ratio.

Table 4-10. Univariate and multivariate Cox regression models of the incidence of vascular dementia for patients with COPD (n=64,280) and subjects without COPD (n=242,605) matched by age, gender, and GP practice

Descriptor	HR (95% CI)	Adjusted HR (95% CI)
Subjects		
Subjects without COPD	**1**	**1**
Patients with COPD	1.29 (1.42 to 1.46)	1.09 (0.89 to 1.33)
Modified CCI		
Score 0-1	**1**	**1**
Score 2	1.23 (1.12 to 1.44)	1.07 (0.91 to 1.27)
Score 3	1.38 (1.14 to 1.69)	1.09 (0.88 to 1.33)
Score 4 and more	1.87 (1.53 to 2.30)	1.39 (1.12 to 1.37)
Smoking Status		
Never	**1**	**1**
Former	1.22 (1.06 to 1.40)	1.14 (0.99 to 1.32)
Current	1.27 (1.03 to 1.57)	1.06 (0.85 to 1.33)
Unknown	0.09 (0.03 to 0.24)	0.13 (0.04 to 0.37)
BMI (kg/m^2)		
Underweight (<18)	2.03 (1.57 to 2.61)	1.99 (1.53 to 2.58)
Normal (18-24.9)	1	
Overweight (25-29.9)	0.86 (0.74 to 0.98)	0.82 (0.71 to 0.94)
Obese (≥30)	0.81 (0.68 to 0.69)	0.77 (0.64 to 0.92)
No records	0.41 (0.30 to 0.56)	0.65 (0.46 to 0.92)
Townsend score		
1 least deprived	**1**	**1**
2	1.04 (0.86 to 1.25)	1.02 (0.84 to 1.24)
3	1.07 (0.88 to 1.29)	1.05 (0.86 to 1.28)
4	1.18 (0.97 to 1.45)	1.11 (0.90 to 1.37)
5 most deprived	1.27 (1.01 to 1.59)	1.25 (0.99 to 1.59)
No records	1.56 (1.11 to 2.19)	1.48 (1.03 to 2.12)
CV disease		
No	1	1
Yes	2.30 (1.03 to 2.60)	2.12 (1.86 to 2.42)
Corticosteroids		
No	1	1
Yes	1.12 (0.94 to 1.34)	1.02 (0.92 to 1.13)

The fully adjusted Hazard Ratio (aHR) was 1.09, 95% CI 0.89 to 0.33, p=0.388– the cox regression model was adjusted for age, gender, GP practice, modified Charlson comorbidity index, smoking status, BMI, socioeconomic class, cardiovascular disease, and oral corticosteroid use.

Abbreviations: BMI: body mass index; CCI: Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; HR: Hazard ratio.

Incidence of either Cognitive Impairment or Dementia

In this analysis, all subjects (patients with COPD and subjects without COPD) with a former code of cognitive impairment and/or dementia were excluded. This has resulted in a total of 61,569 patients with COPD and 227,995 subjects without COPD. Demographics and clinical characteristics remained similar.

There were more patients with COPD with either coded cognitive impairment or dementia (n=5,971; 9.7%) compared to subjects without COPD (n=17,961; 7.3%), $p<0.001$. The incidence rate of either cognitive impairment or dementia in patients with COPD was 27.2 per 1,000 person-years (95% CI: 26.5−27.9) compared with 20.04 per 1,000 person-years (95% CI: 20.1–20.7) in subjects without COPD. Patients with COPD were more likely to have a recorded incidence of either cognitive impairment or dementia compared to subjects without COPD (aHR: 1.11, 95% CI: 1.06 to 1.15; $p <0.001$; Table 4-11).

Table 4-11. Univariate and multivariate Cox regression models of the incidence of either cognitive impairment or dementia for patients with COPD (n=61,569) compared with subjects without COPD (n=227,995) matched by age, gender, and GP practice

Descriptor	HR (95% CI)	Adjusted HR (95% CI)
Subjects		
Subjects without COPD	**1**	**1**
Patients with COPD	1.39 (1.35 to 1.44)	1.11 (1.06 to 1.15)
Modified CCI		
Score 0-1	**1**	**1**
Score 2	1.45 (1.39 to 1.51)	1.20 (1.14 to 1.25)
Score 3	2.04 (1.95 to 1.41)	1.68 (1.60 to 1.77)
Score 4 and more	2.54 (2.42 to 2.68)	1.79 (1.70 to 1.89)
Smoking Status		
Never	**1**	**1**
Former	1.26 (1.22 to 1.31)	1.15 (1.11 to 1.20)
Current	1.13 (1.07 to 1.19)	1.06 (1.01 to 1.12)
Unknown	0.02 (0.01 to 0.04)	0.29 (0.01 to 0.05)
BMI (kg/m^2)		
Underweight (<18)	1.32 (1.21 to 2.45)	1.40 (1.27 to 1.54)
Normal (18-24.9)	1	1
Overweight (25-29.9)	0.98 (0.94 to 1.02)	0.94 (0.90 to 0.98)
Obese (≥30)	1.20 (1.15 to 1.25)	1.08 (1.03 to 1.13)
No records	0.35 (0.32 to 0.40)	0.61 (0.54 to 0.67)
Townsend score		
1 least deprived	**1**	**1**
2	1.01 (0.97 to 1.06)	1.02 (0.97 to 1.07)
3	1.05 (1.01 to 1.10)	1.02 (0.97 to 1.07)
4	1.12 (1.06 to 1.17)	1.07 (1.08 to 1.23)
5 most deprived	1.21 (1.14 to 1.29)	1.15 (1.02 to 1.28)
No records	1.07 (0.96 to 1.19)	1.13 (1.01 to 1.27)
CV disease		
No	**1**	**1**
Yes	2.71 (2.62 to 2.81)	2.34 (2.25 to 2.43)
Corticosteroids		
No	**1**	**1**
Yes	1.15 (1.09 to 1.20)	1.07 (1.02 to 1.12)

The fully adjusted Hazard Ratio (aHR) was 1.11, 95% CI 1.06 to 1.15, p<0.001– the cox regression model was adjusted for age, gender, GP practice, modified Charlson comorbidity index, smoking status, BMI, socioeconomic class, cardiovascular disease, and oral corticosteroid use.

Abbreviations: BMI: body mass index; CCI: Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; HR: Hazard ratio.

Association of MRC dyspnoea score with the incidence of cognitive impairment, dementia, and either

The association of MRC dyspnoea score (recorded at time of COPD diagnosis) with incident cognitive impairment amongst patients with COPD was evaluated. After excluding subjects with former coded cognitive impairment and/or dementia, there were 36,246 patients with MRC score 1-3 and 4,608 with MRC score 4-5.

The incidence of cognitive impairment was greater in patients with MRC dyspnoea score 4-5 (n=444; 9.6%) compared to patients with MRC score 1-3 (n=3,146; 8.7%), p<0.031. Following COPD diagnosis, patients with MRC score 4-5 were 11% more likely to have a recorded incidence of cognitive impairment (aHR, 1.11; 95% CI, 1.02-1.22; p=0.030) following adjustment for age, gender, and socioeconomic class. Further adjustments have diminished the relationship (Table 4-12).

There were 37,942 patients with MRC score 1-3, and 4,932 patients with MRC score 4-5 included in the dementia analysis. Patients with MRC score 4-5 were 27% more likely to have a recorded incidence of dementia compared to patients with MRC score 1-3 (aHR: 1.27; 95% CI: 1.02 to 1.60; p=0.032), Table 4-12.

The incidence of either cognitive impairment or dementia was greater in patients with MRC dyspnoea score 4-5 (n=524; 11.37%) compared to patients with MRC score 1-3 (n=3,514; 9.69%), p<0.001. Following COPD diagnosis, patients with MRC score 4-5 were 13% more likely to have a recorded incidence of either cognitive impairment or dementia (aHR, 1.13; 95% CI, 1.03-1.24; p=0.007) following adjustment for age, gender and socioeconomic class. Further adjustments have diminished the relationship, Table 4-12.

Table 4-12. Comparison of incidence of cognitive impairment, dementia, and either cognitive impairment or dementia in patients with COPD according to MRC dyspnoea score (1–3 vs 4–5)

MRC dyspnoea score	No. events (%)	HR (95% CI)	Adjusted HR (95% CI)	P-value
Cognitive impairment				
MRC 1-3 (n=36,246)	3,146 (8.7%)	1	1	
MRC 4-5 (n=4,608)	444 (9.6%)	1.11 (1.02 to 1.22)	0.98 (0.89 to 1.09)	0.838
Dementia				
MRC 1-3 (n=42,874)	449 (1.2%)	1	1	
MRC 4-5 (n=4,932)	98 (2%)	1.28 (1.02 to 1.60)	1.27 (1.02 to 1.60)	0.032
Either cognitive impairment or dementia				
MRC 1-3 (n=36,246)	3,514 (9.69%)	1	1	
MRC 4-5 (n=4,608)	524 (11.4%)	1.13 (1.03 to 1.24)	0.99 (0.90 to 1.09)	0.905

HR: adjusted for age, gender, and socioeconomic class.
Fully adjusted HR: adjusted for age, gender, modified CCI, smoking socioeconomic class, CV disease.
Abbreviations: CCI, Charlson comorbidity index; CI: confidence interval; CV: cardiovascular; MRC: Medical Research Council; HR: Hazard ratio.

4.4 DISCUSSION

The coded prevalence of cognitive impairment was significantly greater in patients with COPD compared with subjects without COPD matched for age, gender and GP surgery, although the association was attenuated with additional confounder adjustment, becoming non-significant. The incidence of cognitive impairment was significantly greater in patients with COPD. In contrast, the prevalence and incidence of coded dementia were significantly less in patients with COPD. To the best of our knowledge, this is the first study to investigate this in patients with COPD using UK electronic GP records.

Prevalence and incidence of cognitive impairment in COPD

Although a large body of literature has investigated the prevalence of cognitive impairment in COPD, there is no consensus on the overall prevalence. Cognitive impairment is present in 4% of older patients (≥65 years old) with mild COPD [262] and up to 61% in patients with COPD and severe hypoxemia [267]. This wide variation in the current estimates is attributed to the severity of COPD [268], whether cognitive impairment was systematically assessed or self-reported, and the use of different diagnostic criteria and tools for cognitive impairment [129]. In addition, studies had different threshold definitions for cognitive impairment, even when using the same cognitive assessment tool. A unique aspect of this study is that it reported the prevalence of cognitive impairment at the time of COPD diagnosis, and included all patients with COPD, which therefore, making it a representative sample to the general populations of COPD. However, the proportion of coded cognitive impairment at COPD diagnosis in the GP electronic health records presented in this study (4.1%) was far lower than the proportion in clinical studies at 50% when cognitive impairment

was systematically assessed [281, 282]. This gives a cause for concern of subclinical underdiagnosed cognitive impairment, which may lead to a delayed intervention and consequently, a missed opportunity to alleviate the negative effects of cognitive impairment on this vulnerable population.

Current evidence suggests that patients with COPD are at amplified risk of cognitive impairment and even dementia. The finding that patients with COPD had a higher incidence of cognitive impairment is consistent with prior literature [136, 137, 283]. A previous study from Finland showed that a diagnosis of COPD in midlife was associated with 85% increased risk of mild cognitive impairment/dementia in later life [136]. However, the latter study incorporated self-reported COPD as opposed to a COPD diagnosis that is objectively confirmed. The present study also found that patients with COPD and cognitive impairment were at a greater risk of dementia compared with patients with COPD without cognitive impairment. In this context, establishing accurate estimates of the proportion of patients with COPD and cognitive impairment could help to further understand the clinical relevance of cognitive decline in patients with COPD and identify a high-risk group. This is also important to allow for appropriate therapeutic interventions and changes in lifestyle, which could prevent or delay the cognitive deterioration to clinical dementia.

The prevalence of cognitive impairment has been associated with COPD severity. Grant et al. showed that the prevalence of cognitive impairment was 27% in patients with mild hypoxemia compared to 62% in patients with severe hypoxemia [267]. A recent systematic review showed that the relationship between cognitive impairment and COPD severity (as measured by GOLD and blood gases) is mainly seen in patients with severe and very severe COPD [268]. In a longitudinal study, Hung et al. reported that patients with severe COPD (defined by oxygen use and limited physical activity)

were associated with a rapid cognitive decline [271], highlighting the potential increased risk of subsequent dementia. Using MRC dyspnoea score as a severity measure [37], this study is consistent that those with more breathlessness were at greater risk of cognitive impairment and dementia compared to those with a better MRC score. This finding has important clinical implications, as cognitive impairment and dementia interfere with patient's ability to adhere to their medications and manage their own disease [261, 284], which may consequently lead to worse health outcomes [264].

A major pitfall in studying the association of COPD severity with cognitive impairment and dementia is the possibility of misdiagnosis of COPD. To explain, patients with cognitive impairment/dementia may not be able to follow instructions to perform spirometry, which may lead to erroneous estimation to lung function [269]; and consequently a misdiagnosis of COPD and its severity. This highlights the challenge in accurately assessing the relationship between cognitive impairment and COPD severity, and partly accounts for the observed discrepancies in the prevalences of cognitive impairment in COPD across study populations (e.g. severe and very severe airflow obstruction).

Prevalence and Incidence of Dementia in COPD

There is growing evidence linking cognitive impairment with COPD. Nevertheless, the literature on dementia in COPD is lacking, and prior studies are also limited by study population [138], self-reported assessment of COPD [136], short or even undefined follow-up time [134, 138], and inadequate matching group [135]. The most surprising finding in this study is that the prevalence and incidence of dementia were significantly lower in patients with COPD. Although at first glance, these findings

suggest that patients with COPD may be at lower risk of dementia, there is a likelihood that a dementia diagnosis in patients with COPD has been unintentionally missed. It is likely that COPD symptoms may predominate and be the central focus during GP visits. In addition, doctors may find limited explanatory value in attaching a label of dementia to cognitive impairment in the context of multi-system functional decline as COPD progresses. It is, however, possible that treatment opportunities and, in many jurisdictions, the opportunity to access dementia-specific services are being missed, ultimately to the detriment of the patient. Therefore, the formalisation of dementia might not be addressed accordingly. These findings reinforce the need for a systematic assessment of the cognitive state of patients with COPD during routine clinical follow up.

In this study, the cumulative prevalence and incidence of either cognitive impairment or dementia have been investigated as a separate outcome. This is because the term "cognitive impairment" varies across studies. For instance, Rusanen et al. define "cognitive impairment" as the presence of either mild cognitive impairment or dementia [136]. In contrast, a recent systematic review has investigated the prevalence of cognitive impairment, by excluding any study that reported a diagnosis of dementia [129]. Since the analyses of this chapter are based on primary care data (GP records), where comprehensive cognitive assessment may not be performed, recording of these conditions (cognitive impairment and dementia) in the medical records may vary across practices. This means that dementia diagnosis may have been coded as cognitive impairment and vice versa. Thus, it was important to investigate whether this – coding limitations – might have influenced the findings. This study found that patients with COPD were at increased incident risk of either cognitive states. However,

a clear distinction between these cognitive states can only be confirmed by performing a systematic assessment.

Analysis from the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study (n=2,000) showed that a self-reported diagnosis of COPD in later life (≥ 65 years) was inversely related, although not significant, to mild cognitive impairment/dementia [136]. The findings of the latter study were attributed to survival bias as opposed to the effect of COPD. As COPD and cognitive impairment are both associated with an increased risk of death in their own, it is reasonable to assume that the risk of death will be even greater if both conditions coexist. Indeed, cognitive impairment increases the risk of mortality in certain COPD populations [264]. Furthermore, dementia is a progressive condition and may take decades to develop. In the co-existence of COPD with cognitive impairment, there is a possibility that patients may die before they even receive a diagnosis of dementia.

Patients with COPD usually present with a smoking history and have a wide range of comorbidities, one of which is CV disease. As expected, in this study, the proportions of current smoking and CV disease were greater in patients with COPD, and these confounders attenuated the association with vascular dementia. Because COPD and CV comorbidities share similar risk factors and patients with COPD are more likely to be predisposed to cardiovascular events [97], it is, therefore, difficult to determine whether COPD is associated with increased risk of vascular dementia. Although it is unlikely for CV comorbidities or smoking per se to account for vascular dementia in COPD, it is important to encourage healthcare professionals to identify and manage any modifiable risk factors.

4.4.1 Clinical Implications

Both COPD and dementia are public health threats with severe impacts on health and prognosis. Therefore, prevention and treatment for both conditions are of clinical importance. The findings of the current study showed that COPD is associated with increased risk of incident cognitive impairment or dementia. This association was independent of age, gender, and other risk factors, suggesting that COPD may causally be associated with increased risk of cognitive impairment, and even dementia. Recent data from the ARIC study demonstrated that reduced lung function (COPD pattern) was associated with greater risk of either mild cognitive impairment or dementia [137]; in agreement with findings of the current study. It is important to mention that cognitive impairment and dementia in patients with COPD are not only caused – per se- by COPD alone, but rather, it is due to multiple factors. To explain, CV risk and smoking, which are highly prevalent in patients with COPD and contribute to the increased risk of dementia, could play an important role in the increased risk of dementia in COPD. Thus, it is crucial to reinforce the importance of smoking cessation, as it improves lung function and reduces the risk of cognitive impairment and dementia. In addition, the presence of multiple comorbidities, which is also common in patients with COPD, could also magnify the risk of cognitive impairment and dementia in those with COPD. Proper management of these comorbidities with appropriate interventions could reduce the risk.

The increased understanding of the relationships between COPD with cognitive impairment and dementia has important clinical implications. First, cognitive impairment and dementia have a considerable impact on the clinical management of COPD. Cognitively impaired patients have poor adherence to their medications regimens, incorrect use of inhaler techniques [261], which could result in an increased

risk of exacerbation and worse health outcomes [285]. Cognitive impairment and dementia also affect the self-management skills in patients with COPD. Indeed, patients with COPD need to adopt healthy lifestyles (e.g. stop smoking, healthy diet, and be physically active). However, these behavioural changes require healthy cognitive function, which may be limited or even completely impaired in patients with dementia. The co-existence of cognitive impairment in patients with COPD also interfere with participation and adherence to pulmonary rehabilitation programs [125]. In contrast, patients with dementia may not even be referred to a PR program in the first place.

4.4.2 Strengths and limitations

A strength of this study is that using electronic primary care health records provides a representative sample for the general UK COPD population [273]. The data source includes longitudinal data on various potential risk factors, such as demographic factors and medical conditions. Further, the analyses adjusted for a wide range of potential confounders. Patients with COPD from 2006 onwards were included, after QOF had been already established, meaning that COPD diagnoses were based on spirometry [286]. However, there is still a possibility of COPD misdiagnosis [287]. In addition, retrospective analyses based on medical records that were mainly collected for administrative purposes rather than research are subject to some limitations. There is a possibility that free text (which is largely inaccessible for research due to issues around patient confidentiality) instead of READ codes may be used to record this information. Although QOF was introduced to improve the quality of recording, some variables used in this study may have changed from the last recorded coded entry, such as self-reported smoking. This study has investigated the impact of COPD severity on cognitive impairment and dementia using MRC dyspnoea score as opposed to lung

function measures; the latter is poorly recorded in the THIN database. It is however important to mention that dyspnoea is not specific for COPD and may also exist in other conditions, heart failure, for instance. The possibility of residual confounding of important risk factors, such as hypoxia, hypercapnia, oxidative stress, and inflammation, cannot be excluded. Information on oxygen saturations, oxygen therapy, and inflammatory markers are not well recorded in the utilised database (THIN); thus, these factors could not be adjusted for in the analyses.

4.5 **CONCLUSION**

Cognitive impairment was more prevalent in patients with COPD than in subjects without COPD. Moreover, the incidence of cognitive impairment was also greater. In contrast, the prevalence and incidence of coded dementia were lower in patients with COPD, highlighting the potential likelihood of under-diagnosis of dementia with a missed opportunity for proper intervention, and underlining the need to accurately estimate the proportion of patients with COPD and dementia with a systematic assessment.

Chapter 5 Incidence of Depression and Antidepressant Prescription in Patients with COPD: A Large UK Population-based Cohort Study

5.1 **INTRODUCTION**

It is increasingly recognised that the presence of comorbidities play a major role in COPD prognosis and greatly contribute to the severity of the disease [1]. Depression is amongst the most common comorbidities in COPD, resulting in impaired quality of life [288], poor adherence to medication regimens and pulmonary rehabilitation [139, 140], increased risk of COPD exacerbation [289], and mortality [141]. Given this, the UK National Institute for Health and Care Excellence (NICE) COPD guidelines encourage identifying and managing depression [40].

The reported prevalence of depression in COPD ranges from 15% to 36%, depending on the study population and methodological designs [143]. However, there is no recent work on the incidence rate of a new onset of depression following a diagnosis of COPD. Previous studies are also limited to small sample size [146], short follow-up period [148], and inconsistency of definitions for depression [290]. An earlier UK population-based study reported that the incidence rate of depression in patients with COPD was 16.2 per 1,000 person-years on data from 1995 to 2005 [147]. However, this predominantly predated the publication of the first UK COPD and depression NICE guidelines in December 2004 [291, 292] and the introduction of GP Quality and Outcomes Framework (QOF); both of which have impacted on the clinical management and recording of COPD and depression [293].

Mechanisms underlying the association between depression in COPD are not fully understood. Risk factors associated with increased prevalence of depression in COPD are likely multiple and include age, female gender, and smoking [142, 143, 294]. The COPD severity has also been associated with an increased prevalence of depression; however, studies have not been consistent on severity definition [290]. Breathlessness

(dyspnoea) is a core symptom in COPD and has been associated with worse depression symptoms [294]. Lower socioeconomic class is another risk factor that could also contribute to the increased risk of depression in patients with COPD. In fact, separate literature has previously shown that lower socioeconomic class is associated with COPD as well as with depression [28, 295]. Whether the incidence of depression among patients with COPD may be explained, at least in part, through socioeconomic class is worth exploring.

This study hypothesised that the incidence of depression or antidepressant prescription in patients with COPD would be greater than in subjects without COPD. This chapter aims to 1) determine the incidence of newly diagnosed depression or antidepressant prescription following a diagnosis of COPD and compare this to subjects without COPD using a large primary care database; and 2) to assess the incidence of antidepressant prescription in patients with COPD and incident depression compared to those with incident depression from the general population.

5.2 METHODS

5.2.1 Study design

A matched cohort study was conducted to assess the incidence of depression, antidepressant prescription, or either in patients with COPD compared to subjects without COPD.

5.2.2 Data source

The data source for this study has been fully described in the previous chapter. (See subsection 4.2.2).

5.2.3 Study populations

The study population comprised individuals aged ≥40 years with a COPD diagnosis from 1st January 2004 to 31st December 2015, with ≥ 1 year of record prior to the COPD diagnosis. In addition, a comparison group free of COPD was identified at random from THIN. To create a matched cohort, each patient with COPD was matched by age, gender and GP surgery to up to four subjects free of COPD, and each subject without COPD was assigned the same index date as the matched patients with COPD. Subjects with a missing diagnosis date were excluded from this study. Further, those who were censored or left the GP surgery before index date were also excluded.

5.2.4 Ethical approval

Ethical approval for this study was obtained by an independent Scientific Review Committee (SRC), reference number - 18THIN098-A1.

5.2.5 Follow-up and outcome definitions

Patients with COPD and subjects without COPD with a code of depression prior to index date were excluded. Also, subjects with antidepressant prescription codes of more than 2 years prior to COPD diagnosis/index date were excluded.

Subjects were followed up form COPD diagnosis/index date until either they experienced the outcome of interest (first recorded depression, antidepressant prescription or either), left the GP practice, died or reached the end of the follow-up (31/12/2015), whichever came first. Diagnosis for depression was solely defined based on READ codes (Appendix 9-11). Antidepressants were defined based on drug codes (Appendix 9-12).

The incident of either depression or antidepressant was also investigated as a sperate outcome, as antidepressant prescription might have been coded with a depression episode, and also to account for the under-diagnosed (under-recorded) depression in patients with COPD [296].

5.2.6 Covariate and confounders

A series of explanatory variables were determined at baseline, including age, gender and Townsend social deprivation score [278]. In addition, clinical variables such as smoking status and the Medical Research Council (MRC) dyspnoea scale [37] were recorded closest to the index date (whether prior to, or after index date). A modified Charlson Comorbidity Index (CCI) was determined before or at index date. Body mass index (BMI) was determined within 2 years (before and after) of index date.

5.2.7 Statistical analyses

Demographics and clinical characteristics of patients with COPD and subjects without COPD were described at baseline in terms of frequency or mean and standard

deviation as appropriate. Categorical data were compared using McNemar test. P <0.05 was considered significant.

Incidence rates were estimated for both patients with COPD and subjects without COPD. Cox proportional hazard regression model was used to evaluate the risk of incident depression, antidepressant, or either following COPD diagnosis. The assumption of cox regression model was checked using Schoenfeld residuals. Only the first event following the index date was considered. Person-time commenced at the index date and ended when either the outcome of interest (depression, antidepressant prescription, or either) occurred, subjects left the GP clinic, subjects died, or end of the study period (31/12/2015), whichever came first. Confounders were included in the final model if they independently changed the HR for depression, antidepressant prescription, or either by ≥ 5%. All covariates were assessed in separate regression models.

5.2.7.1 Sensitivity analyses

The incidence of the first antidepressant prescription within 1-month following incident depression was calculated and compared between 1) patients with COPD and incident depression and 2) subjects without COPD and incident depression.

To assess the impact of severity, incidence of depression, antidepressant prescription, or either was calculated amongst patients with COPD using the MRC dyspnoea score (1-3 vs 4-5) at time of diagnosis.

Since socioeconomic class has been associated with both COPD and depression, this study assessed the incidence of depression, antidepressant, or either based on socioeconomic class (high (1-2) vs low (3-5)) amongst patients with COPD. STATA 15.0 software was used for data management and statistical analyses.

5.3 **RESULTS**

There were 80,874 patients with COPD and 308,999 subjects without COPD identified in THIN from 1st January 2004 to 31st December 2015 (Figure 5-1). After excluding those with either former coded depression or antidepressant prescription, there were 44,362 patients with COPD and 124,140 subjects without COPD. The mean (SD) age at index date was 67.6 (10.5) years, and 65% were males. The median follow-up period was 5.95 years across the groups. The characteristics of the subjects included in the analyses are presented in Table 5-1.

Figure 5-1. Study population flow diagram

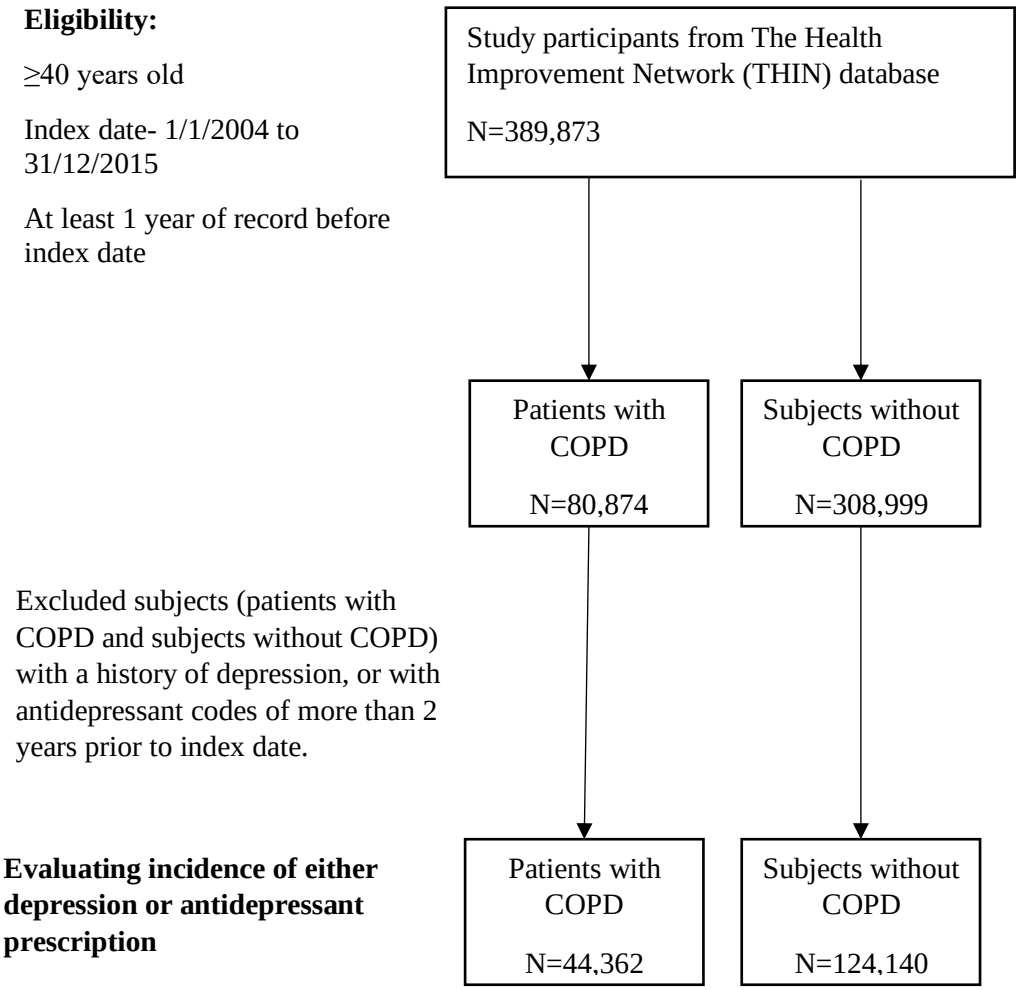


Table 5-1. Baseline characteristics for patients with COPD and up to four subjects without COPD with no prior diagnosis of depression or prescription of any antidepressant matched by age, gender and GP practice

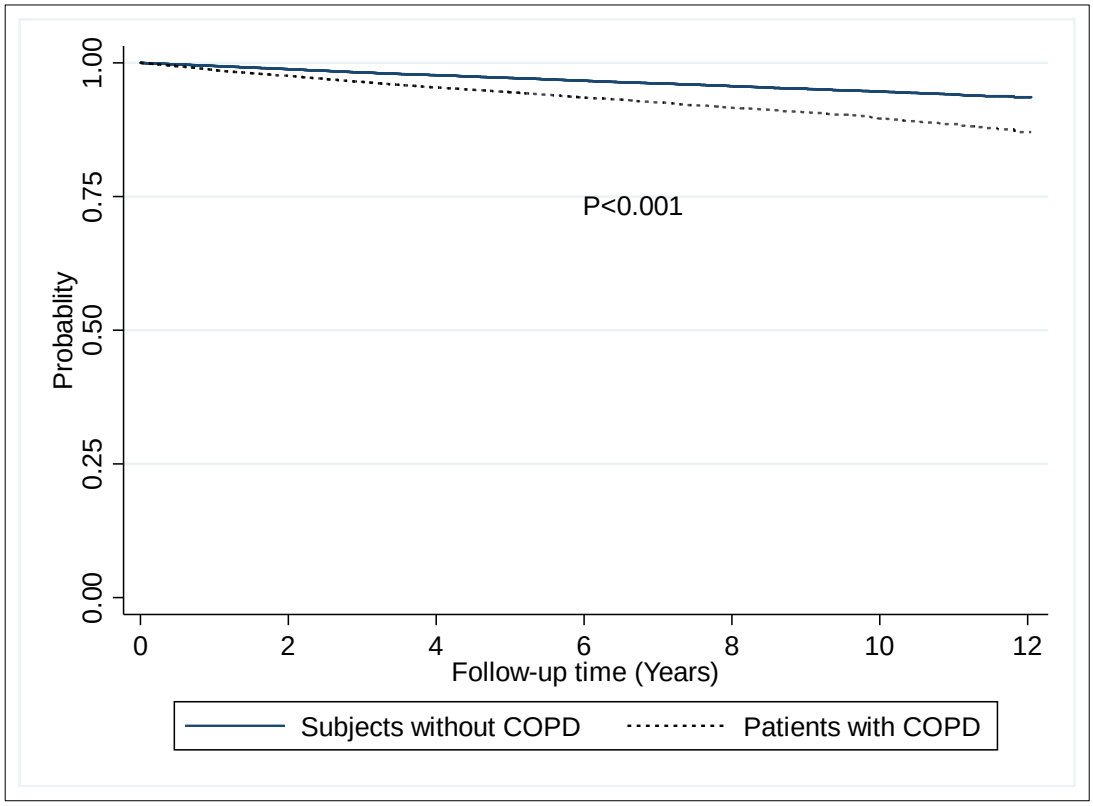
Characteristics	**Patients with COPD**		**Subjects without COPD**		
	n = 44,362	%	n = 124,140	%	p-value
Mean age at index date (years, SD)	67.8 (10.6)		67.5 (10.5)		
Gender					
Male	27,737	62.5	82,270	66.3	
Female	16,625	37.5	41,870	33.7	
Townsend score (prior or at index date)					
1 least deprived	8,071	18.2	31,593	25.4	<0.001
2	8,596	19.4	29,176	23.5	
3	9,239	20.8	24,669	19.9	
4	9,469	21.3	20,352	16.4	
5 most deprived	7,331	16.5	13,064	10.5	
No records	1,656	3.7	5,286	4.3	
MRC dyspnoea score (most recent record whether prior or after index date)					
1	5,571	12.5	413	0.3	<0.001
2	10,234	23.1	313	0.3	
3	5,048	11.4	124	0.1	
4–5	2,339	5.3	38	0.03	
No records	21,170	47.7	123,252	99.31	
BMI (kg/m^2) (2 years either side of index date)					
Underweight (<18)	1,832	4.1	910	0.7	<0.001
Normal (18-24.9)	13,827	31.2	21,407	17.2	
Overweight (25-29.9)	13,196	29.7	31,631	25.5	
Obese (≥30)	9,624	21.7	21,248	17.1	
No records	5,883	13.3	48,944	39.4	
Smoking status					
Never smoked	4,788	10.8	38,506	31.1	<0.001
Ex-smoker	22,970	51.9	30,361	24.5	
Current smoker	15,785	35.6	16,471	13.3	
Unknown	819	1.9	38,802	31.3	
Modified CCI (prior to or at index date)					
0–1	32,713	73.7	97,019	78.2	<0.001
2	6,039	13.6	14,835	11.9	
3	3,079	6.9	7,247	5.8	
≥ 4	2,531	5.7	5,039	4.1	

Abbreviations: BMI: body mass index; CCI, Charlson comorbidity index; MRC: Medical Research Council.

Incidence of depression and antidepressant prescription following index date

Of patients with COPD, 2,155 (4.9%) had an incident diagnosis of depression following the index date compared to 3,400 (2.7%) subjects without COPD, P<0.001. The time to first recorded depression was significantly shorter in patients with COPD than in subjects without COPD, P<0.001. Patients with COPD were 98% more likely to have an incident diagnosis of depression, compared to subjects without COPD (HR: 1.98; 95% CI: 1.87–2.10, Figure 5-2). This association remained significant even after adjusting for BMI, smoking, modified CCI, and socioeconomic class (aHR: 1.42; 95% CI: 1.32 – 1.53; p<0.001; Table 5-2). The incidence rate of depression in patients with COPD was 11.4 per 1,000 person-years (95% CI: 10.9–11.8) compared with 5.7 per 1,000 person-years (95% CI: 5.5–5.8) in subjects without COPD.

Figure 5-2. Kaplan-Meier analysis of the incidence of depression in patients with COPD and subjects without COPD



Kaplan-Meier plots comparing the incidence of depression for patients with COPD and subjects without COPD. The Y-axis represents the probability of subjects free of depression. The X-axis represents the follow-up time in years (2004 to 2015). The solid line represents subjects without COPD. The dashed line represents patients with COPD.

Table 5-2. Univariate and multivariate Cox regression models of the incidence of depression for patients with COPD (n= 44,362) and subjects without COPD (n= 124,140), matched by age, gender, and GP practice

Descriptor	HR (95% CI)	Adjusted HR (95% CI)
Subjects		
Subjects without COPD	1	1
Patients with COPD	1.98 (1.87 to 2.10)	1.42 (1.32 to 1.53)
Modified CCI		
Score 0-1	1	1
Score 2	1.28 (1.15 to 1.42)	1.18 (1.06 to 1.31)
Score 3	1.56 (1.34 to 1.81)	1.32 (1.13 to 1.53)
Score 4 and more	1.43 (1.18 to 1.75)	1.24 (1.02 to 1.51)
BMI (kg/m^2)		
Underweight (<18)	0.96 (0.74 to 1.24)	0.95 (0.73 to 1.23)
Normal (18-24.9)	1	1
Overweight (25-29.9)	0.97 (0.89 to 1.07)	0.97 (0.89 to 1.07)
Obese (≥30)	0.99 (0.89 to 1.09)	0.96 (0.86 to 1.06)
No records	0.48 (0.44 to 0.54)	0.56 (0.50 to 0.62)
Smoking Status		
Never	1	1
Former	1.08 (0.98 to 1.20)	1.07 (0.99 to 1.19)
Current	1.08 (1.06 to 1.32)	1.24 (1.12 to 1.37)
Unknown	0.51 (0.46 to 0.57)	0.66 (0.58 to 0.74)
Townsend score		
1 least deprived	1	1
2	1.14 (1.03 to 1.27)	1.14 (1.02 to 1.27)
3	1.27 (1.14 to 1.41)	1.23 (1.10 to 1.38)
4	1.31 (1.17 to 1.47)	1.27 (1.13 to 1.43)
No records	1.58 (1.28 to 1.96)	1.65 (1.33 to 2.06)

The fully adjusted Hazard Ratio (aHR) was 1.42, 95% CI 1.32 to 1.53, $p<0.001$ – the cox regression model was adjusted for age, gender, GP practice, modified Charlson comorbidity index, BMI smoking status, and socioeconomic class.

Abbreviations: BMI: body mass index; CCI, Charlson comorbidity index.

Following COPD diagnosis, 7,918 (17.9%) patients had a coded antidepressant prescription compared with 14,561 (11.7%) subjects without COPD, $p<0.001$. The incidence rate of antidepressant prescription in patients with COPD was 45.7 per 1,000 person-years (95% CI: 44.7–46.6) compared with 25.7 per 1,000 person-years (95% CI: 25.3–26.1) in subjects without COPD. Patients with COPD were 78% more likely to have a recorded incidence of antidepressant prescription than the subjects without COPD (HR, 1.78; 95% CI, 1.73 – 1.84, Table 5-3). In the fully adjusted model, this association remained significant (aHR: 1.40; 95% CI: 1.35–1.45; $p<0.001$, Table 5-3). In addition, the incidence of either depression or antidepressant was greater in patients with COPD compared with subjects without COPD following adjustment for confounders (aHR: 1.41; 95% CI: 1.36–1.46; $p<0.001$, Table 5-4).

Table 5-3. Univariate and multivariate Cox regression models of the incidence of antidepressant prescription for patients with COPD (n= 44,362) and subjects without COPD (n=124,140), matched by age, gender, and GP practice

Descriptor	HR (95% CI)	Adjusted HR (95% CI)
Subjects		
Subjects without COPD	1	1
Patients with COPD	1.78 (1.73 to 1.84)	1.40 (1.35 to 1.45)
Modified CCI		
Score 0-1	1	1
Score 2	1.33 (1.27 to 1.41)	1.22 (1.16 to 1.29)
Score 3	1.54 (1.42 to 1.66)	1.29 (1.20 to 1.39)
Score 4 and more	1.84 (1.68 to 2.01)	1.55 (1.26 to 1.69)
BMI (kg/m^2)		
Underweight (<18)	0.99 (0.86 to 1.14)	0.97 (0.85 to 1.11)
Normal (18-24.9)	1	1
Overweight (25-29.9)	0.99 (0.86 to 1.08)	0.94 (0.89 to 0.98)
Obese (≥30)	1.01 (0.98 to 1.09)	1.01 (0.95 to 1.05)
No records	0.59 (0.57 to 0.62)	0.68 (0.65 to 0.72)
Smoking Status		
Never	1	1
Former	1.09 (1.04 to 1.14)	1.07 (1.03 to 1.12)
Current	1.15 (1.09 to 1.22)	1.20 (1.13 to 1.26)
Unknown	0.58 (0.54 to 0.61)	0.69 (0.65 to 0.73)
Townsend score		
1 least deprived	1	1
2	1.07 (1.01 to 1.13)	1.05 (1.01 to 1.12)
3	1.09 (1.03 to 1.16)	1.07 (1.02 to 1.13)
4	1.14 (1.08 to 1.21)	1.10 (1.03 to 1.16)
5 most deprived	1.22 (1.14 to 1.31)	1.17 (1.09 to 1.25)
No records	1.14 (1.01 to 1.27)	1.18 (1.05 to 1.32)

The fully adjusted Hazard Ratio (aHR) was 1.40, 95% CI 1.35 to 1.45, p<0.001 – the cox regression model was adjusted for age, gender, GP practice, modified Charlson comorbidity index, BMI smoking status, and socioeconomic class.

Abbreviations: BMI: body mass index; CCI, Charlson comorbidity index.

Table 5-4. Univariate and multivariate Cox regression models of the incidence of either depression or antidepressant prescriptions for patients with COPD (n= 44,362) and subjects without COPD (n=124,140), matched by age, gender, and GP practice

Descriptor	HR (95% CI)	Adjusted HR (95% CI)
Subjects		
Subjects without COPD	1	`1
Patients with COPD	1.81 (1.76 to 1.86)	1.41 (1.36 to 1.46)
Modified CCI		
Score 0-1	1	1
Score 2	1.29 (1.23 to 1.36)	1.22 (1.16 to 1.28)
Score 3	1.51 (1.41 to 1.62)	1.32 (1.23 to 1.42)
Score 4 and more	1.83 (1.76 to 1.92)	1.54 (1.42 to 1.68)
BMI (kg/m^2)		
Underweight (<18)	0.98 (0.86 to 1.11)	0.97 (0.86 to 1.10)
Normal (18-24.9)	1	1
Overweight (25-29.9)	0.96 (0.92 to 1.01)	0.95 (0.91 to 0.99)
Obese (≥30)	1.04 (0.99 to 1.02)	1.01 (0.96 to 1.06)
No records	0.59 (0.55 to 0.61)	0.67 (0.64 to 0.71)
Smoking Status		
Never	1	1
Former	1.09 (1.04 to 1.14)	1.08 (1.04 to 1.13)
Current	1.15 (1.10 to 1.21)	1.20 (1.14 to 1.26)
Unknown	0.57 (0.54 to 0.60)	0.69 (0.65 to 0.72)
Townsend score		
1 least deprived	1	1
2	1.07 (1.02 to 1.24)	1.06 (1.01 to 1.12)
3	1.10 (1.05 to 1.16)	1.08 (1.02 to 1.13)
4	1.14 (1.08 to 1.20)	1.10 (1.04 to 1.16)
5 most deprived	1.23 (1.15 to 1.31)	1.18 (1.11 to 1.26)
No records	1.17 (1.04 to 1.30)	1.21 (1.08 to 1.35)

The fully adjusted Hazard Ratio (aHR) was 1.41, 95% CI 1.36 to 1.46, p<0.001 – the cox regression model was adjusted for age, gender, GP practice, modified Charlson comorbidity index, BMI smoking status, and socioeconomic class.

Abbreviations: BMI: body mass index; CCI, Charlson comorbidity index.

Table 5-5. Summary of the univariate and multivariate Cox regression models of the incidence of depression antidepressant prescription, or either for patients with COPD compared with subjects without COPD matched by age, gender, and GP practice

	Subjects without COPD (n=124,140)	Patients with COPD (n= 44,362)	P-value
Depression			
Rate/1000 person-years (95% CI)	5.7 (5.4 to 5.8)	11.4 (10.9 to 11.8)	
HR (95% CI)	1	1.98 (1.87 to 2.10)	<0.001
Fully adjusted (95% CI)	1	1.42 (1.32 to 1.53) [a]	<0.001
Antidepressant prescription			
Rate/1000 person-years (95% CI)	25.7 (25.3 to 26.1)	45.7 (44.6 to 46.7)	
HR (95% CI)	1	1.78 (1.73 to 1.84)	<0.001
Fully adjusted (95% CI)	1	1.40 (1.35 to 1.45) [a]	<0.001
Either depression or antidepressant prescription			
Rate/1000 person-years (95% CI)	27.4 (26.9 to 27.8)	49.6 (48.5 to 50.6)	
HR (95% CI)	1	1.81 (1.76 to 1.86)	<0.001
Fully adjusted (95% CI)	1	1.41 (1.36 to 1.46) [a]	<0.001

HR – adjusted for age, gender, and GP practice

[a] Fully adjusted for age, gender, GP, BMI, modified CCI, smoking status, and socioeconomic class.

Abbreviations: BMI: body mass index; CCI, Charlson comorbidity index; CI: confidence interval; GP: general practice; HR: hazard ratio.

Of all subjects with incident depression, 51% were prescribed antidepressant within 1-month of a depression diagnosis. The incidence of antidepressant prescription following a diagnosis of depression was significantly higher for patients with COPD compared with subjects without COPD following adjustment for age, gender, BMI, modified CCI, and socioeconomic class (aHR: 1.09; 95% CI: 1.01–1.18; p=0.022). Further adjustments for smoking have attenuated the relationship.

The association of MRC dyspnoea score amongst patients with COPD at the time of diagnosis was evaluated. There were 20,853 patients with MRC score 1-3 and 2,339 with MRC score 4-5. There was a significantly greater incidence of new depression diagnosis (aHR: 1.28; 95% CI: 1.01–1.63; p=0.044), antidepressant prescription (aHR: 1.29; 95% CI: 1.16–1.44, p>0.001), or either (aHR: 1.32; 95% CI: 1.19–1.46; p>0.001) in patients with an MRC score of 4–5 compared with those with an MRC score 1–3 (Table 5-6).

A total of 42,706 patients with COPD with Townsend index score were identified. Patients with lower socioeconomic status (n=26,039) had a greater risk of depression (aHR: 1.12; 95% CI: 1.02–1.23 ;p=0.016), antidepressant prescription (aHR:1.11; 95%CI: 1.05–1.17), or either (aHR:1.08; 95% CI: 1.04–1.13), compared to patients with higher class (n=16,667) (Table 5-7)

Table 5-6. Comparison of incidence of either depression or antidepressant prescription in patients with COPD according to MRC dyspnoea score (1–3 vs 4–5)

	MRC dyspnea score 1-3 (n = 20,853)	MRC dyspnea score 4-5 (n = 2,339)	**P-value**
Depression			
HR (95% CI)	1	1.38 (1.12-1.71)	0.002
Fully adjusted (95% CI)	1	1.28 (1.01–1.63) [a]	0.044
Antidepressant prescription			
HR (95% CI)	1	1.35 (1.22–1.51)	<0.001
Fully adjusted (95% CI)	1	1.29 (1.16–1.44) [a]	<0.001
Either depression or antidepressant prescription			
HR (95% CI)	1	1.38 (1.24–1.53)	<0.001
Fully adjusted (95% CI)	1	1.32 (1.19–1.46) [a]	<0.001

[a] Adjusted for age, gender, BMI, modified CCI, smoking status, and socioeconomic class.

Abbreviations: BMI: body mass index; CCI: Charlson comorbidity index; CI: confidence interval; HR: hazard ratio; MRC: Medical Research Council.

Table 5-7. Comparison of incidence of depression, antidepressant prescription, or either in patients with COPD according to Townsend index score (1–2 vs 3–5)

	High social class (1–2) (n = 16,667)	Low social class (3–5) (n = 26,039)	**P-value**
Depression			
HR (95% CI)	1	1.17 (1.06-1.28)	0.001
Fully adjusted (95% CI)	1	1.12 (1.02–1.23) [a]	0.016
Antidepressant prescription			
HR (95% CI)	1	11.13 (1.08–1.19)	<0.001
Fully adjusted (95% CI)	1	1.11 (1.05–1.17) [a]	<0.001
Either depression or antidepressant prescription			
HR (95% CI)	1	1.11 (1.06–1.17)	<0.001
Fully adjusted (95% CI)	1	1.08 (1.04–1.13) [a]	<0.001

[a] Adjusted for age, gender, BMI, modified CCI, MRC dyspnea score, and smoking status.

Abbreviations: BMI: body mass index; CCI: Charlson comorbidity index; CI: confidence interval; HR: hazard ratio; MRC: Medical Research Council.

5.4 **DISCUSSION**

The coded incidence rates of depression or antidepressant prescription were significantly greater in patients with COPD compared to subjects without COPD, even after adjustments of age, gender, GP surgery, and other confounders. In addition, the risk of depression is further increased in patients with worse breathlessness and in those with a lower socioeconomic class. This study provides contemporaneous information with the current practice of managing patients with COPD.

Studies on the incidence of depression following COPD is currently old. The findings that the incidence rate of depression was greater for patients with COPD compared to subjects without COPD is consistent with existing literature. However, the incidence of depression in the GP medical records reported in this study at 4.9% is slightly lower than the incidence reported in other population-based and clinical studies at 6% to 14%, respectively [146, 297]. The difference is attributed to methodological differences such as sample size, follow-up period, definitions depression, and study designs. This large population-based study was conducted after the publication of NICE COPD guidelines and introduction of QOF recommendations for COPD; thus, reporting the incidence rate of depression according to the current primary care practice.

Several risk factors are contributing to increased risk of depression in patients with COPD; one of which is COPD severity [290]. Using MRC dyspnoea score as a severity measure, the findings that patients with COPD and more breathlessness dyspnoea score were at a greater risk of incident depression are concordant with current literature. Yohannes et al. found that the odds of a new onset of depression was greater in patients with ≥ 2 modified MRC score compared to patients with less breathlessness

in a 3-year follow up study [297]. However, this does not imply that less breathless patients with COPD are not at risk of depression. Indeed, dyspnoea has been suggested as an important risk factor for depression in patients with COPD [36]. Breathlessness is the most burdensome symptom in COPD and is highly prevalent, even in patients with mild airflow limitation [34]. Therefore, it is vital to consider the psychological impact of COPD severity, particularly dyspnoea, and use targeted interventions.

As expected, this study found that patients with COPD from lower socioeconomic status were at increased risk of depression compared to those in the higher class; consistent with previous reports linking low socioeconomic status to increased prevalence of COPD [28], depression [295, 298], and adverse health outcomes [299]. Patients living at more deprived areas are likely to be exposed to several stressors, including financial strain, poor housing, lower level of health literacy, and social isolation. In addition, there are also healthcare inequalities, with patients from more deprived areas having poor health care access, ultimately to the detriment of the patient [300]. Indeed, Steiner et al. found that patients with COPD from more deprived areas were less likely to adhere to pulmonary rehabilitation [301]. The latter study suggested that poor adherence may be due to lack of transport but may also be because these patients are less likely to be referred in the first place. Taken together, the findings of this study suggest that healthcare systems should understand the impact of social disadvantage and be determined to provide equity when addressing issues in patients with COPD.

With regard to depression, this study found that 51% of patients with incident depression were prescribed antidepressant, a proportion that is far lower than previously reported (88%) [147]. The difference in these figures can be attributed to methodological differences (e.g. sample size) but can also be due to a change in clinical

practice after the initiative of the NICE guideline [302]. Antidepressant is not the sole treatment for depression [302], and the current depression NICE guideline recommends a stepwise approach when managing depression starting with the least intrusive and most effective approach first. Therefore, non-pharmacological interventions may be the first-line therapy for treating depression in patients with COPD.

Establishing that patients with COPD are a high-risk group of depression highlights that healthcare professionals involving in the management of COPD need to be aware of this association at the annual review, thereby permitting appropriate treatment strategies and improving the quality of life in this population. Pulmonary rehabilitation, the cornerstone of care in patients with COPD, should be considered in all patients with COPD, particularly for those with MRC dyspnoea score of 3-5 [58] and is effective in reducing dyspnoea, and has also been shown to improve depression in COPD [58, 303].

5.4.1 Strength and limitations

The current large-scale population-based study has several strengths. Firstly, the primary care database is large and provides a representative sample of patients with COPD within the UK [273]; thus, offering high external validity and generalisability. Secondly, patients with COPD from 2004 onwards were included after the initiatives of NICE guidelines and QOF. Thirdly, this study adjusted for a wide range of relevant confounders, in addition to matching patients with COPD to subjects without COPD by age, gender, and GP practice; thus, reducing sources of bias.

Regarding limitations, the actual incidence rate of depression might be underestimated, as it may be recorded as a free-text instead of READ-codes; therefore,

unlikely to appear in the search. In addition, some variables reported in QOF are subject to reporting bias. For instance, smoking, which is a self-reported, may have changed from the last recorded coded entry. This study only considered the first incident of depression or antidepressant prescription and did not consider repeated events. Another limitation is that the THIN database has some missing data, particularly on MRC dyspnoea score, which it may have led to inaccurate estimation. However, only those with MRC dyspnoea score were included in the MRC analysis.

5.5 **CONCLUSION**

This large population-based study demonstrated an increased risk of incident depression and antidepressant prescription in patients with confirmed COPD. This indicates that healthcare providers should be vigilant to this association and target accordingly.

Chapter 6 Association between Antidepressants and Respiratory Related Morbidity in Patients with COPD: A Self-Controlled Case Series

6.1 **INTRODUCTION**

Poor mental health in patients with COPD has a significant impact on health and prognosis. In some cases, antidepressants may be needed for these patients, and the current guidelines recommend using selective serotonin reuptake inhibitors (SSRIs) or serotonin–noradrenaline reuptake inhibitors (SNRIs) [302].

There is growing evidence that antidepressants may be associated with respiratory harm in patients with COPD, even with SSRI/SNRI, which have better overall safety and acceptability records compared to tricyclic antidepressants (TCAs) [151, 304]. In fact, each antidepressant class has its own side-effects. The anticholinergic component of TCAs is associated with dry mouth [305], which may potentially lead to increased risk of pneumonia amongst elderly [306]. Current statistics show that up to 30% of antidepressant (SSRs/SNRIs) users experience side-effects of vomiting and nausea [307, 308], which are risk factors for aspiration pneumonia, and may also contribute to COPD exacerbation. In addition, SSRs/SNRIs may also have immunosuppressant effects, which can lower the threshold of infection [309, 310], making antidepressant recipients (from patients with COPD) more likely to experience a COPD exacerbation.

A recent population-based study examined the association between antidepressant use and adverse respiratory events in the 90 days following antidepressant (SSRI/SNRI) prescription [151]. The findings showed that new users of SSRIs and/or SNRIs with COPD had increased risks of hospitalisation, emergency visits, pneumonia and mortality compared to non-users [151], highlighting a potential concern of antidepressant use in patients with COPD. However, these findings are subject to some limitations such as residual confounding and unmeasured factors. A major issue of studying such an association using traditional observational approach (e.g. cohort study) is the problem of uncontrolled confounding effects. Thus, utilising more

sophisticated analyses to eliminate “between-person” confounding and to further investigate these associations are worthwhile.

The aim of this chapter is to investigate whether antidepressants are associated with an increased risk of pneumonia and COPD exacerbation using primary care electronic health records within the UK.

6.2 **METHODS**

6.2.1 Study Design

A self-controlled case series (SCCS) study design was used to examine the association between incident pneumonia and COPD exacerbation and antidepressant prescription in patients with a diagnosis of COPD.

6.2.1.1 An overview of the SCCS design

The SCCS method is a type of cohort study developed to investigate potential associations between transient exposures and acute outcomes. It estimates the relative incidence of an outcome in the exposure risk periods (exposed periods), with incidence during other baseline times (unexposed) within a person [311]. The main question, therefore, becomes "when" as opposed to "who". A clear definition (e.g. precise timing) of the risk periods (exposed periods) is required for the SCCS, as it is best suited to investigate the temporal association between a time-varying exposure and an outcome event [311, 312]. The analysis is based only on data from cases (e.g. patients with COPD with a record of antidepressant prescription and who have the outcome of interest). The baseline (unexposed) period may include time both before and after the risk periods.

The SCCS estimates the incidence rate ratio (IRR) ─ that is, the rate of an event in a given 'exposed time' compared to the rate of an event in 'unexposed times'. The relative incidence is therefore estimated using a conditional Poisson model of the total number of events and exposures which each 'case' has experienced over a pre-determined observation period. The SCCS was initially developed to study vaccine safety in a variety of settings where control groups are not readily available [313]. Since then, it has been extensively applied in different situations in pharmaco-

epidemiology studies, including studies that used UK primary care data (e.g. THIN) [314-317]. Recently, the SCCS method has been used in studying the incident risk of cardiovascular events associated with infection and inflammation [318, 319].

A major advantage of SCCS is, as the name suggests, that it is self-controlled ─ each participant acts as his/her own control ─ meaning that it accounts for all constant (fixed) confounders (e.g. sex, socioeconomic status, genetics) over the period of observation. In other words, the influence of confounding between subjects is eliminated [311, 320]. In addition, the SCCS allows for the assessment of risk alteration with exposure' duration and provides a statistical power comparable to that of a cohort study [313].

6.2.1.2 Selection of the SCCS method in this study

The decision to select the SCCS method to assess the association between antidepressant prescription and respiratory-related morbidity (pneumonia and COPD exacerbation) was made for two main reasons. First, there are several possible confounding sources when studying the association between the use of antidepressants and pneumonia and COPD exacerbation, including sex, socioeconomic status, and co-existing comorbidities. This is in addition to other unknown/unmeasured confounders which may affect the association and are challenging to determine from electronic health records. However, the SCCS implicitly accounts for these factors as it is based on within-person comparisons. Secondly, the SCCS method permits the study of the duration of hypothesised increased risk in relation to the transient exposure (antidepressant prescription).

Although this study could have been conducted using a cohort approach, confounding effects would have been introduced. There is also another within-person study design

(e.g. case cross-over (CCO) design) which could have been used to eliminate between-person confounding effects associated with cohort study [321], and therefore to conduct this study. In brief, the CCO is analogous to a case-control study, in which all persons who have the outcome of interest (e.g. pneumonia and COPD exacerbation) are identified, and the exposure (antidepressant prescription) during risk period(s) immediately prior to the event is compared with the individual's exposure at an earlier time (control periods) [321, 322]. However, the CCO design requires a strong stationary assumption ─ that is the exposure must have a stable (exchangeable) prevalence over successive time periods intervals (risk periods and baseline periods) [322], which is unlikely to be the case in this study.

Some key features of the SCCS highlighted by Whitaker et al. [312, 320, 323] are as follows:

- It is based on cases only, and the estimates of incidence related to different periods (exposed vs non-exposed).
- It controls for non-varying confounders.
- It can be applied to rare acute events and recurrent events.

6.2.2 Data source and study population

The cohort information was obtained using the THIN dataset, which contains anonymised patients records from over 550 GP practices within the UK [273]. See subsection 4.2.2.

The study included all individuals aged ≥40 years with a new READ-coded COPD diagnosis between 1/01/2004 and 31/12/2015, who have at least one year of data prior to their COPD diagnosis [286] and have at least one record of anti-depressant prescription/dispensing. From those with antidepressant prescription(s), we included

all individuals (cases) with the outcomes of interest (pneumonia and COPD exacerbation) in the SCCS analyses. Outcomes (pneumonia and COPD exacerbations) were identified using a list of READ codes. See subsection 6.2.6.

6.2.3 Ethical approval

Ethical approval for this study was provided by an independent Scientific Review Committee (SRC), reference number - 18THIN098.

6.2.4 Exposure definition

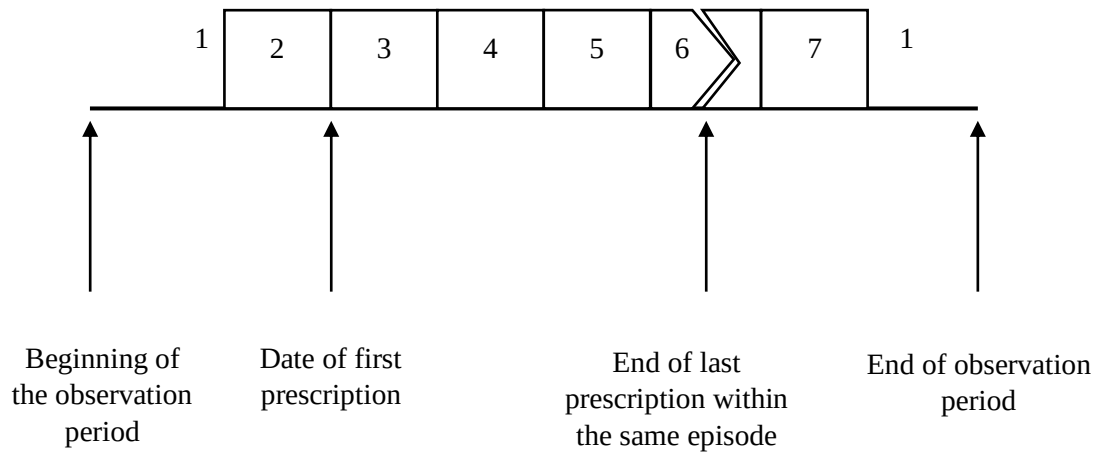
The exposure of interest was the prescription of any antidepressant. Antidepressant prescriptions were further divided into four classes: SSRIs, SNRIs, TCAs, Monoamine oxidase inhibitors (MAOIs), and collectively all together (Appendix 9-12). Data on antidepressant prescriptions were extracted for all cases in the study population.

Detailed recordings of the length of prescriptions are not always found in THIN. In practice, patients are unlikely to collect the subsequent medication prescribed on exactly the day after the last day of the previous dispensing. Rather, they may collect it earlier (overlap between two prescriptions) or later (time gap between two prescriptions). To account for these irregularities, it is advised to allow for a certain number of days between prescriptions [324]. Therefore, to constitute a new episode of antidepressants, a 90-day interval between prescriptions was used, as it has consistently been used in primary care studies [316], and also according to the standard practice in the UK [325]. Thus, this study made a conservative assumption, in which prescriptions were part of the same episode if they were dated within 90 days of the previous prescription.

6.2.5 Exposed and unexposed periods definitions

The follow-up was defined as finishing when patients left the GP practice, date of death, or end of the study period. The core of the SCCS is to estimate the relative incidence risk amongst different risk periods to that in the baseline periods. The outcomes for each case were estimated during 7 different periods (Figure 6-1). Following a previous study [151], the decision was made to include a 90-day "hypothesised risk window" following the day of the first prescription. The selection of the 90-day risk period was made because this study intended to assess the acute effects of antidepressant related adverse events, and since it is acknowledged that antidepressant may take several weeks before it reaches its full effects. To assess the temporal changes associated with antidepressant prescription, this period (90-day) was then divided into 3 segments of 30 days each, where the risk of each period was assessed individually. A period of a variable-length was also included to cover the remainder period of that episode, followed by a 90-day washout period after the end of the antidepressant episode/course. In a situation where a new episode of antidepressant was started within these last two periods, the exposure statuses associated with that episode had taken over.

Figure 6-1. Diagram representing the study design



1- The time when cases are not exposed to antidepressants (baseline).

2- A 30-day pre-exposure period including the first prescription date. Since antidepressants may be prescribed for anxiety or depression caused by the outcomes (pneumonia or COPD exacerbation), this period was added to correct for event-dependent exposure - that is to remove any pneumonia or exacerbation that might have led to prescribing an antidepressant. One approach to account for "a temporary increase in exposure after an event" is to consider a pre-exposure risk period [311]. (See subsection: 6.2.7.1 Assumptions and sensitivity analyses).

3- A 30-day period following the 1st prescription date (from day 1 to day 30 on treatment).

4- A 30-day period (from day 31 to day 60 on treatment).

5- A 30-day period (from day 61 to day 90 on treatment).

6- The remainder of that course to cover the entire exposure period (from day 91 until the end of that course).

7- A 90-day washout period following the end of that course.

6.2.6 Outcome definitions

Two outcomes were assessed. Firstly, we assessed the association between antidepressants with READ-coded pneumonia (Appendix 9-13). All events of pneumonia were considered, and a new event was considered as such if at least 90 days had elapsed from the previous incidence of pneumonia. This was determined after considering the number of days between pneumonia episodes and in line with current literature [326, 327]. Analyses for multiple events assume that an event is independent within an individual, meaning that an occurrence of an event must not change the probability of the following event (see subsection: 6.2.10. Assumption and sensitivity analyses).

Secondly, we assessed the association between antidepressants and COPD exacerbation. Incidents of COPD exacerbation were defined based on algorithms constructed from multiple READ and drug codes as follows: "*1) a medical diagnosis of lower respiratory tract infection (LRTI) or acute exacerbation of COPD (AECOPD), or 2) a prescription of COPD-specific antibiotic combined with oral corticosteroids (OCS) for 5–14 days, or 3) a record of two or more respiratory symptoms of AECOPD along with a prescription of COPD-specific antibiotics and/or OCS on the same day*" [328]. A new COPD exacerbation episode was considered as such if at least 8 weeks (56 days) had elapsed from the previous coded exacerbation [67]. READ and drug codes for constructing COPD exacerbations are available in the appendices (Appendix 9-14).

6.2.7 Statistical analysis

Baseline characteristics and demographics were summarised as relative frequencies for categorical data and mean (SD) for normally distributed continuous variables as appropriate. The incidence rate ratio (IRR) for the outcomes (pneumonia and COPD exacerbation) were calculated using fixed-effects Poisson regression by comparing the incidence ratio during each exposure period with the incidence when the same individual was unexposed (baseline), with an adjustment for age (3-year bands) [320]. The age-adjusted IRR for each antidepressant class was calculated individually, as well as when all antidepressants were collectively combined for each outcome. STATA 15.0 software was used for data management and statistical analyses.

6.2.7.1 Assumptions and sensitivity analyses

For the SCCS model to be valid, the following key assumptions must be fulfilled:

1- The occurrence of an outcome must not alter the probability of subsequent exposure so that there is no short term-dependency between the outcome and the subsequent exposure. As both pneumonia and COPD exacerbations are associated with depression and anxiety [329, 330], which therefore might increase the probability of antidepressants prescriptions, there is a potential short-term dependency that may lead to change in prescription. To account for this, Whitaker et al. proposed including a pre-exposure risk period to remove any outcome events that may have led to antidepressant prescription [312]. This approach has been widely used in previous studies [315-317, 326]. Therefore, a 30-day pre-exposure period was included, wherein there is a significant difference in the IRR at the 30-day pre-exposure period would indicate that the event has influenced the probability of subsequent exposure.

2- The second assumption is that an event should not alter the probability of a subsequent event (occurrence of outcomes is independent), especially for modelling multiple events. Since COPD exacerbation is known to increase the risk of a future exacerbation [66], and pneumonia may also increase the probability of a future event, the assumption might be violated. To overcome this assumption, however, Whitaker et al. proposed another strategy ─ that is to limit the analysis to the first event [312, 323]. Therefore, a sensitivity analysis was conducted restricting the analysis to the first outcome event (e.g. pneumonia and COPD exacerbation). This approach is only valid for rare outcomes, such that the probability of an independent recurrence is trivial relative to that of an outcome-dependent (clustered) recurrence. It is unlikely

that COPD exacerbations meet this assumption, so the true independent IRR with antidepressant use is likely to lie between the two estimates.

3- The outcome should not increase the probability of observation censoring; in other words, it does not lead to increased risk of death ─ which will inevitably alter the probability of subsequent exposures. Indeed, both outcomes (pneumonia and COPD exacerbation) are associated with increased risk of death; thus, the assumption might be violated. A number of approaches have been proposed to circumvent this assumption. Where the exposure of interest is a single fixed event and the exposure statuses that would have applied post-censorship are known, censored observations may simply be extended to encompass the additional exposed time [331]; however, this approach is not viable in this case as the exposure period is of variable duration. An alternative case-series model applicable to event-dependent censoring is available [332]. However, this model relies on the assumption that events are rare and non-recurrent, which is inapplicable to the present study data. Therefore, this study opted to carry out a secondary analysis using a simpler approach wherein patients who died following an event were excluded, similar to previous studies [317, 318, 326, 333, 334]. Thus, the primary analyses were repeated in patients whose follow-up was not censored because of death for 1) 6 months, and 2) 12 months following the outcome event, to observe whether this resulted in a change in the effect size.

6.3 **RESULTS**

Of the 31,253 patients with COPD with at least one record of antidepressant prescription during the study period, 1,969 individuals who had a coded pneumonia, and 18,483 individuals with COPD exacerbation were included in the SCCS analyses (Figure 6-2). The mean age (SD) was 65 (11) years, and more than 50% were females. The baseline characteristics of the study participants are summarised in Table 6-1.

Figure 6-2. Flow chart to the study

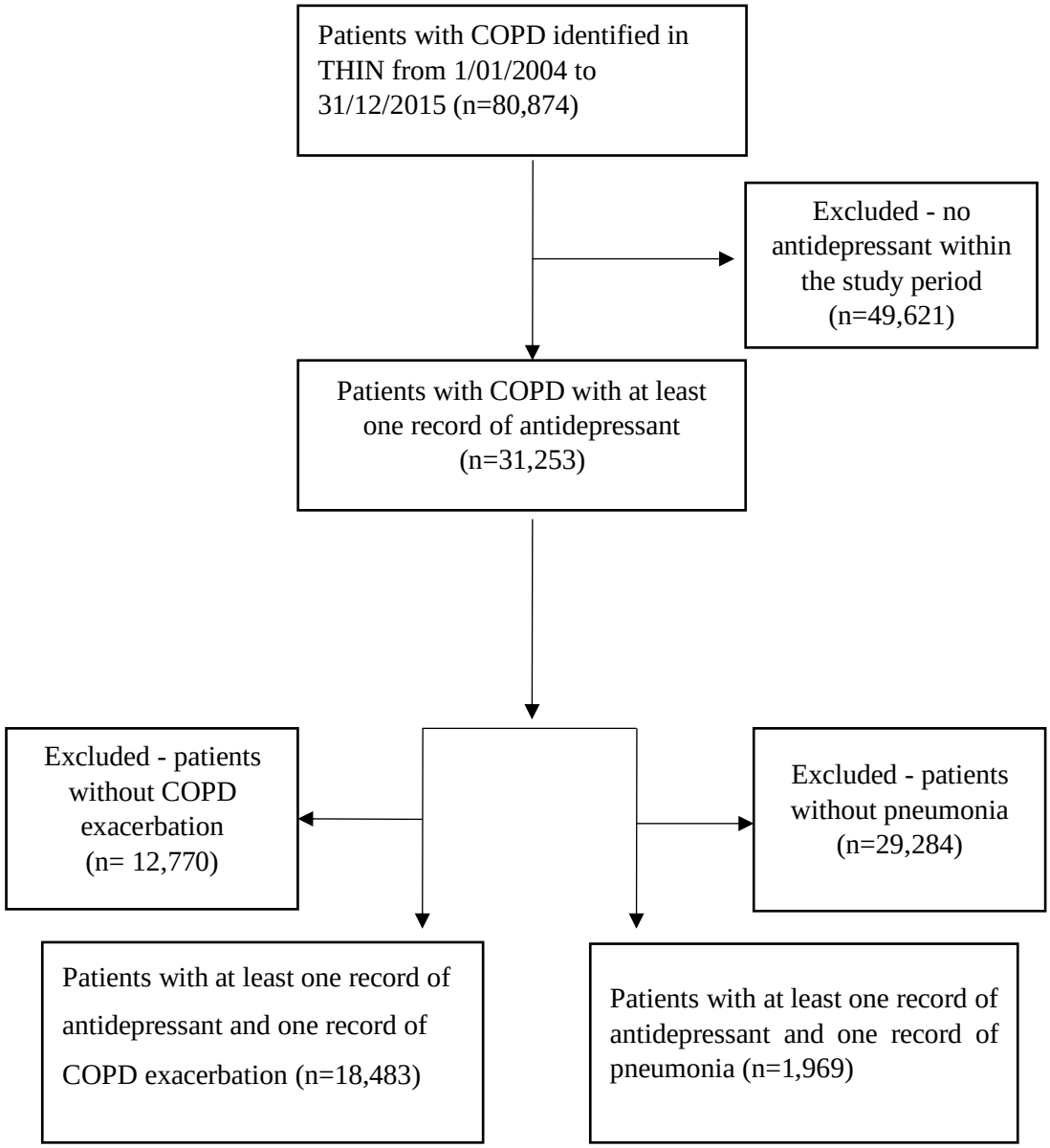


Table 6-1. Baseline characteristics for patients with COPD with a record of antidepressant prescription (n=31,253) with pneumonia (n=1,969) or COPD exacerbation (n=18,483) during the study period

Characteristics	Overall (n=31,253)	Pneumonia (n=1,969)	COPD exacerbation (n=18,483)
Mean Age (years, SD)	65.1 (11.2)	71.8 (10.8)	67.7 (10.9)
Gender			
Male	13,283 (44%)	950 (48%)	7,407 (41%)
Female	17,970 (56%)	1,019 (52%)	11,076 (59%)
Follow-up (years, median, IQR)	5.9 (3.3-8.7)	7.7 (5.5-9.8)	6.7 (4.2-9.1)
Townsend score, n (%)			
1 least deprived	4,300 (14%)	252 (13%)	2,458 (14%)
2	4,927 (16.2%)	300 (15%)	2,884 (16%)
3	6,240 (20%)	386 (20%)	3,694 (20%)
4	7,541 (24%)	513 (26%)	4,494 (24%)
5 most deprived	6,902 (21.3%)	443 (22%)	4,217 (21.6%)
No records	1,343 (4.5%)	75 (4%)	736 (4.4%)
BMI (kg/m^2), n (%)			
underweight (<18)	13,790 (44%)	863 (43%)	13,854 (44%)
normal (18-24.99)	9,758 (31%)	623 (32%)	10,098 (32%)
Overweight (25-29.99)	4,942 (16%)	289 (15%)	4,971 (16%)
Obese (>30)	2,567 (6%)	314 (6%)	1,736 (5%)
No records	952 (3%)	75 (4%)	543 (3%)
MRC dyspnoea score, n (%)			
1	2,821 (10.3%)	94 (5%)	1,364 (7%)
2	6,856 (23.6%)	285 (14%)	3,744 (20%)
3	4,372 (14%)	231 (12%)	2,634 (14%)
4-5	2,419 (7.4%)	174 (9%)	1,463 (8%)
No records	14,785 (44.7%)	1,185 (60%)	9,278 (45.5%)
Smoking status, (%)			
Never smoked	2,754 (9%)	164 (8.3%)	1,551 (8%)
EX-smoker	13,608 (44%)	959 (48.7%)	8,092 (44%)
Current smoker	14,480 (45%)	823 (42%)	8,667 (47%)
Unknown	411 (2%)	23 (1%)	173 (1%)
Modified CCI			
0-1	15,141 (48%)	790 (40%)	9,197 (50%)
2	5,230 (16.5%)	358 (18%)	3,004 (16%)
3	5,397 (17.5%)	368 (19%)	3,270 (18%)
≥ 4	5,485 (18%)	453 (23%)	3,012 (16%)

Abbreviations: BMI: Body Mass Index; CCI, Charlson comorbidity index; MRC: Medical Research Council.

Association with pneumonia

A total of 1,969 patients with COPD and antidepressant prescription had at least one event of pneumonia during the observation period (Table 6-2). The median number of pneumonia events is 1 (IQR: 1-2) per patent. The risk of pneumonia was compared across several risk periods. Compared to an unexposed period, collective antidepressant, SSRI/SNRI, and TCA prescriptions showed marked associations with pneumonia throughout all risk periods. However, the associations were then diminished after withdrawal from the treatment.

The 90-day period following any antidepressant prescription was associated with a 79% increased risk of pneumonia (age-adjusted IRR 1.79, 95% CI: 1.54 to 2.07). The risk also persisted throughout the remainder period (age-adjusted IRR 1.88, 95% CI: 1.68 to 2.11). The initiation of SSRI/SNRI and TCAs, separately, were also associated with increased risk of pneumonia that extended to the remainder period (Table 6-2).

In the sensitivity analysis, when restricting the analysis to the first event of pneumonia following antidepressant prescription, the risk remained across all risk periods and persisted to the remainder period for collective antidepressants, SSRI/SNRI and TCAs. However, no associations were observed after withdrawal of the treatment. Following pneumonia, there were 295 and 388 patients censored within 6 and 12 months, respectively. In those who were not censored within 6 months after incident pneumonia, there was a 48% (1.26 to 1.75) increased risk of pneumonia in the 90 days following the prescription of any antidepressant. In this analyses, the results and trends were mostly similar to the primary analyses but slightly lower in magnitude (Table 6-4 & Table 6-5).

Table 6-2. Age-adjusted incidence rate ratio of pneumonia (multiple events) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,969	1.68 (1.33 to 2.13)	1.83 (1.48 to 2.27)	1.89 (1.43 to 2.49)	1.79 (1.54 to 2.07)	1.88 (1.68 to 2.11)	1.03 (0.76 to 1.40)
SSRI or SNRI	1,218	1.75 (1.29 to 2.38)	1.62 (1.22 to 2.15)	2.56 (1.88 to 3.50)	1.76 (1.46 to 2.12)	1.83 (1.58 to 2.12)	1.02 (0.69 to 1.50)
SSRI	1,143	1.73 (1.62 to 2.39)	1.53 (1.13 to 2.07)	2.65 (1.94 to 3.62)	1.86 (1.54 to 2.4)	1.79 (1.54 to 2.09)	0.95 (0.64 to 1.42)
SNRI	168	1.69 (0.73 to 3.91)	1.23 (0.53 to 2.86)	1.61 (0.59 to 4.36)	1.48 (0.86 to 2.55)	1.91 (1.31 to 2.79)	1.29 (0.52 to 3.2)
TCA	1,318	1.51 (1.10 to 2.03)	1.92 (1.46 to 2.52)	1.40 (0.95 to 2.07)	1.64 (1.35 to 1.98)	1.78 (1.54 to 2.07)	1.29 (0.93 to 1.79)
MAOI	50	0.82 (0.07 to 7.43)	0.93 (0.10 to 8.14)	–	0.62 (0.13 to 2.90)	2.44 (0.95 to 5.7)	1.38 (0.33 to 5.77)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course).
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table 6-3. Age-adjusted incidence rate ratio of pneumonia (first event) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,969	1.54 (1.13 to 2.10)	1.57 (1.18 to 2.08)	1.59 (1.08 to 2.34)	1.51 (1.45 to 2.17)	2.15 (1.86 to 2.48)	0.92 (0.62 to 1.38)
SSRI or NRI	1,218	1.69 (1.21 to 2.35)	1.55 (1.15 to 2.10)	2.51 (1.80 to 3.15)	1.79 (1.46 to 2.18)	1.91 (1.64 to 2.23)	1.02 (0.68 to 1.54)
SSRI	1,143	1.71 (1.21 to 2.41)	1.45 (1.05 to 2.01)	2.60 (1.85 to 3.66)	1.70 (1.38 to 2.08)	1.89 (1.61 to 2.22)	0.95 (0.61 to 1.47)
SNRI	168	1.99 (0.85 to 4.69)	1.42 (0.60 to 2.38)	1.47 (0.46 to 4.66)	1.59 (0.90 to 2.80)	2.20 (1.35 to 3.02)	2.23 (01.03 to 4.84)
TCA	1,318	1.61 (1.17 to 2.21)	1.75 (1.29 to 2.38)	1.28 (0.83 to 1.98)	1.55 (1.26 to 1.90)	1.77 (1.51 to 2.08)	1.28 (0.90 to 1.81)
MAOI	50	1.02 (0.09 to 11.2)	1.22 (0.10 to 12.3)	–	0.95 (0.18 to 4.81)	2.03 (0.66 to 6.21)	1.06 (0.14 to 8.18)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course).
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table 6-4. Age-adjusted incidence rate ratio of pneumonia (excluding cases who died within 6 months following the date of pneumonia diagnosis) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,674	1.33 (1.12 to 1.66)	1.64 (1.30 to 2.07)	1.44 (1.04 to 2.02)	1.48 (1.26 to 1.75)	1.56 (1.37 to 1.77)	0.85 (0.59 to 1.23)
SSRI or SNRI	1,048	1.32 (0.92 to 1.89)	1.44 (1.05 to 1.97)	2.03 (1.41 to 2.91)	1.50 (1.22 to 1.84)	1.51 (1.28 to 1.78)	0.86 (0.55 to 1.34)
SSRI	978	1.26 (0.86 to 1.85)	1.41 (1.02 to 1.95)	2.15 (1.49 to 3.1)	1.55 (1.26 to 1.91)	1.48 (1.26 to 1.75)	0.83 (0.52 to 1.33)
SNRI	157	0.89 (0.30 to 2.70)	1.15 (0.46 to 2.84)	1.72 (0.63 to 4.67)	1.17 (0.64 to 2.15)	1.81 (1.22 to 2.70)	2.03 (0.93 to 4.39)
TCA	1,121	1.24 (0.88 to 1.74)	1.71 (1.27 to 2.30)	1.21 (0.77 to 1.88)	1.42 (1.15 to 1.74)	1.56 (1.32 to 1.83)	1.04 (0.71 to 1.54)
MAOI	45	0.83 (0.08 to 7.86)	0.91 (0.10 to 8.46)	–	0.62 (0.13 to 3.02)	1.70 (0.58 to 4.94)	1.47 (0.36 to 6.14)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table 6-5. Age-adjusted incidence rate ratio of pneumonia (excluding cases who died within 12 months following the date of pneumonia diagnosis) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with Pneumonia	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	1,581	1.32 (1.02 to 1.75)	1.51 (1.18 to 1.92)	1.46 (1.04 to 2.05)	1.43 (1.21 to 1.70)	1.48 (1.30 to 1.68)	0.79 (0.53 to 1.17)
SSRI or SNRI	989	1.33 (0,92 to 1.91)	1.38 (1.01 to 1.89)	1.97 (1.36 to 2.87)	1.48 (1.19 to 1.83)	1.42 (1.20 to 1.68)	0.87 (0.57 to 1.39)
SSRI	922	1.24 (0.85 to 1.84)	1.23 (0.87 to 1.74)	2.02 (1.38 to 2.69)	1.51 (1.22 to 1.86)	1.34 (1.12 to 1.60)	0.86 (0.54 to 1.38)
SNRI	153	0.91 (0.30 to 2.76)	1.16 (0.47 to 2.90)	1.77 (0.65 to 4.82)	1.19 (0.65 to 2.19)	1.75 (1.61 to 2.63)	2.09 (0.97 to 4.54)
TCA	1,065	1.25 (0.88 to 1.76)	1.58 (1.16 to 2.15)	1.19 (0.75 to 1.88)	1.40 (1.13 to 1.72)	1.50 (1.27 to 1.78)	0.95 (0.62 to 1.44)
MAOI	44	0.85 (0.09 to 8.05)	0.93 (0.10 to 8.64)	–	0.64 (0.13 to 3.10)	1.76 (0.60 to 5.16)	1.50 (0.36 to 6.32)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Association with COPD exacerbation

The results of the association of antidepressant use and COPD exacerbation are shown in Table 6-6. There were 18,483 patients with COPD identified who had been prescribed antidepressants and had ≥ 1 COPD exacerbation event. The median number of COPD exacerbations was 3 (IQR; 2-6) events per patient, using validated definitions suggested by Rothnie and colleagues [328].

Compared to a period when patients were not exposed to antidepressant, there was a 16% increased risk of COPD exacerbation (age-adjusted IRR= 1.16, 95% CI: 1.13 to 1.20) in the first 90 days following any antidepressant prescription that slightly increased in the remainder period (age-adjusted IRR= 1.38, 95% CI: 1.34 to 1.41), but the association was diminished after 90 days from stopping the treatment. Similar trends were observed in SSRI/SNRI and TCAs (Table 6-6).

The 90 days following antidepressant prescription were associated with increased risk of the first event of COPD exacerbation (age-adjusted IRR= 1.41, 95% CI: 1.34 to 1.49; Table 6-7) The risk has also extended throughout the remainder period, but then diminished in the washout period.

To assess the impact of COPD exacerbation on increasing the probability of censoring, the analyses were repeated in those who were not censored within 6 and 12 months after COPD exacerbation. The results showed that there were 1331 and 2,078 patients censored within 6 and 12 months, respectively, following a COPD exacerbation. There was 12% increased risk of COPD exacerbation in the 90 days following any antidepressants in those whose observations were not censored within 6 and 12 months after COPD exacerbation, compared to unexposed periods (Table 6-8 & Table 6-9). The risk persisted through the remainder period.

Table 6-6. Age-adjusted incidence rate ratio of COPD exacerbation (multiple events) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressants	No. of exposed cases with exacerbation	Day 1-30 IRR (95%CI)	Day 31-60 IRR (95%CI)	Day 61-90 IRR (95%CI)	Day 1-90 IRR (95%CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective antidepressant	18,483	1.11 (1.06 to 1.17)	1.18 (1.12 to 1.23)	1.23 (1.15 to 1.31)	1.16 (1.13 to 1.20)	1.38 (1.34 to 1.41)	0.98 (0.92 to 1.05)
SSRI or SNRI	11,770	1.10 (1.03 to 1.17)	1.16 (1.09 to 1.23)	1.22 (1.13 to 1.33)	1.15 (1.11 to 1.20)	1.39 (1.35 to 1.43)	0.99 (0.93 to 1.10)
SSRI	10,919	1.07 (1.01 to 1.45)	1.13 (1.06 to 1.21)	1.29 (1.10 to 1.30)	1.12 (1.08 to 1.17)	1.36 (1.32 to 1.41)	1.02 (0.94 to 1.11)
SNRI	1,753	1.14 (0.94 to 1.40)	1.29 (1.10 to 1.52)	1.34 (1.09 to 1.65)	1.23 (1.10 to 1.38)	1.36 (1.26 to 1.47)	1.06 (0.87 to 1.33)
TCA	11,936	1.09 (1.02 to 1.16)	1.16 (1.10 to 1.23)	1.26 (1.17 to 1.37)	1.16 (1.11 to 1.21)	1.27 (1.23 to 1.32)	1.02 (0.93 to 1.09)
MAOI	416	1.14 (0.77 to 1.68)	1.57 (1.11 to 2.23)	1.17 (0.71 to 1.92)	1.33 (1.07 to 1.66)	1.15 (0.89 to 1.50)	0.76 (0.49 to 1.18)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table 6-7. Age-adjusted incidence rate ratio of COPD exacerbation (first event) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressant	No. of exposed cases with exacerbation	Day 1-30 IRR (95% CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	18483	1.41 (1.30 to 1.52)	1.21 (1.12 to 1.31)	1.73 (1.59 to 1.89)	1.41 (1.34 to 1.49)	1.34 (1.28 to 1.39)	0.97 (0.85 to 1.10)
SSRI or SNRI	11,770	1.48 (1.34 to 1.64)	1.19 (1.08 to 1.32)	1.73 (1.54 to 1.93)	1.43 (1.34 to 1.53)	1.39 (1.32 to 1.45)	1.12 (0.98 to 1.27)
SSRI	20,885	1.45 (1.30 to 1.61)	1.18 (1.06 to 1.31)	1.62 (1.44 to 1.83)	1.39 (1.30 to 1.49)	1.37 (1.30 to 1.44)	0.97 (0.85 to 1.10)
SNRI	4,128	1.29 (0.97 to 1.72)	1.56 (1.17 to 2.07)	2.24 (1.71 to 2.92)	1.64 (1.38 to 1.95)	1.32 (1.16 to 1.50)	1.26 (0.88 to 1.78)
TCA	23,786	1.36 (1.22 to 1.51)	1.22 (1.10 to 1.35)	1.70 (1.52 to 1.91)	1.23 (1.16 to 1.30)	1.23 (1.17 to 1.31)	0.98 (0.86 to 1.07)
MAOI	416	0.98 (0.48 to 2.00)	1.18 (0.67 to 2.09)	1.62 (0.83 to 13.1)	1.23 (0.83 to 1.81)	1.15 (0.78 to 1.70)	1.07 (0.54 to 2.10)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90)
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table 6-8. Age-adjusted incidence rate ratio of COPD exacerbation (excluding cases who died within 6 months following the date of COPD exacerbation) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressant	No. of exposed cases with exacerbation	Day 1-30 IRR (95% CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	17,152	1.07 (1.02 to 1.13)	1.12 (1.07 to 1.18)	1.18 (1.11 to 1.26)	1.12 (1.08 to 1.15)	1.30 (1.27 to 1.33)	0.99 (0.93 to 1.07)
SSRI or SNRI	10,938	1.07 (1.01 to 1.15)	1.13 (1.06 to 1.20)	1.18 (1.08 to 1.28)	1.12 (1.07 to 1.17)	1.32 (1.28 to 1.36)	1.01 (0.92 to 1.08)
SSRI	10,133	1.05 (0.97 to 1.12)	1.10 (1.03 to 1.18)	1.16 (1.06 to 1.27)	1.09 (1.05 to 1.14)	1.30 (1.25 to 1.34)	1.02 (0.94 to 1.11)
SNRI	1,666	1.11 (0.90 to 1.36)	1.24 (1.05 to 1.47)	1.27 (1.02 to 1.58)	1.19 (1.06 to 1.33)	1.32 (1.23 to 1.43)	1.08 (0.87 to 1.34)
TCA	11,114	1.05 (0.98 to 1.12)	1.12 (1.05 to 1.19)	1.22 (1.12 to 1.32)	1.11 (1.07 to 1.16)	1.21 (1.17 to 1.25)	1.02 (0.95 to 1.11)
MAOI	394	1.10 (0.74 to 1.65)	1.61 (1.16 to 2.23)	1.22 (0.74 to 1.95)	1.37 (1.10 to 1.71)	1.19 (0.93 to 1.52)	0.95 (0.62 to 1.45)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

Table 6-9. Age-adjusted incidence rate ratio of COPD exacerbation (excluding cases who died within 12 months following the date of COPD exacerbation) in exposure periods after antidepressant prescription relative to unexposed periods in patients with COPD, calculated by case series analytical technique, UK, 2004-2015

Antidepressant	No. of exposed cases with exacerbation	Day 1-30 IRR (95% CI)	Day 31-60 IRR (95% CI)	Day 61-90 IRR (95% CI)	Day 1-90 IRR (95% CI)	Remainder period IRR (95% CI)	90 days washout IRR (95% CI)
Collective Antidepressants	16,405	1.07 (1.02 to 1.13)	1.11 (1.05 to 1.16)	1.17 (1.10 to 1.26)	1.12 (1.07 to 1.15)	1.27 (1.24 to 1.30)	0.99 (0.93 to 1.07)
SSRI or SNRI	10,472	1.06 (0.99 to 1.14)	1.11 (1.04 to 1.18)	1.19 (1.09 to 1.30)	1.11 (1.06 to 1.16)	1.29 (1.25 to 1.33)	1.01 (0.92 to 1.09)
SSRI	9,696	1.04 (0.96 to 1.11)	1.09 (1.02 to 1.16)	1.17 (1.07 to 1.28)	1.09 (1.04 to 1.14)	1.26 (1.22 to 1.31)	1.06 (0.94 to 1.12)
SNRI	1,609	1.10 (0.89 to 1.36)	1.22 (1.03 to 1.44)	1.24 (0.99 to 1.55)	1.17 (1.04 to 1.31)	1.29 (1.20 to 1.40)	1.08 (0.87 to 1.35)
TCA	10,638	1.05 (0.97 to 1.12)	1.10 (1.03 to 1.17)	1.21 (1.11 to 1.31)	1.10 (1.06 to 1.15)	1.18 (1.13 to 1.22)	1.02 (0.96 to 1.11)
MAOI	381	1.11 (0.75 to 1.63)	1.61 (1.16 to 2.24)	1.27 (0.79 to 1.02)	1.39 (1.11 to 1.74)	1.24 (0.97 to 1.59)	0.96 (0.62 to 1.49)

The "Collective Antidepressants" does not equate to the total of all individual class as some subjects received more than one antidepressant in each class

Exposure time periods:

1- Day 1-30: A 30-day risk period starting from the day after the date of prescription.
2- Day 31-60: A 30-day risk period starting from day 31 after the date of prescription.
3- Day 61-90: A 30-day risk period starting from day 61 after the date of prescription.
4- Day 1-90: A 90-day risk period accounts for the entire risk window (day 1 to 90).
5- Remainder period: A period starts 90 days after the date of the prescription until the end of the course (from day 91 after date of prescription until the end of the course)
6- 90 days washout: A 90-day period starting the day after the end of the course and continuing for 90 days (day 1 after the end of the course until day 90 after the end of the course). Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: serotonin-norepinephrine reuptake Inhibitor; TCA: Tricyclic antidepressants; MAOI: Monoamine oxidase inhibitors.

6.4 DISCUSSION

In this self-controlled case series study utilising primary care data, there were increased risks of both pneumonia and COPD exacerbations in the 90 days following the use of antidepressants, including SSRIs or SNRIs, and TCAs among patients with COPD. The increased risk remained even when the analyses were restricted to the first event. However, the risk of pneumonia and COPD exacerbation both diminished once antidepressants are discontinued. This study provides important information on the potential adverse reactions of antidepressants in patients with COPD and adds to the body of literature.

There has been growing evidence that antidepressants may lead to respiratory-related adverse events in patients with COPD. The current study found that there is an increased risk of pneumonia in the 90-day following antidepressant prescription and was also extended as long as patients with COPD were receiving antidepressants. Although this study further supports findings from a previous study that SSRI or SNRI users with COPD have increased risk of pneumonia compared to non-users [151], the risk of pneumonia reported in this study was of a greater magnitude and longer period. In addition, this study also explored these associations in other antidepressant classes and identifying precise timing and duration of amplified risk; something has not been investigated before.

The causal link between antidepressants and the development of pneumonia has not been established. However, there is evidence suggesting that depression/anxiety (which are highly prevalent in COPD [143, 296], and may be accompanied with antidepressants) is independently associated with increased risk of respiratory infection and pneumonia [335]. A previous study reported a 3-fold increased risk of

pneumonia in the 90-day period after hospitalisation for depression [336], highlighting the possibility that antidepressants contribute to the increased risk. Furthermore, Hennessy et al. found an association between antidepressants and increased risk of pneumonia, despite the nullified association upon further adjustments [337]. There is also a possibility that the side effects associated with antidepressants, such as dry mouth, vomiting, and nausea, may contribute to increased risk of pneumonia (e.g. aspiration pneumonia) [307, 308, 338]. It is possible, however, that the increased pneumonia risk observed here may be additive to the risk associated with COPD, as COPD itself is associated with increased risk of pneumonia [339].

COPD exacerbation is an important event in the natural history of COPD. On average, patients with COPD may experience two exacerbation episodes every year [340]. This study found an increased risk of COPD exacerbation in the 90-day period following antidepressant prescriptions, which has also extended during the time when patients were on continues antidepressant. In contrast, a previous study has shown that new users (patients with COPD) of antidepressant (SSRI/SNRI) were at lower risk of COPD exacerbation compared to non-users in the 90-day following antidepressant, owning this to increased and competing risk of other respiratory events and death [151]. Crucially, the current study compared the incidence relative risk of COPD exacerbation during antidepressant exposure periods with the patients' own stable period, not the risk of COPD exacerbation between individuals. Although having a history of COPD exacerbation is the greatest risk factor of future exacerbations [66], this study found a similar relationship ─ there is an increased risk of COPD exacerbation following antidepressant prescriptions ─ when the analysis was restricted to the first COPD exacerbation event, strengthening the robustness of the presented findings.

6.4.1 Strengths and validity of the SCCS method

The use of case-only study designs, such as SCCS, has been widely employed in pharmaco-epidemiological studies. It circumvents the problem of selecting an appropriate comparator group and minimises the effect of unmeasured and unknown confounding that may be seen in the traditional observational designs (e.g. case-control and cohort studies). This is an important point to consider, as there may be systematic differences between subjects. However, the SCCS accounts for the time-independent confounder, making the estimation more robust than traditional observational designs. Indeed, the statistical power of the SCCS is comparable to that of a cohort study [341]. Furthermore, the SCCS method also provides an opportunity to assess the temporal changes in outcome (e.g. pneumonia and COPD exacerbation) risk associated with antidepressants prescriptions, something which has not been fully explored before.

Although the initial research question of this study may seem to violate some assumptions of the SCCS, this study used recommended approaches to overcome these issues, such as 1) including a pre-exposure period, 2) studying the first event, and 3) excluding those whose observations were censored because of death. The 30-day pre-exposure period was designed to exclude any outcomes (e.g. pneumonia and COPD exacerbation) that might have led to prescriptions of antidepressants. It is unsurprising that the IRRs of both pneumonia and COPD exacerbation were significantly increased in this period. This is because both outcomes (pneumonia and COPD exacerbation) have been associated with depression [329, 330], which therefore might increase the probability of antidepressant prescriptions. Because the day of the antidepressant prescription was included in the 30-day pre-exposure period, it is also possible that the increased IRRs were due to behavioural artefact (e.g. GPs may continue a prescription

that started in secondary care) as opposed to the antidepressants causing the pneumonia or COPD exacerbation events. Therefore, it was essential to consider such an adjustment.

The validity of the SCCS analytical approach relies on whether recurrent events occur independently. In an ideal world, the model allows outcomes (pneumonia and COPD exacerbation) to be recurrent, but they must be independent. However, independence is not always present in practice. In fact, the greatest risk factor of COPD exacerbation is a history of previous exacerbation [66]. In this instance, bias might be introduced. It is simpler, however, to consider a non-recurrent event as the first event, even when recurrence is unlikely to happen [323]. Therefore, a sensitivity analysis was conducted by studying the first event, and the results were consistent with the primary analyses; thus, satisfying this assumption.

Another critical assumption for the SCCS method is that both the distribution of exposure and the observation period must be independent of the time of the event. In other words, the occurrence of an event must not censor or disrupt the exposure process, which is inevitable in the case of death [342]. If an event is associated with increased risk of mortality, such as pneumonia or COPD exacerbation, there is a chance that the observation period might be altered, and exposures (e.g. antidepressant) will not be observed. This could possibly produce a biased estimate (e.g. inflation of the IRRs) of pneumonia or COPD exacerbation [331], although a violation of the assumption does not always result in severe bias. It is therefore important to have an applicable method to account for this. It is also worth noting that the alternative approach (which assumes non-recurrence) is equally problematic, as the median number of COPD exacerbations in this study was 3. However, this issue

was circumvented by excluding patients whose observations were censored within 6 and 12 months of their outcome event. This approach has been widely used in the literature [318, 326, 333, 334], as it ensures that only cases who were followed until the end of the observation period were included, and therefore meeting the requirement of the assumption. The results for the 90-day "risk window" were consistent with the primary analyses, although lower in magnitude due to loss of power.

6.4.2 Strengths and limitations of the study

This study has several strengths. First, the primary care database is large and provides a representative sample of patients with COPD within the UK [273]. Second, the use of within-individual comparison has control for time-independent confounders such as sex, socioeconomic status, and genetics; thus, providing a robust estimate. Third, this study used validated definitions for COPD exacerbation in electronic health records [328]. However, this study has some limitations. Although the SCCS does not account for time-varying confounders, this study accounted for these by adjusting for age-bands. Another limitation is that some lifestyle exposures are not regularly updated, making it difficult to exclude confounding factors that are known to accompany the issue of antidepressant prescription. For instance, smoking consumption may become more frequent during depression or anxiety episodes (and hence antidepressant prescription), which could consequently confound the observed relationship. In addition, it was difficult to determine whether patients collected and/or adhered to their antidepressants as prescribed. In fact, THIN does not provide information on whether the antidepressants were dispensed. Moreover, the current analysis only studied pneumonia and COPD exacerbation events reported in general practice but could not determine events that required hospital admission.

6.4.3 Clinical implications

The findings of this study should be interpreted with caution. Instead of completely avoiding prescribing antidepressants to patients with COPD, the findings should raise awareness of the potential respiratory adverse effects associated with antidepressants. Clinicians should adopt a meticulous approach when managing patients with COPD and poor mental health. This includes explaining both the condition and the side effects of the treatment. It is also important for clinicians to stay vigilant and accept the challenges of antidepressants by monitoring each patient closely following the prescription of the treatment. On the other hand, these findings also highlight the importance of considering non-pharmacological therapies that have been shown to improve mental health disorders such as psychological support [343].

6.5 **CONCLUSION**

Compared to the stable period, antidepressants were associated with increased risk of pneumonia and COPD exacerbation in the 90 days following a prescription of antidepressants. If cause and effect relationships are confirmed, clinicians should be cautious when prescribing antidepressants and aware of the potential adverse effects.

Chapter 7 Summary of conclusions, implications, and suggested future studies

7.1 **Summary of findings**

Research in this thesis contributes to the body of knowledge on COPD comorbidities and clinical biomarkers. The findings of each study have led to the following conclusions:

7.1.1 Clinical circulating biomarkers

- In a cross-sectional analysis, soluble Receptor for Advanced Glycation End-products (sRAGE) was not associated with aortic stiffness, carotid intimal media thickness, or coexistent cardiovascular disease in patients with COPD, but there was a weak association between sRAGE and FEV_1% predicted.
- Patients with COPD and either diabetes, ischaemic heart disease, or cerebrovascular disease have increased urinary albumin creatinine ratio compared to patients without these conditions. The prevalence of clinical microalbuminuria in patients with COPD and either diabetes, ischaemic heart disease, or cerebrovascular disease was 22%, and it was 15% in patients without these comorbidities.
- The associations of urinary albumin creatinine ratio with aortic stiffness and carotid intimal media thickness in all patients with COPD were nullified when adjusted for known confounders.
- Aortic stiffness was significantly greater in patients with clinical microalbuminuria compared to patients without microalbuminuria.

7.1.2 COPD comorbidities

- A UK-population-based study demonstrates that the prevalence of cognitive impairment at the time of COPD diagnosis was greater than in subjects without COPD, matched by age, gender, and GP practice.
- Patients with COPD were more likely to have an incident diagnosis of cognitive impairment (incident rate: 23.1 per 1,000 person-years), compared to subjects without COPD (incident rate: 16.3 per 1,000 person-years).
- The prevalence and incidence of dementia were less frequently recorded in patients with COPD compared to matched subjects without COPD.
- Patients with COPD and worse breathlessness were associated with a greater prevalence and incidence of cognitive impairment and dementia compared to patients with less breathlessness.
- In a large cohort study, the risk of incident depression following a COPD diagnosis was greater (incidence rate: 11.4 per 1,000 person-years) than in subjects without COPD (incidence rate: 5.7 per 1,000 person-years) matched by age, gender, and GP practice.
- Patients with COPD with lower socioeconomic status had a greater risk of depression compared to patients with COPD with higher socioeconomic class.
- Patients with COPD and worse breathlessness were associated with increased risk of incident depression compared to patients with less breathlessness.
- Antidepressant use was associated with increased risks of pneumonia and COPD exacerbations in patients with COPD, relative to a period of unexposed to antidepressants.

- The risks of pneumonia and COPD exacerbations both diminished once antidepressants were discontinued.

The co-existence of comorbidities presents a significant challenge in the clinical management of COPD, impacting on patients' health status and affecting the rate of hospitalisations, exacerbations, and mortality [69-74]. Increased knowledge of the burden of COPD comorbidities helps in developing appropriate interventions, improving clinical practice, and reframing guidelines. The findings of this thesis highlight important aspects of recognising, understanding, and managing comorbidities in patients with COPD. The following sections will discuss the implications of the thesis findings and provide recommendations for future research.

7.2 Implications of findings

7.2.1 Cardiovascular risk prognostication in COPD

Cardiovascular (CV) disease is recognised as a significant cause of morbidity and mortality in patients with COPD [73, 87], yet the CV state is not routinely assessed. The burden of CV events in patients with COPD can be significantly ameliorated by preventative strategies (primary and secondary preventions). However, this implies recognising CV disease and CV risk factors (e.g. smoking, cholesterol, and hypertension), and taking necessary actions as early as possible.

Cardiovascular disease often remains underdiagnosed and undertreated in patients with COPD [344]. This may be attributed to the lack of clinical guidelines for managing CV disease in patients with COPD. Although the current COPD guidelines recommend recognising CV disease in patients with COPD [1], there has been no practical guidance or specific information on when and how to screen/assess for CV

risk. This issue has been highlighted in the literature which emphasises on routine assessment to the CV state in patients with COPD [157-159]. We, therefore, should be continuously seeking opportunities for CV risk identification and prevention in primary care as well as in secondary care clinics.

Current recommendations suggest that management of CV disease in patients with COPD should be performed using its own individual guidelines (as if the patient does not have COPD), which have been developed by those specialists. This, however, contrasts other guidelines for other disease groups (e.g. kidney disease, diabetes, and arthritis) where specific recommendations are made available for assessing and managing CV disease [345-347]. As an example, individuals with diabetes (without CV disease) are routinely assessed for the presence of microalbuminuria to identify patients at increased risk of renal impairment and/or future CV events [346]. Patients with COPD are at 2 to 5 times increased risk of CV diseases [97], which is comparable or even greater than these conditions (e.g. subjects with diabetes are at two times increased risk of CV disease) [348]. Therefore, there needs to be more information available on how to perform a CV risk assessment in patients with COPD; and more importantly, how to integrate it into clinical practice.

In current practice, there are considerable gaps in the CV risk detection/prognostication in patients with COPD. Active detection for CV risk should be considered for all patients with COPD. Identifying new and simple biomarkers that can be used to aid the detection of patients with increased CV risk is also of clinical importance. Indeed, if patients at increased CV risk are identified, we can apply preventive strategies before the development of any major CV events. This, in turn, would improve the clinical outcomes of patients, reduce morbidity, hospitalisation,

mortality, and the economic burden. However, it is important to note that preventative strategies (primary and secondary) for CV risk reduction would not be successful if patients do not adhere to medical advice. Indeed, current guidelines state that the most important and effective way to prevent CV risk is by promoting a healthy lifestyle, which includes smoking cessation, physical activity and appropriate diet. These lifestyle modifications should be considered before any pharmacological therapies.

Two biological circulating markers have been investigated in this thesis: blood (soluble RAGE) and urine (microalbuminuria). First, soluble RAGE was not associated with physiological measures of increased CV risk in the ERICA cohort. These findings, although contrary to expectations, do not support that soluble RAGE being a biomarker to address the CV status in patients with COPD. However, these findings add to the existing literature [221].

Second, microalbuminuria is frequent in patients with COPD, highlighting the potential risk of sub-clinical renal damage and future CV events [192, 196, 197]. Screening for microalbuminuria is simple, non-invasive, and inexpensive; and can, therefore, be performed routinely to aid the detection of micro- and macro-vascular abnormalities in patients with COPD. In addition, patients with COPD and confirmed microalbuminuria have increased aortic stiffness compared to those without microalbuminuria (as shown in this thesis), which also reinforces the need to intervene. Optimising the CV state in patients with COPD using aggressive interventions to target microalbuminuria is a potential area of future research.

7.2.2 Cognitive impairment and dementia in COPD

Cognitive impairment and subsequent dementia have negative impacts on COPD clinical outcomes. Nevertheless, little consideration is given for timely detection and

early intervention within the frame of respiratory assessment. Indeed, early identification of cognitively impaired patients is of clinical importance, as it allows for appropriate therapeutic interventions and change in lifestyle (e.g. physical activity, healthy nutrition, and social interaction), which could prevent or at least minimise the cognitive deterioration to clinical dementia.

Dementia is a devastating, irreversible condition, impacting on all aspects of life for both patients and caregivers. Individuals with COPD are at increased risk of neuronal damage leading to cognitive impairment and even subsequent dementia. Establishing an early diagnosis of dementia permits patients to access service that meets their needs. Therefore, healthcare providers involved in the management of COPD should be aware of the increased burden of cognitive impairment and dementia.

The increased prevalence and incidence of cognitive impairment in patients with COPD should extend the clinical focus to identify and manage modifiable risk factors contributing to the development of cognitive impairment and subsequent dementia. For instance, smoking, CV disease, and hypoxemia are common risk factors linked to cognitive impairment in COPD [265], and should, therefore, be evaluated and managed during routine follow-up. Given that cognitive impairment, by itself, is a major risk factor leading to dementia, it is very likely that in the settings of COPD, where the prevalence of smoking and CV disease is high, the risk of dementia will be magnified. This is of clinical importance, particularly as there are no curative therapies for dementia. Early interventions (e.g. smoking cessation, oxygen therapy, and change in lifestyle) to manage these modifiable risk factors should, therefore, be prioritized.

Early intervention also permits dealing with functional impairments, which can pose a barrier to the clinical management of COPD. Cognitive impairment and dementia

significantly affect adherence to medication regimens [261]. For instance, if planning and sequencing (e.g. praxic skills) are impaired, it is unlikely for the patient to be able to self-administer their inhalation therapies. Moreover, patients with COPD and cognitive impairment are less likely to gain benefits from pulmonary rehabilitation programs due to increased functional dependence and poor adherence to instructions [125], whereas patients with confirmed dementia will not be referred at the first place. Cognitive impairment also leads to problems with educational achievements and smoking-abstinence; all of which are vital elements of pulmonary rehabilitation. In these contexts, pulmonary rehabilitation programs may be tailored to meet patients' needs in order to bring greater benefits.

Furthermore, cognitive impairment and dementia also have a considerable impact on dependency and self-management in COPD [126]. Having adequate cognitive functioning is necessary for patients with COPD to maintain independence, uptake information properly, follow instructions, and adhere to medication regimens, which underpin effective care. However, failure to maintain these functions leads to reduce the effectiveness of treatment, which may result in worse outcomes.

Given the considerable impacts of cognitive impairment and dementia on patients with COPD, it is of importance to consider active cognitive screening/assessment. Otherwise, cognitive impairment and dementia will remain under- or even un-diagnosed, with a missed opportunity for timely intervention. Cognitive screening can be performed using a brief cognitive assessment, which will indicate the presence and severity of cognitive impairment, and help determine the type and amount of required support and assistance. Further consideration should also be given to patients presenting with severe respiratory symptoms and comorbidities.

It is important to mention here that the evidence of screening and systematic assessment for cognitive impairment and dementia in patients with COPD is currently scarce. In addition, there are also other factors which may interfere with performing a systematic assessment, such as high workload, staff shortage, and time constraints for patient visit. This opens new doors for researchers to explore the role of cognitive screening/assessment in improving diagnosis for cognitive impairment and dementia, and whether it needs to be implemented/standardised as an element of the respiratory assessment in patients with COPD.

7.2.3 Depression in COPD

Depression is amongst the most common comorbidities in patients with COPD. However, it often remains underdiagnosed and undertreated, which can significantly affect clinical outcomes. Therefore, clinicians caring for patients with COPD should be alert to the existence of depression and aware of its symptoms and consequences.

The very first step to improve outcomes and reduce the impact of depression is to identify depression as early as possible. Although the current guidelines recommend recognising depression in patients with COPD [40], there is no evidence that depression is currently part of the standard assessment. Early identification of depression plays a vital role in the clinical management of COPD. It allows healthcare professionals to develop appropriate treatment strategies, guide the choice of pharmacological and non-pharmacological therapies, and minimise the risk of missing critical patients' symptoms; all of which aim to improve clinical outcomes.

Patients with COPD are offered routine check-ups, mainly at primary care practices. In other words, health care professionals in direct contact with those patients play an important role in identifying COPD comorbidities, one of which is depression. Given

the increased risk of depression, patients with COPD need to be actively screened. To be efficiently performed, screening should be quick and straightforward. There are several validated screening tools for depression which can be simply incorporated within the respiratory assessment. The NICE guideline for depression suggests asking two screening questions: ‘‘during the last month, have you often been bothered by feeling down, depressed or hopeless?’’ and ‘‘during the last month, have you often been bothered by having little interest or pleasure in doing things?’’ [291]. These two questions can be quickly done during COPD assessment, and the answers to these questions will then determine whether further assessment for depression is indicated.

7.2.4 Antidepressants and adverse events in COPD

Antidepressants are associated with multiple side effects, and there is a growing concern that they may contribute to increased risk of respiratory-related morbidities such as pneumonia and COPD exacerbations in patients with COPD [151]. Nevertheless, it is important not to deny the relevant outcomes of antidepressants completely. Therefore, a meticulous approach should be considered when prescribing antidepressants to those patients.

Clinicians are required to stay alert and accept the challenges associated with the therapy. It is also worthwhile that clinicians closely monitor the side effects of antidepressants after prescription. When antidepressants are needed, it is essential to adopt the concept “start low and go slow” to allow patients to tolerate the drug. As patients with COPD often co-exist with multiple comorbidities, prescribers should keep in mind the possible side effects and drug interactions. Prescribers should also educate patients about antidepressants and possible adverse effects and how to manage them. Regular follow-ups after the initiation of antidepressant are vital, particularly at

the first and early stages of the treatment. Thereafter, periodic follow-ups (e.g. phone call) may suffice.

When managing mental health in patients with COPD, pharmacological interventions (e.g. antidepressants) should not be the sole treatment. Patients with COPD and poor mental health may benefit from other forms of non-pharmacological interventions such as cognitive psychological therapies and pulmonary rehabilitation. The current clinical guidelines promote a stepwise approach for poor mental health ─ that is starting with the least intrusive and most effective approach [291].

7.3 **Recommendation for future research**

This thesis has investigated important but inadequately researched aspects of COPD comorbidities and circulating biomarkers. The following sections will suggest directions for future research to build-up on the presented work.

7.3.1 Microalbuminuria in COPD

Since microalbuminuria is common in patients with COPD, studies should be conducted to understand the risk factors of the development of microalbuminuria in patients with COPD and confirmed microalbuminuria. Furthermore, determining whether microalbuminuria is a potential target in the management of patients with COPD at clinical stability and at times of exacerbation is also a potential area for future research. Indeed, aggressive interventions for CV risk factors (e.g. lowering blood pressure, promoting smoking cessation, reducing high cholesterol level, and maintain a healthy lifestyle) are recommended in patients with diabetes and hypertension with confirmed microalbuminuria [257, 258]. Since MAB was prevalent (even in patients without self-reported comorbidities), it is worthwhile to investigate whether similar

aggressive interventions will improve microalbuminuria (and thus the increased CV risk) and clinical outcomes in patients with COPD. It is, however, important to mention that some pharmacological therapies that are used to treat CV disease may alter the natural history of COPD; therefore, careful consideration for this issue should be applied.

7.3.2 Cognitive impairment and dementia in COPD

Understanding the cognitive decline in patients with COPD should be considered for future research. Although a previous study suggested that a self-reported diagnosis of severe COPD was associated with a cognitive decline (assessed by a questionnaire) over time [271], this association is yet to be confirmed. A future longitudinal study should be carried to confirm this association using objective measures to determine COPD severity and assess the impact of which on cognitive function. Understanding such an association will promote more research to develop interventions to slow this rate of decline.

A need also exists for mechanistic studies looking to understand the factors associated with increased risk of cognitive impairment and dementia in COPD. Further work should consider the contribution of comorbidities (e.g. CV disease), hypoxemia, and smoking in relation to cognitive impairment, and which factors affect the cognitive function in COPD the most.

An important area to explore is the role of screening of cognitive impairment in patients with COPD at primary care settings. Whether screening/assessment for cognitive impairment and dementia will improve diagnosis at an early stage, and whether this will promote better care (e.g. opportunity to intervene) and consequently modify/alter the trajectory to dementia. For instance, whether screening for cognitive

impairment will offer a tailored smoking cession program to those patients, and whether this will slow the rate of decline to dementia. It is also worth knowing whether screening for cognitive impairment and dementia will identify a group of patients with COPD, who are struggling with poor adherence to medication or improper techniques for inhaled medications. This can be done by taking a group of patients with COPD, who are failing to use their medications and perform a cognitive assessment to determine the commonality of cognitive impairment in that group. Furthermore, understanding the acceptability (e.g. social, economic, and health benefits and challenges) of cognitive screening in patients with COPD and/or a certain group of COPD is also worth consideration.

7.3.3 Depression in COPD

Given the increased risk of depression in patients with COPD, future research into effective treatment should be considered. Thus, there is a need to understand whether pharmacological or psychological treatments, alone or in combination, are more effective than exercise alone. The evidence of pulmonary rehabilitation in improving depressive symptoms is well-established. However, what remains unknown is how to maximise benefits during a pulmonary rehabilitation program. There is also a need to understand barriers and facilitators for pulmonary rehabilitation adherence, the possibility of uptake and completion in patients with COPD and depression. In other words, whether these outcomes are associated with depression in patients with COPD. Another area worth considering is to understand which other add-on interventions (e.g. psychological therapy) in conjunction with PR in comparison to PR alone are more beneficial to those patients. A future randomised controlled trial should be conducted to address this.

7.3.4 Antidepressants in COPD

Given that antidepressant use is associated with increased risks of both pneumonia and COPD exacerbations, there is a need to understand the mechanisms of these associations further. This can be done by a lab-based approach to understand the pathological pathways. In addition, it remains unknown whether patients with COPD are aware of the side effects associated with antidepressants and whether they are also aware of other forms of non-pharmacological treatments for their mental illness. A cross-sectional, self-administered questionnaire can be used to evaluate patients' awareness.

A further understanding of the observed relationships is required. An observational approach using other appropriate databases (from primary and secondary care) to explore the risk of hospitalisation and mortality in patients with COPD after use of antidepressants is of interest.

7.4 **Concluding remarks**

COPD is associated with multiple comorbidities, which have a substantial effect on health and prognosis. This PhD has utilised different methodologies and datasets to address several areas related to COPD comorbidities, which have not been adequately researched. Increase the understanding of comorbid conditions in patients with COPD has important implications. The findings outlined in this thesis advance our knowledge of different aspects of COPD comorbidities and biomarkers, and provide new evidence into the clinical management of COPD. There is still a need to understand the mechanisms linking these comorbidities to COPD and, how these comorbidities should be assessed and managed in the clinical settings.

Chapter 8 REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. *the Global Strategy for the Diagnosis, Management and Prevention of COPD 2020*. 2020 [cited 2020 18 February]; Available from: https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf.
2. *Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis.* Lancet, 1965. **1**(7389): p. 775-9.
3. Snider, G.L., *Distinguishing among asthma, chronic bronchitis, and emphysema.* Chest, 1985. **87**(1 Suppl): p. 35s-39s.
4. Halbert, R.J., et al., *Global burden of COPD: systematic review and meta-analysis.* Eur Respir J, 2006. **28**(3): p. 523-32.
5. Kohansal, R., et al., *The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort.* Am J Respir Crit Care Med, 2009. **180**(1): p. 3-10.
6. Rennard, S.I. and J. Vestbo, *COPD: the dangerous underestimate of 15%.* Lancet, 2006. **367**(9518): p. 1216-9.
7. Celli, B.R., et al., *An Official American Thoracic Society/European Respiratory Society Statement: Research questions in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2015. **191**(7): p. e4-e27.
8. Lamprecht, B., et al., *COPD in never smokers: results from the population-based burden of obstructive lung disease study.* Chest, 2011. **139**(4): p. 752-763.

9. Lytras, T., et al., *Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey*. Thorax, 2018. **73**(11): p. 1008-1015.

10. Sadhra, S., et al., *Occupational COPD and job exposure matrices: a systematic review and meta-analysis.* Int J Chron Obstruct Pulmon Dis, 2017. **12**: p. 725-734.

11. De Matteis, S., et al., *The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort.* Eur Respir J, 2019. **54**(1).

12. Hnizdo, E., et al., *Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey.* Am J Epidemiol, 2002. **156**(8): p. 738-46.

13. Eisner, M.D., et al., *An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2010. **182**(5): p. 693-718.

14. Schikowski, T., et al., *Ambient air pollution: a cause of COPD?* Eur Respir J, 2014. **43**(1): p. 250-63.

15. Doiron, D., et al., *Air pollution, lung function and COPD: results from the population-based UK Biobank study*. Eur Respir J, 2019. **54**(1).

16. Assad, N.A., et al., *Chronic obstructive pulmonary disease secondary to household air pollution.* Semin Respir Crit Care Med, 2015. **36**(3): p. 408-21.

17. Salvi, S. and P.J. Barnes, *Is exposure to biomass smoke the biggest risk factor for COPD globally?* Chest, 2010. **138**(1): p. 3-6.

18. Pathak, U., N.C. Gupta, and J.C. Suri, *Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis.* Int J Environ Health Res, 2020. **30**(1): p. 75-88.

19. Kurmi, O.P., et al., *COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis.* Thorax, 2010. **65**(3): p. 221-8.

20. Jary, H., et al., *Household Air Pollution and Acute Lower Respiratory Infections in Adults: A Systematic Review.* PLoS One, 2016. **11**(12): p. e0167656.

21. Po, J.Y., J.M. FitzGerald, and C. Carlsten, *Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis.* Thorax, 2011. **66**(3): p. 232-9.

22. Smith, K.R., et al., *Millions dead: how do we know and what does it mean? Methods used in the comparative risk assessment of household air pollution.* Annu Rev Public Health, 2014. **35**: p. 185-206.

23. Lee, K.K., et al., *Adverse health effects associated with household air pollution: a systematic review, meta-analysis, and burden estimation study.* Lancet Glob Health, 2020. **8**(11): p. e1427-e1434.

24. Chan, K.H., et al., *Solid Fuel Use and Risks of Respiratory Diseases. A Cohort Study of 280,000 Chinese Never-Smokers.* Am J Respir Crit Care Med, 2019. **199**(3): p. 352-361.

25. Sana, A., et al., *Chronic obstructive pulmonary disease associated with biomass fuel use in women: a systematic review and meta-analysis.* BMJ Open Respir Res, 2018. **5**(1): p. e000246.

26. Siddharthan, T., et al., *Association between Household Air Pollution Exposure and Chronic Obstructive Pulmonary Disease Outcomes in 13 Low- and Middle-Income Country Settings.* Am J Respir Crit Care Med, 2018. **197**(5): p. 611-620.

27. Regalado, J., et al., *The effect of biomass burning on respiratory symptoms and lung function in rural Mexican women.* Am J Respir Crit Care Med, 2006. **174**(8): p. 901-5.

28. Gershon, A.S., et al., *Chronic obstructive pulmonary disease and socioeconomic status: a systematic review.* Copd, 2012. **9**(3): p. 216-26.

29. Grigsby, M., et al., *Socioeconomic status and COPD among low- and middle-income countries.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 2497-2507.

30. Hakamy, A., et al., *The recording and characteristics of pulmonary rehabilitation in patients with COPD using The Health Information Network (THIN) primary care database.* NPJ Prim Care Respir Med, 2017. **27**(1): p. 58.

31. Wewers, M., *Pathogenesis of emphysema. Assessment of basic science concepts through clinical investigation.* Chest, 1989. **95**(1): p. 190-5.

32. Hall, I.P. and D.A. Lomas, *The genetics of obstructive lung disease: big is beautiful.* Thorax, 2010. **65**(9): p. 760-1.

33. Parshall, M.B., et al., *An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea.* Am J Respir Crit Care Med, 2012. **185**(4): p. 435-52.

34. Müllerová, H., et al., *Prevalence and burden of breathlessness in patients with chronic obstructive pulmonary disease managed in primary care.* PLoS One, 2014. **9**(1): p. e85540.

35. Janssens, T., et al., *Dyspnea perception in COPD: association between anxiety, dyspnea-related fear, and dyspnea in a pulmonary rehabilitation program.* Chest, 2011. **140**(3): p. 618-625.

36. Schuler, M., et al., *The interrelations among aspects of dyspnea and symptoms of depression in COPD patients - a network analysis.* J Affect Disord, 2018. **240**: p. 33-40.

37. Mahler, D.A., et al., *Patient-reported dyspnea in COPD reliability and association with stage of disease.* Chest, 2009. **136**(6): p. 1473-1479.

38. Bestall, J.C., et al., *Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.* Thorax, 1999. **54**(7): p. 581-6.

39. Fletcher, C.M., et al., *The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population.* Br Med J, 1959. **2**(5147): p. 257-66.

40. *Chronic obstructive pulmonary disease in over 16s: diagnosis and management*. 2019 july 2019 12/01/2020]; Available from: https://www.nice.org.uk/guidance/ng115/chapter/Recommendations.

41. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.

42. Salvi, S.S. and P.J. Barnes, *Chronic obstructive pulmonary disease in non-smokers.* Lancet, 2009. **374**(9691): p. 733-43.

43. Adeloye, D., et al., *Global and regional estimates of COPD prevalence: Systematic review and meta-analysis.* J Glob Health, 2015. **5**(2): p. 020415.

44. Organization, W.H. *Chronic obstructive pulmonary disease (COPD)*. 2020 [cited 2020 12 July]; Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).

45. Blanco, I., et al., *Geographical distribution of COPD prevalence in Europe, estimated by an inverse distance weighting interpolation technique.* Int J Chron Obstruct Pulmon Dis, 2018. **13**: p. 57-67.

46. British Lung Foundation. *Chronic obstructive pulmonary disease (COPD) statistics.* 2012 21 July 2020]; Available from: https://statistics.blf.org.uk/copd.

47. Services, N.H. *NHS Information Centre for Health and Social Care. Quality Outcomes Framework: Prevalence Data Tables 2019*. 2019 [cited 2020 15 May]; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2018-19-pas#summary.

48. England, N.H.S. *Factsheet1: Non–invasive ventilation in acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD)*. 2014 [cited 2020 5 April]; Available from: https://www.england.nhs.uk/wp-content/uploads/2014/02/rm-fs-6.pdf.

49. Iacobucci, G., *Hospital readmissions for COPD in England are rising, audit shows.* Bmj, 2017. **356**: p. j557.

50. McLean, S., et al., *Projecting the COPD population and costs in England and Scotland: 2011 to 2030.* Sci Rep, 2016. **6**: p. 31893.

51. Punekar, Y.S., A. Shukla, and H. Mullerova, *COPD management costs according to the frequency of COPD exacerbations in UK primary care.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 65-73.

52. Service, N.H. *COPD Commissioning Toolkit*. 2012 [cited 2020 5 April]; Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/212876/chronic-obstructive-pulmonary-disease-COPD-commissioning-toolkit.pdf.

53. Organization, W.H. *Chronic obstructive pulmonary disease (COPD)*. 2017 [cited 2020 5 April]; Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).

54. *Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015.* Lancet Respir Med, 2017. **5**(9): p. 691-706.

55. World Health Organization. *Projections of mortality and causes of death, 2016 to 2060.* 2020 21 July 2020]; Available from: https://www.who.int/healthinfo/global_burden_disease/projections/en/.

56. Anthonisen, N.R., J.E. Connett, and R.P. Murray, *Smoking and lung function of Lung Health Study participants after 11 years.* Am J Respir Crit Care Med, 2002. **166**(5): p. 675-9.

57. Poole, P.J., et al., *Influenza vaccine for patients with chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2006(1): p. Cd002733.

58. Bolton, C.E., et al., *British Thoracic Society guideline on pulmonary rehabilitation in adults.* Thorax, 2013. **68 Suppl 2**: p. ii1-30.

59. Hurst, J.R. and J.A. Wedzicha, *What is (and what is not) a COPD exacerbation: thoughts from the new GOLD guidelines.* Thorax, 2007. **62**(3): p. 198-9.

60. Miravitlles, M., et al., *Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study.* Thorax, 2004. **59**(5): p. 387-95.

61. Halpin, D.M.G., et al., *Effect of a single exacerbation on decline in lung function in COPD.* Respir Med, 2017. **128**: p. 85-91.

62. Schmidt, S.A., et al., *The impact of exacerbation frequency on mortality following acute exacerbations of COPD: a registry-based cohort study.* BMJ Open, 2014. **4**(12): p. e006720.

63. Hartl, S., et al., *Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit.* Eur Respir J, 2016. **47**(1): p. 113-21.

64. Sprooten, R.T.M., et al., *Risk stratification for short-term mortality at hospital admission for acute exacerbations of COPD.* Respirology, 2019. **24**(8): p. 765-776.

65. Donaldson, G.C., et al., *Impact of Prolonged Exacerbation Recovery in Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2015. **192**(8): p. 943-50.

66. Hurst, J.R., et al., *Susceptibility to exacerbation in chronic obstructive pulmonary disease.* N Engl J Med, 2010. **363**(12): p. 1128-38.

67. Hurst, J.R., et al., *Temporal clustering of exacerbations in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2009. **179**(5): p. 369-74.

68. Decramer, M. and W. Janssens, *Chronic obstructive pulmonary disease and comorbidities.* Lancet Respir Med, 2013. **1**(1): p. 73-83.

69. Huber, M.B., et al., *Comorbid Influences on Generic Health-Related Quality of Life in COPD: A Systematic Review.* PLoS One, 2015. **10**(7): p. e0132670.

70. Burgel, P.R., et al., *Impact of comorbidities on COPD-specific health-related quality of life.* Respir Med, 2013. **107**(2): p. 233-41.

71. Mannino, D.M., et al., *Economic Burden of COPD in the Presence of Comorbidities.* Chest, 2015. **148**(1): p. 138-150.

72. Alqahtani, J.S., et al., *Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis.* Eur Respir Rev, 2020. **29**(156).

73. Divo, M., et al., *Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2012. **186**(2): p. 155-61.

74. Crisafulli, E., et al., *Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation.* Thorax, 2008. **63**(6): p. 487-92.

75. Stallberg, B., et al., *Real-world retrospective cohort study ARCTIC shows burden of comorbidities in Swedish COPD versus non-COPD patients.* NPJ Prim Care Respir Med, 2018. **28**(1): p. 33.

76. Yin, H.L., et al., *Prevalence of comorbidities in chronic obstructive pulmonary disease patients: A meta-analysis.* Medicine (Baltimore), 2017. **96**(19): p. e6836.

77. McGarvey, L.P., et al., *Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee.* Thorax, 2007. **62**(5): p. 411-5.

78. Vanfleteren, L.E., et al., *Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2013. **187**(7): p. 728-35.

79. Divo, M.J., et al., *COPD comorbidities network.* Eur Respir J, 2015. **46**(3): p. 640-50.

80. Almagro, P., et al., *Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study.* Chest, 2012. **142**(5): p. 1126-1133.

81. Miller, J., et al., *Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort.* Respir Med, 2013. **107**(9): p. 1376-84.

82. Schnell, K., et al., *The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999-2008.* BMC Pulm Med, 2012. **12**: p. 26.

83. Agusti, A., et al., *Characterisation of COPD heterogeneity in the ECLIPSE cohort.* Respir Res, 2010. **11**(1): p. 122.

84. Camiciottoli, G., et al., *Prevalence of comorbidities according to predominant phenotype and severity of chronic obstructive pulmonary disease.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 2229-2236.

85. Bolton, C.E., et al., *Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2004. **170**(12): p. 1286-93.

86. Dal Negro, R.W., L. Bonadiman, and P. Turco, *Prevalence of different comorbidities in COPD patients by gender and GOLD stage.* Multidiscip Respir Med, 2015. **10**(1): p. 24.

87. Mannino, D.M., et al., *Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD.* Eur Respir J, 2008. **32**(4): p. 962-9.

88. Lahousse, L., et al., *Cardiac effects of current treatments of chronic obstructive pulmonary disease.* Lancet Respir Med, 2016. **4**(2): p. 149-64.

89. Vespasiani-Gentilucci, U., et al., *The pharmacological treatment of chronic comorbidities in COPD: mind the gap!* Pulm Pharmacol Ther, 2018. **51**: p. 48-58.

90. Ramalho, S.H.R. and A.M. Shah, *Lung function and cardiovascular disease: A link.* Trends Cardiovasc Med, 2020.

91. Sin, D.D., L. Wu, and S.F. Man, *The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature.* Chest, 2005. **127**(6): p. 1952-9.

92. Stavem, K., et al., *Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males.* Eur Respir J, 2005. **25**(4): p. 618-25.

93. Cuttica, M.J., et al., *Lung Function in Young Adults and Risk of Cardiovascular Events Over 29 Years: The CARDIA Study.* J Am Heart Assoc, 2018. **7**(24): p. e010672.

94. Agarwal, S.K., et al., *Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study.* Eur J Heart Fail, 2012. **14**(4): p. 414-22.

95. Silvestre, O.M., et al., *Declining Lung Function and Cardiovascular Risk: The ARIC Study.* J Am Coll Cardiol, 2018. **72**(10): p. 1109-1122.

96. Curkendall, S.M., et al., *Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients.* Ann Epidemiol, 2006. **16**(1): p. 63-70.

97. Chen, W., et al., *Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis.* Lancet Respir Med, 2015. **3**(8): p. 631-9.

98. Feary, J.R., et al., *Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care.* Thorax, 2010. **65**(11): p. 956-62.

99. Portegies, M.L., et al., *Chronic Obstructive Pulmonary Disease and the Risk of Stroke. The Rotterdam Study.* Am J Respir Crit Care Med, 2016. **193**(3): p. 251-8.

100. Rothnie, K.J., et al., *Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis.* BMJ Open, 2015. **5**(9): p. e007824.

101. Goudis, C.A., *Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship.* J Cardiol, 2017. **69**(5): p. 699-705.

102. Morgan, A.D., et al., *Chronic obstructive pulmonary disease and the risk of 12 cardiovascular diseases: a population-based study using UK primary care data*. Thorax, 2018. **73**(9): p. 877-879.

103. Mannino, D.M., et al., *The natural history of chronic obstructive pulmonary disease.* Eur Respir J, 2006. **27**(3): p. 627-43.

104. Anthonisen, N.R., et al., *The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial.* Ann Intern Med, 2005. **142**(4): p. 233-9.

105. Smith, M.C. and J.P. Wrobel, *Epidemiology and clinical impact of major comorbidities in patients with COPD.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 871-88.

106. Dodd, J.W., S.V. Getov, and P.W. Jones, *Cognitive function in COPD.* Eur Respir J, 2010. **35**(4): p. 913-22.

107. Richardson, C., et al., *Two-decade change in prevalence of cognitive impairment in the UK.* Eur J Epidemiol, 2019. **34**(11): p. 1085-1092.

108. Grant, I., et al., *Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease.* Arch Intern Med, 1982. **142**(8): p. 1470-6.

109. Baierle, M., et al., *Relationship between inflammation and oxidative stress and cognitive decline in the institutionalized elderly.* Oxid Med Cell Longev, 2015. **2015**: p. 804198.

110. Nguyen, J.C., A.S. Killcross, and T.A. Jenkins, *Obesity and cognitive decline: role of inflammation and vascular changes.* Front Neurosci, 2014. **8**: p. 375.

111. Abbatecola, A.M., M. Russo, and M. Barbieri, *Dietary patterns and cognition in older persons.* Curr Opin Clin Nutr Metab Care, 2018. **21**(1): p. 10-13.

112. Snyder, H.M., et al., *Vascular contributions to cognitive impairment and dementia including Alzheimer's disease.* Alzheimers Dement, 2015. **11**(6): p. 710-7.

113. Deckers, K., et al., *Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis.* PLoS One, 2017. **12**(9): p. e0184244.

114. Kobayashi, Y., et al., *Decreased Physical Activity Associated with Executive Dysfunction Correlates with Cognitive Impairment among Older Adults in the Community: A Retrospective Analysis from the Kurihara Project.* Dement Geriatr Cogn Dis Extra, 2016. **6**(2): p. 350-360.

115. Anstey, K.J., et al., *Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies.* Am J Epidemiol, 2007. **166**(4): p. 367-78.

116. Wollam, M.E., et al., *Genetic Risk Score Predicts Late-Life Cognitive Impairment.* J Aging Res, 2015. **2015**: p. 267062.

117. Livingston, G., et al., *Dementia prevention, intervention, and care.* Lancet, 2017. **390**(10113): p. 2673-2734.

118. DH/SCLG&CP/SCPI/SR. *Living well with dementia: A National Dementia Strategy*. 2009 [cited 20 Junuary 2021; Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/168220/dh_094051.pdf.

119. Fogg, C., et al., *The relationship between cognitive impairment, mortality and discharge characteristics in a large cohort of older adults with unscheduled admissions to an acute hospital: a retrospective observational study*. Age Ageing, 2017. **46**(5): p. 794-801.

120. Bohlken, J., L. Jacob, and K. Kostev, *Progression of mild cognitive impairment to dementia in German specialist practices.* Dementia (London), 2019. **18**(1): p. 380-390.

121. Farias, S.T., et al., *Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts.* Arch Neurol, 2009. **66**(9): p. 1151-7.

122. Roberts, R.O., et al., *Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal.* Neurology, 2014. **82**(4): p. 317-25.

123. Koch, T. and S. Iliffe, *Rapid appraisal of barriers to the diagnosis and management of patients with dementia in primary care: a systematic review.* BMC Fam Pract, 2010. **11**: p. 52.

124. Dodd, E., et al., *An evaluation of primary care led dementia diagnostic services in Bristol.* BMC Health Serv Res, 2014. **14**: p. 592.

125. Cleutjens, F., et al., *The Impact of Cognitive Impairment on Efficacy of Pulmonary Rehabilitation in Patients With COPD.* J Am Med Dir Assoc, 2017. **18**(5): p. 420-426.

126. Baird, C., et al., *The impact of cognitive impairment on self-management in chronic obstructive pulmonary disease: A systematic review.* Respir Med, 2017. **129**: p. 130-139.

127. Rogliani, P., et al., *Optimizing drug delivery in COPD: The role of inhaler devices.* Respir Med, 2017. **124**: p. 6-14.

128. Sulaiman, I., et al., *Objective Assessment of Adherence to Inhalers by Patients with Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2017. **195**(10): p. 1333-1343.

129. Yohannes, A.M., et al., *Cognitive Impairment in Chronic Obstructive Pulmonary Disease and Chronic Heart Failure: A Systematic Review and Meta-analysis of Observational Studies.* J Am Med Dir Assoc, 2017. **18**(5): p. 451.e1-451.e11.

130. Wimo, A., et al., *The worldwide costs of dementia 2015 and comparisons with 2010.* Alzheimers Dement, 2017. **13**(1): p. 1-7.

131. Alzheimer's Disease International. *Policy Brief: The Global Impact of Dementia 2013-2050.* 2013 22 July 2020]; Available from: https://www.alz.co.uk/research/G8-policy-brief.

132. Prince, M., et al., *The global prevalence of dementia: a systematic review and metaanalysis.* Alzheimers Dement, 2013. **9**(1): p. 63-75.e2.

133. Yeh, J.J., et al., *Effect of the asthma-chronic obstructive pulmonary disease syndrome on the stroke, Parkinson's disease, and dementia: a national cohort study.* Oncotarget, 2018. **9**(15): p. 12418-12431.

134. Liao, K.M., et al., *Increased Risk of Dementia in Patients With Chronic Obstructive Pulmonary Disease.* Medicine (Baltimore), 2015. **94**(23): p. e930.

135. Liao, W.C., et al., *The association between chronic obstructive pulmonary disease and dementia: a population-based retrospective cohort study.* Eur J Neurol, 2015. **22**(2): p. 334-40.

136. Rusanen, M., et al., *Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study.* Curr Alzheimer Res, 2013. **10**(5): p. 549-55.

137. Lutsey, P.L., et al., *Impaired Lung Function, Lung Disease, and Risk of Incident Dementia.* Am J Respir Crit Care Med, 2019. **199**(11): p. 1385-1396.

138. Xie, F. and L. Xie, *COPD and the risk of mild cognitive impairment and dementia: a cohort study based on the Chinese Longitudinal Health Longevity Survey.* Int J Chron Obstruct Pulmon Dis, 2019. **14**: p. 403-408.

139. Khdour, M.R., et al., *Potential risk factors for medication non-adherence in patients with chronic obstructive pulmonary disease (COPD).* Eur J Clin Pharmacol, 2012. **68**(10): p. 1365-73.

140. Keating, A., A. Lee, and A.E. Holland, *What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review.* Chron Respir Dis, 2011. **8**(2): p. 89-99.

141. Laforest, L., et al., *Frequency of comorbidities in chronic obstructive pulmonary disease, and impact on all-cause mortality: A population-based cohort study.* Respir Med, 2016. **117**: p. 33-9.

142. Di Marco, F., et al., *Anxiety and depression in COPD patients: The roles of gender and disease severity.* Respir Med, 2006. **100**(10): p. 1767-74.

143. Matte, D.L., et al., *Prevalence of depression in COPD: A systematic review and meta-analysis of controlled studies.* Respir Med, 2016. **117**: p. 154-61.

144. Yohannes, A.M., et al., *Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles.* Int J Geriatr Psychiatry, 2010. **25**(12): p. 1209-21.

145. Hanania, N.A., et al., *Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort.* Am J Respir Crit Care Med, 2011. **183**(5): p. 604-11.

146. van den Bemt, L., et al., *The risk for depression comorbidity in patients with COPD.* Chest, 2009. **135**(1): p. 108-114.

147. Schneider, C., et al., *COPD and the risk of depression.* Chest, 2010. **137**(2): p. 341-7.

148. Wagena, E.J., et al., *Chronic bronchitis, cigarette smoking, and the subsequent onset of depression and anxiety: results from a prospective population-based cohort study.* Psychosom Med, 2005. **67**(4): p. 656-60.

149. Dury, R., *COPD and emotional distress: not always noticed and therefore untreated.* Br J Community Nurs, 2016. **21**(3): p. 138-41.

150. Kunik, M.E., et al., *Surprisingly high prevalence of anxiety and depression in chronic breathing disorders.* Chest, 2005. **127**(4): p. 1205-11.

151. Vozoris, N.T., et al., *Serotonergic antidepressant use and morbidity and mortality among older adults with COPD.* Eur Respir J, 2018. **52**(1).

152. *Biomarkers and surrogate endpoints: preferred definitions and conceptual framework.* Clin Pharmacol Ther, 2001. **69**(3): p. 89-95.

153. Hollander, Z., et al., *Biomarker Development in COPD: Moving From P Values to Products to Impact Patient Care.* Chest, 2017. **151**(2): p. 455-467.

154. Administration, F.a.D. *Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff*. 2018 [cited 28 Junuary 2021; Available from: https://www.fda.gov/media/119271/download.

155. *The Food and Drug Modernization Act of 1997. Title 21 code of federal regulations part 314 Subpart H Section 314.500.*

156. Folsom, A.R., *Classical and novel biomarkers for cardiovascular risk prediction in the United States.* J Epidemiol, 2013. **23**(3): p. 158-62.

157. Vanfleteren, L., et al., *Management of chronic obstructive pulmonary disease beyond the lungs.* Lancet Respir Med, 2016. **4**(11): p. 911-924.

158. Roversi, S., et al., *Chronic Obstructive Pulmonary Disease and Cardiac Diseases. An Urgent Need for Integrated Care.* Am J Respir Crit Care Med, 2016. **194**(11): p. 1319-1336.

159. Bhatt, S.P., J.M. Wells, and M.T. Dransfield, *Cardiovascular disease in COPD: a call for action.* Lancet Respir Med, 2014. **2**(10): p. 783-5.

160. Celli, B.R., et al., *Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2012. **185**(10): p. 1065-72.

161. Fermont, J.M., et al., *Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis.* Thorax, 2019. **74**(5): p. 439-446.

162. Mannino, D.M., *Biomarkers for chronic obstructive pulmonary disease diagnosis and progression: insights, disappointments and promise.* Curr Opin Pulm Med, 2019. **25**(2): p. 144-149.

163. Cozlea, D.L., et al., *The impact of C reactive protein on global cardiovascular risk on patients with coronary artery disease.* Curr Health Sci J, 2013. **39**(4): p. 225-31.

164. Kaptoge, S., et al., *C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis.* Lancet, 2010. **375**(9709): p. 132-40.

165. Man, S.F., et al., *C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease.* Thorax, 2006. **61**(10): p. 849-53.

166. de Torres, J.P., et al., *C-reactive protein levels and survival in patients with moderate to very severe COPD.* Chest, 2008. **133**(6): p. 1336-1343.

167. Mohan, D., et al., *Fibrinogen does not relate to cardiovascular or muscle manifestations in COPD: cross-sectional data from the ERICA study.* Thorax, 2018. **73**(12): p. 1182-1185.

168. Miller, B.E., et al., *Plasma Fibrinogen Qualification as a Drug Development Tool in Chronic Obstructive Pulmonary Disease. Perspective of the Chronic Obstructive Pulmonary Disease Biomarker Qualification Consortium.* Am J Respir Crit Care Med, 2016. **193**(6): p. 607-13.

169. Duvoix, A., et al., *Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease.* Thorax, 2013. **68**(7): p. 670-6.

170. Nin, J.W., et al., *Higher plasma soluble Receptor for Advanced Glycation End Products (sRAGE) levels are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes: a 12-year follow-up study.* Diabetes, 2010. **59**(8): p. 2027-32.

171. Rebholz, C.M., et al., *Association of plasma levels of soluble receptor for advanced glycation end products and risk of kidney disease: the*

Atherosclerosis Risk in Communities study. Nephrol Dial Transplant, 2015. **30**(1): p. 77-83.

172. Falcone, C., et al., *Soluble RAGE plasma levels in patients with coronary artery disease and peripheral artery disease.* ScientificWorldJournal, 2013. **2013**: p. 584504.

173. Semba, R.D., et al., *Plasma carboxymethyl-lysine, an advanced glycation end product, and all-cause and cardiovascular disease mortality in older community-dwelling adults.* J Am Geriatr Soc, 2009. **57**(10): p. 1874-80.

174. Xie, J., et al., *Cellular signalling of the receptor for advanced glycation end products (RAGE).* Cell Signal, 2013. **25**(11): p. 2185-97.

175. Brett, J., et al., *Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues.* Am J Pathol, 1993. **143**(6): p. 1699-712.

176. Morbini, P., et al., *The receptor for advanced glycation end products and its ligands: a new inflammatory pathway in lung disease?* Mod Pathol, 2006. **19**(11): p. 1437-45.

177. Wu, L., et al., *Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD.* Respir Med, 2011. **105**(3): p. 329-36.

178. Iwamoto, H., et al., *Soluble receptor for advanced glycation end-products and progression of airway disease.* BMC Pulm Med, 2014. **14**: p. 68.

179. Smith, D.J., et al., *Reduced soluble receptor for advanced glycation end-products in COPD.* Eur Respir J, 2011. **37**(3): p. 516-22.

180. Sukkar, M.B., et al., *Soluble RAGE is deficient in neutrophilic asthma and COPD.* Eur Respir J, 2012. **39**(3): p. 721-9.

181. Miniati, M., et al., *Soluble receptor for advanced glycation end products in COPD: relationship with emphysema and chronic cor pulmonale: a case-control study.* Respir Res, 2011. **12**: p. 37.

182. Cheng, D.T., et al., *Systemic soluble receptor for advanced glycation endproducts is a biomarker of emphysema and associated with AGER genetic variants in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2013. **188**(8): p. 948-57.

183. Gopal, P., et al., *Association of plasma sRAGE, but not esRAGE with lung function impairment in COPD.* Respir Res, 2014. **15**: p. 24.

184. Gopal, P., et al., *Decreased plasma sRAGE levels in COPD: influence of oxygen therapy.* Eur J Clin Invest, 2012. **42**(8): p. 807-14.

185. Falcone, C., et al., *Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men.* Arterioscler Thromb Vasc Biol, 2005. **25**(5): p. 1032-7.

186. Selvin, E., et al., *sRAGE and risk of diabetes, cardiovascular disease, and death.* Diabetes, 2013. **62**(6): p. 2116-21.

187. Fujisawa, K., et al., *Circulating soluble RAGE as a predictive biomarker of cardiovascular event risk in patients with type 2 diabetes.* Atherosclerosis, 2013. **227**(2): p. 425-8.

188. Colhoun, H.M., et al., *Total soluble and endogenous secretory receptor for advanced glycation end products as predictive biomarkers of coronary heart disease risk in patients with type 2 diabetes: an analysis from the CARDS trial.* Diabetes, 2011. **60**(9): p. 2379-85.

189. Reichert, S., et al., *Soluble form of receptor for advanced glycation end products and incidence of new cardiovascular events among patients with cardiovascular disease.* Atherosclerosis, 2017. **266**: p. 234-239.

190. Arsenault, B.J., et al., *Prediction of cardiovascular events in statin-treated stable coronary patients of the treating to new targets randomized controlled trial by lipid and non-lipid biomarkers.* PLoS One, 2014. **9**(12): p. e114519.

191. Raposeiras-Roubín, S., et al., *Fluorescent advanced glycation end products and their soluble receptor: the birth of new plasmatic biomarkers for risk stratification of acute coronary syndrome.* PLoS One, 2013. **8**(9): p. e74302.

192. Mogensen, C.E., et al., *Microalbuminuria: an early marker of renal involvement in diabetes.* Uremia Invest, 1985. **9**(2): p. 85-95.

193. Viazzi, F., et al., *Microalbuminuria is a predictor of chronic renal insufficiency in patients without diabetes and with hypertension: the MAGIC study.* Clin J Am Soc Nephrol, 2010. **5**(6): p. 1099-106.

194. Yuyun, M.F., et al., *Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study.* Int J Epidemiol, 2004. **33**(1): p. 189-98.

195. Hillege, H.L., et al., *Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population.* Circulation, 2002. **106**(14): p. 1777-82.

196. Smink, P.A., et al., *Albuminuria, estimated GFR, traditional risk factors, and incident cardiovascular disease: the PREVEND (Prevention of Renal and Vascular Endstage Disease) study.* Am J Kidney Dis, 2012. **60**(5): p. 804-11.

197. Gerstein, H.C., et al., *Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals.* Jama, 2001. **286**(4): p. 421-6.

198. Yokoyama, H., et al., *Subclinical atherosclerosis is increased in type 2 diabetic patients with microalbuminuria evaluated by intima-media thickness and pulse wave velocity.* Kidney Int, 2004. **66**(1): p. 448-54.

199. Liu, C.S., et al., *Albuminuria is strongly associated with arterial stiffness, especially in diabetic or hypertensive subjects--a population-based study (Taichung Community Health Study, TCHS).* Atherosclerosis, 2010. **211**(1): p. 315-21.

200. Kim, B.J., et al., *The association of albuminuria, arterial stiffness, and blood pressure status in nondiabetic, nonhypertensive individuals.* J Hypertens, 2011. **29**(11): p. 2091-8.

201. Arnlov, J., et al., *Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study.* Circulation, 2005. **112**(7): p. 969-75.

202. Matsushita, K., et al., *Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis.* Lancet, 2010. **375**(9731): p. 2073-81.

203. Kömürcüoğlu, A., et al., *Microalbuminuria in chronic obstructive pulmonary disease.* Monaldi Arch Chest Dis, 2003. **59**(4): p. 269-72.

204. Polatli, M., et al., *Microalbuminuria, von Willebrand factor and fibrinogen levels as markers of the severity in COPD exacerbation.* J Thromb Thrombolysis, 2008. **26**(2): p. 97-102.

205. Bozkus, F., N. Dikmen, and A. Samur, *Microalbuminuria in Subjects With COPD: Relationship to the New Version of Global Initiative for Chronic Obstructive Lung Disease Staging.* Respir Care, 2017. **62**(3): p. 307-314.

206. Casanova, C., et al., *Microalbuminuria and hypoxemia in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2010. **182**(8): p. 1004-10.

207. Bulcun, E., et al., *Microalbuminuria in chronic obstructive pulmonary disease.* Copd, 2013. **10**(2): p. 186-92.

208. John, M., et al., *Target renal damage: the microvascular associations of increased aortic stiffness in patients with COPD.* Respir Res, 2013. **14**(1): p. 31.

209. Romundstad, S., et al., *COPD and microalbuminuria: a 12-year follow-up study.* Eur Respir J, 2014. **43**(4): p. 1042-50.

210. Collins, G.S. and D.G. Altman, *Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2.* Bmj, 2012. **344**: p. e4181.

211. Stone, N.J., et al., *2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol, 2014. **63**(25 Pt B): p. 2889-934.

212. Khanji, M.Y., et al., *Cardiovascular Risk Assessment: A Systematic Review of Guidelines.* Ann Intern Med, 2016. **165**(10): p. 713-722.

213. Ben-Shlomo, Y., et al., *Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective*

observational data from 17,635 subjects. J Am Coll Cardiol, 2014. **63**(7): p. 636-646.

214. Vivodtzev, I., et al., *Arterial stiffness in COPD.* Chest, 2014. **145**(4): p. 861-875.

215. Mills, N.L., et al., *Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk.* Thorax, 2008. **63**(4): p. 306-11.

216. Wang, L.Y., et al., *Subclinical atherosclerosis risk markers in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis.* Respir Med, 2017. **123**: p. 18-27.

217. van Gestel, Y.R., et al., *Association of COPD with carotid wall intima-media thickness in vascular surgery patients.* Respir Med, 2010. **104**(5): p. 712-6.

218. Kalea, A.Z., A.M. Schmidt, and B.I. Hudson, *RAGE: a novel biological and genetic marker for vascular disease.* Clin Sci (Lond), 2009. **116**(8): p. 621-37.

219. Monnier, V.M., et al., *Cross-linking of the extracellular matrix by the maillard reaction in aging and diabetes: an update on "a puzzle nearing resolution".* Ann N Y Acad Sci, 2005. **1043**: p. 533-44.

220. Ferhani, N., et al., *Expression of high-mobility group box 1 and of receptor for advanced glycation end products in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2010. **181**(9): p. 917-27.

221. John, M., et al., *Traditional and emerging indicators of cardiovascular risk in chronic obstructive pulmonary disease.* Chron Respir Dis, 2016. **13**(3): p. 247-55.

222. Mohan, D., et al., *Evaluating the role of inflammation in chronic airways disease: the ERICA study.* Copd, 2014. **11**(5): p. 552-9.

223. Levey, A.S., et al., *A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group.* Ann Intern Med, 1999. **130**(6): p. 461-70.

224. Jones, P.W., et al., *Development and first validation of the COPD Assessment Test.* Eur Respir J, 2009. **34**(3): p. 648-54.

225. Lindsey, J.B., et al., *Association between circulating soluble receptor for advanced glycation end products and atherosclerosis: observations from the Dallas Heart Study.* Diabetes Care, 2009. **32**(7): p. 1218-20.

226. Thomas, M.C., et al., *Soluble receptor for AGE (RAGE) is a novel independent predictor of all-cause and cardiovascular mortality in type 1 diabetes.* Diabetologia, 2011. **54**(10): p. 2669-77.

227. Yonchuk, J.G., et al., *Circulating soluble receptor for advanced glycation end products (sRAGE) as a biomarker of emphysema and the RAGE axis in the lung.* Am J Respir Crit Care Med, 2015. **192**(7): p. 785-92.

228. Celli, B.R., et al., *Serum biomarkers and outcomes in patients with moderate COPD: a substudy of the randomised SUMMIT trial.* BMJ Open Respir Res, 2019. **6**(1): p. e000431.

229. Pouwels, S.D., et al., *Cigarette Smoking Acutely Decreases Serum Levels of the Chronic Obstructive Pulmonary Disease Biomarker sRAGE.* Am J Respir Crit Care Med, 2018. **198**(11): p. 1456-1458.

230. Caram, L.M.O., et al., *Tumor necrosis factor receptor 2 as a possible marker of COPD in smokers and ex-smokers.* Int J Chron Obstruct Pulmon Dis, 2017. **12**: p. 2015-2021.

231. Gopal, P., et al., *Association of plasma sRAGE, but not esRAGE with lung function impairment in COPD.* Respir Res, 2014. **15**(1): p. 24.

232. Casanova, C. and B.R. Celli, *Microalbuminuria as a potential novel cardiovascular biomarker in patients with COPD.* Eur Respir J, 2014. **43**(4): p. 951-3.

233. Weir, M.R., *Microalbuminuria and cardiovascular disease.* Clin J Am Soc Nephrol, 2007. **2**(3): p. 581-90.

234. Sarafidis, P.A. and G.L. Bakris, *Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease.* Nephrol Dial Transplant, 2006. **21**(9): p. 2366-74.

235. Kistorp, C., et al., *N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults.* Jama, 2005. **293**(13): p. 1609-16.

236. Shayo, F.K. and J. Lutale, *Albuminuria in patients with chronic obstructive pulmonary disease: a cross-sectional study in an African patient cohort.* BMC Pulm Med, 2018. **18**(1): p. 125.

237. Wilkinson, I.B., et al., *Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis.* J Hypertens, 1998. **16**(12 Pt 2): p. 2079-84.

238. Hui, X., et al., *CKD and cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study: interactions with age, sex, and race.* Am J Kidney Dis, 2013. **62**(4): p. 691-702.

239. Vlachopoulos, C., K. Aznaouridis, and C. Stefanadis, *Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis.* J Am Coll Cardiol, 2010. **55**(13): p. 1318-27.

240. Matsui, Y., et al., *Impact of arterial stiffness reduction on urinary albumin excretion during antihypertensive treatment: the Japan morning Surge-1 study*. J Hypertens, 2010. **28**(8): p. 1752-60.

241. Dwyer, J.P., et al., *Renal Dysfunction in the Presence of Normoalbuminuria in Type 2 Diabetes: Results from the DEMAND Study.* Cardiorenal Med, 2012. **2**(1): p. 1-10.

242. Ruggenenti, P., et al., *Measurable urinary albumin predicts cardiovascular risk among normoalbuminuric patients with type 2 diabetes.* J Am Soc Nephrol, 2012. **23**(10): p. 1717-24.

243. Scirica, B.M., et al., *Cardiovascular Outcomes According to Urinary Albumin and Kidney Disease in Patients With Type 2 Diabetes at High Cardiovascular Risk: Observations From the SAVOR-TIMI 53 Trial.* JAMA Cardiol, 2018. **3**(2): p. 155-163.

244. Chen, S.C., et al., *Brachial-ankle pulse wave velocity and rate of renal function decline and mortality in chronic kidney disease.* Clin J Am Soc Nephrol, 2011. **6**(4): p. 724-32.

245. Hermans, M.M., et al., *Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: the Hoorn Study.* J Am Soc Nephrol, 2007. **18**(6): p. 1942-52.

246. Ford, M.L., et al., *Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4.* Hypertension, 2010. **55**(5): p. 1110-5.

247. Sedaghat, S., et al., *Arterial Stiffness and Decline in Kidney Function.* Clin J Am Soc Nephrol, 2015. **10**(12): p. 2190-7.

248. Hamilton, P.K., et al., *Arterial stiffness: clinical relevance, measurement and treatment.* Clin Sci (Lond), 2007. **113**(4): p. 157-70.

249. Townsend, R.R. and H. Tomiyama, *Arterial Stiffness, Kidney Function, and Chronic Kidney Disease Progression.* Pulse (Basel), 2013. **1**(2): p. 123-30.

250. Incalzi, R.A., et al., *Chronic renal failure: a neglected comorbidity of COPD.* Chest, 2010. **137**(4): p. 831-7.

251. Gjerde, B., et al., *The prevalence of undiagnosed renal failure in a cohort of COPD patients in western Norway.* Respir Med, 2012. **106**(3): p. 361-6.

252. van Gestel, Y.R., et al., *Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients.* Nephrol Dial Transplant, 2009. **24**(9): p. 2763-7.

253. Yoshizawa, T., et al., *Prevalence of chronic kidney diseases in patients with chronic obstructive pulmonary disease: assessment based on glomerular filtration rate estimated from creatinine and cystatin C levels.* Int J Chron Obstruct Pulmon Dis, 2015. **10**: p. 1283-9.

254. Gaddam, S., et al., *Prevalence of chronic kidney disease in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis.* BMC Pulm Med, 2016. **16**(1): p. 158.

255. Glassock, R.J. and C. Winearls, *Screening for CKD with eGFR: doubts and dangers.* Clin J Am Soc Nephrol, 2008. **3**(5): p. 1563-8.

256. Hemmelgarn, B.R., et al., *Relation between kidney function, proteinuria, and adverse outcomes.* Jama, 2010. **303**(5): p. 423-9.

257. *10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020.* Diabetes Care, 2020. **43**(Suppl 1): p. S111-s134.

258. Williams, B., et al., *2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension.* Blood Press, 2018. **27**(6): p. 314-340.

259. Hartley, P., et al., *The association between cognitive impairment and functional outcome in hospitalised older patients: a systematic review and meta-analysis.* Age Ageing, 2017. **46**(4): p. 559-567.

260. Martinez, C.H., et al., *Chronic obstructive pulmonary disease, cognitive impairment, and development of disability: the health and retirement study.* Ann Am Thorac Soc, 2014. **11**(9): p. 1362-70.

261. Allen, S.C., et al., *Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects.* Age Ageing, 2003. **32**(3): p. 299-302.

262. Chang, S.S., et al., *Effect of coexisting chronic obstructive pulmonary disease and cognitive impairment on health outcomes in older adults.* J Am Geriatr Soc, 2012. **60**(10): p. 1839-46.

263. Campbell, S.E., D.G. Seymour, and W.R. Primrose, *A systematic literature review of factors affecting outcome in older medical patients admitted to hospital.* Age Ageing, 2004. **33**(2): p. 110-5.

264. Antonelli-Incalzi, R., et al., *Drawing impairment predicts mortality in severe COPD.* Chest, 2006. **130**(6): p. 1687-94.

265. Dodd, J.W., *Lung disease as a determinant of cognitive decline and dementia.* Alzheimers Res Ther, 2015. **7**(1): p. 32.

266. Lahousse, L., et al., *Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review.* Respir Med, 2015. **109**(11): p. 1371-80.

267. Grant, I., et al., *Progressive neuropsychologic impairment and hypoxemia. Relationship in chronic obstructive pulmonary disease.* Arch Gen Psychiatry, 1987. **44**(11): p. 999-1006.

268. Schou, L., et al., *Cognitive dysfunction in patients with chronic obstructive pulmonary disease--a systematic review.* Respir Med, 2012. **106**(8): p. 1071-81.

269. Pezzoli, L., et al., *Quality of spirometric performance in older people.* Age Ageing, 2003. **32**(1): p. 43-6.

270. Bellia, V., et al., *Quality control of spirometry in the elderly. The SA.R.A. study. SAlute Respiration nell'Anziano = Respiratory Health in the Elderly.* Am J Respir Crit Care Med, 2000. **161**(4 Pt 1): p. 1094-100.

271. Hung, W.W., et al., *Cognitive decline among patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2009. **180**(2): p. 134-7.

272. Dulohery, M.M., D.R. Schroeder, and R.P. Benzo, *Cognitive function and living situation in COPD: is there a relationship with self-management and quality of life?* Int J Chron Obstruct Pulmon Dis, 2015. **10**: p. 1883-9.

273. Blak, B.T., et al., *Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates.* Inform Prim Care, 2011. **19**(4): p. 251-5.

274. IQVIA. *The Heath Improvement Network (THIN)*. 2018 [cited 2018 26 July]; Available from: https://www.iqvia.com/locations/uk-and-ireland/thin.

275. National Services Scotland. *Quality and Outcomes Framework*. 2010 [cited 2018 26 July]; Available from: http://www.isdscotland.org/Health-Topics/General-Practice/Quality-And-Outcomes-Framework/Revisions-To-QOF.asp.

276. Deyo, R.A., D.C. Cherkin, and M.A. Ciol, *Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases.* J Clin Epidemiol, 1992. **45**(6): p. 613-9.

277. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.

278. Townsend, P., P. Phillimore, and A. Beattie, *Health and deprivation: inequality and the North*. 1988: Routledge.

279. National Clinical Guideline, C., *National Institute for Health and Clinical Excellence: Guidance*, in *Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care*. 2010, Royal College of Physicians (UK)

National Clinical Guideline Centre - Acute and Chronic Conditions.: London.

280. NHS Digital. *Dementia diagnosis rate and prescription of antipsychotic medication to people with dementia*. [cited 2018 26 July]; Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/general-practice-data-hub/dementia-diagnosis-rate-and-prescription-of-antipsychotic-medication-to-people-with-dementia.

281. Yohannes, A.M., et al., *Association of mild cognitive impairment and characteristic of COPD and overall health status in a cohort study.* Expert Rev Respir Med, 2020: p. 1-7.

282. Cleutjens, F., et al., *Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease.* Chron Respir Dis, 2018. **15**(2): p. 91-102.

283. Singh, B., et al., *A prospective study of chronic obstructive pulmonary disease and the risk for mild cognitive impairment.* JAMA Neurol, 2014. **71**(5): p. 581-8.

284. Arlt, S., et al., *Adherence to medication in patients with dementia: predictors and strategies for improvement.* Drugs Aging, 2008. **25**(12): p. 1033-47.

285. Dodd, J.W., et al., *Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD.* Chest, 2013. **144**(1): p. 119-127.

286. Quint, J.K., et al., *Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).* BMJ Open, 2014. **4**(7): p. e005540.

287. Strong, M., et al., *Accuracy of diagnosis and classification of COPD in primary and specialist nurse-led respiratory care in Rotherham, UK: a cross-sectional study.* Prim Care Respir J, 2014. **23**(1): p. 67-73.

288. Blakemore, A., et al., *Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 501-12.

289. Xu, W., et al., *Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations.* Am J Respir Crit Care Med, 2008. **178**(9): p. 913-20.

290. Atlantis, E., et al., *Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis.* Chest, 2013. **144**(3): p. 766-777.

291. *Depression: management of depression in primary and secondary care*. 2004 [cited 2020 12/02/2020]; Available from: https://www.nice.org.uk/guidance/cg23.

292. *Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care.* Thorax, 2004. **59 Suppl 1**(Suppl 1): p. 1-232.

293. Campbell, S.M., et al., *Effects of pay for performance on the quality of primary care in England.* N Engl J Med, 2009. **361**(4): p. 368-78.

294. Martinez Rivera, C., et al., *Factors Associated with Depression in COPD: A Multicenter Study.* Lung, 2016. **194**(3): p. 335-43.

295. Domenech-Abella, J., et al., *The association between socioeconomic status and depression among older adults in Finland, Poland and Spain: A comparative cross-sectional study of distinct measures and pathways.* J Affect Disord, 2018. **241**: p. 311-318.

296. Yohannes, A.M., A. Kaplan, and N.A. Hanania, *Anxiety and Depression in Chronic Obstructive Pulmonary Disease: Recognition and Management.* Cleve Clin J Med, 2018. **85**(2 Suppl 1): p. S11-s18.

297. Yohannes, A.M., et al., *Long-term Course of Depression Trajectories in Patients With COPD: A 3-Year Follow-up Analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Cohort.* Chest, 2016. **149**(4): p. 916-26.

298. Lorant, V., et al., *Depression and socio-economic risk factors: 7-year longitudinal population study.* Br J Psychiatry, 2007. **190**: p. 293-8.

299. Johar, M., et al., *Inequality in access to health care, health insurance and the role of supply factors.* Soc Sci Med, 2018. **213**: p. 134-145.

300. Dixon, A., et al., *Is the British National Health Service equitable? The evidence on socioeconomic differences in utilization.* J Health Serv Res Policy, 2007. **12**(2): p. 104-9.

301. Steiner, M.C., et al., *Socioeconomic deprivation and the outcome of pulmonary rehabilitation in England and Wales.* Thorax, 2017. **72**(6): p. 530-537.

302. *Depression in adults: recognition and management*. 2009 April 2018 [cited 2020 February 2]; Available from: https://www.nice.org.uk/guidance/cg90/chapter/1-Guidance#step-2-recognised-depression-persistent-subthreshold-depressive-symptoms-or-mild-to-moderate.

303. Gordon, C.S., et al., *Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis.* Chest, 2019. **156**(1): p. 80-91.

304. von Wolff, A., et al., *Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: a systematic review and meta-analysis.* J Affect Disord, 2013. **144**(1-2): p. 7-15.

305. Cipriani, A., et al., *Sertraline versus other antidepressive agents for depression.* Cochrane Database Syst Rev, 2010(4): p. Cd006117.

306. Chatterjee, S., et al., *Anticholinergic Medication Use and Risk of Pneumonia in Elderly Adults: A Nested Case-Control Study*. J Am Geriatr Soc, 2016. **64**(2): p. 394-400.

307. Cipriani, A., et al., *Duloxetine versus other anti-depressive agents for depression.* Cochrane Database Syst Rev, 2012. **10**: p. Cd006533.

308. Cipriani, A., et al., *Citalopram versus other anti-depressive agents for depression.* Cochrane Database Syst Rev, 2012(7): p. Cd006534.

309. Shenoy, A.R., et al., *Citalopram suppresses thymocyte cytokine production.* J Neuroimmunol, 2013. **262**(1-2): p. 46-52.

310. Taler, M., et al., *Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression.* Eur Neuropsychopharmacol, 2007. **17**(12): p. 774-80.

311. Petersen, I., I. Douglas, and H. Whitaker, *Self controlled case series methods: an alternative to standard epidemiological study designs.* Bmj, 2016. **354**: p. i4515.

312. Whitaker, H.J., et al., *Tutorial in biostatistics: the self-controlled case series method.* Stat Med, 2006. **25**(10): p. 1768-97.

313. Farrington, C.P., *Relative incidence estimation from case series for vaccine safety evaluation.* Biometrics, 1995. **51**(1): p. 228-35.

314. Hubbard, R., et al., *Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture.* Am J Epidemiol, 2003. **158**(1): p. 77-84.

315. Gibson, J.E., et al., *Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes.* Am J Epidemiol, 2009. **169**(6): p. 761-8.

316. Wijlaars, L.P., et al., *Suicide-related events in young people following prescription of SSRIs and other antidepressants: a self-controlled case series analysis.* BMJ Open, 2013. **3**(9): p. e003247.

317. Gribbin, J., et al., *Risk of falls associated with antihypertensive medication: self-controlled case series.* Pharmacoepidemiol Drug Saf, 2011. **20**(8): p. 879-84.

318. Rothnie, K.J., et al., *Myocardial Infarction and Ischemic Stroke after Exacerbations of Chronic Obstructive Pulmonary Disease.* Ann Am Thorac Soc, 2018. **15**(8): p. 935-946.

319. Minassian, C., et al., *Acute Cardiovascular Events after Herpes Zoster: A Self-Controlled Case Series Analysis in Vaccinated and Unvaccinated Older Residents of the United States.* PLoS Med, 2015. **12**(12): p. e1001919.

320. Whitaker, H.J., M.N. Hocine, and C.P. Farrington, *The methodology of self-controlled case series studies.* Stat Methods Med Res, 2009. **18**(1): p. 7-26.

321. Maclure, M., *The case-crossover design: a method for studying transient effects on the risk of acute events.* Am J Epidemiol, 1991. **133**(2): p. 144-53.

322. Mittleman, M.A. and E. Mostofsky, *Exchangeability in the case-crossover design.* Int J Epidemiol, 2014. **43**(5): p. 1645-55.

323. Whitaker, H.J., C.D. Steer, and C.P. Farrington, *Self-controlled case series studies: Just how rare does a rare non-recurrent outcome need to be?* Biom J, 2018. **60**(6): p. 1110-1120.

324. Gardarsdottir, H., et al., *Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length.* J Clin Epidemiol, 2010. **63**(4): p. 422-7.

325. Vinogradova, Y., et al., *Patients who discontinued statin treatment: a protocol for cohort study using primary care data.* BMJ Open, 2015. **5**(10): p. e008701.

326. Othman, F., C.J. Crooks, and T.R. Card, *Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study.* Bmj, 2016. **355**: p. i5813.

327. Niederman, M.S., *Understanding the natural history of community-acquired pneumonia resolution: vital information for optimizing duration of therapy.* Clin Infect Dis, 2004. **39**(12): p. 1791-3.

328. Rothnie, K.J., et al., *Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records.* PLoS One, 2016. **11**(3): p. e0151357.

329. Quint, J.K., et al., *Relationship between depression and exacerbations in COPD.* Eur Respir J, 2008. **32**(1): p. 53-60.

330. Davydow, D.S., et al., *Depression and risk of hospitalization for pneumonia in a cohort study of older Americans.* J Psychosom Res, 2014. **77**(6): p. 528-34.

331. Farrington, C.P. and H.J. Whitaker, *Semiparametric analysis of case series data.* Journal of the Royal Statistical Society: Series C (Applied Statistics), 2006. **55**(5): p. 553-594.

332. Farrington, C.P., et al., *Self-Controlled Case Series Analysis With Event-Dependent Observation Periods.* Journal of the American Statistical Association, 2011. **106**(494): p. 417-426.

333. Langan, S.M., et al., *Risk of stroke following herpes zoster: a self-controlled case-series study.* Clin Infect Dis, 2014. **58**(11): p. 1497-503.

334. Wiese, A.D., et al., *Opioid Analgesics and the Risk of Serious Infections Among Patients With Rheumatoid Arthritis: A Self-Controlled Case Series Study.* Arthritis Rheumatol, 2016. **68**(2): p. 323-31.

335. Seminog, O.O. and M.J. Goldacre, *Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies.* Thorax, 2013. **68**(2): p. 171-6.

336. Baine, W.B. and S.V. Kazakova, *An analysis of administrative data found that proximate clinical event ratios provided a systematic approach to identifying possible iatrogenic risk factors or complications.* J Clin Epidemiol, 2005. **58**(2): p. 162-70.

337. Hennessy, S., et al., *Observed association between antidepressant use and pneumonia risk was confounded by comorbidity measures.* J Clin Epidemiol, 2007. **60**(9): p. 911-8.

338. Carvalho, A.F., et al., *The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature.* Psychother Psychosom, 2016. **85**(5): p. 270-88.

339. Restrepo, M.I., O. Sibila, and A. Anzueto, *Pneumonia in Patients with Chronic Obstructive Pulmonary Disease.* Tuberc Respir Dis (Seoul), 2018. **81**(3): p. 187-197.

340. Donaldson, G.C., et al., *Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease.* Thorax, 2002. **57**(10): p. 847-52.

341. Farrington, C.P., *Control without separate controls: evaluation of vaccine safety using case-only methods.* Vaccine, 2004. **22**(15-16): p. 2064-70.

342. Farrington, C.P., H.J. Whitaker, and M.N. Hocine, *Case series analysis for censored, perturbed, or curtailed post-event exposures.* Biostatistics, 2009. **10**(1): p. 3-16.

343. Usmani, Z.A., et al., *Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2017. **3**(3): p. Cd010673.

344. Morgan, A.D., R. Zakeri, and J.K. Quint, *Defining the relationship between COPD and CVD: what are the implications for clinical practice?* Ther Adv Respir Dis, 2018. **12**: p. 1753465817750524.

345. Agca, R., et al., *EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of*

inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis, 2017. **76**(1): p. 17-28.

346. Cosentino, F., et al., *2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.* Eur Heart J, 2020. **41**(2): p. 255-323.

347. Inker, L.A., et al., *KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD.* Am J Kidney Dis, 2014. **63**(5): p. 713-35.

348. Sarwar, N., et al., *Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.* Lancet, 2010. **375**(9733): p. 2215-22.

Chapter 9 APPENDICES

Appendix 9-1. List of high blood pressure medications

AMLOPADINE
ATENOLOL
ATORVASTATIN
BENDROFLUAZIDE
BENDROFLUMETHIAZIDE
BISOPROLOL
BUMETANIDE
CANDESARTAN
CO-TENIDONE
COZAAR
DILTALIZAM
DOXAZOSIN
ENALAPRIL
IMBARTISN
IRBESARTAN
IRBESARTAN LERCANIDIPINE
ISOSORBIDE MONONITRATE
LERCANDIPINE
LISINOPRIL
LOSARTAN
MOXONIDINE
NICOANDRYL
NIFEDIPINE
OLMESARTAN
PERIDOPRIL
RAMIPIL
TILDIEM
VALSARTAN

Appendix 9-2. COPD codes

Code	Description
H3...00	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H3...11	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
H31..00	CHRONIC BRONCHITIS
H310.00	SIMPLE CHRONIC BRONCHITIS
H310000	CHRONIC CATARRHAL BRONCHITIS
H310z00	SIMPLE CHRONIC BRONCHITIS
H311.00	MUCOPURULENT CHRONIC BRONCHITIS
H311000	PURULENT CHRONIC BRONCHITIS
H311100	FETID CHRONIC BRONCHITIS
H311z00	MUCOPURULENT CHRONIC BRONCHITIS NOS
H312.00	OBSTRUCTIVE CHRONIC BRONCHITIS
H312000	CHRONIC ASTHMATIC BRONCHITIS
H312011	CHRONIC WHEEZY BRONCHITIS
H312100	EMPHYSEMATOUS BRONCHITIS
H312300	BRONCHIOLITIS OBLITERANS
H312z00	OBSTRUCTIVE CHRONIC BRONCHITIS
H313.00	MIXED SIMPLE AND MUCOPURULENT CHRONIC BRONCHITIS
H31y.00	OTHER CHRONIC BRONCHITIS
H31y100	CHRONIC TRACHEOBRONCHITIS
H31yz00	OTHER CHRONIC BRONCHITIS
H31z.00	CHRONIC BRONCHITIS
H32..00	EMPHYSEMA
H320.00	CHRONIC BULLOUS EMPHYSEMA
H320000	SEGMENTAL BULLOUS EMPHYSEMA
H320100	ZONAL BULLOUS EMPHYSEMA
H320200	GIANT BULLOUS EMPHYSEMA
H320300	BULLOUS EMPHYSEMA WITH COLLAPSE
H320311	TENSION PNEUMATOCELE
H320z00	CHRONIC BULLOUS EMPHYSEMA

H321.00	PAN-LOBULAR EMPHYSEMA
H322.00	CENTRILOBULAR EMPHYSEMA
H32y.00	OTHER EMPHYSEMA
H32y000	ACUTE VESICULAR EMPHYSEMA
H32y100	ATROPHIC (SENILE) EMPHYSEMA
H32y111	ACUTE INTERSTITIAL EMPHYSEMA
H32y200	MACLEOD'S UNILATERAL EMPHYSEMA
H32yz00	OTHER EMPHYSEMA NOS
H32z.00	EMPHYSEMA
H36..00	MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H37..00	MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H38..00	SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H39..00	VERY SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H3A..00	END-STAGE CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
H3y..00	OTHER SPECIFIED CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
H3y..11	OTHER SPECIFIED CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H3z..00	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
H3z..11	CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Appendix 9-3. Cognitive impairment codes

Code	Description
14Od.00	AT RISK OF DEMENTIA
1B1A.00	MEMORY LOSS - AMNESIA
1B1A.12	MEMORY LOSS SYMPTOM
1B1A.13	MEMORY DISTURBANCE
28E..00	COGNITIVE DECLINE
28E0.00	MILD COGNITIVE IMPAIRMENT
28E1.00	MODERATE COGNITIVE IMPAIRMENT
28E2.00	SEVERE COGNITIVE IMPAIRMENT
28E3.00	COGNITIVE IMPAIRMENT
38Dv.00	GPCOG - GENERAL PRACTITIONER ASSESSMENT OF COGNITION
3A...11	MEMORY ASSESSMENT
3A10.00	MEMORY: OWN AGE NOT KNOWN
3A20.00	MEMORY: PRESENT TIME NOT KNOWN
3A30.00	MEMORY: PRESENT PLACE NOT KNOWN
3A40.00	MEMORY: PRESENT YEAR NOT KNOWN
3A50.00	MEMORY: OWN DOB NOT KNOWN
3A60.00	MEMORY: PRESENT MONTH NOT KNOWN
3A70.00	MEMORY: IMPORTANT EVENT NOT KNOWN
3A80.00	MEMORY: IMPORTANT PERSON NOT KNOWN
3A91.00	MEMORY: COUNT DOWN UNSUCCESSFUL
3AA1.00	MEMORY: ADDRESS RECALL UNSUCCESSFUL
3AE1.00	GDS LEVEL 2 - VERY MILD COGNITIVE DECLINE
3AE2.00	GDS LEVEL 3 - MILD COGNITIVE DECLINE
3AE3.00	GDS LEVEL 4 - MODERATE COGNITIVE DECLINE
3AE4.00	GDS LEVEL 5 - MODERATELY SEVERE COGNITIVE DECLINE
3AE5.00	GDS LEVEL 6 - SEVERE COGNITIVE DECLINE
3AE6.00	GDS LEVEL 7 - VERY SEVERE COGNITIVE DECLINE
8HTY.00	REFERRAL TO MEMORY CLINIC

9Nk1.00	SEEN IN MEMORY CLINIC
E2A1000	MILD MEMORY DISTURBANCE
E2A1100	ORGANIC MEMORY IMPAIRMENT
Eu05700	MILD COGNITIVE DISORDER
R00z011	MEMORY DEFICIT
Z7C1.00	IMPAIRED COGNITION
Z7CE414	MEMORY DISTURBANCE
Z7CE415	LOSS OF MEMORY
Z7CE611	MEMORY LOSS
Z7CE615	LOSS OF MEMORY
Z7CEH00	MEMORY IMPAIRMENT
Z7CEH11	MEMORY DYSFUNCTION
Z7CEH12	MEMORY DEFICIT
Z7CEH14	MEMORY PROBLEM
Z7CEH15	POOR MEMORY
Z7CEL00	MILD MEMORY DISTURBANCE
Z7CFO00	POOR LONG-TERM MEMORY

Appendix 9-4. Dementia codes

Code	Description
E00..11	SENILE DEMENTIA
E00..12	SENILE/PRESENILE DEMENTIA
E000.00	UNCOMPLICATED SENILE DEMENTIA
E001.00	PRESENILE DEMENTIA
E001000	UNCOMPLICATED PRESENILE DEMENTIA
E001200	PRESENILE DEMENTIA WITH PARANOIA
E001300	PRESENILE DEMENTIA WITH DEPRESSION
E001z00	PRESENILE DEMENTIA
E002.00	SENILE DEMENTIA WITH DEPRESSIVE OR PARANOID FEATURES
E002000	SENILE DEMENTIA WITH PARANOIA
E002100	SENILE DEMENTIA WITH DEPRESSION
E002z00	SENILE DEMENTIA WITH DEPRESSIVE OR PARANOID FEATURES
E041.00	DEMENTIA IN CONDITIONS
Eu00.00	DEMENTIA IN ALZHEIMER'S DISEASE
Eu00000	DEMENTIA IN ALZHEIMER'S DISEASE WITH EARLY ONSET
Eu00011	PRESENILE DEMENTIA, ALZHEIMER'S TYPE
Eu00012	PRIMARY DEMENTIA, ALZHEIMER'S TYPE, PRESENILE ONSET
Eu00013	ALZHEIMER'S DISEASE TYPE 2
Eu00100	DEMENTIA IN ALZHEIMER'S DISEASE WITH LATE ONSET
Eu00111	ALZHEIMER'S DISEASE TYPE 1
Eu00112	SENILE DEMENTIA, ALZHEIMER'S TYPE
Eu00113	PRIMARY DEGEN DEMENTIA OF ALZHEIMER'S TYPE, SENILE ONSET
Eu00200	DEMENTIA IN ALZHEIMER'S DIS, ATYPICAL OR MIXED TYPE

Eu00z00	DEMENTIA IN ALZHEIMER’S DISEASE, UNSPECIFIED
Eu00z11	ALZHEIMER’S DEMENTIA UNSPECIFIC
Eu02.00	DEMENTIA IN OTHER DISEASES CLASSIFIED ELSEWHERE
Eu02000	DEMENTIA IN PICK'S DISEASE
Eu02300	DEMENTIA IN PARKINSON’S DISEASE
Eu02y00	DEMENTIA IN OTHER SPECIFIED DISEASES
Eu02z00	UNSPECIFIED DEMENTIA
Eu02z11	PRESENILE DEMENTIA
Eu02z13	PRIMARY DEGENERATIVE DEMENTIA
Eu02z14	SENILE DEMENTIA
Eu02z16	SENILE DEMENTIA, DEPRESSED OR PARANOID TYPE
F110.00	ALZHEIMER'S DISEASE
F110000	ALZHEIMER'S DISEASE WITH EARLY ONSET
F110100	ALZHEIMER'S DISEASE WITH LATE ONSET
Fyu3000	OTHER ALZHEIMER'S DISEASE
ZS7C500	LANGUAGE DISORDER OF DEMENTIA
Vascular dementia	
E004.00	ARTERIOSCLEROTIC DEMENTIA
E004.11	MULTI INFARCT DEMENTIA
E004000	UNCOMPLICATED ARTERIOSCLEROTIC DEMENTIA
E004100	ARTERIOSCLEROTIC DEMENTIA WITH DELIRIUM
E004200	ARTERIOSCLEROTIC DEMENTIA WITH PARANOIA
E004300	ARTERIOSCLEROTIC DEMENTIA WITH DEPRESSION
E004z00	ARTERIOSCLEROTIC DEMENTIA
Eu01.00	VASCULAR DEMENTIA
Eu01.11	ARTERIOSCLEROTIC DEMENTIA
Eu01000	VASCULAR DEMENTIA OF ACUTE ONSET
Eu01100	MULTI-INFARCT DEMENTIA
Eu01200	SUBCORTICAL VASCULAR DEMENTIA
Eu01300	MIXED CORTICAL AND SUBCORTICAL VASCULAR DEMENTIA

Eu01y00	OTHER VASCULAR DEMENTIA
Eu01z00	VASCULAR DEMENTIA, UNSPECIFIED

Appendix 9-5. MRC score codes

173H.00	MRC BREATHLESSNESS SCALE: GRADE 1
173I.00	MRC BREATHLESSNESS SCALE: GRADE 2
173J.00	MRC BREATHLESSNESS SCALE: GRADE 3
173K.00	MRC BREATHLESSNESS SCALE: GRADE 4
173L.00	MRC BREATHLESSNESS SCALE: GRADE 5

Appendix 9-6. Smoking codes

1371.11	NON-SMOKER	AMBIGUOUS
137L.00	CURRENT NON-SMOKER	AMBIGUOUS
137X.00	CIGARETTE CONSUMPTION	AMBIGUOUS
137Y.00	CIGAR CONSUMPTION	AMBIGUOUS
137Z.00	TOBACCO CONSUMPTION NOS	AMBIGUOUS
137a.00	PIPE TOBACCO CONSUMPTION	AMBIGUOUS
6893.00	TOBACCO USAGE SCREEN	AMBIGUOUS
68T..00	TOBACCO USAGE SCREEN	AMBIGUOUS
ZV4K000	TOBACCO USE	AMBIGUOUS
137..11	SMOKER - AMOUNT SMOKED	CURRENT
1372.00	TRIVIAL SMOKER - < 1 CIG/DAY	CURRENT
1372.11	OCCASIONAL SMOKER	CURRENT
1373.00	LIGHT SMOKER - 1-9 CIGS/DAY	CURRENT
1374.00	MODERATE SMOKER - 10-19 CIGS/D	CURRENT
1375.00	HEAVY SMOKER - 20-39 CIGS/DAY	CURRENT
1376.00	VERY HEAVY SMOKER - 40+CIGS/D	CURRENT
137C.00	KEEPS TRYING TO STOP SMOKING	CURRENT
137G.00	TRYING TO GIVE UP SMOKING	CURRENT
137H.00	PIPE SMOKER	CURRENT
137J.00	CIGAR SMOKER	CURRENT
137M.00	ROLLS OWN CIGARETTES	CURRENT
137P.00	CIGARETTE SMOKER	CURRENT
137P.11	SMOKER	CURRENT
137Q.00	SMOKING STARTED	CURRENT
137Q.11	SMOKING RESTARTED	CURRENT
137R.00	CURRENT SMOKER	CURRENT
137V.00	SMOKING REDUCED	CURRENT
137b.00	READY TO STOP SMOKING	CURRENT
137c.00	THINKING ABOUT STOPPING SMOKING	CURRENT

137d.00	NOT INTERESTED IN STOPPING SMOKING	CURRENT
137e.00	SMOKING RESTARTED	CURRENT
137f.00	REASON FOR RESTARTING SMOKING	CURRENT
137h.00	MINUTES FROM WAKING TO FIRST TOBACCO CONSUMPTION	CURRENT
137m.00	FAILED ATTEMPT TO STOP SMOKING	CURRENT
13p0.00	NEGOTIATED DATE FOR CESSATION OF SMOKING	CURRENT
13p5.00	SMOKING CESSATION PROGRAMME START DATE	CURRENT
13p5000	PRACTICE BASED SMOKING CESSATION PROGRAMME START DATE	CURRENT
6791.00	HEALTH ED. - SMOKING	CURRENT
67A3.00	PREGNANCY SMOKING ADVICE	CURRENT
67H1.00	LIFESTYLE ADVICE REGARDING SMOKING	CURRENT
745H000	NICOTINE REPLACEMENT THERAPY USING NICOTINE PATCHES	CURRENT
745H100	NICOTINE REPLACEMENT THERAPY USING NICOTINE GUM	CURRENT
745H200	NICOTINE REPLACEMENT THERAPY USING NICOTINE INHALATOR	CURRENT
745H300	NICOTINE REPLACEMENT THERAPY USING NICOTINE LOZENGES	CURRENT
745H400	SMOKING CESSATION DRUG THERAPY	CURRENT
745Hy00	OTHER SPECIFIED SMOKING CESSATION THERAPY	CURRENT
8B3Y.00	OVER THE COUNTER NICOTINE REPLACEMENT THERAPY	CURRENT

8B3f.00	NICOTINE REPLACEMENT THERAPY PROVIDED FREE	CURRENT
8BP3.00	NICOTINE REPLACEMENT THERAPY PROVIDED BY COMMUNITY PHARMACIES	CURRENT
8CAL.00	SMOKING CESSATION ADVICE	CURRENT
8CAg.00	SMOKING CESSATION ADVICE PROVIDED BY COMMUNITY PHARMACIST	CURRENT
8H7i.00	REFERRAL TO SMOKING CESSATION ADVISOR	CURRENT
8HTK.00	REFERRAL TO STOP-SMOKING CLINIC	CURRENT
8HkQ.00	REFERRAL TO NHS STOP SMOKING SERVICE	CURRENT
8I2I.00	NICOTINE REPLACEMENT THERAPY CONTRAINDICATED	CURRENT
8I39.00	NICOTINE REPLACEMENT THERAPY REFUSED	CURRENT
9OO7.00	STOP SMOKING MONITOR VERBING.	CURRENT
9OO8.00	STOP SMOKING MONITOR PHONE INV	CURRENT
9ko..00	CURRENT SMOKER ANNUAL REVIEW - ENHANCED SERVICES ADMIN	CURRENT
9ko..11	CURRENT SMOKER ANNUAL REVIEW	CURRENT
E251.00	TOBACCO DEPENDENCE	CURRENT
E251000	TOBACCO DEPENDENCE, UNSPECIFIED	CURRENT
E251100	TOBACCO DEPENDENCE, CONTINUOUS	CURRENT
E251200	TOBACCO DEPENDENCE, EPISODIC	CURRENT
E251z00	TOBACCO DEPENDENCE NOS	CURRENT
ZG23300	ADVICE ON SMOKING	CURRENT

ZRBm200	FAGERSTROM TEST FOR NICOTINE DEPENDENCE	CURRENT
ZRBm211	FTND - FAGERSTROM TEST FOR NICOTINE DEPENDENCE	CURRENT
ZRaM.00	MOTIVES FOR SMOKING SCALE	CURRENT
ZRaM.11	MFS - MOTIVES FOR SMOKING SCALE	CURRENT
ZRao.00	OCCASIONS FOR SMOKING SCALE	CURRENT
ZRao.11	OFS - OCCASIONS FOR SMOKING SCALE	CURRENT
ZRh4.00	REASONS FOR SMOKING SCALE	CURRENT
ZRh4.11	RFS - REASONS FOR SMOKING SCALE	CURRENT
ZV6D800	[V]TOBACCO ABUSE COUNSELLING	CURRENT
1377.00	EX-TRIVIAL SMOKER (<1/DAY)	EX-SMOKER
1378.00	EX-LIGHT SMOKER (1-9/DAY)	EX-SMOKER
1379.00	EX-MODERATE SMOKER (10-19/DAY)	EX-SMOKER
137A.00	EX-HEAVY SMOKER (20-39/DAY)	EX-SMOKER
137B.00	EX-VERY HEAVY SMOKER (40+/DAY)	EX-SMOKER
137F.00	EX-SMOKER - AMOUNT UNKNOWN	EX-SMOKER
137K.00	STOPPED SMOKING	EX-SMOKER
137N.00	EX PIPE SMOKER	EX-SMOKER
137O.00	EX CIGAR SMOKER	EX-SMOKER
137S.00	EX-SMOKER	EX-SMOKER
137T.00	DATE CEASED SMOKING	EX-SMOKER
137l.00	EX ROLL-UP CIGARETTE SMOKER	EX-SMOKER
8HBM.00	STOP SMOKING FACE TO FACE FOLLOW-UP	EX-SMOKER
E251300	TOBACCO DEPENDENCE IN REMISSION	EX-SMOKER
137k.00	REFUSAL TO GIVE SMOKING STATUS	EXCEPTION
9hG..00	EXCEPTION REPORTING: SMOKING QUALITY INDICATORS	EXCEPTION

9hG0.00	EXCEPTED FROM SMOKING QUALITY INDICATORS: PATIENT UNSUITABLE	EXCEPTION
9hG1.00	EXCEPTED FROM SMOKING QUALITY INDICATORS: INFORMED DISSENT	EXCEPTION
1371.00	NEVER SMOKED TOBACCO	NEVER
9kn..00	NON-SMOKER ANNUAL REVIEW - ENHANCED SERVICES ADMINISTRATION	NEVER
9kn..11	NON-SMOKER ANNUAL REVIEW	NEVER
137..00	TOBACCO CONSUMPTION	UNKNOWN
137D.00	ADMITTED TOBACCO CONS UNTRUE	UNKNOWN
137E.00	TOBACCO CONSUMPTION UNKNOWN	UNKNOWN
137g.00	CIGARETTE PACK-YEARS	UNKNOWN
13p..00	SMOKING CESSATION MILESTONES	UNKNOWN
13p1.00	SMOKING STATUS AT 4 WEEKS	UNKNOWN
13p2.00	SMOKING STATUS BETWEEN 4 AND 52 WEEKS	UNKNOWN
13p3.00	SMOKING STATUS AT 52 WEEKS	UNKNOWN
13p4.00	SMOKING FREE WEEKS	UNKNOWN
38DH.00	FAGERSTR TEST FOR NICOTINE DEP	UNKNOWN
67H6.00	BRIEF INTERVENTION FOR SMOKING CESSATION	UNKNOWN
745H.00	SMOKING CESSATION THERAPY	UNKNOWN
745Hz00	SMOKING CESSATION THERAPY NOS	UNKNOWN
8I6H.00	SMOKING REVIEW NOT INDICATED	UNKNOWN
8IAj.00	SMOKING CESSATION ADVICE DECLINED	UNKNOWN
9N2k.00	SEEN BY SMOKING CESSATION ADVISOR	UNKNOWN
9N4M.00	DNA - DID NOT ATTEND SMOKING CESSATION CLINIC	UNKNOWN

9NdV.00	CONSENT GIVEN FOLLOW-UP AFTER SMOKING CESSATION INTERVENTION	UNKNOWN
9NdW.00	CONSENT GIVEN FOR SMOKING CESSATION DATA SHARING	UNKNOWN
9NdY.00	DECLINE CONS FOLLOW-UP EVALUATION AFTER SMOKING CESS INTERVEN	UNKNOWN
9NdZ.00	DECLINED CONSENT FOR SMOKING CESSATION DATA SHARING	UNKNOWN
9Ndf.00	CONSENT GIVEN FOR FOLLOW-UP BY SMOKING CESSATION TEAM	UNKNOWN
9Ndg.00	DECLINED CONSENT FOR FOLLOW-UP BY SMOKING CESSATION TEAM	UNKNOWN
9OO..00	ANTI-SMOKING MONITORING ADMIN.	UNKNOWN
9OO..11	STOP SMOKING CLINIC ADMIN.	UNKNOWN
9OO..12	STOP SMOKING MONITORING ADMIN.	UNKNOWN
9OO1.00	ATTENDS STOP SMOKING MONITOR.	UNKNOWN
9OO2.00	REFUSES STOP SMOKING MONITOR	UNKNOWN
9OO3.00	STOP SMOKING MONITOR DEFAULT	UNKNOWN
9OO4.00	STOP SMOKING MONITOR 1ST LETTER	UNKNOWN
9OO5.00	STOP SMOKING MONITOR 2ND LETTER	UNKNOWN
9OO6.00	STOP SMOKING MONITOR 3RD LETTER	UNKNOWN
9OO9.00	STOP SMOKING MONITORING DELETE	UNKNOWN
9OOA.00	STOP SMOKING MONITOR CHECK DONE	UNKNOWN
9OOZ.00	STOP SMOKING MONITOR ADMIN NOS	UNKNOWN

9kf1.11	REFERRED FOR COPD STRUCTURED SMOKING ASSESSMENT	UNKNOWN
9kf2.00	COPD STRUCTURED SMOKING ASSESSMENT DECLINED - ENHANCED SERVICES ADMIN	UNKNOWN
9kf2.11	COPD STRUCTURED SMOKING ASSESSMENT DECLINED	UNKNOWN
E023.00	NICOTINE WITHDRAWAL	UNKNOWN
ZV11600	[V]PERSONAL HISTORY OF TOBACCO ABUSE	UNKNOWN

Appendix 9-7. Charlson index score codes

Code	Description	Score
Myocardial infarction		
G301.00	OTHER SPECIFIED ANTERIOR MYOCARDIAL INFARCTION	1
G30z.00	ACUTE MYOCARDIAL INFARCTION NOS	1
G30..14	HEART ATTACK	1
G30..15	MI - ACUTE MYOCARDIAL INFARCTION	1
G305.00	LATERAL MYOCARDIAL INFARCTION NOS	1
G307.00	ACUTE SUBENDOCARDIAL INFARCTION	1
14AH.00	H/O: MYOCARDIAL INFARCTION IN LAST YEAR	1
G30y.00	OTHER ACUTE MYOCARDIAL INFARCTION	1
G303.00	ACUTE INFERO-POSTERIOR INFARCTION	1
G30..00	ACUTE MYOCARDIAL INFARCTION	1
G300.00	ACUTE ANTEROLATERAL INFARCTION	1
G32..12	PERSONAL HISTORY OF MYOCARDIAL INFARCTION	1
G30X000	ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION	1
G30..13	CARDIAC RUPTURE FOLLOWING MYOCARDIAL INFARCTION (MI)	1
G307100	ACUTE NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION	1
G307000	ACUTE NON-Q WAVE INFARCTION	1
G301100	ACUTE ANTEROSEPTAL INFARCTION	1
G32..00	OLD MYOCARDIAL INFARCTION	1
G30..17	SILENT MYOCARDIAL INFARCTION	1
G32..11	HEALED MYOCARDIAL INFARCTION	1
G30..12	CORONARY THROMBOSIS	1
G30yz00	OTHER ACUTE MYOCARDIAL INFARCTION NOS	1
G302.00	ACUTE INFEROLATERAL INFARCTION	1
Congestive heart disease		

G582.00	ACUTE HEART FAILURE	1
G580.00	CONGESTIVE HEART FAILURE	1
14A6.00	H/O: HEART FAILURE	1
G58z.11	WEAK HEART	1
G58..11	CARDIAC FAILURE	1
1O1..00	HEART FAILURE CONFIRMED	1
G580000	ACUTE CONGESTIVE HEART FAILURE	1
8H2S.00	ADMIT HEART FAILURE EMERGENCY	1
G58z.00	HEART FAILURE NOS	1
G58..00	HEART FAILURE	1
Peripheral vascular disease		
G714000	JUXTARENAL AORTIC ANEURYSM	1
G711.00	THORACIC AORTIC ANEURYSM WHICH HAS RUPTURED	1
G73z.00	PERIPHERAL VASCULAR DISEASE	1
G73zz00	PERIPHERAL VASCULAR DISEASE	1
G71z.00	AORTIC ANEURYSM	1
G713.00	ABDOMINAL AORTIC ANEURYSM WHICH HAS RUPTURED	1
7A14.11	AORTIC ANEURYSM REPAIR	1
14NB.00	H/O: PERIPHERAL VASCULAR DISEASE PROCEDURE	1
G71..00	AORTIC ANEURYSM	1
G713.11	RUPTURED ABDOMINAL AORTIC ANEURYSM	1
Gyu7200	AORTIC ANEURYSM OF UNSPECIFIED SITE, NON-RUPTURED	1
G732300	GANGRENE OF THUMB	1
R054000	GANGRENE, SPREADING CUTANEOUS	1
G714.11	AAA - ABDOMINAL AORTIC ANEURYSM WITHOUT MENTION OF RUPTURE	1
G714.00	ABDOMINAL AORTIC ANEURYSM WITHOUT MENTION OF RUPTURE	1

Gyu7400	OTHER SPECIFIED PERIPHERAL VASCULAR DISEASES	1
G718.00	LEAKING ABDOMINAL AORTIC ANEURYSM	1
7A14411	TUBE GRAFT OF ABDOMINAL AORTIC ANEURYSM	1
G711.11	RUPTURED THORACIC AORTIC ANEURYSM	1
Cerebrovascular disease		
G61..12	STROKE DUE TO INTRACEREBRAL HAEMORRHAGE	1
G600.00	RUPTURED BERRY ANEURYSM	1
G601.00	SUBARACHNOID HAEMORRHAGE FROM CAROTID SIPHON AND BIFURCATION	1
G61..00	INTRACEREBRAL HAEMORRHAGE	1
G605.00	SUBARACHNOID HAEMORRHAGE FROM BASILAR ARTERY	1
G68..00	LATE EFFECTS OF CEREBROVASCULAR DISEASE	1
Gyu6100	OTHER SUBARACHNOID HAEMORRHAGE	1
S620.00	CLOSED TRAUMATIC SUBARACHNOID HAEMORRHAGE	1
Gyu6000	[X]SUBARACHNOID HAEMORRHAGE FROM OTHER INTRACRANIAL ARTERIES	1
G66..11	CVA UNSPECIFIED	1
G660.00	MIDDLE CEREBRAL ARTERY SYNDROME	1
662M.00	STROKE MONITORING	1
G669.00	CEREBRAL PALSY, NOT CONGENITAL OR INFANTILE, ACUTE	1
G661.00	ANTERIOR CEREBRAL ARTERY SYNDROME	1
G66..00	STROKE AND CEREBROVASCULAR ACCIDENT UNSPECIFIED	1
G667.00	LEFT SIDED CVA	1

G66..13	CVA - CEREBROVASCULAR ACCIDENT UNSPECIFIED	1
G666.00	PURE SENSORY LACUNAR SYNDROME	1
G663.00	BRAIN STEM STROKE SYNDROME	1
G664.00	CEREBELLAR STROKE SYNDROME	1
G665.00	PURE MOTOR LACUNAR SYNDROME	1
G668.00	RIGHT SIDED CVA	1
G66..12	STROKE UNSPECIFIED	1
14A7.00	H/O: CVA/STROKE	1
G662.00	POSTERIOR CEREBRAL ARTERY SYNDROME	1
14A7.12	H/O: STROKE	1
G64..13	STROKE DUE TO CEREBRAL ARTERIAL OCCLUSION	1
Dementia		
E001z00	PRESENILE DEMENTIA NOS	1
E004200	ARTERIOSCLEROTIC DEMENTIA WITH PARANOIA	1
Eu00z11	[X]ALZHEIMER'S DEMENTIA UNSPECIFIC	1
E001000	UNCOMPLICATED PRESENILE DEMENTIA	1
Eu01z00	[X]VASCULAR DEMENTIA, UNSPECIFIED	1
Eu02500	[X]LEWY BODY DEMENTIA	1
Eu00112	[X]SENILE DEMENTIA, ALZHEIMER'S TYPE	1
E004.11	MULTI INFARCT DEMENTIA	1
Eu02z14	[X] SENILE DEMENTIA NOS	1
E041.00	DEMENTIA IN CONDITIONS EC	1
Eu01111	[X]PREDOMINANTLY CORTICAL DEMENTIA	1
Eu02z16	[X] SENILE DEMENTIA, DEPRESSED OR PARANOID TYPE	1
Eu00.00	[X]DEMENTIA IN ALZHEIMER'S DISEASE	1
Eu02z00	[X] UNSPECIFIED DEMENTIA	1
Eu00011	[X]PRESENILE DEMENTIA, ALZHEIMER'S TYPE	1
E004.00	ARTERIOSCLEROTIC DEMENTIA	1

Eu02.00	[X]DEMENTIA IN OTHER DISEASES CLASSIFIED ELSEWHERE	1
Eu01000	[X]VASCULAR DEMENTIA OF ACUTE ONSET	1
Eu01100	[X]MULTI-INFARCT DEMENTIA	1
E000.00	UNCOMPLICATED SENILE DEMENTIA	1
E004z00	ARTERIOSCLEROTIC DEMENTIA NOS	1
Eu02y00	[X]DEMENTIA IN OTHER SPECIFIED DISEASES CLASSIFIED ELSEWHERE	1
E001.00	PRESENILE DEMENTIA	1
Eu00z00	[X]DEMENTIA IN ALZHEIMER'S DISEASE, UNSPECIFIED	1
Eu01y00	[X]OTHER VASCULAR DEMENTIA	1
Eu01.11	[X]ARTERIOSCLEROTIC DEMENTIA	1
Eu00113	[X]PRIMARY DEGEN DEMENTIA OF ALZHEIMER'S TYPE, SENILE ONSET	1
E004000	UNCOMPLICATED ARTERIOSCLEROTIC DEMENTIA	1
E00..12	SENILE/PRESENILE DEMENTIA	1
Eu00200	[X]DEMENTIA IN ALZHEIMER'S DIS, ATYPICAL OR MIXED TYPE	1
E00..11	SENILE DEMENTIA	1
E004300	ARTERIOSCLEROTIC DEMENTIA WITH DEPRESSION	1
E004100	ARTERIOSCLEROTIC DEMENTIA WITH DELIRIUM	1
Eu00100	[X]DEMENTIA IN ALZHEIMER'S DISEASE WITH LATE ONSET	1
Eu01.00	[X]VASCULAR DEMENTIA	1
Eu02z13	[X] PRIMARY DEGENERATIVE DEMENTIA NOS	1
1461.00	H/O: DEMENTIA	1
Eu01200	[X]SUBCORTICAL VASCULAR DEMENTIA	1
E000.00	UNCOMPLICATED SENILE DEMENTIA	1

Eu00012	[X]PRIMARY DEGEN DEMENTIA, ALZHEIMER'S TYPE, PRESENILE ONSET	1
Eu00000	[X]DEMENTIA IN ALZHEIMER'S DISEASE WITH EARLY ONSET	1
Eu01300	[X]MIXED CORTICAL AND SUBCORTICAL VASCULAR DEMENTIA	1
Chronic pulmonary disease		
H41..00	ASBESTOSIS	1
9OJ1.00	ATTENDS ASTHMA MONITORING	1
H352100	PIGEON-FANCIERS' LUNG	1
H331.00	INTRINSIC ASTHMA	1
H331.11	LATE ONSET ASTHMA	1
H31..00	CHRONIC BRONCHITIS	1
H350.00	FARMERS' LUNG	1
H334.00	BRITTLE ASTHMA	1
H582.00	COMPENSATORY EMPHYSEMA	1
H57yz00	LUNG DISEASE WITH DISEASES EC NOS	1
H311.00	MUCOPURULENT CHRONIC BRONCHITIS	1
H31y100	CHRONIC TRACHEOBRONCHITIS	1
H320200	GIANT BULLOUS EMPHYSEMA	1
663N.00	ASTHMA DISTURBING SLEEP	1
H310100	SMOKERS' COUGH	1
H4y1000	CHRONIC PULMONARY FIBROSIS FOLLOWING RADIATION	1
1O2..00	ASTHMA CONFIRMED	1
H464000	CHRONIC EMPHYSEMA DUE TO CHEMICAL FUMES	1
H331000	INTRINSIC ASTHMA WITHOUT STATUS ASTHMATICUS	1
H33z200	LATE-ONSET ASTHMA	1
H340.00	RECURRENT BRONCHIECTASIS	1

H410.00	PLEURAL PLAQUE DISEASE DUE TO ASBESTOSIS	1
H333.00	ACUTE EXACERBATION OF ASTHMA	1
8H2P.00	EMERGENCY ADMISSION, ASTHMA	1
H40..00	COAL WORKERS' PNEUMOCONIOSIS	1
14B4.00	H/O: ASTHMA	1
H320z00	CHRONIC BULLOUS EMPHYSEMA	1
H310000	CHRONIC CATARRHAL BRONCHITIS	1
H313.00	MIXED SIMPLE AND MUCOPURULENT CHRONIC BRONCHITIS	1
H31z.00	CHRONIC BRONCHITIS	1
H331z00	INTRINSIC ASTHMA	1
H434.00	SIDEROSIS	1
H34..00	BRONCHIECTASIS	1
H312100	EMPHYSEMATOUS BRONCHITIS	1
H352z00	BIRD-FANCIER'S LUNG	1
H331100	INTRINSIC ASTHMA WITH STATUS ASTHMATICUS	1
H35yz00	OTHER ALLERGIC ALVEOLITIS NOS	1
H435.00	STANNOSIS	1
H33z111	ASTHMA ATTACK NOS	1
H35y300	FURRIERS' LUNG	1
466 BC	BRONCHITIS SUBACUTE	1
h33z100	ASTHMA ATTACK	1
663r.00	ASTHMA CAUSES NIGHT SYMPTOMS 1 TO 2 TIMES PER MONTH	1
H32z.00	EMPHYSEMA NOS	1
H330z00	EXTRINSIC ASTHMA NOS	1
H33..11	BRONCHIAL ASTHMA	1
H32y000	ACUTE VESICULAR EMPHYSEMA	1
663q.00	ASTHMA DAYTIME SYMPTOMS	1

H464100	OBLITERATIVE BRONCHIOLITIS DUE TO CHEMICAL FUMES	1
Hyu4000	[X]PNEUMOCONIOSIS DUE TO OTHER DUST CONTAINING SILICA	1
H330011	HAY FEVER WITH ASTHMA	1
H43..00	PNEUMOCONIOSIS DUE TO OTHER INORGANIC DUST	1
H423.00	MASSIVE SILICOTIC FIBROSIS	1
H460z00	BRONCHITIS AND PNEUMONITIS DUE TO CHEMICAL FUMES NOS	1
H330000	EXTRINSIC ASTHMA WITHOUT STATUS ASTHMATICUS	1
H35z100	HYPERSENSITIVITY PNEUMONITIS NOS	1
663u.00	ASTHMA CAUSES DAYTIME SYMPTOMS 1 TO 2 TIMES PER WEEK	1
493 AD	ASTHMA OCCASIONAL	1
663P.00	ASTHMA LIMITING ACTIVITIES	1
H57y.00	LUNG DISEASE WITH DISEASES EC	1
5192CM	OBSTRUCTIVE LUNG DISEASE COMPENSATORY	1
H311000	PURULENT CHRONIC BRONCHITIS	1
H581.00	INTERSTITIAL EMPHYSEMA	1
5199CL	OBSTRUCTIVE LUNG DISEASE	1
H45..00	PNEUMOCONIOSIS NOS	1
H311z00	MUCOPURULENT CHRONIC BRONCHITIS NOS	1
SK07.00	SUBCUTANEOUS EMPHYSEMA	1
7832AB	WHEEZING BRONCHIAL	1
Hyu4100	[X]PNEUMOCONIOSIS DUE TO OTHER SPECIFIED INORGANIC DUSTS	1
H300.00	TRACHEOBRONCHITIS NOS	1
663w.00	ASTHMA LIMITS WALKING UP HILLS OR STAIRS	1
H440.00	BYSSINOSIS	1
H356.00	MAPLE BARK STRIPPERS' LUNG	1

H30z.00	BRONCHITIS NOS	1
663p.00	ASTHMA TREATMENT COMPLIANCE UNSATISFACTORY	1
66YC.00	ABSENT FROM WORK OR SCHOOL DUE TO ASTHMA	1
H432.00	BERYLLIOSIS	1
H32..00	EMPHYSEMA	1
H312000	CHRONIC ASTHMATIC BRONCHITIS	1
663W.00	ASTHMA PROPHYLACTIC MEDICATION USED	1
H320000	SEGMENTAL BULLOUS EMPHYSEMA	1
H312011	CHRONIC WHEEZY BRONCHITIS	1
H441.00	CANNABINOSIS	1
H311100	FETID CHRONIC BRONCHITIS	1
H33zz12	ALLERGIC ASTHMA NEC	1
L4930LO	LATE ONSET ASTHMA	1
H430.00	ALUMINOSIS OF LUNG	1
H331111	INTRINSIC ASTHMA WITH ASTHMA ATTACK	1
H431.00	BAUXITE FIBROSIS OF LUNG	1
Hyu3000	[X]OTHER EMPHYSEMA	1
H47y000	DETERGENT ASTHMA	1
H35y.00	OTHER ALLERGIC ALVEOLITIS	1
H330.00	EXTRINSIC (ATOPIC) ASTHMA	1
173A.00	EXERCISE INDUCED ASTHMA	1
Rheumatological disease		
7341AA	LUPUS ERYTHEMATOSUS SYSTEMIC	1
N041.00	FELTY'S SYNDROME	1
Nyu1000	[X]RHEUMATOID ARTHRITIS ORGANS OR SYSTEMS	1
N001200	SYSTEMIC SCLEROSIS INDUCED BY DRUGS AND CHEMICALS	1
N04y011	CAPLAN'S SYNDROME	1
N001000	PROGRESSIVE SYSTEMIC SCLEROSIS	1

N001.12	SYSTEMIC SCLEROSIS	1
N040B00	RHEUMATOID ARTHRITIS OF HIP	1
N000300	SYSTEMIC LUPUS ERYTHEMATOSUS WITH ORGAN OR SYS INVOLVE	1
N04y012	FIBROSING ALVEOLITIS ASSOCIATED WITH RHEUMATOID ARTHRITIS	1
N047.00	SEROPOSITIVE EROSIVE RHEUMATOID ARTHRITIS	1
N000.00	SYSTEMIC LUPUS ERYTHEMATOSUS	1
N040J00	RHEUMATOID ARTHRITIS OF OTHER TARSAL JOINT	1
N04X.00	SEROPOSITIVE RHEUMATOID ARTHRITIS, UNSPECIFIED	1
Nyu1G00	SEROPOSITIVE RHEUMATOID ARTHRITIS, UNSPECIFIED	1
N040A00	RHEUMATOID ARTHRITIS OF DIP JOINT OF FINGER	1
N040300	RHEUMATOID ARTHRITIS OF STERNOCLAVICULAR JOINT	1
N240000	RHEUMATISM UNSPECIFIED	1
N240200	MUSCULAR RHEUMATISM	1
N200.00	GIANT CELL ARTERITIS WITH POLYMYALGIA RHEUMATICA	1
N20..00	POLYMYALGIA RHEUMATICA	1
N040900	RHEUMATOID ARTHRITIS OF PIP JOINT OF FINGER	1
N000100	LIBMAN-SACKS DISEASE	1
2A42.00	SYSTEMIC LUPUS ERYTHEMATOSUS WITH RENAL	1
N000400	SYSTEMIC LUPUS ERYTHEMATOSUS WITH PERICARDITIS	1
N040M00	RHEUMATOID ARTHRITIS OF IP JOINT OF TOE	1

N040800	RHEUMATOID ARTHRITIS OF MCP JOINT	1
N2y..00	OTHER SPECIFIED NONARTICULAR RHEUMATISM	1
H572.00	LUNG DISEASE WITH SYSTEMIC SCLEROSIS	1
N04..00	RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHY	1
N040P00	SERONEGATIVE RHEUMATOID ARTHRITIS	1
G5yA.00	RHEUMATOID CARDITIS	1
H57y400	LUNG DISEASE WITH SYSTEMIC LUPUS ERYTHEMATOSUS	1
K01x411	LUPUS NEPHRITIS	1
N001.11	ACROSCLEROSIS	1
N000000	DISSEMINATED LUPUS ERYTHEMATOSUS	1
N040T00	FLARE OF RHEUMATOID ARTHRITIS	1
N040.00	RHEUMATOID ARTHRITIS	1
N04y111	SERO-NEGATIVE POLYARTHRITIS	1
Nyu4500	[X]OTHER FORMS OF SYSTEMIC SCLEROSIS	1
N240z00	RHEUMATISM OR FIBROSITIS NOS	1
N040L00	RHEUMATOID ARTHRITIS OF LESSER MTP JOINT	1
N231400	POLYMYOSITIS OSSIFICANS	1
Nyu1200	OTHER SPECIFIED RHEUMATOID ARTHRITIS	1
F396600	MYOPATHY DUE TO SCLERODERMA	1
F396400	MYOPATHY DUE TO RHEUMATOID ARTHRITIS	1
N042100	RHEUMATOID LUNG DISEASE	1
N040G00	RHEUMATOID ARTHRITIS OF SUBTALAR JOINT	1
N040200	RHEUMATOID ARTHRITIS OF SHOULDER	1
N040H00	RHEUMATOID ARTHRITIS OF TALONAVICULAR JOINT	1
N040D00	RHEUMATOID ARTHRITIS OF KNEE	1
N040F00	RHEUMATOID ARTHRITIS OF ANKLE	1
N060.11	ENDEMIC POLYARTHRITIS	1

Nyu4300	OTHER FORMS OF SYSTEMIC LUPUS ERYTHEMATOSUS	1
Nyu1100	OTHER SEROPOSITIVE RHEUMATOID ARTHRITIS	1
7179GB	RHEUMATISM NONARTICULAR SHOULDER	1
N004.00	POLYMYOSITIS	1
H57y100	LUNG DISEASE WITH POLYMYOSITIS	1
N040E00	RHEUMATOID ARTHRITIS OF TIBIO-FIBULAR JOINT	1
N040600	RHEUMATOID ARTHRITIS OF DISTAL RADIO-ULNAR JOINT	1
N240.00	RHEUMATISM AND FIBROSITIS UNSPECIFIED	1
N040C00	RHEUMATOID ARTHRITIS OF SACRO-ILIAC JOINT	1
N040K00	RHEUMATOID ARTHRITIS OF 1ST MTP JOINT	1
N001.00	SCLERODERMA	1
N2z..00	NON-ARTICULAR RHEUMATISM NOS	1
N040500	RHEUMATOID ARTHRITIS OF ELBOW	1
N000200	DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS	1
K01x400	NEPHROTIC SYNDROME IN SYSTEMIC LUPUS ERYTHEMATOSUS	1
H570.00	RHEUMATOID LUNG	1
N000z00	SYSTEMIC LUPUS ERYTHEMATOSUS NOS	1
N040700	RHEUMATOID ARTHRITIS OF WRIST	1
N240700	HAND RHEUMATISM	1
N040400	RHEUMATOID ARTHRITIS OF ACROMIOCLAVICULAR JOINT	1
N04y000	RHEUMATOID LUNG	1
F371200	POLYNEUROPATHY IN RHEUMATOID ARTHRITIS	1
Peptic ulcer disease		
J120y00	ACUTE DUODENAL ULCER UNSPECIFIED	1

761D600	ENDOSCOPIC INJECTION HAEMOSTASIS OF GASTRIC ULCER	1
J14y400	UNSPECIFIED GASTROJEJUNAL ULCER WITH OBSTRUCTION	1
J13..00	PEPTIC ULCER - (PU) SITE UNSPECIFIED	1
J102000	PEPTIC ULCER OF OESOPHAGUS	1
J12yz00	UNSPECIFIED DUODENAL ULCER NOS	1
J11..12	PYLORIC ULCER	1
J141200	CHRONIC GASTROJEJUNAL ULCER WITH PERFORATION	1
J110.00	ACUTE GASTRIC ULCER	1
J12y.00	UNSPECIFIED DUODENAL ULCER	1
J121y00	CHRONIC DUODENAL ULCER UNSPECIFIED	1
J110111	BLEEDING ACUTE GASTRIC ULCER	1
J11yy00	UNSPECIFIC GASTRIC ULCER; UNSPECIFIED HAEMORRHAGE AND/OR PERFORATION	1
J111y00	CHRONIC GASTRIC ULCER UNSPECIFIED	1
J111100	CHRONIC GASTRIC ULCER WITH HAEMORRHAGE	1
J14..15	STOMAL ULCER	1
J131y00	CHRONIC PEPTIC ULCER UNSPECIFIED	1
J110y00	ACUTE GASTRIC ULCER UNSPECIFIED	1
J13z.00	PEPTIC ULCER NOS	1
J11..11	PREPYLORIC ULCER	1
J110300	ACUTE GASTRIC ULCER WITH HAEMORRHAGE AND PERFORATION	1
761Jz00	OPERATION ON GASTRIC ULCER NOS	1
J14y100	UNSPECIFIED GASTROJEJUNAL ULCER WITH HAEMORRHAGE	1
J121400	CHRONIC DUODENAL ULCER WITH OBSTRUCTION	1
J130z00	ACUTE PEPTIC ULCER NOS	1

J12y400	UNSPECIFIED DUODENAL ULCER WITH OBSTRUCTION	1
J11y100	UNSPECIFIED GASTRIC ULCER WITH HAEMORRHAGE	1
J140400	ACUTE GASTROJEJUNAL ULCER WITH OBSTRUCTION	1
J12y000	UNSPECIFIED DUODENAL ULCER WITHOUT MENTION OF COMPLICATION	1
J122.00	DUODENAL ULCER DISEASE	1
J121000	CHRONIC DUODENAL ULCER WITHOUT MENTION OF COMPLICATION	1
J14y200	UNSPECIFIED GASTROJEJUNAL ULCER WITH PERFORATION	1
J11..00	GASTRIC ULCER - (GU)	1
J141y00	CHRONIC GASTROJEJUNAL ULCER UNSPECIFIED	1
J141300	CHRONIC GASTROJEJUNAL ULCER WITH HAEMORRHAGE AND PERFORATION	1
J11y400	UNSPECIFIED GASTRIC ULCER WITH OBSTRUCTION	1
J13y.00	UNSPECIFIED PEPTIC ULCER	1
J131.00	CHRONIC PEPTIC ULCER	1
J120z00	ACUTE DUODENAL ULCER NOS	1
J140000	ACUTE GASTROJEJUNAL ULCER WITHOUT MENTION OF COMPLICATION	1
J110200	ACUTE GASTRIC ULCER WITH PERFORATION	1
J111400	CHRONIC GASTRIC ULCER WITH OBSTRUCTION	1
J121.00	CHRONIC DUODENAL ULCER	1
J14yy00	UNSPECIFIC GASTROJEJUNAL ULCER; UNSPECIFIED HAEMORRHAGE/PERFORATION	1
J14..12	GASTROCOLIC ULCER	1
J130.00	ACUTE PEPTIC ULCER	1

J11y200	UNSPECIFIED GASTRIC ULCER WITH PERFORATION	1
J120300	ACUTE DUODENAL ULCER WITH HAEMORRHAGE AND PERFORATION	1
J120100	ACUTE DUODENAL ULCER WITH HAEMORRHAGE	1
J13y300	UNSPECIFIED PEPTIC ULCER WITH HAEMORRHAGE AND PERFORATION	1
J14y300	UNSPECIFIED GASTROJEJUNAL ULCER WITH HAEMORRHAGE AND PERFORATION	1
J131300	CHRONIC PEPTIC ULCER WITH HAEMORRHAGE AND PERFORATION	1
J111111	BLEEDING CHRONIC GASTRIC ULCER	1
761J000	CLOSURE OF PERFORATED GASTRIC ULCER	1
J120200	ACUTE DUODENAL ULCER WITH PERFORATION	1
J130200	ACUTE PEPTIC ULCER WITH PERFORATION	1
761J111	SUTURE OF ULCER OF STOMACH NEC	1
J140100	ACUTE GASTROJEJUNAL ULCER WITH HAEMORRHAGE	1
J12y200	UNSPECIFIED DUODENAL ULCER WITH PERFORATION	1
J111z00	CHRONIC GASTRIC ULCER NOS	1
J11yz00	UNSPECIFIED GASTRIC ULCER NOS	1
J14z.00	GASTROJEJUNAL ULCER NOS	1
J14y000	UNSPECIFIED GASTROJEJUNAL ULCER WITHOUT MENTION COMPLICATION	1
J11z.00	GASTRIC ULCER NOS	1
J14y.00	UNSPECIFIED GASTROJEJUNAL ULCER	1
J141z00	CHRONIC GASTROJEJUNAL ULCER NOS	1
J13yy00	UNSPECIFIED PEPTIC ULCER; UNSPECIFIED HAEMORRHAGE AND/OR PERFORATION	1
7612111	BALFOUR EXCISION OF GASTRIC ULCER	1

J12yy00	UNSPECIFIED DUODENAL ULCER; UNSPECIFIED HAEMORRHAGE AND/OR PERFORATION	1
J111000	CHRONIC GASTRIC ULCER WITHOUT MENTION OF COMPLICATION	1
J110000	ACUTE GASTRIC ULCER WITHOUT MENTION OF COMPLICATION	1
J130000	ACUTE PEPTIC ULCER WITHOUT MENTION OF COMPLICATION	1
J111300	CHRONIC GASTRIC ULCER WITH HAEMORRHAGE AND PERFORATION	1
J140300	ACUTE GASTROJEJUNAL ULCER WITH HAEMORRHAGE AND PERFORATION	1
J13y000	UNSPECIFIED PEPTIC ULCER WITHOUT MENTION OF COMPLICATION	1
J14..00	GASTROJEJUNAL ULCER (GJU)	1
J11y.00	UNSPECIFIED GASTRIC ULCER	1
J120.00	ACUTE DUODENAL ULCER	1
J130400	ACUTE PEPTIC ULCER WITH OBSTRUCTION	1
J141400	CHRONIC GASTROJEJUNAL ULCER WITH OBSTRUCTION	1
J13y100	UNSPECIFIED PEPTIC ULCER WITH HAEMORRHAGE	1
J120000	ACUTE DUODENAL ULCER WITHOUT MENTION OF COMPLICATION	1
J121300	CHRONIC DUODENAL ULCER WITH HAEMORRHAGE AND PERFORATION	1
7627000	CLOSURE OF PERFORATED DUODENAL ULCER	1
J131z00	CHRONIC PEPTIC ULCER NOS	1
J13..11	STRESS ULCER NOS	1
J130y00	ACUTE PEPTIC ULCER UNSPECIFIED	1
J112.00	ANTI-PLATELET INDUCED GASTRIC ULCER	1
J110z00	ACUTE GASTRIC ULCER NOS	1

J111.00	CHRONIC GASTRIC ULCER	1
J110400	ACUTE GASTRIC ULCER WITH OBSTRUCTION	1
J121z00	CHRONIC DUODENAL ULCER NOS	1
J131000	CHRONIC PEPTIC ULCER WITHOUT MENTION OF COMPLICATION	1
J12..00	DUODENAL ULCER - (DU)	1
J141.00	CHRONIC GASTROJEJUNAL ULCER	1
J11y000	UNSPECIFIED GASTRIC ULCER WITHOUT MENTION OF COMPLICATION	1
J111200	CHRONIC GASTRIC ULCER WITH PERFORATION	1
J123.00	DUODENAL EROSION	1
J13y400	UNSPECIFIED PEPTIC ULCER WITH OBSTRUCTION	1
761J100	CLOSURE OF GASTRIC ULCER NEC	1
J131400	CHRONIC PEPTIC ULCER WITH OBSTRUCTION	1
J11z.12	MULTIPLE GASTRIC ULCERS	1
J14yz00	UNSPECIFIED GASTROJEJUNAL ULCER NOS	1
ZV12711	[V]PERSONAL HISTORY OF PEPTIC ULCER	1
J130100	ACUTE PEPTIC ULCER WITH HAEMORRHAGE	1
7612500	RESECTION OF GASTRIC ULCER BY CAUTERY	1
J120400	ACUTE DUODENAL ULCER WITH OBSTRUCTION	1
ZV12C00	[V] PERSONAL HISTORY OF GASTRIC ULCER	1
J12y300	UNSPECIFIED DUODENAL ULCER WITH HAEMORRHAGE AND PERFORATION	1
J13yz00	UNSPECIFIED PEPTIC ULCER NOS	1
761J.11	STOMACH ULCER OPERATIONS	1
J111211	PERFORATED CHRONIC GASTRIC ULCER	1
J12z.00	DUODENAL ULCER NOS	1
J140200	ACUTE GASTROJEJUNAL ULCER WITH PERFORATION	1
J131100	CHRONIC PEPTIC ULCER WITH HAEMORRHAGE	1

J141000	CHRONIC GASTROJEJUNAL ULCER WITHOUT MENTION OF COMPLICATION	1
J131200	CHRONIC PEPTIC ULCER WITH PERFORATION	1
J124.00	RECURRENT DUODENAL ULCER	1
J130300	ACUTE PEPTIC ULCER WITH HAEMORRHAGE AND PERFORATION	1
J11y300	UNSPECIFIED GASTRIC ULCER WITH HAEMORRHAGE AND PERFORATION	1
J141100	CHRONIC GASTROJEJUNAL ULCER WITH HAEMORRHAGE	1
J121111	BLEEDING CHRONIC DUODENAL ULCER	1
761Jy00	OTHER SPECIFIED OPERATION ON GASTRIC ULCER	1
J140z00	ACUTE GASTROJEJUNAL ULCER NOS	1
J140y00	ACUTE GASTROJEJUNAL ULCER UNSPECIFIED	1
J13y200	UNSPECIFIED PEPTIC ULCER WITH PERFORATION	1
J110100	ACUTE GASTRIC ULCER WITH HAEMORRHAGE	1
761J.00	OPERATIONS ON GASTRIC ULCER	1
J140.00	ACUTE GASTROJEJUNAL ULCER	1
Mild liver disease		
J616100	SECONDARY BILIARY CIRRHOSIS	1
J615400	FATTY PORTAL CIRRHOSIS	1
J616z00	BILIARY CIRRHOSIS NOS	1
J614.00	CHRONIC HEPATITIS	1
J614y00	CHRONIC HEPATITIS UNSPECIFIED	1
J615100	MULTI-LOBULAR PORTAL CIRRHOSIS	1
J635600	TOXIC LIVER DISEASE WITH FIBROSIS AND CIRRHOSIS OF LIVER	1
C350012	PIGMENTARY CIRRHOSIS OF LIVER	1
J615z14	LAENNEC'S CIRRHOSIS, NON-ALCOHOLIC	1
J617000	CHRONIC ALCOHOLIC HEPATITIS	1

J615z11	MACRONODULAR CIRRHOSIS OF LIVER	1
J614100	CHRONIC ACTIVE HEPATITIS	1
J615000	UNI-LOBULAR PORTAL CIRRHOSIS	1
J615y00	PORTAL CIRRHOSIS UNSPECIFIED	1
J615z00	NON-ALCOHOLIC CIRRHOSIS NOS	1
J612.00	ALCOHOLIC CIRRHOSIS OF LIVER	1
J615A00	PIPE-STEM PORTAL CIRRHOSIS	1
J615.11	PORTAL CIRRHOSIS	1
J615300	DIFFUSE NODULAR CIRRHOSIS	1
J615C00	XANTHOMATOUS PORTAL CIRRHOSIS	1
J615z13	CIRRHOSIS OF LIVER NOS	1
J614300	RECURRENT HEPATITIS	1
Jyu7100	[X]OTHER AND UNSPECIFIED CIRRHOSIS OF LIVER	1
J61..00	CIRRHOSIS AND CHRONIC LIVER DISEASE	1
J615F00	SYPHILITIC PORTAL CIRRHOSIS	1
C310400	GLYCOGENOSIS WITH HEPATIC CIRRHOSIS	1
J615z12	CRYPTOGENIC CIRRHOSIS OF LIVER	1
J616000	PRIMARY BILIARY CIRRHOSIS	1
J616.00	BILIARY CIRRHOSIS	1
J615.00	CIRRHOSIS - NON ALCOHOLIC	1
J633.00	HEPATITIS UNSPECIFIED	1
J615700	CARDIAC PORTAL CIRRHOSIS	1
J614000	CHRONIC PERSISTENT HEPATITIS	1
J600200	ACUTE YELLOW ATROPHY	1
J615B00	TOXIC PORTAL CIRRHOSIS	1
J61y300	PORTAL FIBROSIS WITHOUT CIRRHOSIS	1
J614200	CHRONIC AGGRESSIVE HEPATITIS	1
J601200	SUBACUTE YELLOW ATROPHY	1
J615111	POSTNECROTIC CIRRHOSIS OF LIVER	1
J612.11	FLORID CIRRHOSIS	1
J614z00	CHRONIC HEPATITIS NOS	1

Diabetes		
66AJ.11	UNSTABLE DIABETES	1
C108600	INSULIN DEPENDENT DIABETES MELLITUS WITH GANGRENE	1
C101100	DIABETES MELLITUS, ADULT ONSET, WITH KETOACIDOSIS	1
C10M.00	LIPOATROPHIC DIABETES MELLITUS	1
C103000	DIABETES MELLITUS, JUVENILE TYPE, WITH KETOACIDOTIC COMA	1
C109500	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH GANGRENE	1
C109900	NON-INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATION	1
C109412	TYPE 2 DIABETES MELLITUS WITH ULCER	1
C10FG00	TYPE 2 DIABETES MELLITUS WITH ARTHROPATHY	1
C109.11	NIDDM - NON-INSULIN DEPENDENT DIABETES MELLITUS	1
C109G11	TYPE II DIABETES MELLITUS WITH ARTHROPATHY	1
C10z.00	DIABETES MELLITUS WITH UNSPECIFIED COMPLICATION	1
C10EM11	TYPE I DIABETES MELLITUS WITH KETOACIDOSIS	1
C107200	DIABETES MELLITUS, ADULT WITH GANGRENE	1
C10FJ00	INSULIN TREATED TYPE 2 DIABETES MELLITUS	1
C108911	TYPE I DIABETES MELLITUS MATURITY ONSET	1
C102z00	DIABETES MELLITUS NOS WITH HYPEROSMOLAR COMA	1
G73y000	DIABETIC PERIPHERAL ANGIOPATHY	1
66AJ.00	DIABETIC - POOR CONTROL	1
C109J12	INSULIN TREATED TYPE II DIABETES MELLITUS	1

C109F12	TYPE 2 DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY	1
C109300	NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH MULTIPLE COMPS	1
C108400	UNSTABLE INSULIN DEPENDENT DIABETES MELLITUS	1
C10F900	TYPE 2 DIABETES MELLITUS WITHOUT COMPLICATION	1
C10y.00	DIABETES MELLITUS WITH OTHER SPECIFIED MANIFESTATION	1
C10F.11	TYPE II DIABETES MELLITUS	1
C10FL00	TYPE 2 DIABETES MELLITUS WITH PERSISTENT PROTEINURIA	1
C109G00	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH ARTHROPATHY	1
C109G12	TYPE 2 DIABETES MELLITUS WITH ARTHROPATHY	1
66A5.00	DIABETIC ON INSULIN	1
C109511	TYPE II DIABETES MELLITUS WITH GANGRENE	1
L180600	PRE-EXISTING DIABETES MELLITUS, NON-INSULIN-DEPENDENT	1
C10FN00	TYPE 2 DIABETES MELLITUS WITH KETOACIDOSIS	1
C10E400	UNSTABLE TYPE 1 DIABETES MELLITUS	1
C10zy00	OTHER SPECIFIED DIABETES MELLITUS WITH UNSPECIFIED COMPS	1
C10D.00	DIABETES MELLITUS AUTOSOMAL DOMINANT TYPE 2	1
C107z00	DIABETES MELLITUS NOS WITH PERIPHERAL CIRCULATORY DISORDER	1
C10EN00	TYPE 1 DIABETES MELLITUS WITH KETOACIDOTIC COMA	1

C101000	DIABETES MELLITUS, JUVENILE TYPE, WITH KETOACIDOSIS	1
C100011	INSULIN DEPENDENT DIABETES MELLITUS	1
C108411	UNSTABLE TYPE I DIABETES MELLITUS	1
C103.00	DIABETES MELLITUS WITH KETOACIDOTIC COMA	1
C107.11	DIABETES MELLITUS WITH GANGRENE	1
C10E500	TYPE 1 DIABETES MELLITUS WITH ULCER	1
C109400	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH ULCER	1
C10yy00	OTHER SPECIFIED DIABETES MELLITUS WITH OTHER SPEC COMPS	1
C109711	TYPE II DIABETES MELLITUS - POOR CONTROL	1
C10A000	MALNUTRITION-RELATED DIABETES MELLITUS WITH COMA	1
C10F.00	TYPE 2 DIABETES MELLITUS	1
C109J11	INSULIN TREATED NON-INSULIN DEPENDENT DIABETES MELLITUS	1
8A13.00	DIABETIC STABILISATION	1
C108.00	INSULIN DEPENDENT DIABETES MELLITUS	1
C10EG00	TYPE 1 DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY	1
C108E12	TYPE 1 DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA	1
C108.13	TYPE I DIABETES MELLITUS	1
C107100	DIABETES MELLITUS, ADULT, PERIPHERAL CIRCULATORY DISORDER	1
C10A100	MALNUTRITION-RELATED DIABETES MELLITUS WITH KETOACIDOSIS	1
C102000	DIABETES MELLITUS, JUVENILE TYPE, WITH HYPEROSMOLAR COMA	1
C109411	TYPE II DIABETES MELLITUS WITH ULCER	1

C10F500	TYPE 2 DIABETES MELLITUS WITH GANGRENE	1
C102100	DIABETES MELLITUS, ADULT ONSET, WITH HYPEROSMOLAR COMA	1
C108E11	TYPE I DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA	1
C109K00	HYPEROSMOLAR NON-KETOTIC STATE IN TYPE 2 DIABETES MELLITUS	1
66AJz00	DIABETIC - POOR CONTROL NOS	1
C10FJ11	INSULIN TREATED TYPE II DIABETES MELLITUS	1
C108500	INSULIN DEPENDENT DIABETES MELLITUS WITH ULCER	1
C109J00	INSULIN TREATED TYPE 2 DIABETES MELLITUS	1
C10E800	TYPE 1 DIABETES MELLITUS - POOR CONTROL	1
C108812	TYPE 1 DIABETES MELLITUS - POOR CONTROL	1
C107400	NIDDM WITH PERIPHERAL CIRCULATORY DISORDER	1
C10G.00	SECONDARY PANCREATIC DIABETES MELLITUS	1
C10EM00	TYPE 1 DIABETES MELLITUS WITH KETOACIDOSIS	1
66AV.00	DIABETIC ON INSULIN AND ORAL TREATMENT	1
L180500	PRE-EXISTING DIABETES MELLITUS, INSULIN-DEPENDENT	1
C10FP00	TYPE 2 DIABETES MELLITUS WITH KETOACIDOTIC COMA	1
C100.00	DIABETES MELLITUS WITH NO MENTION OF COMPLICATION	1
C10E600	TYPE 1 DIABETES MELLITUS WITH GANGRENE	1
C109D12	TYPE 2 DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA	1
C10FF00	TYPE 2 DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY	1
C108.12	TYPE 1 DIABETES MELLITUS	1

C109.00	NON-INSULIN-DEPENDENT DIABETES MELLITUS	1
C109D00	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH HYPOGLYCA COMA	1
C10zz00	DIABETES MELLITUS NOS WITH UNSPECIFIED COMPLICATION	1
C10EE00	TYPE 1 DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA	1
66AS.00	DIABETIC ANNUAL REVIEW	1
C107000	DIABETES MELLITUS, JUVENILE CIRCULATORY DISORDER	1
C10E412	UNSTABLE INSULIN DEPENDENT DIABETES MELLITUS	1
C10E900	TYPE 1 DIABETES MELLITUS MATURITY ONSET	1
C101y00	OTHER SPECIFIED DIABETES MELLITUS WITH KETOACIDOSIS	1
C10FL11	TYPE II DIABETES MELLITUS WITH PERSISTENT PROTEINURIA	1
C109712	TYPE 2 DIABETES MELLITUS - POOR CONTROL	1
Cyu2.00	DIABETES MELLITUS	1
C10..00	DIABETES MELLITUS	1
C10EA00	TYPE 1 DIABETES MELLITUS WITHOUT COMPLICATION	1
C100z00	DIABETES MELLITUS NOS WITH NO MENTION OF COMPLICATION	1
C103z00	DIABETES MELLITUS NOS WITH KETOACIDOTIC COMA	1
C108G00	INSULIN DEPENDENT DIAB MELL WITH PERIPHERAL ANGIOPATHY	1
C108E00	INSULIN DEPENDENT DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA	1
C101.00	DIABETES MELLITUS WITH KETOACIDOSIS	1

C10E812	INSULIN DEPENDENT DIABETES MELLITUS - POOR CONTROL	1
C10F700	TYPE 2 DIABETES MELLITUS - POOR CONTROL	1
66AK.00	DIABETIC - COOPERATIVE PATIENT	1
C10B000	STEROID INDUCED DIABETES MELLITUS WITHOUT COMPLICATION	1
C100111	MATURITY ONSET DIABETES	1
C10E.00	TYPE 1 DIABETES MELLITUS	1
8H2J.00	ADMIT DIABETIC EMERGENCY	1
C108811	TYPE I DIABETES MELLITUS - POOR CONTROL	1
C10E.12	INSULIN DEPENDENT DIABETES MELLITUS	1
C100100	DIABETES MELLITUS, ADULT ONSET, NO MENTION OF COMPLICATION	1
C10F400	TYPE 2 DIABETES MELLITUS WITH ULCER	1
C10z100	DIABETES MELLITUS, ADULT ONSET, UNSPECIFIED COMPLICATION	1
L180X00	PRE-EXISTING DIABETES MELLITUS, UNSPECIFIED	1
8BL2.00	PATIENT ON MAXIMAL TOLERATED THERAPY FOR DIABETES	1
C10yz00	DIABETES MELLITUS NOS WITH OTHER SPECIFIED MANIFESTATION	1
C102.00	DIABETES MELLITUS WITH HYPEROSMOLAR COMA	1
C10A.00	MALNUTRITION-RELATED DIABETES MELLITUS	1
C108.11	IDDM-INSULIN DEPENDENT DIABETES MELLITUS	1
C101z00	DIABETES MELLITUS NOS WITH KETOACIDOSIS	1
C10FD00	TYPE 2 DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA	1
C108800	INSULIN DEPENDENT DIABETES MELLITUS - POOR CONTROL	1

C10EK00	TYPE 1 DIABETES MELLITUS WITH PERSISTENT PROTEINURIA	1
C10H.00	DIABETES MELLITUS INDUCED BY NON-STEROID DRUGS	1
C107.00	DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY DISORDER	1
C10D.11	MATURITY ONSET DIABETES IN YOUTH TYPE 2	1
C107300	IDDM WITH PERIPHERAL CIRCULATORY DISORDER	1
C109F11	TYPE II DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY	1
C109D11	TYPE II DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA	1
C10EL00	TYPE 1 DIABETES MELLITUS WITH PERSISTENT MICROALBUMINURIA	1
C100112	NON-INSULIN DEPENDENT DIABETES MELLITUS	1
C10FM00	TYPE 2 DIABETES MELLITUS WITH PERSISTENT MICROALBUMINURIA	1
Cyu2000	[X]OTHER SPECIFIED DIABETES MELLITUS	1
C109.12	TYPE 2 DIABETES MELLITUS	1
C103y00	OTHER SPECIFIED DIABETES MELLITUS WITH COMA	1
C109.13	TYPE II DIABETES MELLITUS	1
C108511	TYPE I DIABETES MELLITUS WITH ULCER	1
C10EN11	TYPE I DIABETES MELLITUS WITH KETOACIDOTIC COMA	1
C109700	NON-INSULIN DEPENDENT DIABETES MELLITUS - POOR CONTROL	1
C10y100	DIABETES MELLITUS, ADULT, OTHER SPECIFIED MANIFESTATION	1
C10E.11	TYPE I DIABETES MELLITUS	1
C10N.00	SECONDARY DIABETES MELLITUS	1

C10F711	TYPE II DIABETES MELLITUS - POOR CONTROL	1
66AI.00	DIABETIC - GOOD CONTROL	1
C100000	DIABETES MELLITUS, JUVENILE TYPE, NO MENTION OF COMPLICATION	1
Hemiplegia		
F241000	FLACCID PARAPLEGIA	2
F222.00	LEFT HEMIPLEGIA	2
F22z.00	HEMIPLEGIA NOS	2
F230000	CONGENITAL PARAPLEGIA	2
F221.00	SPASTIC HEMIPLEGIA	2
F223.00	RIGHT HEMIPLEGIA	2
F230.11	PARAPLEGIA - CONGENITAL	2
F241100	SPASTIC PARAPLEGIA	2
F241.00	PARAPLEGIA	2
F141.00	HEREDITARY SPASTIC PARAPLEGIA	2
F220.00	FLACCID HEMIPLEGIA	2
F22..00	HEMIPLEGIA	2
Renal disease		
K080000	PHOSPHATE-LOSING TUBULAR DISORDERS	2
K032z00	NEPHRITIS UNSPECIFIC GLOMERULONEPHRITIS LESION NOS	2
K080100	RENAL DWARFISM	2
K04z.00	ACUTE RENAL FAILURE NOS	2
K101100	ACUTE PYELONEPHRITIS WITH MEDULLARY NECROSIS	2
K02z.00	CHRONIC GLOMERULONEPHRITIS NOS	2
K060.11	IMPAIRED RENAL FUNCTION	2
K021.00	CHRONIC MEMBRANOUS GLOMERULONEPHRITIS	2
K023.00	CHRONIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS	2

K032y00	NEPHRITIS UNSPECIFIC MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS LESION	2
1Z11.00	CHRONIC KIDNEY DISEASE STAGE 2	2
K041.00	ACUTE RENAL CORTICAL NECROSIS	2
K032y13	MESANGIO PROLIFERATIVE GLOMERULONEPHRITIS NEC	2
K0...00	NEPHRITIS, NEPHROSIS AND NEPHROTIC SYNDROME	2
K02..12	NEPHROPATHY - CHRONIC	2
K08yz00	OTHER IMPAIRED RENAL FUNCTION DISORDER NOS	2
K081.00	NEPHROGENIC DIABETES INSIPIDUS	2
K080.00	RENAL OSTEODYSTROPHY	2
K0A3400	CHRON NEPHRITIC SYNDROME DIFFUSE ENDOCAP PROLIFERATIVE GLOMERULONEPHRITIS	2
K06..00	RENAL FAILURE UNSPECIFIED	2
K0A3200	CHRON NEPHRITIC SYNDROME DIFFUSE MEMBRANOUS GLOMERULONEPHRITIS	2
K034.00	RENAL CORTICAL NECROSIS UNSPECIFIED	2
K02y200	CHRONIC FOCAL GLOMERULONEPHRITIS	2
K03..00	NEPHRITIS AND NEPHROPATHY UNSPECIFIED	2
K05..00	CHRONIC RENAL FAILURE	2
K0A5500	[X]HEREDITARY NEPHROPATHY NEC DIFFUSE MESANGIOCAPILRY GALUMPH	2
K101000	ACUTE PYELONEPHRITIS WITHOUT MEDULLARY NECROSIS	2
K02..00	CHRONIC GLOMERULONEPHRITIS	2
K080300	RENAL RICKETS	2
1Z13.00	CHRONIC KIDNEY DISEASE STAGE 4	2

K032.00	MEMBRANOPROLIFERATIVE NEPHRITIS UNSPECIFIED	2
K012.00	NEPHROTIC SYNDROME GLOMERULONEPHRITIS	2
K0A3300	CHRON NEPHRITIC SYNDROME DIFFUSE MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS	2
1Z14.00	CHRONIC KIDNEY DISEASE STAGE 5	2
Kyu2.00	[X]RENAL FAILURE	2
K08z.00	IMPAIRED RENAL FUNCTION DISORDER NOS	2
K050.00	END STAGE RENAL FAILURE	2
K100000	CHRONIC PYELONEPHRITIS WITHOUT MEDULLARY NECROSIS	2
K04y.00	OTHER ACUTE RENAL FAILURE	2
14D1.00	H/O: NEPHRITIS	2
K02..11	NEPHRITIS - CHRONIC	2
1Z10.00	CHRONIC KIDNEY DISEASE STAGE 1	2
K032000	FOCAL MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	2
K03..11	NEPHRITIS AND NEPHROPATHY UNSPECIFIED	2
K042.00	ACUTE RENAL MEDULLARY NECROSIS	2
K022.00	CHRONIC MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	2
K032y14	MESANGIOCAPILLARY GLOMERULONEPHRITIS NEC	2
K080200	RENAL INFANTILISM	2
K001.00	ACUTE NEPHRITIS WITH LESIONS OF NECROTISING GLOMERULITIS	2
1Z12.00	CHRONIC KIDNEY DISEASE STAGE 3	2
K02yz00	OTHER CHRONIC GLOMERULONEPHRITIS NOS	2
K02y300	CHRONIC DIFFUSE GLOMERULONEPHRITIS	2
K080z00	RENAL OSTEODYSTROPHY NOS	2

K019.00	NEPHROTIC SYNDROME DIFFUSE MESANGIOCAPILLARY GLOMERULONEPHRITIS	2
K035.00	RENAL MEDULLARY NECROSIS UNSPECIFIED	2
K0A3700	CHRONIC NEPHRITIC SYNDROME DIFFUSE CRESCENTIC GLOMERULONEPHRITIS	2
K08y000	HYPOKALAEMIC NEPHROPATHY	2
Kyu2100	[X]OTHER CHRONIC RENAL FAILURE	2
K0A3500	CHRONIC NEPHRITIC SYNDROME DIFFUSE MESANGIOCAPILLARY GLOMERULONEPHRITIS	2
K02y000	CHRONIC GLOMERULONEPHRITIS DISEASES EC	2
K100100	CHRONIC PYELONEPHRITIS WITH MEDULLARY NECROSIS	2
Kyu2000	[X]OTHER ACUTE RENAL FAILURE	2
Diabetes with complications		
F464000	DIABETIC CATARACT	2
C109212	TYPE 2 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS	2
C104000	DIABETES MELLITUS, JUVENILE TYPE, WITH RENAL MANIFESTATION	2
C109111	TYPE II DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS	2
2BBP.00	O/E - RIGHT EYE BACKGROUND DIABETIC RETINOPATHY	2
C108C11	TYPE I DIABETES MELLITUS WITH POLYNEUROPATHY	2
C108H00	INSULIN DEPENDENT DIABETES MELLITUS WITH ARTHROPATHY	2
C109C00	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH NEPHROPATHY	2
C108B00	INSULIN DEPENDENT DIABETES MELLITUS WITH MONONEUROPATHY	2

C106100	DIABETES MELLITUS, ADULT ONSET, NEUROLOGICAL MANIFESTATION	2
C108000	INSULIN-DEPENDENT DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
C109H00	NON-INSULIN DEPENDENT D M WITH NEUROPATHIC ARTHROPATHY	2
C108200	INSULIN-DEPENDENT DIABETES MELLITUS WITH NEUROLOGICAL COMPS	2
C10F100	TYPE 2 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS	2
2BBQ.00	O/E - LEFT EYE BACKGROUND DIABETIC RETINOPATHY	2
C109011	TYPE II DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
F420200	PRE-PROLIFERATIVE DIABETIC RETINOPATHY	2
C105000	DIABETES MELLITUS, JUVENILE TYPE, OPHTHALMIC MANIFESTATION	2
C10FR00	TYPE 2 DIABETES MELLITUS WITH GASTROPARESIS	2
C109100	NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH OPHTHALMIC COMPS	2
C10FE00	TYPE 2 DIABETES MELLITUS WITH DIABETIC CATARACT	2
C108712	TYPE 1 DIABETES MELLITUS WITH RETINOPATHY	2
C106.13	DIABETES MELLITUS WITH POLYNEUROPATHY	2
F420.00	DIABETIC RETINOPATHY	2
C109612	TYPE 2 DIABETES MELLITUS WITH RETINOPATHY	2
C109B00	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH POLYNEUROPATHY	2
F420600	NON PROLIFERATIVE DIABETIC RETINOPATHY	2

C105y00	OTHER SPECIFIED DIABETES MELLITUS WITH OPHTHALMIC COMPLICATION	2
C109E11	TYPE II DIABETES MELLITUS WITH DIABETIC CATARACT	2
C10FB00	TYPE 2 DIABETES MELLITUS WITH POLYNEUROPATHY	2
C10FA00	TYPE 2 DIABETES MELLITUS WITH MONONEUROPATHY	2
C10F611	TYPE II DIABETES MELLITUS WITH RETINOPATHY	2
C10E200	TYPE 1 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS	2
C108B11	TYPE I DIABETES MELLITUS WITH MONONEUROPATHY	2
C109600	NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RETINOPATHY	2
F381300	MYASTHENIC SYNDROME DUE TO DIABETIC AMYOTROPHY	2
C106z00	DIABETES MELLITUS NOS WITH NEUROLOGICAL MANIFESTATION	2
C104y00	OTHER SPECIFIED DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
2BBV.00	O/E - LEFT EYE PROLIFERATIVE DIABETIC RETINOPATHY	2
C108711	TYPE I DIABETES MELLITUS WITH RETINOPATHY	2
F420400	DIABETIC MACULOPATHY	2
C109C12	TYPE 2 DIABETES MELLITUS WITH NEPHROPATHY	2
C106.11	DIABETIC AMYOTROPHY	2
K01x111	KIMMELSTIEL - WILSON DISEASE	2

C108D00	INSULIN DEPENDENT DIABETES MELLITUS WITH NEPHROPATHY	2
C108212	TYPE 1 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS	2
C108100	INSULIN-DEPENDENT DIABETES MELLITUS WITH OPHTHALMIC COMPS	2
F3y0.00	DIABETIC MONONEUROPATHY	2
F372.12	DIABETIC NEUROPATHY	2
F420300	ADVANCED DIABETIC MACULOPATHY	2
C10F011	TYPE II DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
2BBl.00	O/E - LEFT EYE STABLE TREATED PROLIFERATIVE DIABETIC RETINOPATHY	2
C10FC00	TYPE 2 DIABETES MELLITUS WITH NEPHROPATHY	2
C10EF00	TYPE 1 DIABETES MELLITUS WITH DIABETIC CATARACT	2
C109E12	TYPE 2 DIABETES MELLITUS WITH DIABETIC CATARACT	2
C108D11	TYPE I DIABETES MELLITUS WITH NEPHROPATHY	2
C109B11	TYPE II DIABETES MELLITUS WITH POLYNEUROPATHY	2
C10F200	TYPE 2 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS	2
C10EB00	TYPE 1 DIABETES MELLITUS WITH MONONEUROPATHY	2
C109H12	TYPE 2 DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY	2
F420800	HIGH RISK NON PROLIFERATIVE DIABETIC RETINOPATHY	2

C108700	INSULIN DEPENDENT DIABETES MELLITUS WITH RETINOPATHY	2
C10EC00	TYPE 1 DIABETES MELLITUS WITH POLYNEUROPATHY	2
F374z00	POLYNEUROPATHY IN DISEASE NOS	2
C109112	TYPE 2 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS	2
2BBL.00	O/E - DIABETIC MACULOPATHY PRESENT BOTH EYES	2
C109012	TYPE 2 DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
C109000	NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RENAL COMPS	2
C109200	NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH NEURO COMPS	2
F420700	HIGH RISK PROLIFERATIVE DIABETIC RETINOPATHY	2
C106.12	DIABETES MELLITUS WITH NEUROPATHY	2
2BBS.00	O/E - LEFT EYE PRE-PROLIFERATIVE DIABETIC RETINOPATHY	2
C109E00	NON-INSULIN DEPENDS DIABETES MELLITUS WITH DIABETIC CATARACT	2
C10F600	TYPE 2 DIABETES MELLITUS WITH RETINOPATHY	2
C108C00	INSULIN DEPENDENT DIABETES MELLITUS WITH POLYNEUROPATHY	2
C108211	TYPE I DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS	2
C10E000	TYPE 1 DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
C109H11	TYPE II DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY	2

C106.00	DIABETES MELLITUS WITH NEUROLOGICAL MANIFESTATION	2
C109611	TYPE II DIABETES MELLITUS WITH RETINOPATHY	2
F372.11	DIABETIC POLYNEUROPATHY	2
2BBk.00	O/E - RIGHT EYE STABLE TREATED PROLIFERATIVE DIABETIC RETINOPATHY	2
F420z00	DIABETIC RETINOPATHY NOS	2
C105z00	DIABETES MELLITUS NOS WITH OPHTHALMIC MANIFESTATION	2
C105100	DIABETES MELLITUS, ADULT ONSET, OPHTHALMIC MANIFESTATION	2
C10ED00	TYPE 1 DIABETES MELLITUS WITH NEPHROPATHY	2
C108F11	TYPE I DIABETES MELLITUS WITH DIABETIC CATARACT	2
C108011	TYPE I DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
C10FC11	TYPE II DIABETES MELLITUS WITH NEPHROPATHY	2
C108012	TYPE 1 DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
C109A11	TYPE II DIABETES MELLITUS WITH MONONEUROPATHY	2
F381311	DIABETIC AMYOTROPHY	2
C109C11	TYPE II DIABETES MELLITUS WITH NEPHROPATHY	2
C10EQ00	TYPE 1 DIABETES MELLITUS WITH GASTROPARESIS	2
C109A00	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH MONONEUROPATHY	2

C108F00	INSULIN DEPENDENT DIABETES MELLITUS WITH DIABETIC CATARACT	2
C104.11	DIABETIC NEPHROPATHY	2
2BBR.00	O/E - RIGHT EYE PRE-PROLIFERATIVE DIABETIC RETINOPATHY	2
C108J12	TYPE 1 DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY	2
C10FB11	TYPE II DIABETES MELLITUS WITH POLYNEUROPATHY	2
C106y00	OTHER SPECIFIED DIABETES MELLITUS WITH NEUROLOGICAL COMPS	2
C10FH00	TYPE 2 DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY	2
C10F000	TYPE 2 DIABETES MELLITUS WITH RENAL COMPLICATIONS	2
C105.00	DIABETES MELLITUS WITH OPHTHALMIC MANIFESTATION	2
F420100	PROLIFERATIVE DIABETIC RETINOPATHY	2
C109211	TYPE II DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS	2
C104z00	DIABETES MELLITES WITH NEPHROPATHY NOS	2
C10E100	TYPE 1 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS	2
Any tumour		
B072.00	MALIGNANT NEOPLASM OF LATERAL WALL OF NASOPHARYNX	2
B18y100	MALIGNANT NEOPLASM OF MESOCAECUM	2
B173.00	MALIGNANT NEOPLASM OF PANCREATIC DUCT	2
B337100	MALIGNANT NEOPLASM OF SKIN OF THIGH	2
B335.00	MALIGNANT NEOPLASM OF SKIN OF TRUNK, EXCLUDING SCROTUM	2

B614500	HODGKIN'S NODULAR SCLEROSIS OF INGUINAL REGION AND LEG	2
B63..00	MULTIPLE MYELOMA AND IMMUNOPROLIFERATIVE NEOPLASMS	2
B001.00	MALIGNANT NEOPLASM OF LOWER LIP, VERMILION BORDER	2
B04y.00	MALIGNANT NEOPLASM OF OTHER SITES OF FLOOR OF MOUTH	2
B072100	MALIGNANT NEOPLASM OF OPENING OF AUDITORY TUBE	2
B072000	MALIGNANT NEOPLASM OF PHARYNGEAL RECESS	2
B612600	HODGKIN'S SARCOMA OF INTRAPELVIC LYMPH NODES	2
B626400	MAST CELL MALIGNANCY OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B305700	MALIGNANT NEOPLASM OF CARPAL BONE - HAMATE	2
B49..00	MALIGNANT NEOPLASM OF URINARY BLADDER	2
B430300	MALIGNANT NEOPLASM OF MYOMETRIUM OF CORPUS UTERI	2
B627C11	FOLLICULAR LYMPHOMA NOS	2
Byu3300	[X]MALIGNANT NEOPLASM/BONE CARTILAGE, UNSPECIFIED	2
B03z.00	MALIGNANT NEOPLASM OF GUM NOS	2
B340z00	MALIGNANT NEOPLASM OF NIPPLE OR AREOLA OF FEMALE BREAST NOS	2
B627D00	DIFFUSE NON-HODGKIN'S CENTROBLASTIC LYMPHOMA	2
B332000	MALIGNANT NEOPLASM OF SKIN OF AURICLE (EAR)	2
B600700	RETICULOSARCOMA OF SPLEEN	2

B062100	MALIGNANT NEOPLASM OF GLOSSOPALATINE FOLD	2
B600300	RETICULOSARCOMA OF INTRA-ABDOMINAL LYMPH NODES	2
B000.00	MALIGNANT NEOPLASM OF UPPER LIP, VERMILION BORDER	2
ZV10511	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF BLADDER	2
B41z.00	MALIGNANT NEOPLASM OF CERVIX UTERI NOS	2
B4A1z00	MALIGNANT NEOPLASM OF RENAL PELVIS NOS	2
B304400	MALIGNANT NEOPLASM OF ULNA	2
B00y.00	MALIGNANT NEOPLASM OF OTHER SITES OF LIP	2
B51y100	MALIGNANT NEOPLASM OF TAPETUM	2
Byu1200	[X]MALIGNANT NEOPLASM OF INTESTINAL TRACT, PART UNSPECIFIED	2
B07z.00	MALIGNANT NEOPLASM OF NASOPHARYNX NOS	2
B242.00	MALIGNANT NEOPLASM OF ANTERIOR MEDIASTINUM	2
B333z00	MALIGNANT NEOPLASM SKIN OTHER AND UNSPECIFIC PART OF FACE NOS	2
B42..00	MALIGNANT NEOPLASM OF PLACENTA	2
B471100	TERATOMA OF DESCENDED TESTIS	2
B4A3.00	MALIGNANT NEOPLASM OF URETHRA	2
B626500	MAST CELL MALIGNANCY OF LYMPH NODES INGUINAL REGION AND LEG	2
B616000	HODGKIN'S LYMPHOCYTIC DEPLETION OF UNSPECIFIED SITE	2
B02z.00	MALIGNANT NEOPLASM OF MAJOR SALIVARY GLAND NOS	2
B315300	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE - SACRUM OR COCCYX	2

B308.00	MALIGNANT NEOPLASM OF SHORT BONES OF LEG	2
B675.00	ACUTE MYELOFIBROSIS	2
Byu4.00	[X]MELANOMA AND OTHER MALIGNANT NEOPLASMS OF SKIN	2
Byu9.00	[X]MALIGNANT NEOPLASM OF URINARY TRACT	2
B62x000	T-ZONE LYMPHOMA	2
B17y000	MALIGNANT NEOPLASM OF ECTOPIC PANCREATIC TISSUE	2
B141.12	RECTAL CARCINOMA	2
B132.00	MALIGNANT NEOPLASM OF DESCENDING COLON	2
B330.00	MALIGNANT NEOPLASM OF SKIN OF LIP	2
B627500	DIFFUSE NON-HODGKIN MIXED SML & LGE CELL (DIFFUSE) LYMPHOMA	2
B630.00	MULTIPLE MYELOMA	2
B62x200	PERIPHERAL T-CELL LYMPHOMA	2
B502.00	MALIGNANT NEOPLASM OF LACRIMAL GLAND	2
B62x400	MALIGNANT RETICULOSIS	2
ZV10y11	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF BONE	2
B305000	MALIGNANT NEOPLASM OF CARPAL BONE - SCAPHOID	2
B11..00	MALIGNANT NEOPLASM OF STOMACH	2
B222100	MALIGNANT NEOPLASM OF UPPER LOBE OF LUNG	2
B106.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF OESOPHAGUS	2
ByuD.00	[X]MALIGNANT NEOPLASMS OF LYMPHOID, HAEMATOPOIETIC AND RELA	2
B544.00	MALIGNANT NEOPLASM OF CAROTID BODY	2

B066.00	MALIGNANT NEOPLASM OF LATERAL WALL OF OROPHARYNX	2
B62..00	OTHER MALIGNANT NEOPLASM OF LYMPHOID AND HISTIOCYTIC TISSUE	2
Byu5400	[X]MALIGNANT NEOPLASM/PERIPHERAL NERVES OF TRUNK, UNSPECIFIED	2
B101.00	MALIGNANT NEOPLASM OF THORACIC OESOPHAGUS	2
Byu1000	[X]OTHER SARCOMAS OF THE LIVER	2
B66y000	ALEUKAEMIC MONOCYTIC LEUKAEMIA	2
B68y.00	OTHER LEUKAEMIA OF UNSPECIFIED CELL TYPE	2
B326.00	MALIGNANT MELANOMA OF UPPER LIMB AND SHOULDER	2
B203.00	MALIGNANT NEOPLASM OF ETHMOID SINUS	2
ZV10400	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF GENITAL ORGAN	2
B610600	HODGKIN'S PARAGRANULOMA OF INTRAPELVIC LYMPH NODES	2
B313.00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF THORAX	2
B31z000	KAPOSI'S SARCOMA OF SOFT TISSUE	2
B041.00	MALIGNANT NEOPLASM OF LATERAL PORTION OF FLOOR OF MOUTH	2
B615100	HODGKIN'S MIXED CELLULARITY OF LYMPH NODES HEAD, FACE, NECK	2
B114.00	MALIGNANT NEOPLASM OF BODY OF STOMACH	2
B620.11	RETICULOSARCOMA - FOLLICULAR OR NODULAR	2
Byu5A00	[X]MALIGNANT NEOPLASM OVERLAPPING LESION OF SKIN	2

B3...11	CARCINOMA OF BONE, CONNECTIVE TISSUE, SKIN AND BREAST	2
B613.00	HODGKIN'S DISEASE, LYMPHOCYTIC-HISTIOCYTIC PREDOMINANCE	2
B610200	HODGKIN'S PARAGRANULOMA OF INTRATHORACIC LYMPH NODES	2
B490.00	MALIGNANT NEOPLASM OF TRIGONE OF URINARY BLADDER	2
ZV10112	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF LUNG	2
B523z00	MALIGNANT NEOPLASM OF SPINAL MENINGES NOS	2
B615000	HODGKIN'S DISEASE, MIXED CELLULARITY OF UNSPECIFIED SITE	2
B310200	MALIGNANT NEOPLASM OF SOFT TISSUE OF NECK	2
B220.00	MALIGNANT NEOPLASM OF TRACHEA	2
B336z00	MALIGNANT NEOPLASM OF SKIN OF UPPER LIMB OR SHOULDER NOS	2
B213200	MALIGNANT NEOPLASM OF CUNEIFORM CARTILAGE	2
B339.00	DERMATOFIBROSARCOMA PROTUBERANS	2
B180200	MALIGNANT NEOPLASM OF RETROCAECAL TISSUE	2
B651000	CHRONIC EOSINOPHILIC LEUKAEMIA	2
B441.00	MALIGNANT NEOPLASM OF FALLOPIAN TUBE	2
B231.00	MALIGNANT NEOPLASM OF VISCERAL PLEURA	2
B004100	MALIGNANT NEOPLASM OF LIP UNSPECIFIED, FRENULUM	2
B308900	MALIGNANT NEOPLASM OF SECOND METATARSAL BONE	2

B337z00	MALIGNANT NEOPLASM OF SKIN OF LOWER LIMB OR HIP NOS	2
Byu5100	[X]MESOTHELIOMA, UNSPECIFIED	2
B240.00	MALIGNANT NEOPLASM OF THYMUS	2
B62y500	MALIGNANT LYMPHOMA NOS OF LYMPH NODE INGUINAL REGION AND LEG	2
B30z.00	MALIGNANT NEOPLASM OF BONE AND ARTICULAR CARTILAGE NOS	2
B161.00	MALIGNANT NEOPLASM OF EXTRAHEPATIC BILE DUCTS	2
B322z00	MALIGNANT MELANOMA OF EAR AND EXTERNAL AURICULAR CANAL NOS	2
B311100	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE, UPPER ARM	2
B204.00	MALIGNANT NEOPLASM OF FRONTAL SINUS	2
B325200	MALIGNANT MELANOMA OF BUTTOCK	2
B24y.00	MALIGNANT NEOPLASM OF OTHER SITE OF HEART, THYMUS AND MEDIASTINUM	2
B308.11	MALIGNANT NEOPLASM OF METATARSAL BONES OF FOOT	2
B303.00	MALIGNANT NEOPLASM OF RIBS, STERNUM AND CLAVICLE	2
B225.00	MALIGNANT NEOPLASM OF OVERLAPPING LESION OF BRONCHUS & LUNG	2
B327100	MALIGNANT MELANOMA OF THIGH	2
B1z1100	FIBROSARCOMA OF SPLEEN	2
B620300	NODULAR LYMPHOMA OF INTRA-ABDOMINAL LYMPH NODES	2
B602.00	BURKITT'S LYMPHOMA	2
B224z00	MALIGNANT NEOPLASM OF LOWER LOBE, BRONCHUS OR LUNG NOS	2

B622100	SEZARY'S DISEASE OF LYMPH NODES OF HEAD, FACE AND NECK	2
B163.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF BILIARY TRACT	2
B161200	MALIGNANT NEOPLASM OF COMMON BILE DUCT	2
B515.00	MALIGNANT NEOPLASM OF CEREBRAL VENTRICLES	2
B102.00	MALIGNANT NEOPLASM OF ABDOMINAL OESOPHAGUS	2
B312200	MALIGNANT NEOPLASM CONNECTIVE AND SOFT TISSUE OF POPLITEAL SPACE	2
B454.00	MALIGNANT NEOPLASM OF VULVA UNSPECIFIED	2
B080.00	MALIGNANT NEOPLASM OF POST-CRICOID REGION	2
B03y.00	MALIGNANT NEOPLASM OF OTHER SITES OF GUM	2
B013000	MALIGNANT NEOPLASM OF ANTERIOR 2/3 OF TONGUE VENTRAL SURFACE	2
B327000	MALIGNANT MELANOMA OF HIP	2
B064.00	MALIGNANT NEOPLASM OF ANTERIOR EPIGLOTTIS	2
B013.00	MALIGNANT NEOPLASM OF VENTRAL SURFACE OF TONGUE	2
ZV10018	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF STOMACH	2
B300000	MALIGNANT NEOPLASM OF ETHMOID BONE	2
B6z..00	MALIGNANT NEOPLASM LYMPHATIC OR HAEMATOPOIETIC TISSUE NOS	2
B51yz00	MALIGNANT NEOPLASM OF OTHER PART OF BRAIN NOS	2

B624z00	LEUKAEMIC RETICULO-ENDOTHELIOSIS NOS	2
B412.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF CERVIX UTERI	2
B201000	MALIGNANT NEOPLASM OF AUDITORY (EUSTACHIAN) TUBE	2
B10z.00	MALIGNANT NEOPLASM OF OESOPHAGUS NOS	2
ZV10y00	[V]PERSONAL HISTORY OF OTHER SPECIFIED MALIGNANT NEOPLASM	2
B011z00	MALIGNANT NEOPLASM OF DORSUM OF TONGUE NOS	2
B103.00	MALIGNANT NEOPLASM OF UPPER THIRD OF OESOPHAGUS	2
B310.00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE HEAD, FACE AND NECK	2
B334100	MALIGNANT NEOPLASM OF SKIN OF NECK	2
B61z.00	HODGKIN'S DISEASE NOS	2
B333100	MALIGNANT NEOPLASM OF SKIN OF CHIN	2
B310000	MALIGNANT NEOPLASM OF SOFT TISSUE OF HEAD	2
B612800	HODGKIN'S SARCOMA OF LYMPH NODES OF MULTIPLE SITES	2
B523200	MALIGNANT NEOPLASM OF SPINAL PIA MATER	2
B300700	MALIGNANT NEOPLASM OF SPHENOID BONE	2
B33y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SKIN SITES	2
B653z00	MYELOID SARCOMA NOS	2
B325600	MALIGNANT MELANOMA OF UMBILICUS	2
B601800	LYMPHOSARCOMA OF LYMPH NODES OF MULTIPLE SITES	2
B111.00	MALIGNANT NEOPLASM OF PYLORUS OF STOMACH	2
B22z.11	LUNG CANCER	2

B18y400	MALIGNANT NEOPLASM OF PARIETAL PERITONEUM	2
B521200	MALIGNANT NEOPLASM OF CEREBRAL PIA MATER	2
B180000	MALIGNANT NEOPLASM OF PERIADRENAL TISSUE	2
B641.00	CHRONIC LYMPHOID LEUKAEMIA	2
B072z00	MALIGNANT NEOPLASM OF LATERAL WALL OF NASOPHARYNX NOS	2
B....11	CANCERS	2
B34y000	MALIGNANT NEOPLASM OF ECTOPIC SITE OF FEMALE BREAST	2
B224.00	MALIGNANT NEOPLASM OF LOWER LOBE, BRONCHUS OR LUNG	2
B304000	MALIGNANT NEOPLASM OF SCAPULA	2
B315100	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF INGUINAL REGION	2
B12..00	MALIGNANT NEOPLASM OF SMALL INTESTINE AND DUODENUM	2
B311200	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF FORE-ARM	2
B622600	SEZARY'S DISEASE OF INTRAPELVIC LYMPH NODES	2
B626z00	MALIGNANT MAST CELL TUMOUR NOS	2
B611200	HODGKIN'S GRANULOMA OF INTRATHORACIC LYMPH NODES	2
B550300	MALIGNANT NEOPLASM OF JAW NOS	2
B6y0.11	MYELOPROLIFERATIVE DISEASE	2
B306.00	MALIGNANT NEOPLASM OF PELVIC BONES, SACRUM AND COCCYX	2
B69..00	MYELOMONOCYTIC LEUKAEMIA	2

B613100	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PRED OF HEAD, FACE, NECK	2
B616100	HODGKIN'S LYMPHOCYTIC DEPLETION OF HEAD, FACE AND NECK	2
B624.00	LEUKAEMIC RETICULOENDOTHELIOSIS	2
B410z00	MALIGNANT NEOPLASM OF ENDOCERVIX NOS	2
B524W00	MAL NEOPLASM/PERIPHERAL NERVES NERVOUS SYSTEM, UNSPECIFIC	2
B30W.00	MALIGNANT NEOPLASM/OVERLAP LESION/BONE CARTILAGE	2
B327300	MALIGNANT MELANOMA OF POPLITEAL FOSSA AREA	2
B620600	NODULAR LYMPHOMA OF INTRAPELVIC LYMPH NODES	2
B326100	MALIGNANT MELANOMA OF UPPER ARM	2
B68..00	LEUKAEMIA OF UNSPECIFIED CELL TYPE	2
B482.00	MALIGNANT NEOPLASM OF BODY OF PENIS	2
B327900	MALIGNANT MELANOMA OF GREAT TOE	2
B151000	MALIGNANT NEOPLASM OF INTERLOBULAR BILE DUCTS	2
B67y000	LYMPHOSARCOMA CELL LEUKAEMIA	2
B500100	MALIGNANT NEOPLASM OF IRIS	2
B327.00	MALIGNANT MELANOMA OF LOWER LIMB AND HIP	2
B60..00	LYMPHOSARCOMA AND RETICULOSARCOMA	2
B24..00	MALIGNANT NEOPLASM OF THYMUS, HEART AND MEDIASTINUM	2
B627700	DIFFUSE NON-HODGKIN'S LYMPHOBLASTIC (DIFFUSE) LYMPHOMA	2
B45X.00	MALIGNANT NEOPLASM/OVERLAPPING LESION/FEMALE GENITAL ORGANS	2

B601600	LYMPHOSARCOMA OF INTRAPELVIC LYMPH NODES	2
B601500	LYMPHOSARCOMA OF LYMPH NODES OF INGUINAL REGION AND LEG	2
B510300	MALIGNANT NEOPLASM OF GLOBUS PALLIDUS	2
B21..00	MALIGNANT NEOPLASM OF LARYNX	2
B430211	MALIGNANT NEOPLASM OF ENDOMETRIUM	2
B014.00	MALIGNANT NEOPLASM OF ANTERIOR 2/3 OF TONGUE UNSPECIFIED	2
B326400	MALIGNANT MELANOMA OF FINGER	2
B62z700	UNSPECIFIC MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC OF SPLEEN	2
B337400	MALIGNANT NEOPLASM OF SKIN OF LOWER LEG	2
ZV10414	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF OVARY	2
B200100	MALIGNANT NEOPLASM OF NASAL CONCHAE	2
B201.00	MALIGNANT NEOPLASM AUDITORY TUBE, MIDDLE EAR AND MASTOID AIR CELLS	2
B205.00	MALIGNANT NEOPLASM OF SPHENOIDAL SINUS	2
B21y.00	MALIGNANT NEOPLASM OF LARYNX, OTHER SPECIFIED SITE	2
B220100	MALIGNANT NEOPLASM OF MUCOSA OF TRACHEA	2
B612100	HODGKIN'S SARCOMA OF LYMPH NODES OF HEAD, FACE AND NECK	2
B335200	MALIGNANT NEOPLASM OF SKIN OF BREAST	2
B325100	MALIGNANT MELANOMA OF BREAST	2
B631.00	PLASMA CELL LEUKAEMIA	2
B305100	MALIGNANT NEOPLASM OF CARPAL BONE - LUNATE	2

B500200	MALIGNANT NEOPLASM OF CRYSTALLINE LENS	2
B67yz00	OTHER AND UNSPECIFIED LEUKAEMIA NOS	2
ByuD200	[X]OTHER TYPES OF DIFFUSE NON-HODGKIN'S LYMPHOMA	2
B41..00	MALIGNANT NEOPLASM OF CERVIX UTERI	2
B160.11	CARCINOMA GALLBLADDER	2
B331000	MALIGNANT NEOPLASM OF CANTHUS	2
B323000	MALIGNANT MELANOMA OF EXTERNAL SURFACE OF CHEEK	2
B4...00	MALIGNANT NEOPLASM OF GENITOURINARY ORGAN	2
B302100	MALIGNANT NEOPLASM OF THORACIC VERTEBRA	2
B30X.00	MALIGNANT NEOPLASM/BONES CARTILAGE/LIMB, UNSPECIFIC	2
B322000	MALIGNANT MELANOMA OF AURICLE (EAR)	2
B61..00	HODGKIN'S DISEASE	2
B471.00	MALIGNANT NEOPLASM OF DESCENDED TESTIS	2
B500000	MALIGNANT NEOPLASM OF CILIARY BODY	2
ByuDF00	[X]NON-HODGKIN'S LYMPHOMA, UNSPECIFIED TYPE	2
B62y.00	MALIGNANT LYMPHOMA NOS	2
B523100	MALIGNANT NEOPLASM OF SPINAL ARACHNOID MATER	2
B626300	MAST CELL MALIGNANCY OF INTRA-ABDOMINAL LYMPH NODES	2
B54X.00	MALIGNANT NEOPLASM-PLURIGLANDULAR INVOLVEMENT, UNSPECIFIC	2
B54y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED ENDOCRINE GLAND	2

B18..00	MALIGNANT NEOPLASM OF RETROPERITONEUM AND PERITONEUM	2
B30..11	CHONDROMA	2
B150200	PRIMARY ANGIOSARCOMA OF LIVER	2
B31..00	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE	2
B650.00	ACUTE MYELOID LEUKAEMIA	2
B661.00	CHRONIC MONOCYTIC LEUKAEMIA	2
B306500	MALIGNANT SACRAL TERATOMA	2
B200z00	MALIGNANT NEOPLASM OF NASAL CAVITIES NOS	2
B615200	HODGKIN'S MIXED CELLULARITY OF INTRATHORACIC LYMPH NODES	2
B18z.00	MALIGNANT NEOPLASM OF RETROPERITONEUM AND PERITONEUM NOS	2
B621300	MYCOSIS FUNGOIDES OF INTRA-ABDOMINAL LYMPH NODES	2
B52..00	MALIGNANT NEOPLASM OF OTHER AND UNSPECIFIED PARTS OF NERVOUS SYSTEM	2
B55y000	MALIGNANT NEOPLASM OF BACK NOS	2
B304.00	MALIGNANT NEOPLASM OF SCAPULA AND LONG BONES OF UPPER ARM	2
B62z200	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC OF INTRATHORACIC NODE	2
B55y100	MALIGNANT NEOPLASM OF TRUNK NOS	2
B1z..00	MALIGNANT NEOPLASM OTHER/ILL-DEFINED SITES DIGESTIVE TRACT/PERITONEUM	2
B524300	MALIGNANT NEOPLASM OF PERIPHERAL NERVE OF THORAX	2
B1z1.00	MALIGNANT NEOPLASM OF SPLEEN NEC	2
B55y200	MALIGNANT NEOPLASM OF FLANK NOS	2

B55z.00	MALIGNANT NEOPLASM OF OTHER AND ILL-DEFINED SITE NOS	2
Byu5011	[X]MESOTHELIOMA OF LUNG	2
B303100	MALIGNANT NEOPLASM OF STERNUM	2
B34..00	MALIGNANT NEOPLASM OF FEMALE BREAST	2
B070.00	MALIGNANT NEOPLASM OF ROOF OF NASOPHARYNX	2
B680.00	ACUTE LEUKAEMIA NOS	2
B51z.00	MALIGNANT NEOPLASM OF BRAIN NOS	2
B232.00	MESOTHELIOMA OF PLEURA	2
B302z00	MALIGNANT NEOPLASM OF VERTEBRAL COLUMN NOS	2
B11..11	GASTRIC NEOPLASM	2
B510000	MALIGNANT NEOPLASM OF BASAL GANGLIA	2
Byu7200	[X]MALIGNANT NEOPLASM/OVERLAPPING LESION/FEMALE GENITAL ORGANS	2
B308100	MALIGNANT NEOPLASM OF TALUS	2
B20y.00	MALIGNANT NEOPLASM OTHER SITE NASAL CAVITY, MIDDLE EAR AND SINUSES	2
B662.00	SUBACUTE MONOCYTIC LEUKAEMIA	2
B62y300	MALIGNANT LYMPHOMA NOS OF INTRA-ABDOMINAL LYMPH NODES	2
B314100	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUES OF LUMB SPINE	2
Byu5800	[X]MAL NEOPLASM/CONNECTIVE? TISSUE OF TRUNK, UNSPECIFIED	2
B344.00	MALIGNANT NEOPLASM OF UPPER-OUTER QUADRANT OF FEMALE BREAST	2
B524600	MALIGNANT NEOPLASM, OVERLAP LESION PERIPHERAL NERVE & AUTON	2
B30..12	OSTEOMA	2
B33..12	EPITHELIOMA	2

B550200	MALIGNANT NEOPLASM OF NOSE NOS	2
B337000	MALIGNANT NEOPLASM OF SKIN OF HIP	2
B133.00	MALIGNANT NEOPLASM OF SIGMOID COLON	2
ZV10214	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF NOSE	2
Byu2.00	[X]MALIGNANT NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGAN	2
B454.11	PRIMARY VULVAR CANCER	2
B350z00	MALIGNANT NEOPLASM OF NIPPLE OR AREOLA OF MALE BREAST NOS	2
B2...11	CARCINOMA OF RESPIRATORY TRACT AND INTRATHORACIC ORGANS	2
B06z.00	MALIGNANT NEOPLASM OF OROPHARYNX NOS	2
B52y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED PART OF NERVOUS SYSTEM	2
B41y000	MALIGNANT NEOPLASM OF CERVICAL STUMP	2
B064100	MALIGNANT NEOPLASM OF GLOSSO-EPIGLOTTIC FOLD	2
B222.00	MALIGNANT NEOPLASM OF UPPER LOBE, BRONCHUS OR LUNG	2
B610700	HODGKIN'S PARA-GRANULOMA OF SPLEEN	2
B630200	PLASMACYTOMA NOS	2
B52z.00	MALIGNANT NEOPLASM OF NERVOUS SYSTEM NOS	2
B001000	MALIGNANT NEOPLASM OF LOWER LIP, EXTERNAL	2
B150000	PRIMARY CARCINOMA OF LIVER	2
B222z00	MALIGNANT NEOPLASM OF UPPER LOBE, BRONCHUS OR LUNG NOS	2
B512100	MALIGNANT NEOPLASM OF UNCUS	2
B601200	LYMPHOSARCOMA OF INTRATHORACIC LYMPH NODES	2

B602600	BURKITT'S LYMPHOMA OF INTRAPELVIC LYMPH NODES	2
B....00	NEOPLASMS	2
B000000	MALIGNANT NEOPLASM OF UPPER LIP, EXTERNAL	2
Byu4000	[X]MALIGNANT MELANOMA OF OTHER PARTS OF FACE	2
B524000	MALIGNANT NEOPLASM OF PERIPHERAL NERVES OF HEAD, FACE & NECK	2
B550.00	MALIGNANT NEOPLASM OF HEAD, NECK AND FACE	2
B34y.00	MALIGNANT NEOPLASM OF OTHER SITE OF FEMALE BREAST	2
B308C00	MALIGNANT NEOPLASM OF FIFTH METATARSAL BONE	2
B040.00	MALIGNANT NEOPLASM OF ANTERIOR PORTION OF FLOOR OF MOUTH	2
B303000	MALIGNANT NEOPLASM OF RIB	2
B065.00	MALIGNANT NEOPLASM OF JUNCTIONAL REGION OF EPIGLOTTIS	2
B430z00	MALIGNANT NEOPLASM OF CORPUS UTERI NOS	2
B003.00	MALIGNANT NEOPLASM OF LOWER LIP, INNER ASPECT	2
B137.00	MALIGNANT NEOPLASM OF SPLENIC FLEXURE OF COLON	2
ZV10y14	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF SKIN	2
B625700	LETTERER-SIWE DISEASE OF SPLEEN	2
B300600	MALIGNANT NEOPLASM OF PARIETAL BONE	2
B241.00	MALIGNANT NEOPLASM OF HEART	2
B62y100	MALIGNANT LYMPHOMA NOS OF LYMPH NODES OF HEAD, FACE AND NECK	2

B61z400	HODGKIN'S DISEASE NOS OF LYMPH NODES OF AXILLA AND ARM	2
B510100	MALIGNANT NEOPLASM OF CEREBRAL CORTEX	2
B506.00	MALIGNANT NEOPLASM OF CHOROID	2
ByuD700	[X]OTHER MONOCYTIC LEUKAEMIA	2
B540z00	MALIGNANT NEOPLASM OF ADRENAL GLAND NOS	2
Byu2200	[X]MALIGNANT NEOPLASM/UPPER RESPIRATORY TRACT, PART UNSPECIFIED	2
B410000	MALIGNANT NEOPLASM OF ENDOCERVICAL CANAL	2
B691.00	CHRONIC MYELOMONOCYTIC LEUKAEMIA	2
B326000	MALIGNANT MELANOMA OF SHOULDER	2
B49y.00	MALIGNANT NEOPLASM OF OTHER SITE OF URINARY BLADDER	2
B630300	LAMBDA LIGHT CHAIN MYELOMA	2
B612000	HODGKIN'S SARCOMA OF UNSPECIFIED SITE	2
1841AN	MALIGNANT NEOPLASM CANAL OF NUCK	2
B313300	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUES OF THE SPINE	2
B308700	MALIGNANT NEOPLASM OF NAVICULAR	2
B616.00	HODGKIN'S DISEASE, LYMPHOCYTIC DEPLETION	2
B41..11	CERVICAL CARCINOMA (UTERUS)	2
B430.00	MALIGNANT NEOPLASM OF CORPUS UTERI, EXCLUDING ISTHMUS	2
B483.00	MALIGNANT NEOPLASM OF PENIS, PART UNSPECIFIED	2
B200000	MALIGNANT NEOPLASM OF CARTILAGE OF NOSE	2
B307z00	MALIGNANT NEOPLASM OF LONG BONES OF LEG NOS	2

B17yz00	MALIGNANT NEOPLASM OF SPECIFIED SITE OF PANCREAS NOS	2
B323100	MALIGNANT MELANOMA OF CHIN	2
B05..00	MALIGNANT NEOPLASM OF OTHER AND UNSPECIFIED PARTS OF MOUTH	2
B513.00	MALIGNANT NEOPLASM OF PARIETAL LOBE	2
By...00	NEOPLASMS OTHERWISE SPECIFIED	2
B507.00	MALIGNANT NEOPLASM OF LACRIMAL DUCT	2
B616z00	HODGKIN'S DISEASE, LYMPHOCYTIC DEPLETION NOS	2
B311300	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF HAND	2
B305z00	MALIGNANT NEOPLASM OF HAND BONES NOS	2
Byu3200	[X]MALIGNANT NEOPLASM/OVERLAP LESION/BONE??? CARTILAGE	2
B010.00	MALIGNANT NEOPLASM OF BASE OF TONGUE	2
B602200	BURKITT'S LYMPHOMA OF INTRATHORACIC LYMPH NODES	2
B0z..00	MALIGNANT NEOPLASM OTHER/ILL-DEFINED SITES LIP, ORAL CAVITY, PHARYNX	2
B134.11	CARCINOMA OF CAECUM	2
B030.00	MALIGNANT NEOPLASM OF UPPER GUM	2
B621500	MYCOSIS FUNGOIDES OF LYMPH NODES OF INGUINAL REGION AND LEG	2
B071.00	MALIGNANT NEOPLASM OF POSTERIOR WALL OF NASOPHARYNX	2
B625200	LETTERER-SIWE DISEASE OF INTRATHORACIC LYMPH NODES	2
B625300	LETTERER-SIWE DISEASE OF INTRA-ABDOMINAL LYMPH NODES	2
B625.00	LETTERER-SIWE DISEASE	2

B113.00	MALIGNANT NEOPLASM OF FUNDUS OF STOMACH	2
B501.00	MALIGNANT NEOPLASM OF ORBIT	2
B213000	MALIGNANT NEOPLASM OF ARYTENOID CARTILAGE	2
B62x100	LYMPHO-EPITHELIOID LYMPHOMA	2
B322.00	MALIGNANT MELANOMA OF EAR AND EXTERNAL AURICULAR CANAL	2
Byu0.00	[X]MALIGNANT NEOPLASM OF LIP, ORAL CAVITY AND PHARYNX	2
B316.00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE TRUNK UNSPECIFIED	2
B06y.00	MALIGNANT NEOPLASM OF OROPHARYNX, OTHER SPECIFIED SITES	2
B3...00	MALIGNANT NEOPLASM OF BONE, CONNECTIVE TISSUE, SKIN AND BREAST	2
B510400	MALIGNANT NEOPLASM OF HYPOTHALAMUS	2
ByuD900	[X]OTHER LEUKAEMIA OF UNSPECIFIED CELL TYPE	2
B141.00	MALIGNANT NEOPLASM OF RECTUM	2
B63z.00	IMMUNOPROLIFERATIVE NEOPLASM OR MYELOMA NOS	2
B545z00	MALIGNANT NEOPLASM OF AORTIC BODY OR PARAGANGLIA NOS	2
B073000	MALIGNANT NEOPLASM OF FLOOR OF NASOPHARYNX	2
B306z00	MALIGNANT NEOPLASM OF PELVIS, SACRUM OR COCCYX NOS	2
B18y700	MALIGNANT NEOPLASM OF MESENTERY	2
B326z00	MALIGNANT MELANOMA OF UPPER LIMB OR SHOULDER NOS	2

B6y1.00	MYELO-SCLEROSIS WITH MYELOID METAPLASIA	2
B611600	HODGKIN'S GRANULOMA OF INTRAPELVIC LYMPH NODES	2
B41y100	MALIGNANT NEOPLASM OF SQUAMOCOLUMNAR JUNCTION OF CERVIX	2
B62x.00	MALIGNANT LYMPHOMA OTHERWISE SPECIFIED	2
B4z..00	MALIGNANT NEOPLASM OF GENITOURINARY ORGAN NOS	2
B333500	MALIGNANT NEOPLASM OF SKIN OF TEMPLE	2
ZV10411	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF CERVIX UTERI	2
B004300	MALIGNANT NEOPLASM OF LIP, ORAL ASPECT	2
B600000	RETICULO-SARCOMA OF UNSPECIFIED SITE	2
B651.11	CHRONIC GRANULOCYTIC LEUKAEMIA	2
B150z00	PRIMARY MALIGNANT NEOPLASM OF LIVER NOS	2
B326300	MALIGNANT MELANOMA OF HAND	2
ZV10713	[V]PERSONAL HISTORY OF OTHER HAEMATOPOIETIC NEOPLASM	2
B496.00	MALIGNANT NEOPLASM OF URETERIC ORIFICE	2
1419AA	LINGUAL/TONGUE CANCER	2
B337.00	MALIGNANT NEOPLASM OF SKIN OF LOWER LIMB AND HIP	2
B43..00	MALIGNANT NEOPLASM OF BODY OF UTERUS	2
B626200	MAST CELL MALIGNANCY OF INTRATHORACIC LYMPH NODES	2
B0zz.00	MALIGNANT NEOPLASM OF LIP, ORAL CAVITY AND PHARYNX NOS	2
B345.00	MALIGNANT NEOPLASM OF LOWER-OUTER QUADRANT OF FEMALE BREAST	2

ByuA100	[X]MALIGNANT NEOPLASM/CENTRAL NERVOUS SYSTEM, UNSPECIFIED	2
B2z..00	MALIGNANT NEOPLASM OTHER/ILL-DEFINED SITES RESP/INTRATHORACIC ORGANS	2
B337600	MALIGNANT NEOPLASM OF SKIN OF HEEL	2
B313z00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF THORAX NOS	2
B44z.00	MALIGNANT NEOPLASM OF UTERINE ADNEXA NOS	2
Byu5200	[X]KAPOSI'S SARCOMA OF MULTIPLE ORGANS	2
B64y100	PROLYMPHOCYTIC LEUKAEMIA	2
ByuDE00	[X]UNSPECIFIED B-CELL NON-HODGKIN'S LYMPHOMA	2
B622.00	SEZARY'S DISEASE	2
B180100	MALIGNANT NEOPLASM OF PERINEPHRIC TISSUE	2
B410.00	MALIGNANT NEOPLASM OF ENDOCERVIX	2
B325700	MALIGNANT MELANOMA OF BACK	2
B16y.00	MALIGNANT NEOPLASM OTHER GALLBLADDER/EXTRAHEPATIC BILE DUCT	2
B615500	HODGKIN'S MIXED CELLULARITY OF LYMPH NODES INGUINAL AND LEG	2
B241100	MALIGNANT NEOPLASM OF EPICARDIUM	2
B004z00	MALIGNANT NEOPLASM OF LIP, INNER ASPECT NOS	2
B02y.00	MALIGNANT NEOPLASM OF OTHER MAJOR SALIVARY GLANDS	2
B201z00	MALIGNANT NEOPLASM AUDITORY TUBE, MIDDLE EAR, MASTOID AIR CELLS NOS	2
B616200	HODGKIN'S LYMPHOCYTIC DEPLETION OF INTRATHORACIC LYMPH NODES	2

B335100	MALIGNANT NEOPLASM OF SKIN OF CHEST, EXCLUDING BREAST	2
B005.00	MALIGNANT NEOPLASM OF COMMISSURE OF LIP	2
B517200	MALIGNANT NEOPLASM OF MIDBRAIN	2
B0z1.00	MALIGNANT NEOPLASM OF WALDEYER'S RING	2
B600100	RETICULO-SARCOMA OF LYMPH NODES OF HEAD, FACE AND NECK	2
B492.00	MALIGNANT NEOPLASM OF LATERAL WALL OF URINARY BLADDER	2
B161z00	MALIGNANT NEOPLASM OF EXTRAHEPATIC BILE DUCTS NOS	2
B5...00	MALIGNANT NEOPLASM OF OTHER AND UNSPECIFIED SITES	2
B61z000	HODGKIN'S DISEASE NOS, UNSPECIFIED SITE	2
B2...00	MALIGNANT NEOPLASM OF RESPIRATORY TRACT AND INTRATHORACIC ORGANS	2
B622z00	SEZARY'S DISEASE NOS	2
B335400	MALIGNANT NEOPLASM OF SKIN OF UMBILICUS	2
B4A1000	MALIGNANT NEOPLASM OF RENAL CALYCES	2
Byu2400	[X]MALIGNANT NEOPLASM/ILL-DEFINED SITES WITHIN RESP SYSTEM	2
B411.00	MALIGNANT NEOPLASM OF EXOCERVIX	2
ByuA.00	[X]MALIGNANT NEOPLASM OF EYE, BRAIN AND OTHER PARTS OF CENT	2
ByuDD00	[X]OTHER AND UNSPECIFIC PERIPHERAL & CUTANEOUS T-CELL LYMPHOMAS	2
B315000	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF BUTTOCK	2
B495.00	MALIGNANT NEOPLASM OF BLADDER NECK	2

B340100	MALIGNANT NEOPLASM OF AREOLA OF FEMALE BREAST	2
B542000	MALIGNANT NEOPLASM OF PITUITARY GLAND	2
B333000	MALIGNANT NEOPLASM OF SKIN OF CHEEK, EXTERNAL	2
B010z00	MALIGNANT NEOPLASM OF FIXED PART OF TONGUE NOS	2
B324100	MALIGNANT MELANOMA OF NECK	2
B65y100	ACUTE PROMYELOCYTIC LEUKAEMIA	2
B314z00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF ABDOMEN NOS	2
B500z00	MALIGNANT NEOPLASM OF EYEBALL NOS	2
B312400	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF FOOT	2
B311000	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF SHOULDER	2
B340.00	MALIGNANT NEOPLASM OF NIPPLE AND AREOLA OF FEMALE BREAST	2
B00zz00	MALIGNANT NEOPLASM OF LIP, VERMILION BORDER NOS	2
B241000	MALIGNANT NEOPLASM OF ENDOCARDIUM	2
B241300	MALIGNANT NEOPLASM OF PERICARDIUM	2
ZV10416	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF TESTIS	2
B630.12	MYELOMATOSIS	2
B350.00	MALIGNANT NEOPLASM OF NIPPLE AND AREOLA OF MALE BREAST	2
B690.00	ACUTE MYELOMONOCYTIC LEUKAEMIA	2
B181.00	MESOTHELIOMA OF PERITONEUM	2
B508.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF EYE AND ADNEXA	2
B486.00	MALIGNANT NEOPLASM OF SCROTUM	2

B62y600	MALIGNANT LYMPHOMA NOS OF INTRAPELVIC LYMPH NODES	2
B554.00	MALIGNANT NEOPLASM OF UPPER LIMB NOS	2
B150.00	PRIMARY MALIGNANT NEOPLASM OF LIVER	2
B524X00	MALIGNANT NEOPLASM/PERIPHERAL NERVES OF TRUNK, UNSPECIFIED	2
B443.00	MALIGNANT NEOPLASM OF PARAMETRIUM	2
B342.00	MALIGNANT NEOPLASM OF UPPER-INNER QUADRANT OF FEMALE BREAST	2
B213100	MALIGNANT NEOPLASM OF CRICOID CARTILAGE	2
B620800	NODULAR LYMPHOMA OF LYMPH NODES OF MULTIPLE SITES	2
B337300	MALIGNANT NEOPLASM OF SKIN OF POPLITEAL FOSSA AREA	2
B551200	MALIGNANT NEOPLASM OF INTRATHORACIC SITE NOS	2
B311500	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF THUMB	2
B613300	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PRED INTRA-ABDOMINAL NODE	2
Byu2300	[X] MALIGNANT NEOPLASM /OVERLAPPING LES/RESP ORGANS	2
ByuE.00	[X]MALIGNANT NEOPLASMS/INDEPENDENT (PRIMARY) MULTIPLE SITES	2
B410100	MALIGNANT NEOPLASM OF ENDOCERVICAL GLAND	2
Byu6.00	[X]MALIGNANT NEOPLASM OF BREAST	2
B660.00	ACUTE MONOCYTIC LEUKAEMIA	2
B311z00	MALIGNANT NEOPLASM CONNECTIVE SOFT TISSUE UPPER LIMB/SHOULDER NOS	2

B624300	LEUKAEMIC RETICULOEND OF INTRA-ABDOMINAL LYMPH NODES	2
B305.11	MALIGNANT NEOPLASM OF CARPAL BONES	2
B620000	NODULAR LYMPHOMA OF UNSPECIFIED SITE	2
B621100	MYCOSIS FUNGOIDES OF THE LYMPH NODES OF HEAD, FACE AND NECK	2
B621400	MYCOSIS FUNGOIDES OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B00z100	MALIGNANT NEOPLASM OF LIP, UNSPECIFIED, LIPSTICK AREA	2
B622700	SEZARY'S DISEASE OF SPLEEN	2
B230.00	MALIGNANT NEOPLASM OF PARIETAL PLEURA	2
B10z.11	OESOPHAGEAL CANCER	2
B62zz00	LYMPHOID AND HISTIOCYTIC MALIGNANCY NOS	2
B224100	MALIGNANT NEOPLASM OF LOWER LOBE OF LUNG	2
ZV10000	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF GASTROINTESTINAL TRACT	2
B504.00	MALIGNANT NEOPLASM OF CORNEA	2
Byu5.00	[X]MALIGNANT NEOPLASM OF MESOTHELIAL AND SOFT TISSUE	2
B653000	CHLOROMA	2
B334000	MALIGNANT NEOPLASM OF SCALP	2
B66..00	MONOCYTIC LEUKAEMIA	2
B622500	SEZARY'S DISEASE OF LYMPH NODES OF INGUINAL REGION AND LEG	2
B22y.00	MALIGNANT NEOPLASM OF OTHER SITES OF BRONCHUS OR LUNG	2
B540.11	PHEOCHROMOCYTOMA	2
B440.00	MALIGNANT NEOPLASM OF OVARY	2

ZV10714	[V]PERSONAL HISTORY OF RETICULO-SARCOMA	2
B307100	MALIGNANT NEOPLASM OF FIBULA	2
B612.00	HODGKIN'S SARCOMA	2
B613z00	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PREDOMINANCE NOS	2
B55y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES	2
B420.00	CHORIOCARCINOMA	2
B331200	MALIGNANT NEOPLASM OF LOWER EYELID	2
B62z600	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC OF INTRAPELVIC NODES	2
B300C00	MALIGNANT NEOPLASM OF VOMER	2
B4A1.00	MALIGNANT NEOPLASM OF RENAL PELVIS	2
ByuDC00	[X]DIFFUSE NON-HODGKIN'S LYMPHOMA, UNSPECIFIED	2
B625600	LETTERER-SIWE DISEASE OF INTRAPELVIC LYMPH NODES	2
B5...11	CARCINOMA OF OTHER AND UNSPECIFIED SITES	2
B110.00	MALIGNANT NEOPLASM OF CARDIA OF STOMACH	2
B553z00	MALIGNANT NEOPLASM OF PELVIS NOS	2
B221100	MALIGNANT NEOPLASM OF HILUS OF LUNG	2
B550z00	MALIGNANT NEOPLASM OF HEAD, NECK AND FACE NOS	2
B517z00	MALIGNANT NEOPLASM OF BRAIN STEM NOS	2
B33z.00	MALIGNANT NEOPLASM OF SKIN NOS	2
ByuDA00	[X]OTHER SPECIFIC MALIGNANT NEOPLASM /LYMPHOID, HAEMATO-POIETIC TISSUE	2

B6...00	MALIGNANT NEOPLASM OF LYMPHATIC AND HAEMOPOIETIC TISSUE	2
B672.00	MEGAKARYOCYTIC LEUKAEMIA	2
B67..00	OTHER SPECIFIED LEUKAEMIA	2
B142000	MALIGNANT NEOPLASM OF CLOACOGENIC ZONE	2
B521000	MALIGNANT NEOPLASM OF CEREBRAL DURA MATER	2
Byu2500	[X]MALIGNANT NEOPLASM OF MEDIASTINUM, PART UNSPECIFIED	2
B337200	MALIGNANT NEOPLASM OF SKIN OF KNEE	2
B612400	HODGKIN'S SARCOMA OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B211.00	MALIGNANT NEOPLASM OF SUPRA-GLOTTIS	2
B337500	MALIGNANT NEOPLASM OF SKIN OF ANKLE	2
B333300	MALIGNANT NEOPLASM OF SKIN OF FOREHEAD	2
B17z.00	MALIGNANT NEOPLASM OF PANCREAS NOS	2
B524400	MALIGNANT NEOPLASM OF PERIPHERAL NERVE OF ABDOMEN	2
B011000	MALIGNANT NEOPLASM OF ANTERIOR 2/3 OF TONGUE DORSAL SURFACE	2
B501100	MALIGNANT NEOPLASM OF EXTRAOCULAR MUSCLE OF ORBIT	2
B073z00	MALIGNANT NEOPLASM OF ANTERIOR WALL OF NASOPHARYNX NOS	2
B06yz00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE OF OROPHARYNX NOS	2
B64y000	ALEUKAEMIC LYMPHOID LEUKAEMIA	2
B062200	MALIGNANT NEOPLASM OF PALATOGLOSSAL ARCH	2
B553.00	MALIGNANT NEOPLASM OF PELVIS	2
B327500	MALIGNANT MELANOMA OF ANKLE	2

B622000	SEZARY'S DISEASE OF UNSPECIFIED SITE	2
B32y000	OVERLAPPING MALIGNANT MELANOMA OF SKIN	2
B47z.00	MALIGNANT NEOPLASM OF TESTIS NOS	2
B517100	MALIGNANT NEOPLASM OF MEDULLA OBLONGATA	2
B337700	MALIGNANT NEOPLASM OF SKIN OF FOOT	2
B500300	MALIGNANT NEOPLASM OF SCLERA	2
B32z.00	MALIGNANT MELANOMA OF SKIN NOS	2
B4A..00	MALIGNANT NEOPLASM OF KIDNEY AND OTHER UNSPECIFIED URINARY ORGANS	2
B615600	HODGKIN'S MIXED CELLULARITY OF INTRAPELVIC LYMPH NODES	2
B623100	MALIGNANT HISTIOCYTOSIS OF LYMPH NODES HEAD, FACE AND NECK	2
B514.00	MALIGNANT NEOPLASM OF OCCIPITAL LOBE	2
B515100	MALIGNANT NEOPLASM OF FLOOR OF CEREBRAL VENTRICLE	2
B315200	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF PERINEUM	2
Byu5000	[X]MESOTHELIOMA OF OTHER SITES	2
B325500	MALIGNANT MELANOMA OF PERINEUM	2
B524.00	MALIGNANT NEOPLASM PERIPHERAL NERVES AND AUTONOMIC NERVOUS SYSTEM	2
B315z00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF PELVIS NOS	2
B517.00	MALIGNANT NEOPLASM OF BRAIN STEM	2
B303400	MALIGNANT NEOPLASM OF COSTO-VERTEBRAL JOINT	2
B524100	MALIGNANT NEOPLASM OF PERIPHERAL NERVE, UPPER LIMB	2

B627400	DIFFUSE NON-HODGKIN'S SMALL CLEAVED CELL (DIFFUSE) LYMPHOMA	2
B323.00	MALIGNANT MELANOMA OF OTHER AND UNSPECIFIED PARTS OF FACE	2
B450000	MALIGNANT NEOPLASM OF GARTNER'S DUCT	2
B444.00	MALIGNANT NEOPLASM OF ROUND LIGAMENT	2
B3y..00	MALIGNANT NEOPLASM OF BONE, CONNECTIVE TISSUE, SKIN AND BREAST OS	2
B30..00	MALIGNANT NEOPLASM OF BONE AND ARTICULAR CARTILAGE	2
B45y000	MALIGNANT NEOPLASM OF OVERLAPPING LESION OF VULVA	2
B175.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF PANCREAS	2
B174.00	MALIGNANT NEOPLASM OF ISLETS OF LANGERHANS	2
B4Az.00	MALIGNANT NEOPLASM OF KIDNEY OR URINARY ORGANS NOS	2
B335000	MALIGNANT NEOPLASM OF SKIN OF AXILLARY FOLD	2
B056.00	MALIGNANT NEOPLASM OF RETROMOLAR AREA	2
B452.00	MALIGNANT NEOPLASM OF LABIA MINORA	2
B03..00	MALIGNANT NEOPLASM OF GUM	2
B18y600	MALIGNANT NEOPLASM OF THE POUCH OF DOUGLAS	2
B627600	DIFFUSE NON-HODGKIN'S IMMUNOBLASTIC (DIFFUSE) LYMPHOMA	2
ZV10700	[V]PERSONAL HISTORY OTHER LYMPHATIC/HAEMATOPOIETIC NEOPLASM	2
B305.12	MALIGNANT NEOPLASM OF METACARPAL BONES	2

B336200	MALIGNANT NEOPLASM OF SKIN OF FORE-ARM	2
B611z00	HODGKIN'S GRANULOMA NOS	2
ZV10y16	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF TONGUE	2
B62z.00	MALIGNANT NEOPLASMS OF LYMPHOID AND HISTIOCYTIC TISSUE NOS	2
B140.00	MALIGNANT NEOPLASM OF RECTOSIGMOID JUNCTION	2
B681.00	CHRONIC LEUKAEMIA NOS	2
ZV10011	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF ANUS	2
B341.00	MALIGNANT NEOPLASM OF CENTRAL PART OF FEMALE BREAST	2
B0zy.00	MALIGNANT NEOPLASM OF OTHER SITES LIP, ORAL CAVITY, PHARYNX	2
B300z00	MALIGNANT NEOPLASM OF BONES OF SKULL AND FACE NOS	2
B431z00	MALIGNANT NEOPLASM OF ISTHMUS OF UTERINE BODY NOS	2
B062z00	MALIGNANT NEOPLASM OF TONSILLAR FOSSA NOS	2
B004000	MALIGNANT NEOPLASM OF LIP UNSPECIFIED, BUCCAL ASPECT	2
B4A2.00	MALIGNANT NEOPLASM OF URETER	2
B310z00	MALIGNANT NEOPLASM CONNECTIVE AND SOFT TISSUE HEAD, FACE, NECK NOS	2
B003100	MALIGNANT NEOPLASM OF LOWER LIP, FRENULUM	2
B223100	MALIGNANT NEOPLASM OF MIDDLE LOBE OF LUNG	2
B182.00	OVERLAPPING MALIGN LESION OF RETROPERITONEUM AND PERITONEUM	2

B305600	MALIGNANT NEOPLASM OF CARPAL BONE - CAPITATE	2
B651z00	CHRONIC MYELOID LEUKAEMIA NOS	2
B003300	MALIGNANT NEOPLASM OF LOWER LIP, ORAL ASPECT	2
B002200	MALIGNANT NEOPLASM OF UPPER LIP, MUCOSA	2
B060000	MALIGNANT NEOPLASM OF FAUCIAL TONSIL	2
B521.00	MALIGNANT NEOPLASM OF CEREBRAL MENINGES	2
B00z.00	MALIGNANT NEOPLASM OF VERMILION BORDER OF LIP UNSPECIFIED	2
B431.00	MALIGNANT NEOPLASM OF ISTHMUS OF UTERINE BODY	2
ZV10012	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF GASTROINTESTINAL TRACT	2
ByuE000	[X]MALIGNANT NEOPLASMS/INDEPENDENT(PRIMARY)MULTIPLE SITES	2
B470000	MALIGNANT NEOPLASM OF ECTOPIC TESTIS	2
B304300	MALIGNANT NEOPLASM OF RADIUS	2
B11y000	MALIGNANT NEOPLASM OF ANTERIOR WALL OF STOMACH NEC	2
B600400	RETICULO-SARCOMA OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B117.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF STOMACH	2
B305800	MALIGNANT NEOPLASM OF FIRST METACARPAL BONE	2
B611000	HODGKIN'S GRANULOMA OF UNSPECIFIED SITE	2
B212.00	MALIGNANT NEOPLASM OF SUB-GLOTTIS	2

B100.00	MALIGNANT NEOPLASM OF CERVICAL OESOPHAGUS	2
B62y400	MALIGNANT LYMPHOMA NOS OF LYMPH NODES OF AXILLA AND ARM	2
B430000	MALIGNANT NEOPLASM OF CORNU OF CORPUS UTERI	2
B507100	MALIGNANT NEOPLASM OF NASOLACRIMAL DUCT	2
B612500	HODGKIN'S SARCOMA OF LYMPH NODES OF INGUINAL REGION AND LEG	2
B61zz00	HODGKIN'S DISEASE NOS	2
B303200	MALIGNANT NEOPLASM OF CLAVICLE	2
B601700	LYMPHOSARCOMA OF SPLEEN	2
B66z.00	MONOCYTIC LEUKAEMIA NOS	2
B180.00	MALIGNANT NEOPLASM OF RETROPERITONEUM	2
B60z.00	RETICULO-SARCOMA OR LYMPHOSARCOMA NOS	2
B50z.00	MALIGNANT NEOPLASM OF EYE NOS	2
B620500	NODULAR LYMPHOMA OF LYMPH NODES OF INGUINAL REGION AND LEG	2
B600.00	RETICULO-SARCOMA	2
B516.00	MALIGNANT NEOPLASM OF CEREBELLUM	2
B523.00	MALIGNANT NEOPLASM OF SPINAL MENINGES	2
B001z00	MALIGNANT NEOPLASM OF LOWER LIP, VERMILION BORDER NOS	2
Byu1100	[X]OTHER SPECIFIED CARCINOMAS OF LIVER	2
B1...11	CARCINOMA OF DIGESTIVE ORGANS AND PERITONEUM	2
B52W.00	MALIGNANT NEOPLASM, OVERLAP LESION BRAIN & OTHER PART OF CNS	2

B616800	HODGKIN'S LYMPHOCYTIC DEPLETION LYMPH NODES MULTIPLE SITES	2
B49y000	MALIGNANT NEOPLASM, OVERLAPPING LESION OF BLADDER	2
B067.00	MALIGNANT NEOPLASM OF POSTERIOR WALL OF OROPHARYNX	2
B621z00	MYCOSIS FUNGOIDES NOS	2
B624400	LEUKAEMIC RETICULOEND OF LYMPH NODES OF AXILLA AND ARM	2
B4y..00	MALIGNANT NEOPLASM OF GENITOURINARY ORGAN OS	2
B65z.00	MYELOID LEUKAEMIA NOS	2
B110100	MALIGNANT NEOPLASM OF CARDIO-OESOPHAGEAL JUNCTION OF STOMACH	2
B302.00	MALIGNANT NEOPLASM OF VERTEBRAL COLUMN	2
B011100	MALIGNANT NEOPLASM OF MIDLINE OF TONGUE	2
B334z00	MALIGNANT NEOPLASM OF SCALP OR SKIN OF NECK NOS	2
B011.00	MALIGNANT NEOPLASM OF DORSAL SURFACE OF TONGUE	2
B64y200	ADULT T-CELL LEUKAEMIA	2
ByuD300	[X]OTHER SPECIFIED TYPES OF NON-HODGKIN'S LYMPHOMA	2
B337800	MALIGNANT NEOPLASM OF SKIN OF TOE	2
B610800	HODGKIN'S PARAGRANULOMA OF LYMPH NODES OF MULTIPLE SITES	2
B23y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED PLEURA	2
B346.00	MALIGNANT NEOPLASM OF AXILLARY TAIL OF FEMALE BREAST	2

B17..00	MALIGNANT NEOPLASM OF PANCREAS	2
B1z2.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF DIGESTIVE SYSTEM	2
B063.00	MALIGNANT NEOPLASM OF VALLECULA	2
B623300	MALIGNANT HISTIOCYTOSIS OF INTRA-ABDOMINAL LYMPH NODES	2
B313100	MALIGNANT NEOPLASM OF DIAPHRAGM	2
B303500	MALIGNANT NEOPLASM OF XIPHOID PROCESS	2
B64..00	LYMPHOID LEUKAEMIA	2
B150100	HEPATOBLASTOMA OF LIVER	2
B49z.00	MALIGNANT NEOPLASM OF URINARY BLADDER NOS	2
B48..00	MALIGNANT NEOPLASM OF PENIS AND OTHER MALE GENITAL ORGANS	2
B682.00	SUBACUTE LEUKAEMIA NOS	2
B450100	MALIGNANT NEOPLASM OF VAGINAL VAULT	2
B602800	BURKITT'S LYMPHOMA OF LYMPH NODES OF MULTIPLE SITES	2
B620400	NODULAR LYMPHOMA OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B302200	MALIGNANT NEOPLASM OF LUMBAR VERTEBRA	2
B62y000	MALIGNANT LYMPHOMA NOS OF UNSPECIFIED SITE	2
B347.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF BREAST	2
B22z.00	MALIGNANT NEOPLASM OF BRONCHUS OR LUNG NOS	2
B625000	LETTERER-SIWE DISEASE OF UNSPECIFIED SITES	2
B323300	MALIGNANT MELANOMA OF FOREHEAD	2
B060100	MALIGNANT NEOPLASM OF PALATINE TONSIL	2

B223000	MALIGNANT NEOPLASM OF MIDDLE LOBE BRONCHUS	2
B471000	SEMINOMA OF DESCENDED TESTIS	2
B615800	HODGKIN'S MIXED CELLULARITY OF LYMPH NODES OF MULTIPLE SITES	2
B17y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF PANCREAS	2
B213.00	MALIGNANT NEOPLASM OF LARYNGEAL CARTILAGE	2
B062300	MALIGNANT NEOPLASM OF PALATOPHARYNGEAL ARCH	2
B68z.00	LEUKAEMIA NOS	2
B610400	HODGKIN'S PARAGRANULOMA OF LYMPH NODES OF AXILLA AND ARM	2
B18y000	MALIGNANT NEOPLASM OF MESOCOLON	2
B61z300	HODGKIN'S DISEASE NOS OF INTRA-ABDOMINAL LYMPH NODES	2
ZV10712	[V]PERSONAL HISTORY OF LYMPHOSARCOMA	2
B002300	MALIGNANT NEOPLASM OF UPPER LIP, ORAL ASPECT	2
B1zy.00	MALIGNANT NEOPLASM OTHER SPEC DIGESTIVE TRACT AND PERITONEUM	2
B442.00	MALIGNANT NEOPLASM OF BROAD LIGAMENT	2
B042.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF FLOOR OF MOUTH	2
Byu1.00	[X]MALIGNANT NEOPLASM OF DIGESTIVE ORGANS	2
B12z.00	MALIGNANT NEOPLASM OF SMALL INTESTINE NOS	2
B21z.00	MALIGNANT NEOPLASM OF LARYNX NOS	2
B517000	MALIGNANT NEOPLASM OF CEREBRAL PEDUNCLE	2

B08..00	MALIGNANT NEOPLASM OF HYPOPHARYNX	2
B111100	MALIGNANT NEOPLASM OF PYLORIC CANAL OF STOMACH	2
B317.00	MALIGNANT NEOPLASM, OVERLAP LESION CONNECTIVE & SOFT TISSUE	2
B13z.00	MALIGNANT NEOPLASM OF COLON NOS	2
B10..00	MALIGNANT NEOPLASM OF OESOPHAGUS	2
B301.00	MALIGNANT NEOPLASM OF MANDIBLE	2
B335500	MALIGNANT NEOPLASM OF SKIN OF GROIN	2
B306100	MALIGNANT NEOPLASM OF ISCHIUM	2
B335A00	MALIGNANT NEOPLASM OF SKIN OF SCAPULAR REGION	2
B325800	MALIGNANT MELANOMA OF CHEST WALL	2
B327800	MALIGNANT MELANOMA OF TOE	2
B623600	MALIGNANT HISTIOCYTOSIS OF INTRAPELVIC LYMPH NODES	2
Byu4300	[X]MALIGNANT NEOPLASM OF SKIN, UNSPECIFIED	2
ZV10y13	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF EYE	2
B304200	MALIGNANT NEOPLASM OF HUMERUS	2
B04z.00	MALIGNANT NEOPLASM OF FLOOR OF MOUTH NOS	2
ZV10111	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF BRONCHUS	2
B550400	MALIGNANT NEOPLASM OF NECK NOS	2
B551000	MALIGNANT NEOPLASM OF AXILLA NOS	2
B670.11	DI GUGLIELMO'S DISEASE	2
B620.00	NODULAR LYMPHOMA (BRILL - SYMMERS DISEASE)	2
B61z600	HODGKIN'S DISEASE NOS OF INTRAPELVIC LYMPH NODES	2

B66..12	MONOBLASTIC LEUKAEMIA	2
B652.00	SUBACUTE MYELOID LEUKAEMIA	2
B63y.00	OTHER IMMUNOPROLIFERATIVE NEOPLASMS	2
B630000	MALIGNANT PLASMA CELL NEOPLASM, EXTRAMEDULLARY PLASMACYTOMA	2
B11z.00	MALIGNANT NEOPLASM OF STOMACH NOS	2
B48z.00	MALIGNANT NEOPLASM OF PENIS AND OTHER MALE GENITAL ORGAN NOS	2
B540.00	MALIGNANT NEOPLASM OF ADRENAL GLAND	2
B312100	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE THIGH AND UPPER LEG	2
B626100	MAST CELL MALIGNANCY OF LYMPH NODES OF HEAD, FACE AND NECK	2
B305D00	MALIGNANT NEOPLASM OF PHALANGES OF HAND	2
B223z00	MALIGNANT NEOPLASM OF MIDDLE LOBE, BRONCHUS OR LUNG NOS	2
B623700	MALIGNANT HISTIOCYTOSIS OF SPLEEN	2
B0...11	CARCINOMA OF LIP, ORAL CAVITY AND PHARYNX	2
B222000	MALIGNANT NEOPLASM OF UPPER LOBE BRONCHUS	2
B327z00	MALIGNANT MELANOMA OF LOWER LIMB OR HIP NOS	2
B55yz00	MALIGNANT NEOPLASM OF SPECIFIED SITE NOS	2
B013100	MALIGNANT NEOPLASM OF FRENULUM LINGUAE	2
Byu7300	[X]MALIGNANT NEOPLASM OF FEMALE GENITAL ORGAN, UNSPECIFIED	2
B023.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF MAJOR SALIV GLAND	2

B310500	MALIGNANT NEOPLASM SOFT TISSUES OF CERVICAL SPINE	2
Byu5600	[X]MAL NEOPLASM/PERIPH NERVES NERVOUS SYSTEM, UNSPECIFIC	2
ByuD000	[X]OTHER HODGKIN'S DISEASE	2
B552.00	MALIGNANT NEOPLASM OF ABDOMEN	2
B520z00	MALIGNANT NEOPLASM OF CRANIAL NERVES NOS	2
B082.00	MALIGNANT NEOPLASM ARYEPIGLOTTIC FOLD, HYPOPHARYNGEAL ASPECT	2
B625.11	HISTIOCYTOSIS X (ACUTE, PROGRESSIVE)	2
B312000	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF HIP	2
B501000	MALIGNANT NEOPLASM OF CONNECTIVE TISSUE OF ORBIT	2
B201200	MALIGNANT NEOPLASM OF TYMPANIC ANTRUM	2
B241400	MESOTHELIOMA OF PERICARDIUM	2
ByuC000	[X]MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES	2
B67z.00	OTHER SPECIFIED LEUKAEMIA NOS	2
B18y.00	MALIGNANT NEOPLASM OF SPECIFIED PARTS OF PERITONEUM	2
B620z00	NODULAR LYMPHOMA NOS	2
B327200	MALIGNANT MELANOMA OF KNEE	2
B53..00	MALIGNANT NEOPLASM OF THYROID GLAND	2
B545200	MALIGNANT NEOPLASM OF COCCYGEAL BODY	2
B65yz00	OTHER MYELOID LEUKAEMIA NOS	2
B431000	MALIGNANT NEOPLASM OF LOWER UTERINE SEGMENT	2
ByuDF11	[X]NON-HODGKIN'S LYMPHOMA NOS	2

B337900	MALIGNANT NEOPLASM OF SKIN OF GREAT TOE	2
B308600	MALIGNANT NEOPLASM OF CUBOID	2
Byu2100	[X]MALIGNANT NEOPLASM/OVERLAP LESION/HEART, MEDIASTINUM	2
B62x300	MALIGNANT RETICULO-ENDOTHELIOSIS	2
ZV10100	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF TRACHEA/BRONCHUS/LUNG	2
B000100	MALIGNANT NEOPLASM OF UPPER LIP, LIPSTICK AREA	2
B611700	HODGKIN'S GRANULOMA OF SPLEEN	2
B061.00	MALIGNANT NEOPLASM OF TONSILLAR FOSSA	2
Byu8.00	[X]MALIGNANT NEOPLASM OF MALE GENITAL ORGANS	2
B335700	MALIGNANT NEOPLASM OF SKIN OF BACK	2
Byu9000	[X]MALIGNANT NEOPLASM OF URINARY ORGAN, UNSPECIFIED	2
B65y000	ALEUKAEMIC MYELOID LEUKAEMIA	2
B01z.00	MALIGNANT NEOPLASM OF TONGUE NOS	2
B33z000	KAPOSI'S SARCOMA OF SKIN	2
B41y.00	MALIGNANT NEOPLASM OF OTHER SITE OF CERVIX	2
B43z.00	MALIGNANT NEOPLASM OF BODY OF UTERUS NOS	2
B517300	MALIGNANT NEOPLASM OF PONS	2
B201100	MALIGNANT NEOPLASM OF TYMPANIC CAVITY	2
B20..00	MALIGNANT NEOPLASM NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES	2
B143.00	MALIGNANT NEOPLASM OF ANUS UNSPECIFIED	2
B623z00	MALIGNANT HISTIOCYTOSIS NOS	2
B14..00	MALIGNANT NEOPLASM OF RECTUM, RECTOSIGMOID JUNCTION AND ANUS	2

B520100	MALIGNANT NEOPLASM OF OPTIC NERVE	2
B485.00	MALIGNANT NEOPLASM OF SPERMATIC CORD	2
B510500	MALIGNANT NEOPLASM OF THALAMUS	2
B540000	MALIGNANT NEOPLASM OF ADRENAL CORTEX	2
B314000	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF ABDOMINAL WALL	2
B308D00	MALIGNANT NEOPLASM OF PHALANGES OF FOOT	2
B48y200	MALIGNANT NEOPLASM, OVERLAPPING LESION MALE GENITAL ORGS	2
B050.11	MALIGNANT NEOPLASM OF BUCCAL MUCOSA	2
B003z00	MALIGNANT NEOPLASM OF LOWER LIP, INNER ASPECT NOS	2
B612300	HODGKIN'S SARCOMA OF INTRA-ABDOMINAL LYMPH NODES	2
ZV10513	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF KIDNEY	2
B450z00	MALIGNANT NEOPLASM OF VAGINA NOS	2
B62z000	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC OF UNSPECIFIED SITE	2
B020.00	MALIGNANT NEOPLASM OF PAROTID GLAND	2
B67y.00	OTHER AND UNSPECIFIED LEUKAEMIA	2
B000z00	MALIGNANT NEOPLASM OF UPPER LIP, VERMILION BORDER NOS	2
B622800	SEZARY'S DISEASE OF LYMPH NODES OF MULTIPLE SITES	2
B01y.00	MALIGNANT NEOPLASM OF OTHER SITES OF TONGUE	2
B64y.00	OTHER LYMPHOID LEUKAEMIA	2
B055000	MALIGNANT NEOPLASM OF JUNCTION OF HARD AND SOFT PALATE	2

B051.00	MALIGNANT NEOPLASM OF VESTIBULE OF MOUTH	2
B614100	HODGKIN'S NODULAR SCLEROSIS OF HEAD, FACE AND NECK	2
B004200	MALIGNANT NEOPLASM OF LIP UNSPECIFIED, MUCOSA	2
B05z.00	MALIGNANT NEOPLASM OF MOUTH NOS	2
B497.00	MALIGNANT NEOPLASM OF URACHUS	2
B073.00	MALIGNANT NEOPLASM OF ANTERIOR WALL OF NASOPHARYNX	2
B670.00	ACUTE ERYTHRAEMIA AND ERYTHRON-LEUKAEMIA	2
B24X.00	MALIGNANT NEOPLASM OF MEDIASTINUM, PART UNSPECIFIED	2
B45z.00	MALIGNANT NEOPLASM OF FEMALE GENITAL ORGAN NOS	2
B221000	MALIGNANT NEOPLASM OF CARINA OF BRONCHUS	2
B138.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF COLON	2
B451.00	MALIGNANT NEOPLASM OF LABIA MAJORA	2
B512000	MALIGNANT NEOPLASM OF HIPPOCAMPUS	2
B620100	NODULAR LYMPHOMA OF LYMPH NODES OF HEAD, FACE AND NECK	2
B310300	MALIGNANT NEOPLASM OF CARTILAGE OF EAR	2
B002000	MALIGNANT NEOPLASM OF UPPER LIP, BUCCAL ASPECT	2
B430200	MALIGNANT NEOPLASM OF ENDOMETRIUM OF CORPUS UTERI	2
B002z00	MALIGNANT NEOPLASM OF UPPER LIP, INNER ASPECT NOS	2
B161000	MALIGNANT NEOPLASM OF CYSTIC DUCT	2

B062.00	MALIGNANT NEOPLASM OF TONSILLAR PILLAR	2
ZV10200	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OTHER INTRATHORACIC ORGAN	2
B24z.00	MALIGNANT NEOPLASM OF HEART, THYMUS AND MEDIASTINUM NOS	2
B307000	MALIGNANT NEOPLASM OF FEMUR	2
B308200	MALIGNANT NEOPLASM OF CALCANEUM	2
B308A00	MALIGNANT NEOPLASM OF THIRD METATARSAL BONE	2
B022.00	MALIGNANT NEOPLASM OF SUBLINGUAL GLAND	2
B32..00	MALIGNANT MELANOMA OF SKIN	2
B627200	FOLLICULAR NON-HODGKIN'S LARGE CELL LYMPHOMA	2
B600600	RETICULO-SARCOMA OF INTRAPELVIC LYMPH NODES	2
B630.11	KAHLER'S DISEASE	2
B335z00	MALIGNANT NEOPLASM OF SKIN OF TRUNK, EXCLUDING SCROTUM, NOS	2
B111000	MALIGNANT NEOPLASM OF PREPYLORUS OF STOMACH	2
B35z000	MALIGNANT NEOPLASM OF ECTOPIC SITE OF MALE BREAST	2
B055z00	MALIGNANT NEOPLASM OF PALATE NOS	2
B11y100	MALIGNANT NEOPLASM OF POSTERIOR WALL OF STOMACH NEC	2
B300200	MALIGNANT NEOPLASM OF MALAR BONE	2
B50..00	MALIGNANT NEOPLASM OF EYE	2
B123.00	MALIGNANT NEOPLASM OF MECKEL'S DIVERTICULUM	2
B50y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE OF EYE	2

B071z00	MALIGNANT NEOPLASM OF POSTERIOR WALL OF NASOPHARYNX NOS	2
B625500	LETTERER-SIWE DISEASE OF LYMPH NODES INGUINAL REGION AND LEG	2
B51y200	MALIGNANT NEOPLASM, OVERLAPPING LESION OF BRAIN	2
B054.00	MALIGNANT NEOPLASM OF UVULA	2
B120.00	MALIGNANT NEOPLASM OF DUODENUM	2
B553000	MALIGNANT NEOPLASM OF INGUINAL REGION NOS	2
ZV10.00	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM	2
B23z.00	MALIGNANT NEOPLASM OF PLEURA NOS	2
ZV10016	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF OESOPHAGUS	2
B602300	BURKITT'S LYMPHOMA OF INTRA-ABDOMINAL LYMPH NODES	2
B54..00	MALIGNANT NEOPLASM OF OTHER ENDOCRINE GLANDS AND RELATED STRUCTURES	2
B22..00	MALIGNANT NEOPLASM OF TRACHEA, BRONCHUS AND LUNG	2
B61z500	HODGKIN'S DISEASE NOS OF LYMPH NODES INGUINAL REGION AND LEG	2
B51..00	MALIGNANT NEOPLASM OF BRAIN	2
B600200	RETICULO-SARCOMA OF INTRATHORACIC LYMPH NODES	2
B35..00	MALIGNANT NEOPLASM OF MALE BREAST	2
B602000	BURKITT'S LYMPHOMA OF UNSPECIFIED SITE	2
Byu8100	[X]MALIGNANT NEOPLASM/OVERLAPPING LESION/MALE GENITAL ORGANS	2
B071000	MALIGNANT NEOPLASM OF ADENOID	2

Byu4100	[X]MALIGNANT MELANOMA OF SKIN, UNSPECIFIED	2
ZV10412	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF GENITAL ORGAN	2
B621.00	MYCOSIS FUNGOIDES	2
B62z100	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC LYMPH NODE HEAD/NECK	2
B25..00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF HEART, MEDIASTINUM & PLEURA	2
ZV10017	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF RECTUM	2
B623000	MALIGNANT HISTIOCYTOSIS OF UNSPECIFIED SITE	2
B6y..00	MALIGNANT NEOPLASM LYMPHATIC OR HAEMATOPOIETIC TISSUE OS	2
B627300	DIFFUSE NON-HODGKIN'S SMALL CELL (DIFFUSE) LYMPHOMA	2
B308000	MALIGNANT NEOPLASM OF PATELLA	2
B610100	HODGKIN'S PARAGRANULOMA OF LYMPH NODES OF HEAD, FACE, NECK	2
ZV10500	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF URINARY ORGAN	2
B51y000	MALIGNANT NEOPLASM OF CORPUS CALLOSUM	2
B523000	MALIGNANT NEOPLASM OF SPINAL DURA MATER	2
B310100	MALIGNANT NEOPLASM OF SOFT TISSUE OF FACE	2
B051100	MALIGNANT NEOPLASM OF LOWER BUCCAL SULCUS	2
B327400	MALIGNANT MELANOMA OF LOWER LEG	2

B555.00	MALIGNANT NEOPLASM OF LOWER LIMB NOS	2
B35zz00	MALIGNANT NEOPLASM OF MALE BREAST NOS	2
B326500	MALIGNANT MELANOMA OF THUMB	2
B1zz.00	MALIGNANT NEOPLASM OF DIGESTIVE TRACT AND PERITONEUM NOS	2
B332.00	MALIGNANT NEOPLASM SKIN OF EAR AND EXTERNAL AURICULAR CANAL	2
ZV10019	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF TONGUE	2
B335900	MALIGNANT NEOPLASM OF PERIANAL SKIN	2
Byu1300	[X] MALIGNANT NEOPLASM /ILL-DEFINED SITES WITHIN DIGESTIVE SYSTEM	2
B013z00	MALIGNANT NEOPLASM OF VENTRAL TONGUE SURFACE NOS	2
B601400	LYMPHOSARCOMA OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B323500	MALIGNANT MELANOMA OF TEMPLE	2
B51..11	CEREBRAL TUMOUR - MALIGNANT	2
B226.00	MESOTHELIOMA	2
B0...00	MALIGNANT NEOPLASM OF LIP, ORAL CAVITY AND PHARYNX	2
B26..00	MALIGNANT NEOPLASM, OVERLAP LESION OF RESPIRATORY & INTRATHORACIC ORGANS	2
B220z00	MALIGNANT NEOPLASM OF TRACHEA NOS	2
B62z500	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC NODES INGUINAL/LEG	2
B616400	HODGKIN'S LYMPHOCYTIC DEPLETION LYMPH NODES AXILLA AND ARM	2
B611.00	HODGKIN'S GRANULOMA	2
B16..00	MALIGNANT NEOPLASM GALLBLADDER AND EXTRAHEPATIC BILE DUCTS	2

B553100	MALIGNANT NEOPLASM OF PRESACRAL REGION	2
B332z00	MALIGNANT NEOPLASM SKIN OF EAR AND EXTERNAL AURICULAR CANAL NOS	2
B333200	MALIGNANT NEOPLASM OF SKIN OF EYEBROW	2
B2z0.00	MALIGNANT NEOPLASM OF UPPER RESPIRATORY TRACT, PART UNSPECIFIED	2
B501z00	MALIGNANT NEOPLASM OF ORBIT NOS	2
B300500	MALIGNANT NEOPLASM OF ORBITAL BONE	2
B521z00	MALIGNANT NEOPLASM OF CEREBRAL MENINGES NOS	2
B624200	LEUKAEMIC RETICULOENDOTHELIOSIS OF INTRATHORACIC LYMPH NODES	2
B305.00	MALIGNANT NEOPLASM OF HAND BONES	2
B315.00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF PELVIS	2
B615300	HODGKIN'S MIXED CELLULARITY OF INTRA-ABDOMINAL LYMPH NODES	2
B200300	MALIGNANT NEOPLASM OF VESTIBULE OF NOSE	2
ZV10417	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF UTERINE BODY	2
B060.00	MALIGNANT NEOPLASM OF TONSIL	2
B627C00	FOLLICULAR NON-HODGKIN'S LYMPHOMA	2
B136.00	MALIGNANT NEOPLASM OF ASCENDING COLON	2
B221.00	MALIGNANT NEOPLASM OF MAIN BRONCHUS	2
B615400	HODGKIN'S MIXED CELLULARITY OF LYMPH NODES OF AXILLA AND ARM	2
B00..00	MALIGNANT NEOPLASM OF LIP	2
B003000	MALIGNANT NEOPLASM OF LOWER LIP, BUCCAL ASPECT	2
B671.11	HEILMEYER - SCHONER DISEASE	2

B303z00	MALIGNANT NEOPLASM OF RIB, STERNUM AND CLAVICLE NOS	2
B131.00	MALIGNANT NEOPLASM OF TRANSVERSE COLON	2
Byu5700	[X]MALIGNANT NEOPLASM OF PERITONEUM, UNSPECIFIED	2
B010000	MALIGNANT NEOPLASM OF BASE OF TONGUE DORSAL SURFACE	2
B305400	MALIGNANT NEOPLASM OF CARPAL BONE - TRAPEZIUM	2
B141.11	CARCINOMA OF RECTUM	2
Byu3.00	[X]MALIGNANT NEOPLASM OF BONE AND ARTICULAR CARTILAGE	2
B060z00	MALIGNANT NEOPLASM TONSIL NOS	2
B336500	MALIGNANT NEOPLASM OF SKIN OF THUMB	2
B300.00	MALIGNANT NEOPLASM OF BONES OF SKULL AND FACE	2
B625400	LETTERER-SIWE DISEASE OF LYMPH NODES OF AXILLA AND ARM	2
B624800	LEUKAEMIC RETICULOEND OF LYMPH NODES OF MULTIPLE SITES	2
B626800	MAST CELL MALIGNANCY OF LYMPH NODES OF MULTIPLE SITES	2
Byu3100	[X]MALIGNANT NEOPLASM/BONES??? CARTILAGE/LIMB, UNSPECIFIC	2
B006.00	MALIGNANT NEOPLASM OF OVERLAPPING LESION OF LIP	2
ZV10413	[V]PERSONAL HISTORY MALIGNANT NEOPLASM - MALE GENITAL ORGAN	2
ZV10113	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF TRACHEA	2

ZV10014	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF LARGE INTESTINE	2
B62x500	MALIGNANT IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE	2
B470z00	MALIGNANT NEOPLASM OF UNDESCENDED TESTIS NOS	2
ByuD600	[X]OTHER MYELOID LEUKAEMIA	2
B616700	HODGKIN'S DISEASE, LYMPHOCYTIC DEPLETION OF SPLEEN	2
B306200	MALIGNANT NEOPLASM OF PUBIS	2
B613800	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PRED OF MULTIPLE SITES	2
B520200	MALIGNANT NEOPLASM OF ACOUSTIC NERVE	2
B621800	MYCOSIS FUNGOIDES OF LYMPH NODES OF MULTIPLE SITES	2
B62z800	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC OF MULTIPLE SITES	2
B622300	SEZARY'S DISEASE OF INTRA-ABDOMINAL LYMPH NODES	2
B18yz00	MALIGNANT NEOPLASM OF SPECIFIED PARTS OF PERITONEUM NOS	2
B626.00	MALIGNANT MAST CELL TUMOURS	2
B324000	MALIGNANT MELANOMA OF SCALP	2
B621000	MYCOSIS FUNGOIDES OF UNSPECIFIED SITE	2
B121.00	MALIGNANT NEOPLASM OF JEJUNUM	2
B1z1000	ANGIOSARCOMA OF SPLEEN	2
B480.00	MALIGNANT NEOPLASM OF PREPUCE (FORESKIN)	2
B332100	MALIGNANT NEOPLASM OF SKIN OF EXTERNAL AUDITORY MEATUS	2
B601.00	LYMPHOSARCOMA	2
B65..00	MYELOID LEUKAEMIA	2

B170.00	MALIGNANT NEOPLASM OF HEAD OF PANCREAS	2
B325000	MALIGNANT MELANOMA OF AXILLA	2
B02..00	MALIGNANT NEOPLASM OF MAJOR SALIVARY GLANDS	2
B051300	MALIGNANT NEOPLASM OF LOWER LABIAL SULCUS	2
B307.00	MALIGNANT NEOPLASM OF LONG BONES OF LEG	2
ZV10600	[V]PERSONAL HISTORY OF LEUKAEMIA	2
B124.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF SMALL INTESTINE	2
B611800	HODGKIN'S GRANULOMA OF LYMPH NODES OF MULTIPLE SITES	2
B614800	HODGKIN'S NODULAR SCLEROSIS OF LYMPH NODES OF MULTIPLE SITES	2
B62z400	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC LYMPH NODE AXILLA/ARM	2
ZV10212	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF LARYNX	2
B45y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED FEMALE GENITAL ORGAN	2
B007.00	MALIGNANT NEOPLASM OF LIP, UNSPECIFIED	2
B512z00	MALIGNANT NEOPLASM OF TEMPORAL LOBE NOS	2
B310400	MALIGNANT NEOPLASM OF TARSUS OF EYELID	2
B13z.11	COLONIC CANCER	2
B623800	MALIGNANT HISTIOCYTOSIS OF LYMPH NODES OF MULTIPLE SITES	2
Byu7100	[X]MALIGNANT NEOPLASM/OTHER SPECIFIED FEMALE GENITAL ORGANS	2

B051200	MALIGNANT NEOPLASM OF UPPER LABIAL SULCUS	2
B430100	MALIGNANT NEOPLASM OF FUNDUS OF CORPUS UTERI	2
B610500	HODGKIN'S PARA-GRANULOMA LYMPH NODES INGUINAL REGION AND LEG	2
B223.00	MALIGNANT NEOPLASM OF MIDDLE LOBE, BRONCHUS OR LUNG	2
B545100	MALIGNANT NEOPLASM OF AORTIC BODY	2
B08z.00	MALIGNANT NEOPLASM OF HYPOPHARYNX NOS	2
B152.00	MALIGNANT NEOPLASM OF LIVER UNSPECIFIED	2
B1...00	MALIGNANT NEOPLASM OF DIGESTIVE ORGANS AND PERITONEUM	2
B323400	MALIGNANT MELANOMA OF EXTERNAL SURFACE OF NOSE	2
B615z00	HODGKIN'S DISEASE, MIXED CELLULARITY NOS	2
B613200	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PRED INTRATHORACIC NODES	2
B322100	MALIGNANT MELANOMA OF EXTERNAL AUDITORY MEATUS	2
B321.00	MALIGNANT MELANOMA OF EYELID INCLUDING CANTHUS	2
B651200	CHRONIC NEUTROPHILIC LEUKAEMIA	2
Byu..00	[X]ADDITIONAL NEOPLASM CLASSIFICATION TERMS	2
Byu2000	[X]MALIGNANT NEOPLASM OF BRONCHUS OR LUNG, UNSPECIFIED	2
B6y1.11	MEGAKARYOCYTIC MYELOSCLEROSIS	2
B626000	MAST CELL MALIGNANCY OF UNSPECIFIED SITE	2

B215.00	MALIGNANT NEOPLASM OF EPIGLOTTIS NOS	2
B0z0.00	MALIGNANT NEOPLASM OF PHARYNX UNSPECIFIED	2
ByuD800	[X]OTHER SPECIFIED LEUKAEMIAS	2
B671.00	CHRONIC ERYTHRAEMIA	2
B624100	LEUKAEMIC RETICULOEND OF LYMPH NODES OF HEAD, FACE AND NECK	2
B541.00	MALIGNANT NEOPLASM OF PARATHYROID GLAND	2
B545.00	MALIGNANT NEOPLASM OF AORTIC BODY AND OTHER PARAGANGLIA	2
ZV10613	[V]PERSONAL HISTORY OF MYELOID LEUKAEMIA	2
B470200	SEMINOMA OF UNDESCENDED TESTIS	2
B626600	MAST CELL MALIGNANCY OF INTRAPELVIC LYMPH NODES	2
ByuA000	[X]MALIGNANT NEOPLASM/OTHER AND UNSPECIFIED CRANIAL NERVES	2
B6z0.00	KAPOSI'S SARCOMA OF LYMPH NODES	2
B674.00	ACUTE PANMYELOSIS	2
B614400	HODGKIN'S NODULAR SCLEROSIS OF LYMPH NODES OF AXILLA AND ARM	2
B312z00	MALIGNANT NEOPLASM CONNECTIVE AND SOFT TISSUE HIP AND LEG NOS	2
B06y000	MALIGNANT NEOPLASM OF BRANCHIAL CLEFT	2
B602400	BURKITT'S LYMPHOMA OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B494.00	MALIGNANT NEOPLASM OF POSTERIOR WALL OF URINARY BLADDER	2
B335600	MALIGNANT NEOPLASM OF SKIN OF PERINEUM	2
B45..00	MALIGNANT NEOPLASM OF OTHER AND UNSPECIFIED FEMALE GENITAL ORGANS	2

B336300	MALIGNANT NEOPLASM OF SKIN OF HAND	2
B470300	TERATOMA OF UNDESCENDED TESTIS	2
B3...12	SARCOMA OF BONE AND CONNECTIVE TISSUE	2
B62y700	MALIGNANT LYMPHOMA NOS OF SPLEEN	2
B134.00	MALIGNANT NEOPLASM OF CAECUM	2
B510200	MALIGNANT NEOPLASM OF CORPUS STRIATUM	2
ZV10512	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF KIDNEY	2
B615.00	HODGKIN'S DISEASE, MIXED CELLULARITY	2
Byu5500	[X]MAL NEOPLASM/OVERLAP LES/PERIPHERAL NERVE SYSTEM	2
B48y.00	MALIGNANT NEOPLASM OF OTHER MALE GENITAL ORGAN	2
B051000	MALIGNANT NEOPLASM OF UPPER BUCCAL SULCUS	2
B062000	MALIGNANT NEOPLASM OF FAUCIAL PILLAR	2
B503.00	MALIGNANT NEOPLASM OF CONJUNCTIVA	2
ByuD400	[X]OTHER MALIGNANT IMMUNOPROLIFERATIVE DISEASES	2
B610.00	HODGKIN'S PARAGRANULOMA	2
Byu5900	[X]MALIGNANT NEOPLASM/CONNECTIVE SOFT TISSUE, UNSPECIFIED	2
B220000	MALIGNANT NEOPLASM OF CARTILAGE OF TRACHEA	2
B305300	MALIGNANT NEOPLASM OF CARPAL BONE - PISIFORM	2
B54z.00	MALIGNANT NEOPLASM OF ENDOCRINE GLAND OR RELATED STRUCTURE NOS	2
B13y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF COLON	2
B450.00	MALIGNANT NEOPLASM OF VAGINA	2

B40..00	MALIGNANT NEOPLASM OF UTERUS, PART UNSPECIFIED	2
B001100	MALIGNANT NEOPLASM OF LOWER LIP, LIPSTICK AREA	2
B51y.00	MALIGNANT NEOPLASM OF OTHER PARTS OF BRAIN	2
B545000	MALIGNANT NEOPLASM OF GLOMUS JUGULAR	2
B312300	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF LOWER LEG	2
B12y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE SMALL INTESTINE	2
B602z00	BURKITT'S LYMPHOMA NOS	2
B160.00	MALIGNANT NEOPLASM OF GALLBLADDER	2
B520000	MALIGNANT NEOPLASM OF OLFACTORY BULB	2
B13..00	MALIGNANT NEOPLASM OF COLON	2
B542.00	MALIGNANT NEOPLASM PITUITARY GLAND AND CRANIO-PHARYNGEAL DUCT	2
B335300	MALIGNANT NEOPLASM OF SKIN OF ABDOMINAL WALL	2
B52X.00	MALIGNANT NEOPLASM OF MENINGES, UNSPECIFIED	2
B333.00	MALIGNANT NEOPLASM SKIN OF OTHER AND UNSPECIFIED PARTS FACE	2
B110111	MALIGNANT NEOPLASM OF GASTRO-OESOPHAGEAL JUNCTION	2
B306300	MALIGNANT NEOPLASM OF SACRAL VERTEBRA	2
B481.00	MALIGNANT NEOPLASM OF GLANS PENIS	2
B61z800	HODGKIN'S DISEASE NOS OF LYMPH NODES OF MULTIPLE SITES	2
B62y200	MALIGNANT LYMPHOMA NOS OF INTRATHORACIC LYMPH NODES	2

B507z00	MALIGNANT NEOPLASM OF LACRIMAL DUCT NOS	2
B612z00	HODGKIN'S SARCOMA NOS	2
B18y500	MALIGNANT NEOPLASM OF PELVIC PERITONEUM	2
B602700	BURKITT'S LYMPHOMA OF SPLEEN	2
B614z00	HODGKIN'S DISEASE, NODULAR SCLEROSIS NOS	2
B073100	MALIGNANT NEOPLASM OF NASOPHARYNGEAL SOFT PALATE SURFACE	2
B616500	HODGKIN'S LYMPHOCYTIC DEPLETION LYMPH NODES INGUINAL AND LEG	2
B334.00	MALIGNANT NEOPLASM OF SCALP AND SKIN OF NECK	2
B620700	NODULAR LYMPHOMA OF SPLEEN	2
B61z700	HODGKIN'S DISEASE NOS OF SPLEEN	2
B64yz00	OTHER LYMPHOID LEUKAEMIA NOS	2
B612700	HODGKIN'S SARCOMA OF SPLEEN	2
B551z00	MALIGNANT NEOPLASM OF THORAX NOS	2
B610300	HODGKIN'S PARA-GRANULOMA OF INTRA-ABDOMINAL LYMPH NODES	2
ZV10211	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM - ACCESSORY SINUS	2
B180z00	MALIGNANT NEOPLASM OF RETROPERITONEUM NOS	2
B304100	MALIGNANT NEOPLASM OF ACROMION	2
B627W00	UNSPECIFIED B-CELL NON-HODGKIN'S LYMPHOMA	2
B081.00	MALIGNANT NEOPLASM OF PYRIFORM SINUS	2
B512.00	MALIGNANT NEOPLASM OF TEMPORAL LOBE	2
B064z00	MALIGNANT NEOPLASM OF ANTERIOR EPIGLOTTIS NOS	2

B213300	MALIGNANT NEOPLASM OF THYROID CARTILAGE	2
ZV10612	[V]PERSONAL HISTORY OF MONOCYTIC LEUKAEMIA	2
B627100	FOLLICULAR NON-HODG MIXED SML CLEAVD & LGE CELL LYMPHOMA	2
B084.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF HYPOPHARYNX	2
B491.00	MALIGNANT NEOPLASM OF DOME OF URINARY BLADDER	2
B522.00	MALIGNANT NEOPLASM OF SPINAL CORD	2
B312600	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF GREAT TOE	2
B308800	MALIGNANT NEOPLASM OF FIRST METATARSAL BONE	2
B308z00	MALIGNANT NEOPLASM OF SHORT BONES OF LEG NOS	2
B309.00	MALIGNANT NEOPLASM, OVERLAP LES BONE AND ARTIC CART OF LIMBS	2
B313000	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF AXILLA	2
B18y300	MALIGNANT NEOPLASM OF OMENTUM	2
B47z.12	TERATOMA OF TESTIS	2
B62xX00	OTHER AND UNSPECIFIC PERIPHERAL & CUTANEOUS T-CELL LYMPHOMAS	2
B303300	MALIGNANT NEOPLASM OF COSTAL CARTILAGE	2
B451000	MALIGNANT NEOPLASM OF GREATER VESTIBULAR (BARTHOLIN'S) GLAND	2
B620200	NODULAR LYMPHOMA OF INTRATHORACIC LYMPH NODES	2

B627000	FOLLICULAR NON-HODGKIN'S SMALL CLEAVED CELL LYMPHOMA	2
B331.00	MALIGNANT NEOPLASM OF EYELID INCLUDING CANTHUS	2
B33..15	MALIGNANT NEOPLASM OF SWEAT GLAND	2
B327700	MALIGNANT MELANOMA OF FOOT	2
B304z00	MALIGNANT NEOPLASM OF SCAPULA AND LONG BONES OF UPPER ARM NOS	2
Byu8200	[X]MALIGNANT NEOPLASM OF MALE GENITAL ORGAN, UNSPECIFIED	2
B610z00	HODGKIN'S PARA-GRANULOMA NOS	2
B055100	MALIGNANT NEOPLASM OF ROOF OF MOUTH	2
B600z00	RETICULOSARCOMA NOS	2
B336400	MALIGNANT NEOPLASM OF SKIN OF FINGER	2
Byu7000	[X]MALIGNANT NEOPLASM OF UTERINE ADNEXA, UNSPECIFIED	2
B105.00	MALIGNANT NEOPLASM OF LOWER THIRD OF OESOPHAGUS	2
B470.00	MALIGNANT NEOPLASM OF UNDESCENDED TESTIS	2
B616600	HODGKIN'S LYMPHOCYTIC DEPLETION OF INTRAPELVIC LYMPH NODES	2
B66y.00	OTHER MONOCYTIC LEUKAEMIA	2
B11yz00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE OF STOMACH NOS	2
B23..00	MALIGNANT NEOPLASM OF PLEURA	2
B602500	BURKITT'S LYMPHOMA OF LYMPH NODES OF INGUINAL REGION AND LEG	2
B060200	MALIGNANT NEOPLASM OF OVERLAPPING LESION OF TONSIL	2
B4Ay.00	MALIGNANT NEOPLASM OF OTHER URINARY ORGANS	2

B614300	HODGKIN'S NODULAR SCLEROSIS OF INTRA-ABDOMINAL LYMPH NODES	2
B004.00	MALIGNANT NEOPLASM OF LIP UNSPECIFIED, INNER ASPECT	2
B511.00	MALIGNANT NEOPLASM OF FRONTAL LOBE	2
B336000	MALIGNANT NEOPLASM OF SKIN OF SHOULDER	2
B61z100	HODGKIN'S DISEASE NOS OF LYMPH NODES OF HEAD, FACE AND NECK	2
B221z00	MALIGNANT NEOPLASM OF MAIN BRONCHUS NOS	2
B43y.00	MALIGNANT NEOPLASM OF OTHER SITE OF UTERINE BODY	2
B00..11	CARCINOMA OF LIP	2
B33..14	MALIGNANT NEOPLASM OF SEBACEOUS GLAND	2
B305C00	MALIGNANT NEOPLASM OF FIFTH METACARPAL BONE	2
B614.00	HODGKIN'S DISEASE, NODULAR SCLEROSIS	2
B172.00	MALIGNANT NEOPLASM OF TAIL OF PANCREAS	2
B59zX00	KAPOSI'S SARCOMA, UNSPECIFIED	2
B150300	HEPATOCELLULAR CARCINOMA	2
B611100	HODGKIN'S GRANULOMA OF LYMPH NODES OF HEAD, FACE AND NECK	2
B621600	MYCOSIS FUNGOIDES OF INTRAPELVIC LYMPH NODES	2
B015.00	MALIGNANT NEOPLASM OF TONGUE, JUNCTIONAL ZONE	2
B213z00	MALIGNANT NEOPLASM OF LARYNGEAL CARTILAGE NOS	2
B04..00	MALIGNANT NEOPLASM OF FLOOR OF MOUTH	2
B331100	MALIGNANT NEOPLASM OF UPPER EYELID	2
B30z000	OSTEOSARCOMA	2

B6y0.00	MYELOPROLIFERATIVE DISORDER	2
B624500	LEUKAEMIC RETICULOEND OF LYMPH NODES INGUINAL REGION AND LEG	2
B012.00	MALIGNANT NEOPLASM OF TONGUE, TIP AND LATERAL BORDER	2
B305A00	MALIGNANT NEOPLASM OF THIRD METACARPAL BONE	2
B33..00	OTHER MALIGNANT NEOPLASM OF SKIN	2
ByuA200	[X]MALIGNANT NEOPLASM OF MENINGES, UNSPECIFIED	2
B640.00	ACUTE LYMPHOID LEUKAEMIA	2
B62z300	UNSPECIFIED MALIGNANT NEOPLASM LYMPHOID/HISTIOCYTIC INTRA-ABDOMINAL NODES	2
B614000	HODGKIN'S DISEASE, NODULAR SCLEROSIS OF UNSPECIFIED SITE	2
B010.11	MALIGNANT NEOPLASM OF POSTERIOR THIRD OF TONGUE	2
B48yz00	MALIGNANT NEOPLASM OF OTHER MALE GENITAL ORGAN NOS	2
B510z00	MALIGNANT NEOPLASM OF CEREBRUM NOS	2
B053.00	MALIGNANT NEOPLASM OF SOFT PALATE	2
B311.00	MALIGNANT NEOPLASM CONNECTIVE AND SOFT TISSUE UPPER LIMB/SHOULDER	2
B083.00	MALIGNANT NEOPLASM OF POSTERIOR PHARYNX	2
B550100	MALIGNANT NEOPLASM OF CHEEK NOS	2
ZV10013	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF INTESTINE	2
B135.00	MALIGNANT NEOPLASM OF APPENDIX	2
B487.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF PENIS	2

B151z00	MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS NOS	2
B65y.00	OTHER MYELOID LEUKAEMIA	2
B64..11	LYMPHATIC LEUKAEMIA	2
B151300	MALIGNANT NEOPLASM OF INTRAHEPATIC CANALICULI	2
B01..00	MALIGNANT NEOPLASM OF TONGUE	2
B074.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF NASOPHARYNX	2
B110z00	MALIGNANT NEOPLASM OF CARDIA OF STOMACH NOS	2
B326200	MALIGNANT MELANOMA OF FOREARM	2
B308300	MALIGNANT NEOPLASM OF MEDIAL CUNEIFORM	2
B122.00	MALIGNANT NEOPLASM OF ILEUM	2
B064000	MALIGNANT NEOPLASM OF EPIGLOTTIS, FREE BORDER	2
B017.00	MALIGNANT OVERLAPPING LESION OF TONGUE	2
B2zz.00	MALIGNANT NEOPLASM OF RESPIRATORY TRACT NOS	2
ZV10300	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF BREAST	2
B651.00	CHRONIC MYELOID LEUKAEMIA	2
B300400	MALIGNANT NEOPLASM OF OCCIPITAL BONE	2
B32y.00	MALIGNANT MELANOMA OF OTHER SPECIFIED SKIN SITE	2
B44y.00	MALIGNANT NEOPLASM OF OTHER SITE OF UTERINE ADNEXA	2
B10y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED PART OF OESOPHAGUS	2
B46..00	MALIGNANT NEOPLASM OF PROSTATE	2

B00z000	MALIGNANT NEOPLASM OF LIP, UNSPECIFIED, EXTERNAL	2
B210.00	MALIGNANT NEOPLASM OF GLOTTIS	2
B162.00	MALIGNANT NEOPLASM OF AMPULLA OF VATER	2
B206.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF ACCESSORY SINUSES	2
B110000	MALIGNANT NEOPLASM OF CARDIAC ORIFICE OF STOMACH	2
B11y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE OF STOMACH	2
B306400	MALIGNANT NEOPLASM OF COCCYGEAL VERTEBRA	2
B325z00	MALIGNANT MELANOMA OF TRUNK, EXCLUDING SCROTUM, NOS	2
B300100	MALIGNANT NEOPLASM OF FRONTAL BONE	2
B300300	MALIGNANT NEOPLASM OF NASAL BONE	2
ZV10711	[V]PERSONAL HISTORY OF HODGKIN'S DISEASE	2
B142.11	ANAL CARCINOMA	2
B305500	MALIGNANT NEOPLASM OF CARPAL BONE - TRAPEZOID	2
B308400	MALIGNANT NEOPLASM OF INTERMEDIATE CUNEIFORM	2
B551.00	MALIGNANT NEOPLASM OF THORAX	2
B4...11	CARCINOMA OF GENITOURINARY ORGAN	2
B500.00	MALIGNANT NEOPLASM EYEBALL EXCL CONJUNCTIVA, CORNEA, RETINA, CHOROID	2
B314.00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF ABDOMEN	2
B335800	MALIGNANT NEOPLASM OF SKIN OF BUTTOCK	2
B642.00	SUBACUTE LYMPHOID LEUKAEMIA	2

B312500	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF TOE	2
B305900	MALIGNANT NEOPLASM OF SECOND METACARPAL BONE	2
B325400	MALIGNANT MELANOMA OF PERIANAL SKIN	2
B484.00	MALIGNANT NEOPLASM OF EPIDIDYMIS	2
B48y100	MALIGNANT NEOPLASM OF TUNICA VAGINALIS	2
B60y.00	OTHER SPECIFIED RETICULOSARCOMA OR LYMPHOSARCOMA	2
B624700	LEUKAEMIC RETICULOENDOTHELIOSIS OF SPLEEN	2
B142.00	MALIGNANT NEOPLASM OF ANAL CANAL	2
B300A00	MALIGNANT NEOPLASM OF MAXILLA	2
Byu4200	[X]OTHER MALIGNANT NEOPLASM/SKIN OF OTHER PARTS OF FACE	2
B336100	MALIGNANT NEOPLASM OF SKIN OF UPPER ARM	2
ZV10015	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF LIVER	2
B47..00	MALIGNANT NEOPLASM OF TESTIS	2
B611400	HODGKIN'S GRANULOMA OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B4A4.00	MALIGNANT NEOPLASM OF PARAURETHRAL GLANDS	2
B515z00	MALIGNANT NEOPLASM OF CEREBRAL VENTRICLE NOS	2
B332200	MALIGNANT NEOPLASM OF PINNA NEC	2
B540100	MALIGNANT NEOPLASM OF ADRENAL MEDULLA	2
B300900	MALIGNANT NEOPLASM OF ZYGOMATIC BONE	2
B325.00	MALIGNANT MELANOMA OF TRUNK (EXCLUDING SCROTUM)	2

B1z0.00	MALIGNANT NEOPLASM OF INTESTINAL TRACT, PART UNSPECIFIED	2
B161300	MALIGNANT NEOPLASM OF SPHINCTER OF ODDI	2
B002100	MALIGNANT NEOPLASM OF UPPER LIP, FRENULUM	2
B621700	MYCOSIS FUNGOIDES OF SPLEEN	2
B542z00	MALIGNANT NEOPLASM PITUITARY GLAND OR CRANIO-PHARYNGEAL DUCT NOS	2
Bz...00	NEOPLASMS NOS	2
B151100	MALIGNANT NEOPLASM OF INTERLOBULAR BILIARY CANALS	2
B601300	LYMPHOSARCOMA OF INTRA-ABDOMINAL LYMPH NODES	2
B112.00	MALIGNANT NEOPLASM OF PYLORIC ANTRUM OF STOMACH	2
B507000	MALIGNANT NEOPLASM OF LACRIMAL SAC	2
B623500	MALIGNANT HISTIOCYTOSIS OF LYMPH NODES INGUINAL AND LEG	2
B2zy.00	MALIGNANT NEOPLASM OF OTHER SITE OF RESPIRATORY TRACT	2
B055.00	MALIGNANT NEOPLASM OF PALATE UNSPECIFIED	2
B630100	SOLITARY MYELOMA	2
B672.11	THROMBOCYTIC LEUKAEMIA	2
B016.00	MALIGNANT NEOPLASM OF LINGUAL TONSIL	2
B002.00	MALIGNANT NEOPLASM OF UPPER LIP, INNER ASPECT	2
B613000	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PREDOMINANCE UNSPECIFIC SITE	2
B350100	MALIGNANT NEOPLASM OF AREOLA OF MALE BREAST	2

B622200	SEZARY'S DISEASE OF INTRATHORACIC LYMPH NODES	2
B115.00	MALIGNANT NEOPLASM OF LESSER CURVE OF STOMACH UNSPECIFIED	2
B505.00	MALIGNANT NEOPLASM OF RETINA	2
B130.00	MALIGNANT NEOPLASM OF HEPATIC FLEXURE OF COLON	2
B692.00	SUBACUTE MYELOMONOCYTIC LEUKAEMIA	2
B1z0.11	CANCER OF BOWEL	2
B601100	LYMPHOSARCOMA OF LYMPH NODES OF HEAD, FACE AND NECK	2
B493.00	MALIGNANT NEOPLASM OF ANTERIOR WALL OF URINARY BLADDER	2
B6...11	MALIGNANT NEOPLASM OF HISTIOCYTIC TISSUE	2
B62yz00	MALIGNANT LYMPHOMA NOS	2
B641.11	CHRONIC LYMPHATIC LEUKAEMIA	2
B243.00	MALIGNANT NEOPLASM OF POSTERIOR MEDIASTINUM	2
B625800	LETTERER-SIWE DISEASE OF LYMPH NODES OF MULTIPLE SITES	2
B33X.00	MALIGNANT NEOPLASM OVERLAPPING LESION OF SKIN	2
B161211	CARCINOMA COMMON BILE DUCT	2
B613700	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PREDOMINANCE OF SPLEEN	2
B623400	MALIGNANT HISTIOCYTOSIS OF LYMPH NODES OF AXILLA AND ARM	2
B612200	HODGKIN'S SARCOMA OF INTRATHORACIC LYMPH NODES	2
Byu7.00	[X]MALIGNANT NEOPLASM OF FEMALE GENITAL ORGANS	2

B1z1z00	MALIGNANT NEOPLASM OF SPLEEN NOS	2
B673.00	MAST CELL LEUKAEMIA	2
B4A0000	HYPERNEPHROMA	2
ByuD100	[X]OTHER TYPES OF FOLLICULAR NON-HODGKIN'S LYMPHOMA	2
B453.00	MALIGNANT NEOPLASM OF CLITORIS	2
B47z.11	SEMINOMA OF TESTIS	2
B623200	MALIGNANT HISTIOCYTOSIS OF INTRATHORACIC LYMPH NODES	2
B15z.00	MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCTS NOS	2
B627.00	NON - HODGKIN'S LYMPHOMA	2
B07y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE OF NASOPHARYNX	2
B600500	RETICULOSARCOMA OF LYMPH NODES OF INGUINAL REGION AND LEG	2
B470100	MALIGNANT NEOPLASM OF RETAINED TESTIS	2
B611500	HODGKIN'S GRANULOMA LYMPH NODES OF INGUINAL REGION AND LEG	2
B520.00	MALIGNANT NEOPLASM OF CRANIAL NERVES	2
B14z.00	MALIGNANT NEOPLASM RECTUM,RECTOSIGMOID JUNCTION AND ANUS NOS	2
B151400	MALIGNANT NEOPLASM OF INTRAHEPATIC GALL DUCT	2
B16z.00	MALIGNANT NEOPLASM GALLBLADDER/EXTRAHEPATIC BILE DUCTS NOS	2
B241200	MALIGNANT NEOPLASM OF MYOCARDIUM	2
ByuA300	[X] MALIGNANT NEOPLASM, OVERLAP LESION BRAIN & OTHER PART OF CNS	2

B057.00	OVERLAPPING LESION OF OTHER AND UNSPECIFIED PARTS OF MOUTH	2
B302000	MALIGNANT NEOPLASM OF CERVICAL VERTEBRA	2
B524200	MALIGNANT NEOPLASM OF PERIPHERAL NERVE OF LOW LIMB, INCL HIP	2
ZV10611	[V]PERSONAL HISTORY OF LYMPHOID LEUKAEMIA	2
B051z00	MALIGNANT NEOPLASM OF VESTIBULE OF MOUTH NOS	2
B050.00	MALIGNANT NEOPLASM OF CHEEK MUCOSA	2
B161100	MALIGNANT NEOPLASM OF HEPATIC DUCT	2
B66yz00	OTHER MONOCYTIC LEUKAEMIA NOS	2
B325300	MALIGNANT MELANOMA OF GROIN	2
B336.00	MALIGNANT NEOPLASM OF SKIN OF UPPER LIMB AND SHOULDER	2
ByuD500	[X]OTHER LYMPHOID LEUKAEMIA	2
B116.00	MALIGNANT NEOPLASM OF GREATER CURVE OF STOMACH UNSPECIFIED	2
B41yz00	MALIGNANT NEOPLASM OF OTHER SITE OF CERVIX NOS	2
B003200	MALIGNANT NEOPLASM OF LOWER LIP, MUCOSA	2
B4A1100	MALIGNANT NEOPLASM OF URETEROPELVIC JUNCTION	2
B510.00	MALIGNANT NEOPLASM CEREBRUM (EXCLUDING LOBES AND VENTRICLES)	2
B151.00	MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS	2
B200.00	MALIGNANT NEOPLASM OF NASAL CAVITIES	2
B104.00	MALIGNANT NEOPLASM OF MIDDLE THIRD OF OESOPHAGUS	2

B111z00	MALIGNANT NEOPLASM OF PYLORUS OF STOMACH NOS	2
B553200	MALIGNANT NEOPLASM OF SACROCOCCYGEAL REGION	2
B241z00	MALIGNANT NEOPLASM OF HEART NOS	2
B440.11	CANCER OF OVARY	2
B34z.00	MALIGNANT NEOPLASM OF FEMALE BREAST NOS	2
B542100	MALIGNANT NEOPLASM OF CRANIOPHARYNGEAL DUCT	2
Byu3000	[X]MAL NEOPLASM/OVERLAP LESION/BONE CARTILAGE/LIMB	2
B622400	SEZARY'S DISEASE OF LYMPH NODES OF AXILLA AND UPPER LIMB	2
B625z00	LETTERER-SIWE DISEASE NOS	2
1959CC	MALIGNANT NEOPLASM HAND	2
B3z..00	MALIGNANT NEOPLASM OF BONE, CONNECTIVE TISSUE, SKIN AND BREAST NOS	2
B515000	MALIGNANT NEOPLASM OF CHOROID PLEXUS	2
B653.00	MYELOID SARCOMA	2
B222.11	PANCOAST'S SYNDROME	2
B62x600	TRUE HISTIOCYTIC LYMPHOMA	2
B616300	HODGKIN'S LYMPHOCYTIC DEPLETION INTRA-ABDOMINAL LYMPH NODES	2
B600800	RETICULOSARCOMA OF LYMPH NODES OF MULTIPLE SITES	2
B624.11	LEUKAEMIC RETICULOENDOTHELIOSIS	2
B4A0.00	MALIGNANT NEOPLASM OF KIDNEY PARENCHYMA	2
B07..00	MALIGNANT NEOPLASM OF NASOPHARYNX	2
B601000	LYMPHOSARCOMA OF UNSPECIFIED SITE	2

B615700	HODGKIN'S DISEASE, MIXED CELLULARITY OF SPLEEN	2
B324z00	MALIGNANT MELANOMA OF SCALP AND NECK NOS	2
B601z00	LYMPHOSARCOMA NOS	2
B653100	GRANULOCYTIC SARCOMA	2
Byu5300	[X]KAPOSI'S SARCOMA, UNSPECIFIED	2
ZV10415	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF PROSTATE	2
B05z000	KAPOSI'S SARCOMA OF PALATE	2
B61z200	HODGKIN'S DISEASE NOS OF INTRATHORACIC LYMPH NODES	2
B307200	MALIGNANT NEOPLASM OF TIBIA	2
B627X00	DIFFUSE NON-HODGKIN'S LYMPHOMA, UNSPECIFIED	2
ZV10y12	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF BRAIN	2
B621200	MYCOSIS FUNGOIDES OF INTRATHORACIC LYMPH NODES	2
B300800	MALIGNANT NEOPLASM OF TEMPORAL BONE	2
B214.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF LARYNX	2
B200200	MALIGNANT NEOPLASM OF SEPTUM OF NOSE	2
B306000	MALIGNANT NEOPLASM OF ILIUM	2
B48y000	MALIGNANT NEOPLASM OF SEMINAL VESICLE	2
B06..00	MALIGNANT NEOPLASM OF OROPHARYNX	2
B55..00	MALIGNANT NEOPLASM OF OTHER AND ILL-DEFINED SITES	2
B350000	MALIGNANT NEOPLASM OF NIPPLE OF MALE BREAST	2
B31y.00	MALIGNANT NEOPLASM CONNECTIVE AND SOFT TISSUE OTHER SPECIFIED SITE	2

Byu8000	[X]MALIGNANT NEOPLASM/OTHER SPECIFIED MALE GENITAL ORGANS	2
B613500	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PRED INGUINAL AND LEG	2
B312.00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF HIP AND LEG	2
B613600	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PRED INTRAPELVIC NODES	2
B550000	MALIGNANT NEOPLASM OF HEAD NOS	2
B071100	MALIGNANT NEOPLASM OF PHARYNGEAL TONSIL	2
B05y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED MOUTH PARTS	2
B44..00	MALIGNANT NEOPLASM OF OVARY AND OTHER UTERINE ADNEXA	2
B0z2.00	MALIGNANT NEOPLASM OF LARYNGOPHARYNX	2
B432.00	MALIGNANT NEOPLASM OF OVERLAPPING LESION OF CORPUS UTERI	2
B20z.00	MALIGNANT NEOPLASM OF ACCESSORY SINUS NOS	2
ZV10z00	[V]PERSONAL HISTORY OF UNSPECIFIED MALIGNANT NEOPLASM	2
ZV10y15	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF THYROID	2
B14y.00	MALIGNANT NEOPLASM OTHER SITE RECTUM, RECTOSIGMOID JUNCTION AND ANUS	2
B171.00	MALIGNANT NEOPLASM OF BODY OF PANCREAS	2
B624600	LEUKAEMIC RETICULOENDOTHELIOSIS OF INTRAPELVIC LYMPH NODES	2
B626700	MAST CELL MALIGNANCY OF SPLEEN	2

B64z.00	LYMPHOID LEUKAEMIA NOS	2
B201300	MALIGNANT NEOPLASM OF MASTOID AIR CELLS	2
B614200	HODGKIN'S NODULAR SCLEROSIS OF INTRATHORACIC LYMPH NODES	2
B543.00	MALIGNANT NEOPLASM OF PINEAL GLAND	2
B151200	MALIGNANT NEOPLASM OF INTRAHEPATIC BILIARY PASSAGES	2
B551100	MALIGNANT NEOPLASM OF CHEST WALL NOS	2
B524500	MALIGNANT NEOPLASM OF PERIPHERAL NERVE OF PELVIS	2
B623.00	MALIGNANT HISTIOCYTOSIS	2
B610000	HODGKIN'S PARA-GRANULOMA OF UNSPECIFIED SITE	2
B614700	HODGKIN'S DISEASE, NODULAR SCLEROSIS OF SPLEEN	2
B4A..11	RENAL MALIGNANT NEOPLASM	2
B550500	MALIGNANT NEOPLASM OF SUPRACLAVICULAR FOSSA NOS	2
B624000	LEUKAEMIC RETICULOENDOTHELIOSIS OF UNSPECIFIED SITES	2
B320.00	MALIGNANT MELANOMA OF LIP	2
B08y.00	MALIGNANT NEOPLASM OF OTHER SPECIFIED HYPOPHARYNGEAL SITE	2
B62y800	MALIGNANT LYMPHOMA NOS OF LYMPH NODES OF MULTIPLE SITES	2
B340000	MALIGNANT NEOPLASM OF NIPPLE OF FEMALE BREAST	2
B625100	LETTERER-SIWE DISEASE OF LYMPH NODES OF HEAD, FACE AND NECK	2
B323200	MALIGNANT MELANOMA OF EYEBROW	2
B327600	MALIGNANT MELANOMA OF HEEL	2

B34..11	CANCER FEMALE BREAST	2
B525.00	MALIGNANT NEOPLASM OF CAUDA EQUINA	2
B66..11	HISTIOCYTIC LEUKAEMIA	2
B18y200	MALIGNANT NEOPLASM OF MESORECTUM	2
B4Ay000	MALIGNANT NEOPLASM OF OVERLAPPING LESION OF URINARY ORGANS	2
B224000	MALIGNANT NEOPLASM OF LOWER LOBE BRONCHUS	2
B31z.00	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE, SITE NOS	2
B311400	MALIGNANT NEOPLASM OF CONNECTIVE AND SOFT TISSUE OF FINGER	2
B323z00	MALIGNANT MELANOMA OF FACE NOS	2
B333400	MALIGNANT NEOPLASM OF SKIN OF NOSE (EXTERNAL)	2
B073200	MALIGNANT NEOPLASM POSTERIOR MARGIN NASAL SEPTUM AND CHOANAE	2
B313200	MALIGNANT NEOPLASM OF GREAT VESSELS	2
B052.00	MALIGNANT NEOPLASM OF HARD PALATE	2
B305200	MALIGNANT NEOPLASM OF CARPAL BONE - TRIQUETRUM	2
B343.00	MALIGNANT NEOPLASM OF LOWER-INNER QUADRANT OF FEMALE BREAST	2
B62zz11	IMMUNOPROLIFERATIVE NEOPLASM	2
B602100	BURKITT'S LYMPHOMA OF LYMPH NODES OF HEAD, FACE AND NECK	2
B521100	MALIGNANT NEOPLASM OF CEREBRAL ARACHNOID MATER	2
B35z.00	MALIGNANT NEOPLASM OF OTHER SITE OF MALE BREAST	2
B627800	DIFFUSE NON-HODGKIN'S LYMPHOMA UNDIFFERENTIATED (DIFFUSE)	2

B611300	HODGKIN'S GRANULOMA OF INTRA-ABDOMINAL LYMPH NODES	2
B021.00	MALIGNANT NEOPLASM OF SUBMANDIBULAR GLAND	2
B031.00	MALIGNANT NEOPLASM OF LOWER GUM	2
B324.00	MALIGNANT MELANOMA OF SCALP AND NECK	2
B451z00	MALIGNANT NEOPLASM OF LABIA MAJORA NOS	2
B34yz00	MALIGNANT NEOPLASM OF OTHER SITE OF FEMALE BREAST NOS	2
B15..00	MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCTS	2
B308500	MALIGNANT NEOPLASM OF LATERAL CUNEIFORM	2
B202.00	MALIGNANT NEOPLASM OF MAXILLARY SINUS	2
B613400	HODGKIN'S, LYMPHOCYTIC-HISTIOCYTIC PRED AXILLA AND ARM	2
B614600	HODGKIN'S NODULAR SCLEROSIS OF INTRAPELVIC LYMPH NODES	2
ZV10213	[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF MIDDLE EAR	2
Moderate to severe liver disease		
G852300	OESOPHAGEAL VARICES IN ALCOHOLIC CIRRHOSIS OF THE LIVER	3
J62z.00	LIVER ABSCESS AND CHRONIC LIVER DISEASE CAUSING SEQUELAE NOS	3
G851.00	OESOPHAGEAL VARICES WITHOUT BLEEDING	3
Gyu9400	[X]OESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE	3
J62y.00	OTHER SEQUELAE OF CHRONIC LIVER DISEASE	3
G852000	OESOPHAGEAL VARICES WITH BLEEDING IN DISEASES EC	3

J624.00	HEPATORENAL SYNDROME	3
G850.00	OESOPHAGEAL VARICES WITH BLEEDING	3
G852.00	OESOPHAGEAL VARICES IN DISEASES EC	3
J622.00	HEPATIC COMA	3
G858.00	OESOPHAGEAL VARICES NOS	3
G85..11	OESOPHAGEAL VARICES	3
J623.00	PORTAL HYPERTENSION	3
G852200	OESOPHAGEAL VARICES IN CIRRHOSIS OF THE LIVER	3
A704z00	OTHER SPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA NOS	3
760F300	RIGID OESOPHAGOSCOPIC INJECTION SCLEROTHERAPY OESOPH VARICES	3
G852100	OESOPHAGEAL VARICES WITHOUT BLEEDING IN DISEASES EC	3
G852z00	OESOPHAGEAL VARICES IN DISEASES EC NOS	3
Metastatic tumour		
B561400	SECONDARY AND UNSPECIFIED MALIGNANT NEOPLASM POST MEDIASTINAL LYMPH NODES	6
B58y900	SECONDARY MALIGNANT NEOPLASM OF TONGUE	6
B5y..00	MALIGNANT NEOPLASM OF OTHER AND UNSPECIFIED SITE OS	6
B562300	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM COMMON ILIAC LYMPH NODES	6
B563300	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM PECTORAL LYMPH NODES	6
B575.00	SECONDARY MALIGNANT NEOPLASM OF LARGE INTESTINE AND RECTUM	6
B575100	SECONDARY MALIGNANT NEOPLASM OF RECTUM	6

B58y300	SECONDARY MALIGNANT NEOPLASM OF VAGINA	6
B5z..00	MALIGNANT NEOPLASM OF OTHER AND UNSPECIFIED SITE NOS	6
B58y411	SECONDARY CANCER OF THE VULVA	6
B564200	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM POPLITEAL LYMPH NODES	6
B58y600	SECONDARY MALIGNANT NEOPLASM OF TESTIS	6
B586.00	SECONDARY MALIGNANT NEOPLASM OF OVARY	6
B573.00	SECONDARY MALIGNANT NEOPLASM OF OTHER RESPIRATORY ORGANS	6
B593.00	PRIMARY MALIGNANT NEOPLASM OF UNKNOWN SITE	6
B58..00	SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES	6
B581200	SECONDARY MALIGNANT NEOPLASM OF URETHRA	6
B563100	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM SUPRATROCHLEAR LYMPH NODES	6
B56..11	LYMPH NODE METASTASES	6
B574200	SECONDARY MALIGNANT NEOPLASM OF ILEUM	6
ByuC.00	[X]MALIGNANT NEOPLASM OF ILL-DEFINED, SECONDARY AND UNSPECIFIC	6
B58y800	SECONDARY MALIGNANT NEOPLASM OF EPIDIDYMIS AND VAS DEFERENS	6
B561300	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM ANT MEDIASTINAL LYMPH NODES	6
B58yz00	SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE NOS	6

B574z00	SECONDARY MALIGNANT NEOPLASM OF SMALL INTESTINE OR DUODENUM NOS	6
B560500	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM SUBMANDIBULAR LYMPH NODES	6
B562.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTRA-ABDOMINAL LYMPH NODES	6
B562000	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM COELIAC LYMPH NODES	6
B576z00	SECONDARY MALIGNANT NEOPLASM OF RETROPERITONEUM OR PERITONEUM NOS	6
B561800	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM BRONCHOPULMONARY LYMPH NODES	6
B560700	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM SUBMENTAL LYMPH NODES	6
B562100	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM SUPERFICIAL MESENTERIC LN	6
B56..00	SECONDARY AND UNSPECIFIED MALIGNANT NEOPLASM OF LYMPH NODES	6
B574000	SECONDARY MALIGNANT NEOPLASM OF DUODENUM	6
B564000	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM SUPERFICIAL INGUINAL LN	6
B582100	SECONDARY MALIGNANT NEOPLASM OF SKIN OF FACE	6
B577.11	LIVER METASTASES	6
B564100	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM DEEP INGUINAL LYMPH NODES	6
B574100	SECONDARY MALIGNANT NEOPLASM OF JEJUNUM	6
B56y.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM LYMPH NODES MULTIPLE SITES	6

B590.11	CARCINOMATOSIS	6
B582000	SECONDARY MALIGNANT NEOPLASM OF SKIN OF HEAD	6
B583z00	SECONDARY MALIGNANT NEOPLASM OF BRAIN OR SPINAL CORD NOS	6
B576.00	SECONDARY MALIGNANT NEOPLASM OF RETROPERITONEUM AND PERITONEUM	6
B153.00	SECONDARY MALIGNANT NEOPLASM OF LIVER	6
B565.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTRAPELVIC LYMPH NODES	6
B563z00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM AXILLA AND UPPER LIMB LN NOS	6
B58y.00	SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES	6
B572.00	SECONDARY MALIGNANT NEOPLASM OF PLEURA	6
B57..12	SECONDARY CARCINOMA OF RESPIRATORY AND/OR DIGESTIVE SYSTEMS	6
B560100	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM MASTOID LYMPH NODES	6
B582300	SECONDARY MALIGNANT NEOPLASM OF SKIN OF TRUNK	6
B57..00	SECONDARY MALIGNANT NEOPLASM OF RESPIRATORY AND DIGESTIVE SYSTEMS	6
B561200	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM DIAPHRAGMATIC LYMPH NODES	6
B592.00	MALIGNANT NEOPLASMS OF INDEPENDENT (PRIMARY) MULTIPLE SITES	6
B582500	SECONDARY MALIGNANT NEOPLASM OF SKIN OF HIP AND LEG	6
B581100	SECONDARY MALIGNANT NEOPLASM OF BLADDER	6

B560200	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM SUPERFICIAL CERVICAL LN	6
B583100	SECONDARY MALIGNANT NEOPLASM OF SPINAL CORD	6
B59z.00	MALIGNANT NEOPLASM OF UNSPECIFIED SITE NOS	6
B561600	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM TRACHEOBRONCHIAL LN	6
B564.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INGUINAL AND LOWER LIMB LN	6
B576000	SECONDARY MALIGNANT NEOPLASM OF RETROPERITONEUM	6
B560000	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM OF SUPERFICIAL PAROTID LN	6
B561700	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INFERIOR TRACHEOBRONCHIAL LN	6
B563.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM AXILLA AND UPPER LIMB LN	6
B592X00	KAPOSI'S SARCOMA OF MULTIPLE ORGANS	6
B58y500	SECONDARY MALIGNANT NEOPLASM OF PROSTATE	6
B58y200	SECONDARY MALIGNANT NEOPLASM OF CERVIX UTERI	6
B58y211	SECONDARY CANCER OF THE CERVIX	6
B57z.00	SECONDARY MALIGNANT NEOPLASM OF RESPIRATORY OR DIGESTIVE SYSTEM NOS	6
B582400	SECONDARY MALIGNANT NEOPLASM OF SKIN OF SHOULDER AND ARM	6
B587.00	SECONDARY MALIGNANT NEOPLASM OF ADRENAL GLAND	6
B582200	SECONDARY MALIGNANT NEOPLASM OF SKIN OF NECK	6

B581.00	SECONDARY MALIGNANT NEOPLASM OF OTHER URINARY ORGANS	6
B58y000	SECONDARY MALIGNANT NEOPLASM OF BREAST	6
B590.00	DISSEMINATED MALIGNANCY NOS	6
B57..11	METASTASES OF RESPIRATORY AND/OR DIGESTIVE SYSTEMS	6
B58y700	SECONDARY MALIGNANT NEOPLASM OF PENIS	6
B565200	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM CIRCUMFLEX ILIAC LN	6
B58y400	SECONDARY MALIGNANT NEOPLASM OF VULVA	6
B575000	SECONDARY MALIGNANT NEOPLASM OF COLON	6
B561000	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTERNAL MAMMARY LYMPH NODES	6
B583000	SECONDARY MALIGNANT NEOPLASM OF BRAIN	6
B58y100	SECONDARY MALIGNANT NEOPLASM OF UTERUS	6
B565300	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM SACRAL LYMPH NODES	6
B582z00	SECONDARY MALIGNANT NEOPLASM OF SKIN NOS	6
B565100	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INFERIOR EPIGASTRIC LN	6
B582600	SECONDARY MALIGNANT NEOPLASM OF SKIN OF BREAST	6
B585000	PATHOLOGICAL FRACTURE DUE TO METASTATIC BONE DISEASE	6
ByuC100	[X]MALIGNANT NEOPLASM/OVERLAP LESION/OTHER DEFINED SITES	6

B560600	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM OF FACIAL LYMPH NODES	6
B560900	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM DEEP CERVICAL LN	6
ByuC700	[X]SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES	6
B562z00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTRA-ABDOMINAL LN NOS	6
B571.00	SECONDARY MALIGNANT NEOPLASM OF MEDIASTINUM	6
B560800	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM ANTERIOR CERVICAL LN	6
B580.00	SECONDARY MALIGNANT NEOPLASM OF KIDNEY	6
B563000	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM AXILLARY LYMPH NODES	6
B560.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM LYMPH NODES HEAD/FACE/NECK	6
ByuC800	[X]MALIGNANT NEOPLASM WITHOUT SPECIFICATION OF SITE	6
B560z00	SECONDARY UNSPECIFIC MALIGNANT NEOPLASM LYMPH NODES HEAD/FACE/NECK NOS	6
B575z00	SECONDARY MALIGNANT NEOPLASM OF LARGE INTESTINE OR RECTUM NOS	6
B583200	CEREBRAL METASTASIS	6
ByuC500	[X]2NDRY MALIGNANT NEOPLASM/BLADDER URINARY ORGANS	6
B570.00	SECONDARY MALIGNANT NEOPLASM OF LUNG	6
B58z.00	SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITE NOS	6
B577.00	SECONDARY MALIGNANT NEOPLASM OF LIVER	6

B56z.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM LYMPH NODES NOS	6
B565000	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTERNAL ILIAC LYMPH NODES	6
B591.00	OTHER MALIGNANT NEOPLASM NOS	6
ByuC400	[X]SECONDARY MALIGNANT NEOPLASM/OTHER DIGESTIVE ORGANS	6
B563200	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INFRACLAVICULAR LYMPH NODES	6
B564z00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM OF INGUINAL AND LEG LN NOS	6
ByuC300	[X]SECONDARY MALIGNANT NEOPLASM/OTHER RESPIRATORY ORGANS	6
B582.00	SECONDARY MALIGNANT NEOPLASM OF SKIN	6
B581z00	SECONDARY MALIGNANT NEOPLASM OF OTHER URINARY ORGAN NOS	6
B561100	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTERCOSTAL LYMPH NODES	6
B581000	SECONDARY MALIGNANT NEOPLASM OF URETER	6
B585.00	SECONDARY MALIGNANT NEOPLASM OF BONE AND BONE MARROW	6
B565z00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTRAPELVIC LN NOS	6
B562400	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM EXTERNAL ILIAC LYMPH NODES	6
B583.00	SECONDARY MALIGNANT NEOPLASM OF BRAIN AND SPINAL CORD	6
B561.00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTRATHORACIC LYMPH NODES	6
B576200	MALIGNANT ASCITES	6

B574.00	SECONDARY MALIGNANT NEOPLASM OF SMALL INTESTINE AND DUODENUM	6
B594.00	SECONDARY MALIGNANT NEOPLASM OF UNKNOWN SITE	6
B584.00	SECONDARY MALIGNANT NEOPLASM OF OTHER PART OF NERVOUS SYSTEM	6
B562200	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INFERIOR MESENTERIC LN	6
B58..11	SECONDARY CARCINOMA OF OTHER SPECIFIED SITES	6
ByuC200	[X]2NDRY MALIGNANT NEOPLASM LYMPH NODES/MULTI REGIONS	6
B57y.00	SECONDARY MALIGNANT NEOPLASM OF OTHER DIGESTIVE ORGAN	6
B59..00	MALIGNANT NEOPLASM OF UNSPECIFIED SITE	6
B561900	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM PULMONARY LYMPH NODES	6
B561z00	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM INTRATHORACIC LN NOS	6
B561500	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM PARATRACHEAL LYMPH NODES	6
B565400	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM OBTURATOR LYMPH NODES	6
ByuC600	[X]2NDRY MALIGNANT NEOPLASM/OTHER PARTS/NERVOUS SYSTEM	6
B560400	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM DEEP PAROTID LYMPH NODES	6
B576100	SECONDARY MALIGNANT NEOPLASM OF PERITONEUM	6
B560300	SECONDARY AND UNSPECIFIC MALIGNANT NEOPLASM OCCIPITAL LYMPH NODE	6
AIDS		

A788W00	HIV DISEASE RESULTING IN UNSPECIFIED MALIGNANT NEOPLASM	6
A788V00	HIV DISEASE RESULTING IN MULTIPLE DISEASES CE	6
AyuC.00	[X]HUMAN IMMUNODEFICIENCY VIRUS DISEASE	6
A789000	HIV DISEASE RESULTING IN MYCOBACTERIAL INFECTION	6
A788400	HUMAN IMMUNODEFICIENCY VIRUS WITH NEUROLOGICAL DISEASE	6
AyuC600	[X]HIV DISEASE RESULTING IN OTHER NON-HODGKIN'S LYMPHOMA	6
A788X00	HIV DISEASE RESULTING/ UNSPECIFIC INFECTIOUS DISEASE	6
A788z00	ACQUIRED HUMAN IMMUNODEFICIENCY VIRUS INFECTION SYNDROME NOS	6
AyuC900	[X]HIV DISEASE RESULTING IN UNSPECIFIED MALIGNANT NEOPLASM	6
AyuC300	[X]HIV DISEASE RESULTING IN MULTIPLE INFECTIONS	6
A789200	HIV DISEASE RESULTING IN CANDIDIASIS	6
A788500	HUMAN IMMUNODEFICIENCY VIRUS WITH SECONDARY INFECTION	6
AyuC000	[X]HIV DISEASE RESULTING IN OTHER BACTERIAL INFECTIONS	6
AyuCD00	[X]UNSPECIFIED HUMAN IMMUNODEFICIENCY VIRUS [HIV] DISEASE	6
AyuCC00	[X]HIV DISEASE RESULTING IN OTHER SPECIFIED CONDITIONS	6
A789600	HIV DISEASE RESULTING IN BURKITT'S LYMPHOMA	6

AyuC200	[X]HIV DISEASE RESULTING IN OTHER MYCOSES	6
A789900	HIV DISEASE RESULTING IN LYMPHOID INTERSTITIAL PNEUMONITIS	6
A789.00	HUMAN IMMUNODEFICIENCY VIRUS RESULTING IN OTHER DISEASE	6
A789A00	HIV DISEASE RESULTING IN WASTING SYNDROME	6
AyuC100	[X]HIV DISEASE RESULTING IN OTHER VIRAL INFECTIONS	6
A788300	HUMAN IMMUNODEFICIENCY VIRUS WITH CONSTITUTIONAL DISEASE	6
A788.00	ACQUIRED IMMUNE DEFICIENCY SYNDROME	6
AyuCB00	[X]HIV DISEASE RESULT/HAEMATOLOGICAL ABNORMS, NEC	6
A789100	HIV DISEASE RESULTING IN CYTOMEGALOVIRAL DISEASE	6
A789500	HIV DISEASE RESULTING IN KAPOSI'S SARCOMA	6
A788200	HIV INFECTION WITH PERSISTENT GENERALISED LYMPHADENOPATHY	6
A788U00	HIV DISEASE RESULT/HAEMATOLOGICAL ABNORMS,NEC	6
A788y00	HUMAN IMMUNODEFICIENCY VIRUS WITH OTHER CLINICAL FINDINGS	6
A788600	HUMAN IMMUNODEFICIENCY VIRUS WITH SECONDARY CANCERS	6
A789300	HIV DISEASE RESULTING IN PNEUMOCYSTIS CARINII PNEUMONIA	6
AyuC500	[X]HIV DISEASE RESULTING/ UNSPECIFIC INFECTIOUS DISEASE	6

A789X00	HIV DIS RESULT/OTHER MALIGNANT NEOPLASM / LYMPHOID, HEMATOPOIETIC TISSUE	6
AyuC700	[X]HIV DISSIEASE RESULT/OTHER MALIGNANT NEOPLASM / LYMPHOID, HEMATOPOIETIC TISSUE	6
A788100	ASYMPTOMATIC HUMAN IMMUNODEFICIENCY VIRUS INFECTION	6
AyuC800	[X]HIV DISEASE RESULTING IN OTHER MALIGNANT NEOPLASMS	6
AyuC400	[X]HIV DISEASE RESULTING/OTHER INFECTIOUS DISEASES	6
A789400	HIV DISEASE RESULTING IN MULTIPLE INFECTIONS	6
A789800	HIV DISEASE RESULTING IN MULTIPLE MALIGNANT NEOPLASMS	6
AyuCA00	[X]HIV DISEASE RESULTING IN MULTIPLE DISEASES CE	6

Appendix 9-8. Inhaled corticosteroids (ICS) codes

95964996	BETAMETHASONE VALERATE 100MICROGRAMS/ACTUATION
99887998	BETAMETHASONE VALERATE 100MICROGRAMS/ACTUATION
85830998	BECLOMETASONE CFC FREE 50MICROGRAMS/ACTUATION
87986997	BECLOMETASONE EXTRAFINE PARTICLE CFC/FREE B/ACT 100MICROGRAMS/ACTUATION
87986998	BECLOMETASONE EXTRAFINE PARTICLE CFC/FREE B/ACT 50MICROGRAMS/ACTUATION
87988997	BECLOMETASONE EXTRAFINE PARTICLE CFC/FREE B/ACT 100MICROGRAMS/ACTUATION
87988998	BECLOMETASONE EXTRAFINE PARTICLE CFC/FREE B/ACT 50MICROGRAMS/ACTUATION
88832998	BECLOMETASONE BREATH ACT 250MICROGRAMS/ACTUATION
88833997	BECLOMETASONE BREATH ACT 100MICROGRAMS/ACTUATION
86569998	BECLOMETASONE DRY POWDER 200MICROGRAMS/ACTUATION
87173998	BECLOMETASONE EXTRAFINE PARTICLE CFC/FREE B/ACT 100MICROGRAMS/ACTUATION
88305998	BUDESONIDE + FORMOTEROL DRY POWDER 100MICROGRAMS + 6MICROGRAMS/ACTUATION
88434996	BECLOMETASONE DRY POWDER 250MICROGRAMS/ACTUATION
88434997	BECLOMETASONE DRY POWDER 100MICROGRAMS/ACTUATION
88434998	BECLOMETASONE DRY POWDER 50MICROGRAMS/ACTUATION

91088996	BECLOMETASONE DRY POWDER 400MICROGRAMS/ACTUATION
91088997	BECLOMETASONE DRY POWDER 200MICROGRAMS/ACTUATION
91088998	BECLOMETASONE DRY POWDER 100MICROGRAMS/ACTUATION
91363996	BECLOMETASONE DRY POWDER 100MICROGRAMS/ACTUATION
92285996	BECLOMETASONE DRY POWDER 400MICROGRAMS/ACTUATION
92285997	BECLOMETASONE DRY POWDER 200MICROGRAMS/ACTUATION
92285998	BECLOMETASONE DRY POWDER 250MICROGRAMS/ACTUATION
93066997	BECLOMETASONE BREATH ACT 100MICROGRAMS/ACTUATION
93066998	BECLOMETASONE BREATH ACT 50MICROGRAMS/ACTUATION
96626989	BECLOMETASONE 100MICROGRAMS/ACTUATION
85823998	BECLOMETASONE CFC FREE 250MICROGRAMS/ACTUATION
85824998	BECLOMETASONE CFC FREE 200MICROGRAMS/ACTUATION
85825998	BECLOMETASONE CFC FREE 100MICROGRAMS/ACTUATION
85826998	BECLOMETASONE CFC FREE 50MICROGRAMS/ACTUATION
85827998	BECLOMETASONE CFC FREE 250MICROGRAMS/ACTUATION
85828998	BECLOMETASONE CFC FREE 200MICROGRAMS/ACTUATION
84871998	BECLOMETASONE POWDER 400MICROGRAMS

84873998	BECLOMETASONE POWDER 400MICROGRAMS
84875998	BECLOMETASONE POWDER 200MICROGRAMS
84877998	BECLOMETASONE POWDER 200MICROGRAMS
84879998	BECLOMETASONE POWDER 100MICROGRAMS
84881998	BECLOMETASONE POWDER 100MICROGRAMS
94847996	BECLOMETASONE DISC 400MICROGRAMS
94847997	BECLOMETASONE DISC 200MICROGRAMS
94847998	BECLOMETASONE DISC 100MICROGRAMS
97517998	BECLOMETASONE DISC 400MICROGRAMS
84869998	BECLOMETASONE POWDER BLISTERS REF 400MICROGRAMS
84872998	BECLOMETASONE POWDER BLISTERS REF 400MICROGRAMS
84874998	BECLOMETASONE POWDER BLISTERS REF 200MICROGRAMS
84876998	BECLOMETASONE POWDER BLISTERS REF 200MICROGRAMS
84878998	BECLOMETASONE POWDER BLISTERS REF 100MICROGRAMS
84880998	BECLOMETASONE POWDER BLISTERS REF 100MICROGRAMS
93620992	BECLOMETHASONE DIPROPRIONATE CART 200 MCG
93621992	BECLOMETHASONE DIPROPRIONATE CART 100 MCG
94456996	BECLOMETASONE DISC 400MICROGRAMS
94456997	BECLOMETASONE DISC 200MICROGRAMS
94456998	BECLOMETASONE DISC 100MICROGRAMS
94557996	BECLOMETASONE 400MICROGRAMS/ACTUATION
94558996	BECLOMETASONE 400MICROGRAMS
94558997	BECLOMETASONE 200MICROGRAMS
94558998	BECLOMETASONE 100MICROGRAMS
94849997	SALBUTAMOL + BECLOMETASONE CAPS 200MICROGRAMS + 100MICROGRAMS

94849998	SALBUTAMOL + BECLOMETASONE CAPS 400MICROGRAMS + 200MICROGRAMS
94941996	SALBUTAMOL + BECLOMETASONE CAPS 200MICROGRAMS + 100MICROGRAMS
94941997	SALBUTAMOL + BECLOMETASONE CAPS 400MICROGRAMS + 200MICROGRAMS
95983996	BECLOMETASONE + SALBUTAMOL CAPS 100MICROGRAMS + 200MICROGRAMS
95983997	BECLOMETASONE + SALBUTAMOL CAPS 200MICROGRAMS + 400MICROGRAMS
96027990	BECLOMETASONE 400MICROGRAMS
96028990	BECLOMETASONE 200MICROGRAMS
96029990	BECLOMETASONE 100MICROGRAMS
98590996	BECLOMETASONE 400MICROGRAMS
98590997	BECLOMETASONE 200MICROGRAMS
98590998	BECLOMETASONE 100MICROGRAMS
83447998	BECLOMETASONE BREATH ACT 250MICROGRAMS/ACTUATION
84238998	BECLOMETASONE EXTRAFINE PARTICLE + FORMOTEROL CFC FREE 100MICROGRAMS + 6MICROGRAMS/ACTUATION
84239998	BECLOMETASONE EXTRAFINE PARTICLE + FORMOTEROL CFC FREE100MICROGRAMS + 6MICROGRAMS/ACTUATION
85829998	BECLOMETASONE CFC FREE 100MICROGRAMS/ACTUATION
87990997	BECLOMETASONE EXTRAFINE PARTICLE CFC FREE 100MICROGRAMS/ACTUATION
87990998	BECLOMETASONE EXTRAFINE PARTICLE CFC FREE 50MICROGRAMS/ACTUATION
87991997	BECLOMETASONE EXTRAFINE PARTICLE CFC FREE 100MICROGRAMS/ACTUATION

87991998	BECLOMETASONE EXTRAFINE PARTICLE CFC FREE 50MICROGRAMS/ACTUATION
89862996	BECLOMETASONE 250MICROGRAMS/ACTUATION
89862997	BECLOMETASONE 100MICROGRAMS/ACTUATION
89862998	BECLOMETASONE 50MICROGRAMS/ACTUATION
90588998	BECLOMETASONE 200MICROGRAMS/ACTUATION
91363997	BECLOMETASONE DRY POWDER 50MICROGRAMS/ACTUATION
91403996	BECLOMETASONE BREATH ACT 250MICROGRAMS/ACTUATION
91403997	BECLOMETASONE BREATH ACT 100MICROGRAMS/ACTUATION
91403998	BECLOMETASONE BREATH ACT 50MICROGRAMS/ACTUATION
92836990	BECLOMETASONE 50MICROGRAMS/ACTUATION
92837990	BECLOMETASONE 250MICROGRAMS/ACTUATION
92838990	BECLOMETASONE 100MICROGRAMS/ACTUATION
93066996	BECLOMETASONE BREATH ACT 250MICROGRAMS/ACTUATION
94557997	BECLOMETASONE 200MICROGRAMS/ACTUATION
94559996	BECLOMETASONE 100MICROGRAMS/ACTUATION
94559997	BECLOMETASONE 50MICROGRAMS/ACTUATION
94559998	BECLOMETASONE 250MICROGRAMS/ACTUATION
94941998	SALBUTAMOL + BECLOMETASONE 100MCG + 50MCG
95111998	BECLOMETASONE 200MICROGRAMS/ACTUATION
95162990	BECLOMETASONE 250MICROGRAMS/ACTUATION
95163990	BECLOMETASONE 100MICROGRAMS/ACTUATION
95164990	BECLOMETASONE 50MICROGRAMS/ACTUATION
95536990	BECLOMETASONE 200MICROGRAMS/ACTUATION
95983998	BECLOMETASONE + SALBUTAMOL 50MICROGRAMS + 100MICROGRAMS/INHALATION
96130990	BECLOMETASONE 250MICROGRAMS/ACTUATION

96131990	BECLOMETASONE 100MICROGRAMS/ACTUATION
96132990	BECLOMETASONE 50MICROGRAMS/ACTUATION
96626988	BECLOMETASONE 250MICROGRAMS/ACTUATION
96626990	BECLOMETASONE 50MICROGRAMS/ACTUATION
96935988	BECLOMETASONE 250MICROGRAMS/ACTUATION
96935989	BECLOMETASONE 100MICROGRAMS/ACTUATION
96935990	BECLOMETASONE 50MICROGRAMS/ACTUATION
97006988	BECLOMETASONE 250MICROGRAMS/ACTUATION
97006989	BECLOMETASONE 100MICROGRAMS/ACTUATION
97006990	BECLOMETASONE 50MICROGRAMS/ACTUATION
97255988	BECLOMETASONE 100MICROGRAMS/ACTUATION
97255989	BECLOMETASONE 50MICROGRAMS/ACTUATION
97255990	BECLOMETASONE 250MICROGRAMS/ACTUATION
97698998	BECLOMETASONE 100MICROGRAMS/ACTUATION
97872996	BECLOMETASONE 250MICROGRAMS/ACTUATION
97872997	BECLOMETASONE 100MICROGRAMS/ACTUATION
97872998	BECLOMETASONE 50MICROGRAMS/ACTUATION
98288998	BECLOMETASONE 250MICROGRAMS/ACTUATION
98332996	BECLOMETASONE BREATH ACT 100MICROGRAMS/ACTUATION
98332997	BECLOMETASONE BREATH ACT 250MICROGRAMS/ACTUATION
98332998	BECLOMETASONE BREATH ACT 50MICROGRAMS/ACTUATION
98580998	SALBUTAMOL + BECLOMETASONE 100MCG + 50MCG
99910998	BECLOMETASONE 50MICROGRAMS/ACTUATION
99914998	BECLOMETASONE 250MICROGRAMS/ACTUATION
99965997	BECLOMETASONE 100MICROGRAMS/ACTUATION
99965998	BECLOMETASONE 50MICROGRAMS/ACTUATION
99914997	BECLOMETASONE 250MICROGRAMS/ACTUATION
94557998	BECLOMETASONE NEB SUSP 50MICROGRAMS/ML
98588998	BECLOMETASONE NEB SUSP 50MICROGRAMS/ML

88833998	BECLOMETASONE BREATH ACT 50MICROGRAMS/ACTUATION
86195998	BUDESONIDE DRY POWDER 400MICROGRAMS/ACTUATION
86196998	BUDESONIDE DRY POWDER 200MICROGRAMS/ACTUATION
86197998	BUDESONIDE DRY POWDER 100MICROGRAMS/ACTUATION
87174998	BECLOMETASONE EXTRAFINE PARTICLE CFC/FREE B/ACT 50MICROGRAMS/ACTUATION
91493998	BUDESONIDE + FORMOTEROL DRY POWDER 400MICROGRAMS + 12MICROGRAMS/ACTUATION
92411998	BUDESONIDE + FORMOTEROL DRY POWDER 400MICROGRAMS + 12MICROGRAMS/ACTUATION
93302998	BUDESONIDE 400MICROGRAMS/ACTUATION
93303996	BUDESONIDE DRY POWDER 100MICROGRAMS/ACTUATION
93303997	BUDESONIDE DRY POWDER 400MICROGRAMS/ACTUATION
93303998	BUDESONIDE DRY POWDER 200MICROGRAMS/ACTUATION
95938996	BUDESONIDE 100MICROGRAMS/ACTUATION
98887996	BUDESONIDE DRY POWDER 100MICROGRAMS/ACTUATION
98887997	BUDESONIDE DRY POWDER 400MICROGRAMS/ACTUATION
98887998	BUDESONIDE DRY POWDER 200MICROGRAMS/ACTUATION
83268998	BUDESONIDE CFC FREE 200MICROGRAMS
83269998	BUDESONIDE CFC FREE 100MICROGRAMS
83306998	BUDESONIDE CFC FREE 200MICROGRAMS
83307998	BUDESONIDE CFC FREE 100MICROGRAMS

82890998	BUDESONIDE DRY POWDER CART REF 400MICROGRAMS
82891998	BUDESONIDE DRY POWDER 400MICROGRAMS
88156998	BUDESONIDE 200MICROGRAMS
89121998	BUDESONIDE 400MICROGRAMS
95982990	BUDESONIDE 400MICROGRAMS
95983990	BUDESONIDE 200MICROGRAMS
85036998	BUDESONIDE DRY POWDER CART REF 200MICROGRAMS
85037998	BUDESONIDE DRY POWDER 200MICROGRAMS
85045998	BUDESONIDE DRY POWDER 200MICROGRAMS
87438998	BUDESONIDE REFILLABLE BREATH ACT POWDER 200MICROGRAMS/ACTUATION
95526992	PULMICORT COMPLETE 50 MCG INH
95528992	PULMICORT COMPLETE 200 MCG INH
95938997	BUDESONIDE 50MICROGRAMS/ACTUATION
95938998	BUDESONIDE 200MICROGRAMS/ACTUATION
98595998	BUDESONIDE 50MICROGRAMS/ACTUATION
98596998	BUDESONIDE 200MICROGRAMS/ACTUATION
93302996	BUDESONIDE REFILL CANISTER 50MICROGRAMS/ACTUATION
95527992	PULMICORT REFIL 50 MG INH
98595997	BUDESONIDE REFILL CANISTER 50MICROGRAMS/ACTUATION
93546990	BUDESONIDE NEB SUSP 1MG/2ML
93547990	BUDESONIDE NEB SUSP 0.5MG/2ML
93555990	BUDESONIDE NEB SUSP 0.5MG/2ML
95492997	BUDESONIDE NEB SUSP 1MG/2ML
95492998	BUDESONIDE NEB SUSP 0.5MG/2ML
95493997	BUDESONIDE NEB SUSP 1MG/2ML
95493998	BUDESONIDE NEB SUSP 0.5MG/2ML

87439998	BUDESONIDE REFILLABLE BREATH ACT POWDER 200MICROGRAMS/ACTUATION
88305997	BUDESONIDE + FORMOTEROL DRY POWDER 200MICROGRAMS + 6MICROGRAMS/ACTUATION
90394997	BUDESONIDE + FORMOTEROL DRY POWDER 200MICROGRAMS + 6MICROGRAMS/ACTUATION
90394998	BUDESONIDE + FORMOTEROL DRY POWDER 100MICROGRAMS + 6MICROGRAMS/ACTUATION
87062998	CICLESONIDE CFC FREE 160MICROGRAMS/ACTUATION
87063998	CICLESONIDE CFC FREE 80MICROGRAMS/ACTUATION
87065998	CICLESONIDE CFC FREE 160MICROGRAMS/ACTUATION
87069998	CICLESONIDE CFC FREE 80MICROGRAMS/ACTUATION
84751998	FLUTICASONE POWDER 500 MICROGRAMS
84753998	FLUTICASONE POWDER 500 MICROGRAMS
84755998	FLUTICASONE POWDER 250MICROGRAMS
84757998	FLUTICASONE POWDER 250MICROGRAMS
84760998	FLUTICASONE POWDER 100MICROGRAMS
84763998	FLUTICASONE POWDER 100MICROGRAMS
84768998	FLUTICASONE POWDER 50MICROGRAMS
84771998	FLUTICASONE POWDER 50MICROGRAMS
96041992	FLIXOTIDE DISKHALER-COMMUNITY PACK 50 MCG
96884992	FLIXOTIDE DISKHALER-COMMUNITY PACK 250 MCG
96885992	FLIXOTIDE DISKHALER-COMMUNITY PACK 100 MCG
84750998	FLUTICASONE POWDER BLISTERS REF 500 MICROGRAMS
84752998	FLUTICASONE POWDER BLISTERS REF 500 MICROGRAMS
84754998	FLUTICASONE POWDER BLISTERS REF 250MICROGRAMS
84756998	FLUTICASONE POWDER BLISTERS REF 250MICROGRAMS

84759998	FLUTICASONE POWDER BLISTERS REF 100MICROGRAMS
84762998	FLUTICASONE POWDER BLISTERS REF 100MICROGRAMS
84767998	FLUTICASONE POWDER BLISTERS REF 50MICROGRAMS
84770998	FLUTICASONE POWDER BLISTERS REF 50MICROGRAMS
92843998	FLUTICASONE DISC 500MICROGRAMS
92844998	FLUTICASONE DISC 500MICROGRAMS
93056996	FLUTICASONE DISC 250MICROGRAMS
93056997	FLUTICASONE DISC 100MICROGRAMS
93056998	FLUTICASONE DISC 50MICROGRAMS
93057996	FLUTICASONE DISC 250MICROGRAMS
93057997	FLUTICASONE DISC 100MICROGRAMS
93057998	FLUTICASONE DISC 50MICROGRAMS
82254998	FLUTICASONE DRY POWDER 500MICROGRAMS/INHALATION
82255998	FLUTICASONE DRY POWDER 250MICROGRAMS/INHALATION
82257998	FLUTICASONE DRY POWDER 100MICROGRAMS/INHALATION
82258998	FLUTICASONE DRY POWDER 50MICROGRAMS/INHALATION
87979998	SALMETEROL + FLUTICASONE CFC FREE 25MICROGRAMS + 50MICROGRAMS/ACTUATION
87980996	SALMETEROL + FLUTICASONE CFC FREE 25MICROGRAMS + 250MICROGRAMS/ACTUATION
87980997	SALMETEROL + FLUTICASONE CFC FREE 25MICROGRAMS + 125MICROGRAMS/ACTUATION
87980998	SALMETEROL + FLUTICASONE CFC FREE 25MICROGRAMS + 50MICROGRAMS/ACTUATION

88522998	SALMETEROL + FLUTICASONE DRY POWDER 50MICROGRAMS + 100MICROGRAMS/INHALATION
88524996	FLUTICASONE + SALMETEROL DRY POWDER 500MICROGRAMS + 50MICROGRAMS/INHALATION
88524997	FLUTICASONE + SALMETEROL DRY POWDER 250MICROGRAMS + 50MICROGRAMS/INHALATION
88524998	FLUTICASONE + SALMETEROL DRY POWDER 100MICROGRAMS + 50MICROGRAMS/INHALATION
88525996	SALMETEROL + FLUTICASONE DRY POWDER 50MICROGRAMS+ 500MICROGRAMS/INHALATION
88525997	SALMETEROL + FLUTICASONE DRY POWDER 50MICROGRAMS + 250MICROGRAMS/INHALATION
88525998	SALMETEROL + FLUTICASONE DRY POWDER 50MICROGRAMS + 100MICROGRAMS/INHALATION
91322997	FLUTICASONE DRY POWDER 500MICROGRAMS/INHALATION
91322998	FLUTICASONE DRY POWDER 250MICROGRAMS/INHALATION
91334997	FLUTICASONE DRY POWDER 500MICROGRAMS/INHALATION
91334998	FLUTICASONE DRY POWDER 250MICROGRAMS/INHALATION
91348998	SALMETEROL + FLUTICASONE DRY POWDER 50MICROGRAMS + 250MICROGRAMS/INHALATION
91547998	SALMETEROL + FLUTICASONE CFC FREE 25MICROGRAMS + 125MICROGRAMS/ACTUATION
91619996	FLUTICASONE CFC FREE 50MICROGRAMS/ACTUATION
91619997	FLUTICASONE CFC FREE 250MICROGRAMS/ACTUATION
91619998	FLUTICASONE CFC FREE 125MICROGRAMS/ACTUATION

92199998	SALMETEROL + FLUTICASONE DRY POWDER 50MICROGRAMS+ 500MICROGRAMS/INHALATION
92473996	FLUTICASONE CFC FREE 50MICROGRAMS/ACTUATION
92473997	FLUTICASONE CFC FREE 250MICROGRAMS/ACTUATION
92473998	FLUTICASONE CFC FREE 125MICROGRAMS/ACTUATION
92842996	FLUTICASONE DRY POWDER 100MICROGRAMS/INHALATION
92842997	FLUTICASONE DRY POWDER 50MICROGRAMS/INHALATION
92842998	FLUTICASONE 250MICROGRAMS/ACTUATION
92845996	FLUTICASONE DRY POWDER 100MICROGRAMS/INHALATION
92845997	FLUTICASONE DRY POWDER 50MICROGRAMS/INHALATION
92845998	FLUTICASONE 250MICROGRAMS/ACTUATION
92899996	FLUTICASONE 125MICROGRAMS/ACTUATION
92899997	FLUTICASONE 50MICROGRAMS/ACTUATION
92899998	FLUTICASONE 25MICROGRAMS/ACTUATION
92900996	FLUTICASONE 125MICROGRAMS/ACTUATION
92900997	FLUTICASONE 50MICROGRAMS/ACTUATION
92900998	FLUTICASONE 25MICROGRAMS/ACTUATION
93983996	FLUTICASONE + SALMETEROL CFC FREE 250MICROGRAMS + 25MICROGRAMS/ACTUATION
93983997	FLUTICASONE + SALMETEROL CFC FREE 125MICROGRAMS + 25MICROGRAMS/ACTUATION
93983998	FLUTICASONE + SALMETEROL CFC FREE 50MICROGRAMS + 25MICROGRAMS/ACTUATION
94625998	SALMETEROL + FLUTICASONE CFC FREE 25MICROGRAMS + 250MICROGRAMS/ACTUATION

97672997	FLUTICASONE UNIT DOSE NEB SUSP 500MICROGRAMS/2ML
97672998	FLUTICASONE UNIT DOSE NEB SUSP 2MG/2ML
97680997	FLUTICASONE UNIT DOSE NEB SUSP 500MICROGRAMS/2ML
97680998	FLUTICASONE UNIT DOSE NEB SUSP 2MG/2ML
88727998	MOMETASONE FUROATE DRY POWDER 200MICROGRAMS/ACTUATION
89229998	MOMETASONE FUROATE DRY POWDER 400MICROGRAMS/ACTUATION
90758998	MOMETASONE FUROATE DRY POWDER 200MICROGRAMS/ACTUATION
90968998	MOMETASONE FUROATE DRY POWDER 400MICROGRAMS/ACTUATION

Appendix 9-9. Cerebrovascular disease codes

Code	Description
1477.00	H/O: CEREBROVASCULAR DISEASE
14A7.00	H/O: CVA/STROKE
14A7.11	H/O: CVA
14A7.12	H/O: STROKE
14AF.00	H/O SUBARACHNOID HAEMORRHAGE
14AK.00	H/O: STROKE IN LAST YEAR
662M.00	STROKE MONITORING
7A23.00	CEREBRAL ARTERY AND CIRCLE OF WILLIS ANEURYSM OPERATIONS
7A23.11	CEREBRAL ARTERY ANEURYSM OPERATIONS
7A23000	EXCISION OF ANEURYSM OF CEREBRAL ARTERY
7A23200	CLIPPING OF ANEURYSM OF CEREBRAL ARTERY
7A23400	LIGATION OF ANEURYSM OF CEREBRAL ARTERY NEC
7A23600	OBLITERATION OF ANEURYSM OF CEREBRAL ARTERY NEC
7A23y00	OPERATION ON CEREBRAL ARTERY/ CIRCLE OF WILLIS ANEURYSM OS
7A23z00	OPERATION ON CEREBRAL ARTERY/ CIRCLE OF WILLIS ANEURYSM NOS
7A24.00	OTHER OPEN OPERATIONS ON CEREBRAL ARTERY OR CIRCLE OF WILLIS
7A24.11	OTHER OPEN OPERATIONS ON CEREBRAL ARTERY
7A24000	RECONSTRUCTION OF CEREBRAL ARTERY
7A24200	ANASTOMOSIS OF CEREBRAL ARTERY
7A24400	OPEN EMBOLECTOMY OF CEREBRAL ARTERY
7A24600	OPEN EMBOLISATION OF CEREBRAL ARTERY
7A24y00	OTHER OPEN OPERATION ON CEREBRAL ARTERY/CIRCLE OF WILLIS OS
7A24z00	OTHER OPEN OPERATION ON CEREBRAL ARTERY/CIRCLE OF WILLIS NOS

7A25.00	TRANSLUMINAL OPERATIONS ON CEREBRAL ARTERY/ CIRCLE OF WILLIS
7A25000	PERCUTANEOUS TRANSLUMINAL EMBOLISATION OF CEREBRAL ARTERY
7A25200	EMBOLISATION OF CEREBRAL ARTERY NEC
7A25400	ARTERIOGRAPHY OF CEREBRAL ARTERY
7A25y00	TRANSLUMINAL OPERATION ON CEREBRAL ART/CIRCLE OF WILLIS OS
7A25z00	TRANSLUMINAL OPERATION ON CEREBRAL ART/CIRCLE OF WILLIS NOS
E030400	ACUTE CONFUSIONAL STATE, OF CEREBROVASCULAR ORIGIN
E031400	SUBACUTE CONFUSIONAL STATE, OF CEREBROVASCULAR ORIGIN
F11x200	CEREBRAL DEGENERATION DUE TO CEREBROVASCULAR DISEASE
Fyu5500	[X]OTHER TRANSNT CEREBRAL ISCHAEMIC ATTACKS+RELATED SYNDROMS
Fyu5600	[X]OTHER LACUNAR SYNDROMES
Fyu5700	[X]OTHER VASCULAR SYNDROMS/BRAIN IN CEREBROVASCULR DISEASES
G6...00	CEREBROVASCULAR DISEASE
G60..00	SUBARACHNOID HAEMORRHAGE
G600.00	RUPTURED BERRY ANEURYSM
G601.00	SUBARACHNOID HAEMORRHAGE FROM CAROTID SIPHON AND BIFURCATION
G602.00	SUBARACHNOID HAEMORRHAGE FROM MIDDLE CEREBRAL ARTERY
G603.00	SUBARACHNOID HAEMORRHAGE FROM ANTERIOR COMMUNICATING ARTERY
G604.00	SUBARACHNOID HAEMORRHAGE FROM POSTERIOR COMMUNICATING ARTERY

G605.00	SUBARACHNOID HAEMORRHAGE FROM BASILAR ARTERY
G606.00	SUBARACHNOID HAEMORRHAGE FROM VERTEBRAL ARTERY
G60X.00	SUBARACHNOID HAEMORRH FROM INTRACRANIAL ARTERY, UNSPECIF
G60z.00	SUBARACHNOID HAEMORRHAGE NOS
G61..00	INTRACEREBRAL HAEMORRHAGE
G61..11	CVA - CEREBROVASCULAR ACCID DUE TO INTRACEREBRAL HAEMORRHAGE
G61..12	STROKE DUE TO INTRACEREBRAL HAEMORRHAGE
G610.00	CORTICAL HAEMORRHAGE
G611.00	INTERNAL CAPSULE HAEMORRHAGE
G612.00	BASAL NUCLEUS HAEMORRHAGE
G613.00	CEREBELLAR HAEMORRHAGE
G614.00	PONTINE HAEMORRHAGE
G615.00	BULBAR HAEMORRHAGE
G616.00	EXTERNAL CAPSULE HAEMORRHAGE
G617.00	INTRACEREBRAL HAEMORRHAGE, INTRAVENTRICULAR
G618.00	INTRACEREBRAL HAEMORRHAGE, MULTIPLE LOCALIZED
G619.00	LOBAR CEREBRAL HAEMORRHAGE
G61X.00	INTRACEREBRAL HAEMORRHAGE IN HEMISPHERE, UNSPECIFIED
G61X000	LEFT SIDED INTRACEREBRAL HAEMORRHAGE, UNSPECIFIED
G61X100	RIGHT SIDED INTRACEREBRAL HAEMORRHAGE, UNSPECIFIED
G61z.00	INTRACEREBRAL HAEMORRHAGE NOS
G62..00	OTHER AND UNSPECIFIED INTRACRANIAL HAEMORRHAGE

G620.00	EXTRADURAL HAEMORRHAGE - NONTRAUMATIC
G621.00	SUBDURAL HAEMORRHAGE - NONTRAUMATIC
G622.00	SUBDURAL HAEMATOMA - NONTRAUMATIC
G62z.00	INTRACRANIAL HAEMORRHAGE NOS
G63..00	PRECEREBRAL ARTERIAL OCCLUSION
G63..11	INFARCTION - PRECEREBRAL
G63..12	STENOSIS OF PRECEREBRAL ARTERIES
G630.00	BASILAR ARTERY OCCLUSION
G631.00	CAROTID ARTERY OCCLUSION
G631.11	STENOSIS, CAROTID ARTERY
G631.12	THROMBOSIS, CAROTID ARTERY
G633.00	MULTIPLE AND BILATERAL PRECEREBRAL ARTERIAL OCCLUSION
G634.00	CAROTID ARTERY STENOSIS
G63y.00	OTHER PRECEREBRAL ARTERY OCCLUSION
G63y000	CEREBRAL INFARCT DUE TO THROMBOSIS OF PRECEREBRAL ARTERIES
G63y100	CEREBRAL INFARCTION DUE TO EMBOLISM OF PRECEREBRAL ARTERIES
G63z.00	PRECEREBRAL ARTERY OCCLUSION NOS
G64..00	CEREBRAL ARTERIAL OCCLUSION
G64..11	CVA - CEREBRAL ARTERY OCCLUSION
G64..12	INFARCTION - CEREBRAL
G64..13	STROKE DUE TO CEREBRAL ARTERIAL OCCLUSION
G640.00	CEREBRAL THROMBOSIS
G640000	CEREBRAL INFARCTION DUE TO THROMBOSIS OF CEREBRAL ARTERIES
G641.00	CEREBRAL EMBOLISM
G641.11	CEREBRAL EMBOLUS
G641000	CEREBRAL INFARCTION DUE TO EMBOLISM OF CEREBRAL ARTERIES
G64z.00	CEREBRAL INFARCTION NOS

G64z.12	CEREBELLAR INFARCTION
G64z100	WALLENBERG SYNDROME
G64z111	LATERAL MEDULLARY SYNDROME
G64z200	LEFT SIDED CEREBRAL INFARCTION
G64z300	RIGHT SIDED CEREBRAL INFARCTION
G65..00	TRANSIENT CEREBRAL ISCHAEMIA
G65..12	TRANSIENT ISCHAEMIC ATTACK
G65..13	VERTEBRO-BASILAR INSUFFICIENCY
G650.00	BASILAR ARTERY SYNDROME
G650.11	INSUFFICIENCY - BASILAR ARTERY
G651.00	VERTEBRAL ARTERY SYNDROME
G651000	VERTEBRO-BASILAR ARTERY SYNDROME
G652.00	SUBCLAVIAN STEAL SYNDROME
G653.00	CAROTID ARTERY SYNDROME HEMISPHERIC
G654.00	MULTIPLE AND BILATERAL PRECEREBRAL ARTERY SYNDROMES
G655.00	TRANSIENT GLOBAL AMNESIA
G65y.00	OTHER TRANSIENT CEREBRAL ISCHAEMIA
G65z.00	TRANSIENT CEREBRAL ISCHAEMIA NOS
G65z000	IMPENDING CEREBRAL ISCHAEMIA
G65z100	INTERMITTENT CEREBRAL ISCHAEMIA
G65zz00	TRANSIENT CEREBRAL ISCHAEMIA NOS
G66..00	STROKE AND CEREBROVASCULAR ACCIDENT UNSPECIFIED
G66..11	CVA UNSPECIFIED
G66..12	STROKE UNSPECIFIED
G66..13	CVA - CEREBROVASCULAR ACCIDENT UNSPECIFIED
G660.00	MIDDLE CEREBRAL ARTERY SYNDROME
G661.00	ANTERIOR CEREBRAL ARTERY SYNDROME
G662.00	POSTERIOR CEREBRAL ARTERY SYNDROME
G663.00	BRAIN STEM STROKE SYNDROME
G664.00	CEREBELLAR STROKE SYNDROME

G665.00	PURE MOTOR LACUNAR SYNDROME
G666.00	PURE SENSORY LACUNAR SYNDROME
G667.00	LEFT SIDED CVA
G668.00	RIGHT SIDED CVA
G67..00	OTHER CEREBROVASCULAR DISEASE
G670.00	CEREBRAL ATHEROSCLEROSIS
G670.11	PRECEREBRAL ATHEROSCLEROSIS
G671.00	GENERALISED ISCHAEMIC CEREBROVASCULAR DISEASE NOS
G671000	ACUTE CEREBROVASCULAR INSUFFICIENCY NOS
G671100	CHRONIC CEREBRAL ISCHAEMIA
G671z00	GENERALISED ISCHAEMIC CEREBROVASCULAR DISEASE NOS
G673.00	CEREBRAL ANEURYSM, NONRUPTURED
G673000	DISSECTION OF CEREBRAL ARTERIES, NONRUPTURED
G674.00	CEREBRAL ARTERITIS
G675.00	MOYAMOYA DISEASE
G676.00	NONPYOGENIC VENOUS SINUS THROMBOSIS
G676000	CEREB INFARCT DUE CEREBRAL VENOUS THROMBOSIS, NONPYOGENIC
G677.00	OCCLUSION/STENOSIS CEREBRAL ARTS NOT RESULT CEREBRAL INFARCT
G677000	OCCLUSION AND STENOSIS OF MIDDLE CEREBRAL ARTERY
G677100	OCCLUSION AND STENOSIS OF ANTERIOR CEREBRAL ARTERY
G677200	OCCLUSION AND STENOSIS OF POSTERIOR CEREBRAL ARTERY
G677300	OCCLUSION AND STENOSIS OF CEREBELLAR ARTERIES
G677400	OCCLUSION+STENOSIS OF MULTIPLE AND BILAT CEREBRAL ARTERIES

G679.00	SMALL VESSEL CEREBROVASCULAR DISEASE
G67y.00	OTHER CEREBROVASCULAR DISEASE
G67z.00	OTHER CEREBROVASCULAR DISEASE
G68..00	LATE EFFECTS OF CEREBROVASCULAR DISEASE
G680.00	SEQUELAE OF SUBARACHNOID HAEMORRHAGE
G681.00	SEQUELAE OF INTRACEREBRAL HAEMORRHAGE
G682.00	SEQUELAE OF OTHER NONTRAUMATIC INTRACRANIAL HAEMORRHAGE
G683.00	SEQUELAE OF CEREBRAL INFARCTION
G68W.00	SEQUELAE/OTHER + UNSPECIFIED CEREBROVASCULAR DISEASES
G68X.00	SEQUELAE OF STROKE,NOT SPECFD AS H'MORRHAGE OR INFARCTION
G6W..00	CEREB INFARCT DUE UNSP OCCLUS/STENOS PRECEREBR ARTERIES
G6X..00	CEREBRL INFARCTN DUE/UNSPCF OCCLUSN OR STEN/CEREBRL ARTRS
G6y..00	OTHER SPECIFIED CEREBROVASCULAR DISEASE
G6z..00	CEREBROVASCULAR DISEASE NOS
Gyu6.00	CEREBROVASCULAR DISEASES
Gyu6000	SUBARACHNOID HAEMORRHAGE FROM OTHER INTRACRANIAL ARTERIES
Gyu6100	OTHER SUBARACHNOID HAEMORRHAGE
Gyu6200	OTHER INTRACEREBRAL HAEMORRHAGE
Gyu6300	CEREBRL INFARCTN DUE/UNSPCF OCCLUSN OR STEN/CEREBRL ARTRS
Gyu6400	OTHER CEREBRAL INFARCTION
Gyu6500	OCCLUSION AND STENOSIS OF OTHER PRECEREBRAL ARTERIES
Gyu6600	OCCLUSION AND STENOSIS OF OTHER CEREBRAL ARTERIES
Gyu6700	OTHER SPECIFIED CEREBROVASCULAR DISEASES

Gyu6800	CEREBRAL ARTERITIS IN INFECTIOUS AND PARASITIC DISEASES
Gyu6900	CEREBRAL ARTERITIS IN OTHER DISEASES CE
Gyu6A00	OTHER CEREBROVASCULAR DISORDERS IN DISEASES CE
Gyu6B00	SEQUELAE OF OTHER NONTRAUMATIC INTRACRANIAL HAEMORRHAGE
Gyu6C00	SEQUELAE OF STROKE, NOT SPECFD AS H'MORRHAGE OR INFARCTION
Gyu6D00	SEQUELAE/OTHER + UNSPECIFIED CEREBROVASCULAR DISEASES
Gyu6E00	SUBARACHNOID HAEMORRH FROM INTRACRANIAL ARTERY, UNSPECIF
Gyu6F00	INTRACEREBRAL HAEMORRHAGE IN HEMISPHERE, UNSPECIFIED
Gyu6G00	CEREB INFARCT DUE UNSP OCCLUS/STENOS PRECEREBR ARTERIES
L417.00	OBSTETRIC CEREBRAL VENOUS THROMBOSIS
L417000	CEREBRAL VENOUS THROMBOSIS IN PREGNANCY
L417100	CEREBRAL VENOUS THROMBOSIS IN THE PUERPERIUM
L440.00	CEREBROVASCULAR DISORDERS IN THE PUERPERIUM
L440.11	CVA- CEREBROVASCULAR ACCIDENT IN THE PUERPERIUM
L440.12	STROKE IN THE PUERPERIUM
L440000	PUERPERAL CEREBROVASCULAR DISORDER UNSPECIFIED
L440100	PUERPERAL CEREBROVASCULAR DISORDER - DELIVERED
L440200	PUERPERAL CEREBROVASCULAR DISORDER - DELIVERED WITH P/N COMP

L440300	PUERPERAL CEREBROVASCULAR DISORDER WITH ANTENATAL COMP
L440400	PUERPERAL CEREBROVASCULAR DISORDER WITH POSTNATAL COMP
L440z00	PUERPERAL CEREBROVASCULAR DISORDER NOS
P7y0.00	CEREBROVASCULAR SYSTEM ANOMALIES
P7y0100	CONGENITAL CEREBRAL ARTERIOVENOUS ANEURYSM
P7y0112	CONGENITAL CEREBRAL ARTERIOVENOUS MALFORMATION
P7y0300	CONGENITAL STRICTURE OF CEREBRAL ARTERY
P7y0y00	OTHER SPECIFIED CEREBROVASCULAR ANOMALY
P7y0z00	CEREBROVASCULAR SYSTEM ANOMALY NOS
Pyu2C00	[X]OTHER MALFORMATIONS OF PRECEREBRAL VESSELS
Pyu2D00	[X]OTHER MALFORMATIONS OF CEREBRAL VESSELS
S62..00	CEREBRAL HAEMORRHAGE FOLLOWING INJURY
S62..11	EXTRADURAL HAEMORRHAGE FOLLOWING INJURY
S62..12	SUBARACHNOID HAEMORRHAGE FOLLOWING INJURY
S62..13	SUBDURAL HAEMORRHAGE FOLLOWING INJURY
S62..14	TRAUMATIC CEREBRAL HAEMORRHAGE
S620.00	CLOSED TRAUMATIC SUBARACHNOID HAEMORRHAGE
S620.11	MIDDLE MENINGEAL HAEMMORHAGE FOLLOWING INJURY
S620000	SUBARACHNOID H'GE INJ NO OPEN INTRACRAN WOUND + UNSPEC CONSC
S620100	SUBARACHNOID H'GE INJ NO OPEN INTRACRAN WND+NO LOSS CONSC
S620200	SUBARACHNOID H'GE INJ NO OPEN INTRACRAN WND+<1HR LOSS CONSC

S620300	SUBARACHNOID H'GE INJ NO OPEN INTRACRAN WOUND + 1-24HR LOC
S620400	SUBARACHNOID H'GE INJ NO OPEN INTRACRAN WND+>24 LOC+RECOVERY
S620500	SUBARACH H'GE INJ NO OPEN INTRACRAN WND+>24HRS LOC-RESTORED
S620600	SUBARACH H'GE INJ NO OPEN INTRACRAN WND+LOC UNSPEC DURATION
S620z00	SUBARACH H'GE INJ NO OPEN INTRACRAN WND + CONCUSSION UNSPEC
S621.00	OPEN TRAUMATIC SUBARACHNOID HAEMORRHAGE
S621000	SUBARACHNOID H'GE INJ + OPEN INTRACRAN WOUND + UNSPEC CONSC
S621100	SUBARACHNOID H'GE INJ + OPEN INTRACRANIAL WOUND + NO LOC
S621200	SUBARACHNOID H'GE INJ + OPEN INTRACRAN WOUND+<1HR LOSS CONSC
S621300	SUBARACHNOID H'GE INJ + OPEN INTRACRAN WND+1-24HR LOSS CONSC
S621400	SUBARACH H'GE INJ + OPEN INTRACRAN WND +>24HR LOC + RECOVERY
S621500	SUBARACH H'GE INJ + OPEN INTRACRAN WND+>24HR LOC -RESTORED
S621600	SUBARACH H'GE INJ + OPEN INTRACRAN WND+LOC UNSPEC DURATION
S621z00	SUBARACHNOID H'GE INJ + OPEN INTRACRAN WND+CONCUSSION UNSPEC
S622.00	CLOSED TRAUMATIC SUBDURAL HAEMORRHAGE
S622000	SUBDURAL H'GE INJ NO OPEN INTRACRANIAL WND + UNSPEC CONSC
S622100	SUBDURAL H'GE INJ NO OPEN INTRACRANIAL WOUND+NO LOSS CONSC

S622200	SUBDURAL H'GE INJ NO OPEN INTRACRANIAL WOUND+<1HR LOSS CONSC
S622300	SUBDURAL H'GE INJ NO OPEN INTRACRAN WND+1-24HR LOSS CONSC
S622400	SUBDURAL H'GE INJ NO OPEN INTRACRANIAL WND+>24 LOC +RECOVERY
S622500	SUBDURAL H'GE INJ NO OPEN INTRACRAN WND+>24HR LOC -RESTORED
S622600	SUBDURAL H'GE INJ NO OPEN INTRACRAN WND+LOC UNSPEC DURATION
S622z00	SUBDURAL H'GE INJ NO OPEN INTRACRAN WOUND+CONCUSSION UNSPEC
S623.00	OPEN TRAUMATIC SUBDURAL HAEMORRHAGE
S623000	SUBDURAL H'GE INJ + OPEN INTRACRANIAL WOUND + UNSPEC CONSC
S623100	SUBDURAL H'GE INJ + OPEN INTRACRANIAL WOUND+NO LOSS CONSC
S623200	SUBDURAL H'GE INJ + OPEN INTRACRANIAL WOUND+<1HR LOSS CONSC
S623300	SUBDURAL H'GE INJ + OPEN INTRACRANIAL WND+1-24HR LOSS CONSC
S623400	SUBDURAL H'GE INJ + OPEN INTRACRAN WOUND+>24HR LOC +RECOVERY
S623500	SUBDURAL H'GE INJ + OPEN INTRACRAN WND+>24HR LOC -RESTORED
S623600	SUBDURAL H'GE INJ + OPEN INTRACRAN WND+LOC UNSPEC DURATION
S623z00	SUBDURAL H'GE INJ + OPEN INTRACRANIAL WND+CONCUSSION UNSPEC
S624.00	CLOSED TRAUMATIC EXTRADURAL HAEMORRHAGE
S624000	EXTRADURAL H'GE INJ NO OPEN INTRACRANIAL WND + UNSPEC CONSC

S624100	EXTRADURAL H'GE INJ NO OPEN INTRACRANIAL WND + NO LOSS CONSC
S624200	EXTRADURAL H'GE INJ NO OPEN INTRACRANIAL WND+<1HR LOSS CONSC
S624300	EXTRADURAL H'GE INJ NO OPEN INTRACRAN WND+1-24HR LOSS CONSC
S624400	EXTRADURAL H'GE INJ NO OPEN INTRACRAN WND+>24HR LOC+RECOVERY
S624500	EXTRADURAL H'GE INJ NO OPEN INTRACRAN WND+>24HR LOC-RESTORED
S624600	EXTRADURAL H'GE INJ NO OPEN INTRACRA WND+LOC UNSPEC DURATION
S624z00	EXTRADURAL H'GE INJ NO OPEN INTRACRAN WND+CONCUSSION UNSPEC
S625.00	OPEN TRAUMATIC EXTRADURAL HAEMORRHAGE
S625000	EXTRADURAL H'GE INJ + OPEN INTRACRANIAL WND + UNSPEC CONSC
S625100	EXTRADURAL H'GE INJ + OPEN INTRACRANIAL WOUND+NO LOSS CONSC
S625200	EXTRADURAL H'GE INJ + OPEN INTRACRANIAL WND+<1HR LOSS CONSC
S625300	EXTRADURAL H'GE INJ + OPEN INTRACRAN WND+1-24HR LOSS CONSC
S625400	EXTRADURAL H'GE INJ + OPEN INTRACRAN WND+>24HR LOC+RECOVERY
S625500	EXTRADURAL H'GE INJ + OPEN INTRACRAN WND+>24HR LOC -RESTORED
S625600	EXTRADURAL H'GE INJ + OPEN INTRACRAN WND+LOC UNSPEC DURATION
S625z00	EXTRADURAL H'GE INJ + OPEN INTRACRAN WND+CONCUSSION UNSPEC
S627.00	TRAUMATIC SUBARACHNOID HAEMORRHAGE

S628.00	TRAUMATIC SUBDURAL HAEMORRHAGE
S629.00	TRAUMATIC SUBDURAL HAEMATOMA
S629000	TRAUMATIC SUBDURAL HAEMATOMA WITHOUT OPEN INTRACRANIAL WOUND
S629100	TRAUMATIC SUBDURAL HAEMATOMA WITH OPEN INTRACRANIAL WOUND
S62A.00	TRAUMATIC EXTRADURAL HAEMATOMA
S62A000	TRAUMATIC EXTRADURAL HAEMAT WITHOUT OPEN INTRACRANIAL WOUND
S62A100	TRAUMATIC EXTRADURAL HAEMATOMA WITH OPEN INTRACRANIAL WOUND
S62z.00	CEREBRAL HAEMORRHAGE FOLLOWING INJURY NOS
S63..00	OTHER CEREBRAL HAEMORRHAGE FOLLOWING INJURY
S630.00	OTHER CEREBRAL H'GE AFTER INJURY NO OPEN INTRACRANIAL WOUND
S630.12	INTRACRANIAL HAEMATOMA FOLLOWING INJURY
S630000	OTH CEREBRAL H'GE INJ NO OPEN INTRACRAN WND+UNSPEC CONSC
S630100	OTH CEREBRAL H'GE INJ NO OPEN INTRACRANIAL WND+NO LOSS CONSC
S630200	OTH CEREBRAL H'GE INJ NO OPEN INTRACRAN WND+<1HR LOSS CONSC
S630300	OTH CEREBRAL H'GE INJ NO OPEN INTRACRAN WND+1-24HR LOC
S630400	OTH CEREB H'GE INJ NO OPEN INTRACRAN WND+>24HR LOC +RECOVERY
S630500	OTH CEREB H'GE INJ NO OPEN INTRACRAN WND+>24HR LOC -RESTORED
S630600	OTH CEREB H'GE INJ NO OPEN INTRACRAN WND+LOC UNSPEC DURATION

S630z00	OTH CEREB H'GE INJ NO OPEN INTRACRAN WND+CONCUSSION UNSPEC
S631.00	OTHER CEREBRAL H'GE AFTER INJURY + OPEN INTRACRANIAL WOUND
S631000	OTH CEREBRAL H'GE INJ + OPEN INTRACRAN WND + UNSPEC CONSC
S631100	OTH CEREBRAL H'GE INJ + OPEN INTRACRANIAL WND+NO LOSS CONSC
S631200	OTH CEREBRAL H'GE INJ + OPEN INTRACRAN WND+<1HR LOSS CONSC
S631300	OTH CEREBRAL H'GE INJ + OPEN INTRACRAN WND+1-24HR LOSS CONSC
S631400	OTH CEREB H'GE INJ + OPEN INTRACRAN WND+>24HR LOC + RECOVERY
S631500	OTH CEREB H'GE INJ + OPEN INTRACRAN WND+>24HR LOC -RESTORED
S631600	OTH CEREB H'GE INJ + OPEN INTRACRAN WND+LOC UNSPEC DURATION
S631z00	OTH CEREB H'GE INJ + OPEN INTRACRAN WND+CONCUSSION UNSPEC
S63z.00	OTHER CEREBRAL HAEMORRHAGE FOLLOWING INJURY NOS
ZV12511	PERSONAL HISTORY OF STROKE
ZV12512	PERSONAL HISTORY OF CEREBROVASCULAR ACCIDENT (CVA)

Appendix 9-10. Cardiovascular (CV) disease codes

Code	Description
14A..00	H/O: CARDIOVASCULAR DISEASE
14AH.00	H/O: MYOCARDIAL INFARCTION IN LAST YEAR
G3...00	ISCHAEMIC HEART DISEASE
G3...11	ARTERIOSCLEROTIC HEART DISEASE
G3...12	ATHEROSCLEROTIC HEART DISEASE
G3...13	IHD - ISCHAEMIC HEART DISEASE
G30..00	ACUTE MYOCARDIAL INFARCTION
G30..11	ATTACK - HEART
G30..12	CORONARY THROMBOSIS
G30..13	CARDIAC RUPTURE FOLLOWING MYOCARDIAL INFARCTION (MI)
G30..14	HEART ATTACK
G30..15	MI - ACUTE MYOCARDIAL INFARCTION
G30..16	THROMBOSIS - CORONARY
G30..17	SILENT MYOCARDIAL INFARCTION
G300.00	ACUTE ANTEROLATERAL INFARCTION
G301.00	OTHER SPECIFIED ANTERIOR MYOCARDIAL INFARCTION
G301000	ACUTE ANTEROAPICAL INFARCTION
G301100	ACUTE ANTEROSEPTAL INFARCTION
G301z00	ANTERIOR MYOCARDIAL INFARCTION NOS
G302.00	ACUTE INFEROLATERAL INFARCTION
G303.00	ACUTE INFEROPOSTERIOR INFARCTION
G304.00	POSTERIOR MYOCARDIAL INFARCTION NOS
G305.00	LATERAL MYOCARDIAL INFARCTION NOS
G306.00	TRUE POSTERIOR MYOCARDIAL INFARCTION
G307.00	ACUTE SUBENDOCARDIAL INFARCTION
G307000	ACUTE NON-Q WAVE INFARCTION
G307100	ACUTE NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

G308.00	INFERIOR MYOCARDIAL INFARCTION NOS
G309.00	ACUTE Q-WAVE INFARCT
G30A.00	MURAL THROMBOSIS
G30B.00	ACUTE POSTEROLATERAL MYOCARDIAL INFARCTION
G30X.00	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF UNSPECIFIC SITE
G30X000	ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION
G30y.00	OTHER ACUTE MYOCARDIAL INFARCTION
G30y000	ACUTE ATRIAL INFARCTION
G30y200	ACUTE SEPTAL INFARCTION
G30yz00	OTHER ACUTE MYOCARDIAL INFARCTION NOS
G30z.00	ACUTE MYOCARDIAL INFARCTION NOS
G311.11	CRESCENDO ANGINA
G311.13	UNSTABLE ANGINA
G311.14	ANGINA AT REST
G311100	UNSTABLE ANGINA
G311200	ANGINA AT REST
G311300	REFRACTORY ANGINA
G311400	WORSENING ANGINA
G311500	ACUTE CORONARY SYNDROME
G312.00	CORONARY THROMBOSIS NOT RESULTING IN MYOCARDIAL INFARCTION
G31y.00	OTHER ACUTE AND SUBACUTE ISCHAEMIC HEART DISEASE
G31y000	ACUTE CORONARY INSUFFICIENCY
G32..00	OLD MYOCARDIAL INFARCTION
G33..00	ANGINA PECTORIS
G33z.00	ANGINA PECTORIS NOS
G33z300	ANGINA ON EFFORT
G33z400	ISCHAEMIC CHEST PAIN
G33z700	STABLE ANGINA

G33zz00	ANGINA PECTORIS NOS
G340.00	CORONARY ATHEROSCLEROSIS
G340.11	TRIPLE VESSEL DISEASE OF THE HEART
G340.12	CORONARY ARTERY DISEASE
G340000	SINGLE CORONARY VESSEL DISEASE
G340100	DOUBLE CORONARY VESSEL DISEASE
G343.00	ISCHAEMIC CARDIOMYOPATHY
G34z000	ASYMPTOMATIC CORONARY HEART DISEASE
G3z..00	ISCHAEMIC HEART DISEASE NOS
G70y011	CAROTID ARTERY DISEASE
G32..11	HEALED MYOCARDIAL INFARCTION
G32..12	PERSONAL HISTORY OF MYOCARDIAL INFARCTION
G211100	BENIGN HYPERTENSIVE HEART DISEASE WITH CCF
G21z100	HYPERTENSIVE HEART DISEASE NOS WITH CCF
G232.00	HYPERTENSIVE HEART & RENAL DIS WITH (CONGESTIVE) HEART FAILURE
G234.00	HYPERTENSIVE HEART & RENAL DIS +BOTH(CONGESTIVE)HEART AND RENAL FAIL
G343.00	ISCHAEMIC CARDIOMYOPATHY
G55..00	CARDIOMYOPATHY
G550.00	ENDOMYOCARDIAL FIBROSIS
G58..00	HEART FAILURE
G58..11	CARDIAC FAILURE
G580.00	CONGESTIVE HEART FAILURE
G580.11	CONGESTIVE CARDIAC FAILURE
G580.14	BIVENTRICULAR FAILURE
G580000	ACUTE CONGESTIVE HEART FAILURE
G580100	CHRONIC CONGESTIVE HEART FAILURE
G580200	DECOMPENSATED CARDIAC FAILURE
G580300	COMPENSATED CARDIAC FAILURE
G581.00	LEFT VENTRICULAR FAILURE
G581.12	PULMONARY OEDEMA - ACUTE

G581.13	IMPAIRED LEFT VENTRICULAR FUNCTION
G581000	ACUTE LEFT VENTRICULAR FAILURE
G582.00	ACUTE HEART FAILURE
G58z.00	HEART FAILURE NOS
G58z.12	CARDIAC FAILURE NOS
1O1..00	HEART FAILURE CONFIRMED
8B29.00	CARDIAC FAILURE THERAPY
8CL3.00	HEART FAILURE CARE PLAN DISCUSSED WITH PATIENT
8H2S.00	ADMIT HEART FAILURE EMERGENCY
G554000	CONGESTIVE CARDIOMYOPATHY
G631.11	STENOSIS, CAROTID ARTERY
G634.00	CAROTID ARTERY STENOSIS
G65z.00	TRANSIENT CEREBRAL ISCHAEMIA NOS
G70z.00	ARTERIOSCLEROTIC VASCULAR DISEASE NOS
G73..00	OTHER PERIPHERAL VASCULAR DISEASE
G73..11	PERIPHERAL ISCHAEMIC VASCULAR DISEASE
G73..12	ISCHAEMIA OF LEGS
G73..13	PERIPHERAL ISCHAEMIA
G732.00	PERIPHERAL GANGRENE
G732000	GANGRENE OF TOE
G732100	GANGRENE OF FOOT
G73yz00	OTHER SPECIFIED PERIPHERAL VASCULAR DISEASE NOS
G734.00	PERIPHERAL ARTERIAL DISEASE
G73z.00	PERIPHERAL VASCULAR DISEASE NOS
G73z000	INTERMITTENT CLAUDICATION
G73z011	CLAUDICATION
G73zz00	PERIPHERAL VASCULAR DISEASE NOS
G71z.00	AORTIC ANEURYSM
G713.00	ABDOMINAL AORTIC ANEURYSM WHICH HAS RUPTURED

7A14.11	AORTIC ANEURYSM REPAIR
14NB.00	H/O: PERIPHERAL VASCULAR DISEASE PROCEDURE
G71..00	AORTIC ANEURYSM
G713.11	RUPTURED ABDOMINAL AORTIC ANEURYSM
Gyu7400	OTHER SPECIFIED PERIPHERAL VASCULAR DISEASES
G3...11	ARTERIOSCLEROTIC HEART DISEASE
G309.00	ACUTE Q-WAVE INFARCT
G30y100	ACUTE PAPILLARY MUSCLE INFARCTION
G31..00	OTHER ACUTE AND SUBACUTE ISCHAEMIC HEART DISEASE
G311.00	PREINFARCTION SYNDROME
G311.12	IMPENDING INFARCTION
G311000	MYOCARDIAL INFARCTION ABORTED
G311011	MI - MYOCARDIAL INFARCTION ABORTED
G311100	UNSTABLE ANGINA
G311z00	PREINFARCTION SYNDROME NOS
G31y100	MICROINFARCTION OF HEART
G31y200	SUBENDOCARDIAL ISCHAEMIA
G31y300	TRANSIENT MYOCARDIAL ISCHAEMIA
G31yz00	OTHER ACUTE AND SUBACUTE ISCHAEMIC HEART DISEASE NOS
G33z100	STENOCARDIA
G330.00	ANGINA DECUBITUS
G33z000	STATUS ANGINOSUS
G330z00	ANGINA DECUBITUS NOS
G330000	NOCTURNAL ANGINA
G33zz00	ANGINA PECTORIS NOS
G33z200	SYNCOPE ANGINOSA
G33z500	POST INFARCT ANGINA
G33z600	NEW ONSET ANGINA
G34..00	OTHER CHRONIC ISCHAEMIC HEART DISEASE
G342.00	ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

G344.00	SILENT MYOCARDIAL ISCHAEMIA
G34y.00	OTHER SPECIFIED CHRONIC ISCHAEMIC HEART DISEASE
G34y000	CHRONIC CORONARY INSUFFICIENCY
G34y100	CHRONIC MYOCARDIAL ISCHAEMIA
G34yz00	OTHER SPECIFIED CHRONIC ISCHAEMIC HEART DISEASE NOS
G34z.00	OTHER CHRONIC ISCHAEMIC HEART DISEASE NOS
G35..00	SUBSEQUENT MYOCARDIAL INFARCTION
G350.00	SUBSEQUENT MYOCARDIAL INFARCTION OF ANTERIOR WALL
G351.00	SUBSEQUENT MYOCARDIAL INFARCTION OF INFERIOR WALL
G353.00	SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES
G35X.00	SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
G360.00	HAEMOPERICARDIUM/CURRENT COMP FOLOW ACUT MYOCARD INFARCT
G362.00	VENTRIC SEPTAL DEFECT/CURR COMP FOL ACUT MYOCARDAL INFARCTN
G363.00	RUPTURE CARDIAC WALL W'OUT HAEMOPERICARD/CUR COMP FOL AC MI
G364.00	RUPTURE CHORDAE TENDINAE/CURR COMP FOL ACUTE MI
G365.00	RUPTURE PAPILLARY MUSCLE/CURR COMP FOL ACUTE MI
G38..00	POSTOPERATIVE MYOCARDIAL INFARCTION
G380.00	POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION ANTERIOR WALL
G381.00	POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION INFERIOR WALL

G382.00	POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION OTHER SITES
G383.00	POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION UNSPECIFIC SITE
G38z.00	POSTOPERATIVE MYOCARDIAL INFARCTION, UNSPECIFIED
G39..00	CORONARY MICROVASCULAR DISEASE
G3y..00	OTHER SPECIFIED ISCHAEMIC HEART DISEASE
G574011	CARDIAC ARREST-VENTRICULAR FIBRILLATION
G575.00	CARDIAC ARREST
G575.11	CARDIO-RESPIRATORY ARREST
Gyu3.00	[X]ISCHAEMIC HEART DISEASES
Gyu3000	[X]OTHER FORMS OF ANGINA PECTORIS
Gyu3200	[X]OTHER FORMS OF ACUTE ISCHAEMIC HEART DISEASE
G384.00	POSTOPERATIVE SUBENDOCARDIAL MYOCARDIAL INFARCTION
Gyu3300	[X]OTHER FORMS OF CHRONIC ISCHAEMIC HEART DISEASE
Gyu3500	[X]SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES
Gyu3400	[X]ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF UNSPECIFIC SITE
Gyu3600	[X]SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
Fyu5500	[X]OTHER TRANSIT CEREBRAL ISCHAEMIC ATTACKS + RELATED SYNDROMES
G657.00	CAROTID TERRITORY TRANSIENT ISCHAEMIC ATTACK
ZV12D00	[V]PERSONAL HISTORY OF TRANSIENT ISCHAEMIC ATTACK

Appendix 9-11. Depression codes

146D.00	H/O: MANIC DEPRESSIVE DISORDER
1B17.00	DEPRESSED
62T1.00	PUERPERAL DEPRESSION
8BK0.00	DEPRESSION MANAGEMENT PROGRAMME
8CAa.00	PATIENT GIVEN ADVICE ABOUT MANAGEMENT OF DEPRESSION
8HHq.00	REFERRAL FOR GUIDED SELF-HELP FOR DEPRESSION
9H90.00	DEPRESSION ANNUAL REVIEW
9H91.00	DEPRESSION MEDICATION REVIEW
9H92.00	DEPRESSION INTERIM REVIEW
9HA0.00	ON DEPRESSION REGISTER
9k4..00	DEPRESSION - ENHANCED SERVICES ADMINISTRATION
9k40.00	DEPRESSION - ENHANCED SERVICE COMPLETED
9kQ..00	ON FULL DOSE LONG TERM TREATMENT DEPRESSION
E001300	PRESENILE DEMENTIA WITH DEPRESSION
E002.00	SENILE DEMENTIA WITH DEPRESSIVE OR PARANOID FEATURES
E002100	SENILE DEMENTIA WITH DEPRESSION
E002z00	SENILE DEMENTIA WITH DEPRESSIVE OR PARANOID FEATURES
E004300	ARTERIOSCLEROTIC DEMENTIA WITH DEPRESSION
E11..12	DEPRESSIVE PSYCHOSES
E112.00	SINGLE MAJOR DEPRESSIVE EPISODE
E112.11	AGITATED DEPRESSION
E112.12	ENDOGENOUS DEPRESSION FIRST EPISODE
E112.13	ENDOGENOUS DEPRESSION FIRST EPISODE
E112.14	ENDOGENOUS DEPRESSION
E112000	SINGLE MAJOR DEPRESSIVE EPISODE, UNSPECIFIED
E112100	SINGLE MAJOR DEPRESSIVE EPISODE, MILD
E112200	SINGLE MAJOR DEPRESSIVE EPISODE, MODERATE

E112300	SINGLE MAJOR DEPRESSIVE EPISODE, SEVERE, WITHOUT PSYCHOSIS
E112400	SINGLE MAJOR DEPRESSIVE EPISODE, SEVERE, WITH PSYCHOSIS
E112500	SINGLE MAJOR DEPRESSIVE EPISODE, PARTIAL OR UNSPECIFIC REMISSION
E112600	SINGLE MAJOR DEPRESSIVE EPISODE, IN FULL REMISSION
E112z00	SINGLE MAJOR DEPRESSIVE EPISODE NOS
E113.00	RECURRENT MAJOR DEPRESSIVE EPISODE
E113.11	ENDOGENOUS DEPRESSION - RECURRENT
E113000	RECURRENT MAJOR DEPRESSIVE EPISODES, UNSPECIFIED
E113100	RECURRENT MAJOR DEPRESSIVE EPISODES, MILD
E113200	RECURRENT MAJOR DEPRESSIVE EPISODES, MODERATE
E113300	RECURRENT MAJOR DEPRESSIVE EPISODES, SEVERE, NO PSYCHOSIS
E113400	RECURRENT MAJOR DEPRESSIVE EPISODES, SEVERE, WITH PSYCHOSIS
E113500	RECURRENT MAJOR DEPRESSIVE EPISODES, PARTIAL/UNSPECIFIC REMISSION
E113600	RECURRENT MAJOR DEPRESSIVE EPISODES, IN FULL REMISSION
E113700	RECURRENT DEPRESSION
E113z00	RECURRENT MAJOR DEPRESSIVE EPISODE NOS
E114.11	MANIC-DEPRESSIVE - NOW MANIC
E115.00	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED
E115.11	MANIC-DEPRESSIVE - NOW DEPRESSED
E115000	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED, UNSPECIFIED

E115100	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED, MILD
E115200	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED, MODERATE
E115300	BIPOLAR AFFECT DISORDER, NOW DEPRESSED, SEVERE, NO PSYCHOSIS
E115600	BIPOLAR AFFECTIVE DISORDER, NOW DEPRESSED, IN FULL REMISSION
E115z00	BIPOLAR AFFECTIVE DISORDER, CURRENTLY DEPRESSED
E11y.00	OTHER AND UNSPECIFIED MANIC-DEPRESSIVE PSYCHOSES
E11y000	UNSPECIFIED MANIC-DEPRESSIVE PSYCHOSES
E11y200	ATYPICAL DEPRESSIVE DISORDER
E11y300	OTHER MIXED MANIC-DEPRESSIVE PSYCHOSES
E11yz00	OTHER AND UNSPECIFIED MANIC-DEPRESSIVE PSYCHOSES
E11z200	MASKED DEPRESSION
E130.00	REACTIVE DEPRESSIVE PSYCHOSIS
E130.11	PSYCHOTIC REACTIVE DEPRESSION
E135.00	AGITATED DEPRESSION
E200300	ANXIETY WITH DEPRESSION
E204.00	NEUROTIC DEPRESSION REACTIVE TYPE
E204.11	POSTNATAL DEPRESSION
E211200	DEPRESSIVE PERSONALITY DISORDER
E290.00	BRIEF DEPRESSIVE REACTION
E290z00	BRIEF DEPRESSIVE REACTION NOS
E291.00	PROLONGED DEPRESSIVE REACTION
E2B..00	DEPRESSIVE DISORDER NEC
E2B0.00	DEPRESSIVE DISORDER NEC
E2B1.00	CHRONIC DEPRESSION
Eu02z16	SENILE DEMENTIA, DEPRESSED OR PARANOID TYPE

Eu20400	POST-SCHIZOPHRENIC DEPRESSION
Eu32.00	DEPRESSIVE EPISODE
Eu32.11	SINGLE EPISODE OF DEPRESSIVE REACTION
Eu32.12	SINGLE EPISODE OF PSYCHOGENIC DEPRESSION
Eu32.13	SINGLE EPISODE OF REACTIVE DEPRESSION
Eu32000	MILD DEPRESSIVE EPISODE
Eu32100	MODERATE DEPRESSIVE EPISODE
Eu32200	SEVERE DEPRESSIVE EPISODE WITHOUT PSYCHOTIC SYMPTOMS
Eu32211	SINGLE EPISODE AGITATED DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS
Eu32212	SINGLE EPISODE MAJOR DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS
Eu32213	SINGLE EPISODE VITAL DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS
Eu32300	SEVERE DEPRESSIVE EPISODE WITH PSYCHOTIC SYMPTOMS
Eu32311	SINGLE EPISODE OF MAJOR DEPRESSION AND PSYCHOTIC SYMPTOMS
Eu32312	SINGLE EPISODE OF PSYCHOGENIC DEPRESSIVE PSYCHOSIS
Eu32313	SINGLE EPISODE OF PSYCHOTIC DEPRESSION
Eu32314	SINGLE EPISODE OF REACTIVE DEPRESSIVE PSYCHOSIS
Eu32400	MILD DEPRESSION
Eu32500	MAJOR DEPRESSION, MILD
Eu32600	MAJOR DEPRESSION, MODERATELY SEVERE
Eu32700	MAJOR DEPRESSION, SEVERE WITHOUT PSYCHOTIC SYMPTOMS
Eu32800	MAJOR DEPRESSION, SEVERE WITH PSYCHOTIC SYMPTOMS
Eu32y00	OTHER DEPRESSIVE EPISODES
Eu32y11	ATYPICAL DEPRESSION

Eu32y12	SINGLE EPISODE OF MASKED DEPRESSION NOS
Eu32z00	DEPRESSIVE EPISODE, UNSPECIFIED
Eu32z11	DEPRESSION
Eu32z12	DEPRESSIVE DISORDER NOS
Eu32z13	PROLONGED SINGLE EPISODE OF REACTIVE DEPRESSION
Eu32z14	REACTIVE DEPRESSION
Eu33.00	RECURRENT DEPRESSIVE DISORDER
Eu33.11	RECURRENT EPISODES OF DEPRESSIVE REACTION
Eu33.12	RECURRENT EPISODES OF PSYCHOGENIC DEPRESSION
Eu33.13	RECURRENT EPISODES OF REACTIVE DEPRESSION
Eu33.14	SEASONAL DEPRESSIVE DISORDER
Eu33000	RECURRENT DEPRESSIVE DISORDER, CURRENT EPISODE MILD
Eu33100	RECURRENT DEPRESSIVE DISORDER, CURRENT EPISODE MODERATE
Eu33200	RECURRENT DEPRESS DISORDER CUR EPI SEVERE WITHOUT PSYCHOTIC SYMPTOMS
Eu33211	ENDOGENOUS DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS
Eu33212	MAJOR DEPRESSION, RECURRENT WITHOUT PSYCHOTIC SYMPTOMS
Eu33213	MANIC-DEPRESS PSYCHOSIS, DEPRESSED PSYCHOTIC SYMPTOMS
Eu33300	RECURRENT DEPRESS DISORDER CUR EPI SEVERE WITH PSYCHOTIC SYMPTOMS
Eu33311	ENDOGENOUS DEPRESSION WITH PSYCHOTIC SYMPTOMS
Eu33312	MANIC-DEPRESS PSYCHOSIS, DEPRESSED TYPE + PSYCHOTIC SYMPTOMS
Eu33313	RECURRENT SEVERE EPISODES/MAJOR DEPRESSION + PSYCHOTIC SYMPTOM

Eu33315	RECURRENT SEVERE EPISODES OF PSYCHOTIC DEPRESSION
Eu33316	RECURRENT SEVERE EPISODES/REACTIVE DEPRESSIVE PSYCHOSIS
Eu33400	RECURRENT DEPRESSIVE DISORDER, CURRENTLY IN REMISSION
Eu33y00	OTHER RECURRENT DEPRESSIVE DISORDERS
Eu33z00	RECURRENT DEPRESSIVE DISORDER, UNSPECIFIED
Eu34.00	PERSISTENT MOOD AFFECTIVE DISORDERS
Eu34111	DEPRESSIVE NEUROSIS
Eu34112	DEPRESSIVE PERSONALITY DISORDER
Eu34113	NEUROTIC DEPRESSION
Eu34114	PERSISTENT ANXIETY DEPRESSION
Eu34z00	PERSISTENT MOOD AFFECTIVE DISORDER, UNSPECIFIED
Eu3y111	RECURRENT BRIEF DEPRESSIVE EPISODES
Eu41200	MIXED ANXIETY AND DEPRESSIVE DISORDER
Eu41211	MILD ANXIETY DEPRESSION
Eu53011	POSTNATAL DEPRESSION
Eu53012	POSTPARTUM DEPRESSION
Eu92000	DEPRESSIVE CONDUCT DISORDER
R007z13	POSTOPERATIVE DEPRESSION

Appendix 9-12. Antidepression codes

Selective Serotonin Reuptake Inhibitor (SSRI)	
86222020	CIPRALEX 10MG TABLETS
90873020	CIPRALEX 10MG/ML ORAL DROPS
55602020	CIPRALEX 20MG TABLETS
97171020	CIPRALEX 20MG/ML ORAL DROPS
87526020	CIPRALEX 5MG TABLETS
79421020	CIPRAMIL 10MG TABLETS
79420020	CIPRAMIL 20MG TABLETS
79422020	CIPRAMIL 40MG TABLETS
77312020	CIPRAMIL 40MG/ML DROPS
65254020	CITALOPRAM 10MG TABLET
79463020	CITALOPRAM 10MG TABLETS
87251998	CITALOPRAM 10MG TABLETS
91380997	CITALOPRAM 10MG TABLETS
91395997	CITALOPRAM 10MG TABLETS
93948990	CITALOPRAM 10MG TABLETS
93994990	CITALOPRAM 10MG TABLETS
94895990	CITALOPRAM 10MG TABLETS
95271990	CITALOPRAM 10MG TABLETS
95335990	CITALOPRAM 10MG TABLETS
95421990	CITALOPRAM 10MG TABLETS
95633990	CITALOPRAM 10MG TABLETS
95668990	CITALOPRAM 10MG TABLETS
95705990	CITALOPRAM 10MG TABLETS
95995979	CITALOPRAM 10MG TABLETS
65376020	CITALOPRAM 10MG TABLETS
67890020	CITALOPRAM 10MG TABLETS
71373020	CITALOPRAM 10MG TABLETS
66451020	CITALOPRAM 10MG TABLETS
71225020	CITALOPRAM 10MG TABLETS
66680020	CITALOPRAM 10MG TABLETS

71214020	CITALOPRAM 10MG TABLETS
65125020	CITALOPRAM 10MG TABLETS
68042020	CITALOPRAM 10MG TABLETS
66149020	CITALOPRAM 10MG TABLETS
69605979	CITALOPRAM 10MG/5ML ORAL SUSPENSION
69606979	CITALOPRAM 10MG/5ML ORAL SUSPENSION
65257020	CITALOPRAM 20MG TABLET
79462020	CITALOPRAM 20MG TABLETS
91380998	CITALOPRAM 20MG TABLETS
91395998	CITALOPRAM 20MG TABLETS
93996990	CITALOPRAM 20MG TABLETS
94894990	CITALOPRAM 20MG TABLETS
94937990	CITALOPRAM 20MG TABLETS
95270990	CITALOPRAM 20MG TABLETS
95334990	CITALOPRAM 20MG TABLETS
95420990	CITALOPRAM 20MG TABLETS
95632990	CITALOPRAM 20MG TABLETS
95667990	CITALOPRAM 20MG TABLETS
95704990	CITALOPRAM 20MG TABLETS
65381020	CITALOPRAM 20MG TABLETS
67893020	CITALOPRAM 20MG TABLETS
71376020	CITALOPRAM 20MG TABLETS
38526020	CITALOPRAM 20MG TABLETS
66454020	CITALOPRAM 20MG TABLETS
66685020	CITALOPRAM 20MG TABLETS
65128020	CITALOPRAM 20MG TABLETS
68045020	CITALOPRAM 20MG TABLETS
66152020	CITALOPRAM 20MG TABLETS
69604979	CITALOPRAM 20MG/5ML ORAL SUSPENSION
65262020	CITALOPRAM 40MG TABLET
79464020	CITALOPRAM 40MG TABLETS
91380996	CITALOPRAM 40MG TABLETS

91395996	CITALOPRAM 40MG TABLETS
94880990	CITALOPRAM 40MG TABLETS
94893990	CITALOPRAM 40MG TABLETS
94936990	CITALOPRAM 40MG TABLETS
95269990	CITALOPRAM 40MG TABLETS
95333990	CITALOPRAM 40MG TABLETS
95418990	CITALOPRAM 40MG TABLETS
95631990	CITALOPRAM 40MG TABLETS
95666990	CITALOPRAM 40MG TABLETS
95703990	CITALOPRAM 40MG TABLETS
65386020	CITALOPRAM 40MG TABLETS
67898020	CITALOPRAM 40MG TABLETS
66459020	CITALOPRAM 40MG TABLETS
66688020	CITALOPRAM 40MG TABLETS
65131020	CITALOPRAM 40MG TABLETS
68049020	CITALOPRAM 40MG TABLETS
66160020	CITALOPRAM 40MG TABLETS
92172998	CITALOPRAM 40MG/ML ORAL DROPS
77306020	CITALOPRAM 40MG/ML ORAL DROPS SUGAR FREE
92174998	CITALOPRAM 40MG/ML ORAL DROPS SUGAR FREE
78768020	ESCITALOPRAM 10MG TABLETS
88285998	ESCITALOPRAM 10MG TABLETS
91671998	ESCITALOPRAM 10MG TABLETS
85970998	ESCITALOPRAM 10MG/ML ORAL DROPS
85971998	ESCITALOPRAM 10MG/ML ORAL DROPS SUGAR FREE
90871020	ESCITALOPRAM 10MG/ML ORAL DROPS SUGAR FREE
53823020	ESCITALOPRAM 20MG TABLETS
98088998	ESCITALOPRAM 20MG TABLETS
98561998	ESCITALOPRAM 20MG TABLETS
82790998	ESCITALOPRAM 20MG/ML ORAL DROPS
82791998	ESCITALOPRAM 20MG/ML ORAL DROPS SUGAR FREE
97169020	ESCITALOPRAM 20MG/ML ORAL DROPS SUGAR FREE

87524020	ESCITALOPRAM 5MG TABLETS
87662998	ESCITALOPRAM 5MG TABLETS
87663998	ESCITALOPRAM 5MG TABLETS
62074020	FAVERIN 100MG TABLETS
62073020	FAVERIN 50MG TABLETS
49680020	FELICIUM 20MG CAPSULES
82367998	FLUOXETINE 10MG TABLETS
98001020	FLUOXETINE 10MG TABLETS
74425020	FLUOXETINE 20MG CAPSULE
69654020	FLUOXETINE 20MG CAPSULES
90159998	FLUOXETINE 20MG CAPSULES
90814998	FLUOXETINE 20MG CAPSULES
93066990	FLUOXETINE 20MG CAPSULES
93905990	FLUOXETINE 20MG CAPSULES
94447998	FLUOXETINE 20MG CAPSULES
94490998	FLUOXETINE 20MG CAPSULES
95388990	FLUOXETINE 20MG CAPSULES
96162979	FLUOXETINE 20MG CAPSULES
96168979	FLUOXETINE 20MG CAPSULES
96272990	FLUOXETINE 20MG CAPSULES
96281990	FLUOXETINE 20MG CAPSULES
96606990	FLUOXETINE 20MG CAPSULES
96644990	FLUOXETINE 20MG CAPSULES
96647990	FLUOXETINE 20MG CAPSULES
96651990	FLUOXETINE 20MG CAPSULES
96654990	FLUOXETINE 20MG CAPSULES
96659990	FLUOXETINE 20MG CAPSULES
96674990	FLUOXETINE 20MG CAPSULES
96709990	FLUOXETINE 20MG CAPSULES
96729990	FLUOXETINE 20MG CAPSULES
99592998	FLUOXETINE 20MG CAPSULES
61084020	FLUOXETINE 20MG CAPSULES

61452020	FLUOXETINE 20MG CAPSULES
62975020	FLUOXETINE 20MG CAPSULES
61409020	FLUOXETINE 20MG CAPSULES
61455020	FLUOXETINE 20MG CAPSULES
61167020	FLUOXETINE 20MG CAPSULES
61420020	FLUOXETINE 20MG CAPSULES
63016020	FLUOXETINE 20MG CAPSULES
61387020	FLUOXETINE 20MG CAPSULES
61319020	FLUOXETINE 20MG CAPSULES
66273020	FLUOXETINE 20MG CAPSULES
61439020	FLUOXETINE 20MG CAPSULES
61616020	FLUOXETINE 20MG CAPSULES
90766998	FLUOXETINE 20MG/5ML ORAL LIQ
94490997	FLUOXETINE 20MG/5ML ORAL LIQ
69655020	FLUOXETINE 20MG/5ML ORAL SOLUTION
91928990	FLUOXETINE 20MG/5ML ORAL SOLUTION
94447997	FLUOXETINE 20MG/5ML ORAL SOLUTION
95426990	FLUOXETINE 20MG/5ML ORAL SOLUTION
95813990	FLUOXETINE 20MG/5ML ORAL SOLUTION
95820990	FLUOXETINE 20MG/5ML ORAL SOLUTION
64717020	FLUOXETINE 20MG/5ML ORAL SOLUTION
66129020	FLUOXETINE 20MG/5ML ORAL SOLUTION
64692020	FLUOXETINE 20MG/5ML ORAL SOLUTION
84403998	FLUOXETINE 20MG/5ML ORAL SOLUTION SUGAR FREE
84436998	FLUOXETINE 20MG/5ML ORAL SOLUTION SUGAR FREE
93984020	FLUOXETINE 20MG/5ML ORAL SOLUTION SUGAR FREE
69656020	FLUOXETINE 60MG CAPSULES
94447996	FLUOXETINE 60MG CAPSULES
94490996	FLUOXETINE 60MG CAPSULES
95610990	FLUOXETINE 60MG CAPSULES
65464020	FLUOXETINE 60MG CAPSULES
62070020	FLUVOXAMINE 100MG TABLETS

96345989	FLUVOXAMINE 100MG TABLETS
96493997	FLUVOXAMINE 100MG TABLETS
96810989	FLUVOXAMINE 100MG TABLETS
66244020	FLUVOXAMINE 100MG TABLETS
62693020	FLUVOXAMINE 100MG TABLETS
60735020	FLUVOXAMINE 100MG TABLETS
62069020	FLUVOXAMINE 50MG TABLETS
96493998	FLUVOXAMINE 50MG TABLETS
96492997	FLUVOXAMINE MALEATE 100MG TABS
96492998	FLUVOXAMINE MALEATE 50MG TABS
74047020	LUSTRAL 100MG TABLETS
74046020	LUSTRAL 50MG TABLETS
80679020	OXACTIN 20MG CAPSULES
54495979	PAROXETINE 10MG TABLETS
84807998	PAROXETINE 10MG TABLETS
85382998	PAROXETINE 10MG TABLETS
92043020	PAROXETINE 10MG TABLETS
72934020	PAROXETINE 10MG/5ML ORAL SUSPENSION SUGAR FREE
93490996	PAROXETINE 10MG/5ML ORAL SUSPENSION SUGAR FREE
93489996	PAROXETINE 10MG/5ML S/F LIQ
72932020	PAROXETINE 20MG TABLETS
93489998	PAROXETINE 20MG TABLETS
93490998	PAROXETINE 20MG TABLETS
95051990	PAROXETINE 20MG TABLETS
95332990	PAROXETINE 20MG TABLETS
95350990	PAROXETINE 20MG TABLETS
95578990	PAROXETINE 20MG TABLETS
96087990	PAROXETINE 20MG TABLETS
66464020	PAROXETINE 20MG TABLETS
65578020	PAROXETINE 20MG TABLETS

66399020	PAROXETINE 20MG TABLETS
69754020	PAROXETINE 20MG TABLETS
63703020	PAROXETINE 20MG TABLETS
72933020	PAROXETINE 30MG TABLETS
93487990	PAROXETINE 30MG TABLETS
93489997	PAROXETINE 30MG TABLETS
93490997	PAROXETINE 30MG TABLETS
95007990	PAROXETINE 30MG TABLETS
95028990	PAROXETINE 30MG TABLETS
67650020	PAROXETINE 30MG TABLETS
67575020	PAROXETINE 30MG TABLETS
88346020	PAXORAN 10MG TABLET
88348020	PAXORAN 20MG TABLET
69506020	PROZAC 20MG CAPSULES
69507020	PROZAC 20MG/5ML LIQUID
69508020	PROZAC 60MG CAPSULES
93918020	PROZEP 20MG/5ML ORAL SOLUTION
80777020	PROZIT 20MG/5ML ORAL SOLUTION
82055020	RANFLUTIN 20MG CAPSULES
93187020	SEROXAT 10MG TABLETS
72937020	SEROXAT 20MG TABLETS
72939020	SEROXAT 20MG/10ML LIQUID
72938020	SEROXAT 30MG TABLETS
74051020	SERTRALINE 100MG TABLETS
92729990	SERTRALINE 100MG TABLETS
93173997	SERTRALINE 100MG TABLETS
93174997	SERTRALINE 100MG TABLETS
93732990	SERTRALINE 100MG TABLETS
93842990	SERTRALINE 100MG TABLETS
72095020	SERTRALINE 100MG TABLETS
20738020	SERTRALINE 100MG/5ML ORAL SUSPENSION
79261979	SERTRALINE 100MG/5ML ORAL SUSPENSION

66187979	SERTRALINE 150MG/5ML ORAL SUSPENSION
33816020	SERTRALINE 25MG/5ML ORAL SUSPENSION
66183979	SERTRALINE 25MG/5ML ORAL SUSPENSION
74050020	SERTRALINE 50MG TABLETS
92728990	SERTRALINE 50MG TABLETS
93173998	SERTRALINE 50MG TABLETS
93174998	SERTRALINE 50MG TABLETS
93694990	SERTRALINE 50MG TABLETS
93749990	SERTRALINE 50MG TABLETS
71725020	SERTRALINE 50MG TABLETS
72034020	SERTRALINE 50MG TABLETS
75620020	SERTRALINE 50MG TABLETS
86159998	SERTRALINE 50MG/5ML ORAL SUSPENSION
90497020	SERTRALINE 50MG/5ML ORAL SUSPENSION
Serotonin–norepinephrine reuptake inhibitor (SNRI)	
3977020	ALVENTA XL 150MG CAPSULES
3966020	ALVENTA XL 75MG CAPSULES
88849020	CYMBALTA 30MG GASTRO-RESISTANT CAPSULES
88851020	CYMBALTA 60MG GASTRO-RESISTANT CAPSULES
98863020	DEPEFEX XL 150MG CAPSULES
98861020	DEPEFEX XL 75MG CAPSULES
87335998	DULOXETINE 20MG G/R CAPSULES
87337998	DULOXETINE 20MG GASTRO-RESISTANT CAPSULES
86997998	DULOXETINE 30MG G/R CAPSULES
86999998	DULOXETINE 30MG GASTRO-RESISTANT CAPSULES
88845020	DULOXETINE 30MG GASTRO-RESISTANT CAPSULES
87334998	DULOXETINE 40MG G/R CAPSULES
87336998	DULOXETINE 40MG GASTRO-RESISTANT CAPSULES
86996998	DULOXETINE 60MG G/R CAPSULES
86998998	DULOXETINE 60MG GASTRO-RESISTANT CAPSULES
88847020	DULOXETINE 60MG GASTRO-RESISTANT CAPSULES
10967020	DULOXETINE 60MG GASTRO-RESISTANT CAPSULES

84961020	EDRONAX 4MG TABLETS
48376020	EFEXOR 37.5MG TABLETS
48377020	EFEXOR 75MG TABLETS
85164020	EFEXOR XL 150MG CAPSULES
3970020	EFEXOR XL 150MG CAPSULES
85163020	EFEXOR XL 75MG CAPSULES
97351020	FORAVEN XL 75MG CAPSULES
97656020	RANFAXINE XL 75MG CAPSULES
84955020	REBOXETINE 4MG TABLETS
88836998	REBOXETINE 4MG TABLETS
88838998	REBOXETINE 4MG TABLETS
96241020	RODOMEL XL 150MG CAPSULES
96239020	RODOMEL XL 75MG CAPSULES
96331020	TARDCAPS XL 150MG CAPSULES
96329020	TARDCAPS XL 75MG CAPSULES
97030020	VALDOXAN 25MG TABLETS
97005020	VENAXX XL 150MG CAPSULES
97003020	VENAXX XL 75MG CAPSULES
3976020	VENLABLUE XL 150MG CAPSULES
3965020	VENLABLUE XL 75MG CAPSULES
82190998	VENLAFAXINE 150MG M/R CAPSULES
82874998	VENLAFAXINE 150MG M/R CAPSULES
83114998	VENLAFAXINE 150MG M/R CAPSULES
83149998	VENLAFAXINE 150MG M/R CAPSULES
83204998	VENLAFAXINE 150MG M/R CAPSULES
83217998	VENLAFAXINE 150MG M/R CAPSULES
83264998	VENLAFAXINE 150MG M/R CAPSULES
88755997	VENLAFAXINE 150MG M/R CAPSULES
96022979	VENLAFAXINE 150MG M/R CAPSULES
96029979	VENLAFAXINE 150MG M/R CAPSULES
52165979	VENLAFAXINE 150MG M/R TABLETS
80024978	VENLAFAXINE 150MG M/R TABLETS

82962998	VENLAFAXINE 150MG M/R TABLETS
83157998	VENLAFAXINE 150MG M/R TABLETS
81749998	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
81929998	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
83074998	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
83145998	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
85109020	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
88776997	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
96023979	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
96616020	VENLAFAXINE 150MG MODIFIED-RELEASE CAPSULES
83159998	VENLAFAXINE 150MG MODIFIED-RELEASE TABLETS
96447020	VENLAFAXINE 150MG MODIFIED-RELEASE TABLETS
35355020	VENLAFAXINE 150MG/5ML ORAL SOLUTION
82959998	VENLAFAXINE 225MG M/R TABLETS
82961998	VENLAFAXINE 225MG MODIFIED-RELEASE TABLETS
96838020	VENLAFAXINE 225MG MODIFIED-RELEASE TABLETS
81505998	VENLAFAXINE 37.5MG M/R TABLETS
79303978	VENLAFAXINE 37.5MG MODIFIED-RELEASE CAPSULES
79304978	VENLAFAXINE 37.5MG MODIFIED-RELEASE CAPSULES
81506998	VENLAFAXINE 37.5MG MODIFIED-RELEASE TABLETS
99679020	VENLAFAXINE 37.5MG MODIFIED-RELEASE TABLETS
54686020	VENLAFAXINE 37.5MG TABLETS
83163998	VENLAFAXINE 37.5MG TABLETS
98336998	VENLAFAXINE 37.5MG TABLETS
99896998	VENLAFAXINE 37.5MG TABLETS
3942020	VENLAFAXINE 37.5MG TABLETS
35357020	VENLAFAXINE 37.5MG/5ML ORAL SOLUTION
64642979	VENLAFAXINE 37.5MG/5ML ORAL SOLUTION
86431998	VENLAFAXINE 37.5MG/5ML ORAL SUSPENSION
89954020	VENLAFAXINE 37.5MG/5ML ORAL SUSPENSION
98336996	VENLAFAXINE 50MG TABLETS
99896996	VENLAFAXINE 50MG TABLETS

82191998	VENLAFAXINE 75MG M/R CAPSULES
82875998	VENLAFAXINE 75MG M/R CAPSULES
83115998	VENLAFAXINE 75MG M/R CAPSULES
83150998	VENLAFAXINE 75MG M/R CAPSULES
83205998	VENLAFAXINE 75MG M/R CAPSULES
83218998	VENLAFAXINE 75MG M/R CAPSULES
83265998	VENLAFAXINE 75MG M/R CAPSULES
88755998	VENLAFAXINE 75MG M/R CAPSULES
96033979	VENLAFAXINE 75MG M/R CAPSULES
80023978	VENLAFAXINE 75MG M/R TABLETS
82963998	VENLAFAXINE 75MG M/R TABLETS
83158998	VENLAFAXINE 75MG M/R TABLETS
83162998	VENLAFAXINE 75MG M/R TABLETS
81750998	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
81930998	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
82540998	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
83075998	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
83146998	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
85108020	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
88776998	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
96034979	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
96614020	VENLAFAXINE 75MG MODIFIED-RELEASE CAPSULES
83160998	VENLAFAXINE 75MG MODIFIED-RELEASE TABLETS
96445020	VENLAFAXINE 75MG MODIFIED-RELEASE TABLETS
54687020	VENLAFAXINE 75MG TABLETS
98336997	VENLAFAXINE 75MG TABLETS
99896997	VENLAFAXINE 75MG TABLETS
35359020	VENLAFAXINE 75MG/5ML ORAL SOLUTION
64640979	VENLAFAXINE 75MG/5ML ORAL SOLUTION
96836020	VENLALIC XL 150MG TABLETS
96841020	VENLALIC XL 225MG TABLETS
99681020	VENLALIC XL 37.5MG TABLETS

96834020	VENLALIC XL 75MG TABLETS
99210020	VENLANEO XL 150MG CAPSULES
99208020	VENLANEO XL 75MG CAPSULES
96357020	VENSIR XL 150MG CAPSULES
96355020	VENSIR XL 75MG CAPSULES
96536020	VEXARIN XL 150MG CAPSULES
96534020	VEXARIN XL 75MG CAPSULES
96439020	VIEPAX 37.5MG TABLETS
96441020	VIEPAX 75MG TABLETS
96451020	VIEPAX XL 150MG TABLETS
96449020	VIEPAX XL 75MG TABLETS
Tricyclic (TCA)	
55355020	ALLEGRON 10MG TABLETS
55356020	ALLEGRON 25MG TABLETS
99824992	AMITRIPTYLINE 100 MG TAB
98129998	AMITRIPTYLINE 100MG/10ML
94703998	AMITRIPTYLINE 10MG / PERPHENAZINE 2MG TABLETS
48490020	AMITRIPTYLINE 10MG TABLET
48533020	AMITRIPTYLINE 10MG TABLET
58949020	AMITRIPTYLINE 10MG TABLETS
97223998	AMITRIPTYLINE 10MG TABLETS
98130998	AMITRIPTYLINE 10MG TABLETS
98150998	AMITRIPTYLINE 10MG TABLETS
99861990	AMITRIPTYLINE 10MG TABLETS
99863990	AMITRIPTYLINE 10MG TABLETS
99864990	AMITRIPTYLINE 10MG TABLETS
99866990	AMITRIPTYLINE 10MG TABLETS
99868990	AMITRIPTYLINE 10MG TABLETS
99869990	AMITRIPTYLINE 10MG TABLETS
99870990	AMITRIPTYLINE 10MG TABLETS
99871990	AMITRIPTYLINE 10MG TABLETS
48496020	AMITRIPTYLINE 10MG TABLETS

48507020	AMITRIPTYLINE 10MG TABLETS
48522020	AMITRIPTYLINE 10MG TABLETS
48516020	AMITRIPTYLINE 10MG TABLETS
48479020	AMITRIPTYLINE 10MG TABLETS
48484020	AMITRIPTYLINE 10MG TABLETS
81085998	AMITRIPTYLINE 10MG/5ML ORAL SOLUTION
55688020	AMITRIPTYLINE 10MG/5ML ORAL SOLUTION
81084998	AMITRIPTYLINE 10MG/5ML ORAL SUSPENSION
75331020	AMITRIPTYLINE 10MG/5ML SUGAR FREE ORAL SOLUTION
92808996	AMITRIPTYLINE 10MG/5ML SUGAR FREE ORAL SOLUTION
98067988	AMITRIPTYLINE 10MG/5ML SUGAR FREE ORAL SOLUTION
98128998	AMITRIPTYLINE 10MG/5ML SUGAR FREE ORAL SOLUTION
60229020	AMITRIPTYLINE 10MG/ML INJECTION
96924998	AMITRIPTYLINE 10MG/ML INJECTION
68724020	AMITRIPTYLINE 12.5MG / CHLORDIAZEPOXIDE 5MG CAPSULES
94704998	AMITRIPTYLINE 12.5MG / CHLORDIAZEPOXIDE 5MG CAPSULES
99826992	AMITRIPTYLINE 200 MG TAB
68725020	AMITRIPTYLINE 25MG / CHLORDIAZEPOXIDE 10MG CAPSULES
94704997	AMITRIPTYLINE 25MG / CHLORDIAZEPOXIDE 10MG CAPSULES
98343998	AMITRIPTYLINE 25MG / CHLORDIAZEPOXIDE 10MG CAPSULES
68729020	AMITRIPTYLINE 25MG / PERPHENAZINE 2MG TABLETS
94703997	AMITRIPTYLINE 25MG / PERPHENAZINE 2MG TABLETS
98138998	AMITRIPTYLINE 25MG M/R CAPS

96925998	AMITRIPTYLINE 25MG MODIFIED-RELEASE CAPSULES
48492020	AMITRIPTYLINE 25MG TABLET
48502020	AMITRIPTYLINE 25MG TABLET
48513020	AMITRIPTYLINE 25MG TABLET
48528020	AMITRIPTYLINE 25MG TABLET
48534020	AMITRIPTYLINE 25MG TABLET
58950020	AMITRIPTYLINE 25MG TABLETS
94076990	AMITRIPTYLINE 25MG TABLETS
94771990	AMITRIPTYLINE 25MG TABLETS
97223997	AMITRIPTYLINE 25MG TABLETS
98130997	AMITRIPTYLINE 25MG TABLETS
98150997	AMITRIPTYLINE 25MG TABLETS
99861989	AMITRIPTYLINE 25MG TABLETS
99863989	AMITRIPTYLINE 25MG TABLETS
99864989	AMITRIPTYLINE 25MG TABLETS
99865990	AMITRIPTYLINE 25MG TABLETS
99866989	AMITRIPTYLINE 25MG TABLETS
99867989	AMITRIPTYLINE 25MG TABLETS
99868989	AMITRIPTYLINE 25MG TABLETS
99869988	AMITRIPTYLINE 25MG TABLETS
99870989	AMITRIPTYLINE 25MG TABLETS
99871989	AMITRIPTYLINE 25MG TABLETS
48497020	AMITRIPTYLINE 25MG TABLETS
48508020	AMITRIPTYLINE 25MG TABLETS
70948020	AMITRIPTYLINE 25MG TABLETS
48523020	AMITRIPTYLINE 25MG TABLETS
48517020	AMITRIPTYLINE 25MG TABLETS
48480020	AMITRIPTYLINE 25MG TABLETS
48485020	AMITRIPTYLINE 25MG TABLETS
75330020	AMITRIPTYLINE 25MG/5ML ORAL SOLUTION SUGAR FREE

92808997	AMITRIPTYLINE 25MG/5ML ORAL SOLUTION SUGAR FREE
98067990	AMITRIPTYLINE 25MG/5ML ORAL SOLUTION SUGAR FREE
55686020	AMITRIPTYLINE 25MG/5ML ORAL SOLUTION SUGAR FREE
99825992	AMITRIPTYLINE 300 MG TAB
98138997	AMITRIPTYLINE 50MG M/R CAPS
96925997	AMITRIPTYLINE 50MG MODIFIED-RELEASE CAPSULES
48491020	AMITRIPTYLINE 50MG TABLET
58951020	AMITRIPTYLINE 50MG TABLETS
97223996	AMITRIPTYLINE 50MG TABLETS
98130996	AMITRIPTYLINE 50MG TABLETS
98150996	AMITRIPTYLINE 50MG TABLETS
99863988	AMITRIPTYLINE 50MG TABLETS
99864988	AMITRIPTYLINE 50MG TABLETS
99866988	AMITRIPTYLINE 50MG TABLETS
99868988	AMITRIPTYLINE 50MG TABLETS
99869989	AMITRIPTYLINE 50MG TABLETS
99870988	AMITRIPTYLINE 50MG TABLETS
99871988	AMITRIPTYLINE 50MG TABLETS
48498020	AMITRIPTYLINE 50MG TABLETS
48509020	AMITRIPTYLINE 50MG TABLETS
48524020	AMITRIPTYLINE 50MG TABLETS
48518020	AMITRIPTYLINE 50MG TABLETS
48481020	AMITRIPTYLINE 50MG TABLETS
48486020	AMITRIPTYLINE 50MG TABLETS
75329020	AMITRIPTYLINE 50MG/5ML ORAL SOLUTION SUGAR FREE
92808998	AMITRIPTYLINE 50MG/5ML ORAL SOLUTION SUGAR FREE

98067989	AMITRIPTYLINE 50MG/5ML ORAL SOLUTION SUGAR FREE
55687020	AMITRIPTYLINE 50MG/5ML ORAL SOLUTION SUGAR FREE
94067992	AMITRIPTYLINE 75 MG TAB
98129997	AMITRIPTYLINE 75MG M/R CAPS
60224020	AMITRIPTYLINE 75MG MODIFIED-RELEASE CAPSULES
96925996	AMITRIPTYLINE 75MG MODIFIED-RELEASE CAPSULES
92481020	AMITRIPTYLINE ORAL SOLUTION
96891992	AMITRIPTYLINE S/F 25 MG/5ML
55386020	ANAFRANIL 10MG CAPSULES
55387020	ANAFRANIL 25MG CAPSULES
55392020	ANAFRANIL 25MG/5ML SYRUP
55388020	ANAFRANIL 50MG CAPSULES
55396020	ANAFRANIL SR 75MG TABLETS
61463020	CLOMIPRAMINE 10MG CAPSULES
96640998	CLOMIPRAMINE 10MG CAPSULES
97548990	CLOMIPRAMINE 10MG CAPSULES
98340990	CLOMIPRAMINE 10MG CAPSULES
99297990	CLOMIPRAMINE 10MG CAPSULES
50946020	CLOMIPRAMINE 10MG CAPSULES
57824020	CLOMIPRAMINE 10MG CAPSULES
54669020	CLOMIPRAMINE 10MG CAPSULES
97167992	CLOMIPRAMINE 25 MG TAB
61464020	CLOMIPRAMINE 25MG CAPSULES
96640997	CLOMIPRAMINE 25MG CAPSULES
97548989	CLOMIPRAMINE 25MG CAPSULES
97773989	CLOMIPRAMINE 25MG CAPSULES
98340989	CLOMIPRAMINE 25MG CAPSULES
99297989	CLOMIPRAMINE 25MG CAPSULES
50947020	CLOMIPRAMINE 25MG CAPSULES
57825020	CLOMIPRAMINE 25MG CAPSULES

54670020	CLOMIPRAMINE 25MG CAPSULES
61469020	CLOMIPRAMINE 25MG/5ML ORAL SOLUTION
96639998	CLOMIPRAMINE 25MG/5ML ORAL SOLUTION
61465020	CLOMIPRAMINE 50MG CAPSULES
96640996	CLOMIPRAMINE 50MG CAPSULES
96901988	CLOMIPRAMINE 50MG CAPSULES
97548988	CLOMIPRAMINE 50MG CAPSULES
98340988	CLOMIPRAMINE 50MG CAPSULES
99297988	CLOMIPRAMINE 50MG CAPSULES
50948020	CLOMIPRAMINE 50MG CAPSULES
57826020	CLOMIPRAMINE 50MG CAPSULES
19451020	CLOMIPRAMINE 50MG/5ML ORAL SOLUTION
80548979	CLOMIPRAMINE 50MG/5ML ORAL SOLUTION
83878998	CLOMIPRAMINE 50MG/5ML ORAL SUSPENSION
95021020	CLOMIPRAMINE 50MG/5ML ORAL SUSPENSION
61473020	CLOMIPRAMINE 75MG MODIFIED-RELEASE TABLETS
96638998	CLOMIPRAMINE 75MG MODIFIED-RELEASE TABLETS
93360992	CLOMIPRAMINE HCL 10MG CAPSULES
98144998	CLOMIPRAMINE HCL 10MG CAPSULES
98144997	CLOMIPRAMINE HCL 25MG CAPSULES
96637998	CLOMIPRAMINE HCL 25MG/2ML
99794992	CLOMIPRAMINE HCL 25MG/2ML
98143998	CLOMIPRAMINE HCL 25MG/5ML SYR
93358992	CLOMIPRAMINE HCL 50MG CAPSULES
98144996	CLOMIPRAMINE HCL 50MG CAPSULES
98142998	CLOMIPRAMINE HCL 75MG M/R TABS
62833020	DOSULEPIN 25MG CAPSULES
94801990	DOSULEPIN 25MG CAPSULES
96158990	DOSULEPIN 25MG CAPSULES
96311998	DOSULEPIN 25MG CAPSULES
96467990	DOSULEPIN 25MG CAPSULES
96868990	DOSULEPIN 25MG CAPSULES

96964990	DOSULEPIN 25MG CAPSULES
97762990	DOSULEPIN 25MG CAPSULES
98351989	DOSULEPIN 25MG CAPSULES
98563989	DOSULEPIN 25MG CAPSULES
98783990	DOSULEPIN 25MG CAPSULES
99614990	DOSULEPIN 25MG CAPSULES
49588020	DOSULEPIN 25MG CAPSULES
56942020	DOSULEPIN 25MG CAPSULES
68380020	DOSULEPIN 25MG CAPSULES
60464020	DOSULEPIN 25MG CAPSULES
53818020	DOSULEPIN 25MG CAPSULES
63443020	DOSULEPIN 25MG CAPSULES
66765020	DOSULEPIN 25MG CAPSULES
62179020	DOSULEPIN 25MG CAPSULES
54621020	DOSULEPIN 25MG CAPSULES
54728020	DOSULEPIN 25MG/5ML MIXTURE
98327997	DOSULEPIN 25MG/5ML MIXTURE
19725020	DOSULEPIN 25MG/5ML ORAL SOLUTION
80274979	DOSULEPIN 25MG/5ML ORAL SOLUTION
55642020	DOSULEPIN 25MG/5ML ORAL SOLUTION
62835020	DOSULEPIN 25MG/5ML ORAL SOLUTION SUGAR FREE
96311996	DOSULEPIN 25MG/5ML ORAL SOLUTION SUGAR FREE
98078990	DOSULEPIN 25MG/5ML ORAL SOLUTION SUGAR FREE
62834020	DOSULEPIN 75MG TABLETS
94800990	DOSULEPIN 75MG TABLETS
96311997	DOSULEPIN 75MG TABLETS
96868989	DOSULEPIN 75MG TABLETS
97762989	DOSULEPIN 75MG TABLETS
98351990	DOSULEPIN 75MG TABLETS
98563990	DOSULEPIN 75MG TABLETS
99614989	DOSULEPIN 75MG TABLETS
49589020	DOSULEPIN 75MG TABLETS

56943020	DOSULEPIN 75MG TABLETS
68383020	DOSULEPIN 75MG TABLETS
60465020	DOSULEPIN 75MG TABLETS
53817020	DOSULEPIN 75MG TABLETS
54620020	DOSULEPIN 75MG TABLETS
80278979	DOSULEPIN 75MG/5ML ORAL SOLUTION
54727020	DOSULEPIN 75MG/5ML ORAL SOLUTION SUGAR FREE
98078989	DOSULEPIN 75MG/5ML ORAL SOLUTION SUGAR FREE
98327998	DOSULEPIN 75MG/5ML ORAL SOLUTION SUGAR FREE
88906998	DOSULEPIN 25MG CAPSULES
97722998	DOSULEPIN 25MG CAPSULES
97818998	DOSULEPIN 25MG CAPSULES
98126998	DOSULEPIN 25MG CAPSULES
88906997	DOSULEPIN 75MG TABLETS
97722997	DOSULEPIN 75MG TABLETS
97818997	DOSULEPIN 75MG TABLETS
98126997	DOSULEPIN 75MG TABLETS
56698020	DOTHAPAX 25 CAPSULES
56699020	DOTHAPAX 75 TABLETS
62850020	DOXEPIN 10MG CAPSULES
96308998	DOXEPIN 10MG CAPSULES
98124998	DOXEPIN 10MG CAPSULES
62851020	DOXEPIN 25MG CAPSULES
85172998	DOXEPIN 25MG CAPSULES
96308997	DOXEPIN 25MG CAPSULES
98124997	DOXEPIN 25MG CAPSULES
83206998	DOXEPIN 25MG/5ML ORAL SUSPENSION
96353020	DOXEPIN 25MG/5ML ORAL SUSPENSION
89407998	DOXEPIN 5% CREAM
62852020	DOXEPIN 50MG CAPSULES
85171998	DOXEPIN 50MG CAPSULES
96308996	DOXEPIN 50MG CAPSULES

98124996	DOXEPIN 50MG CAPSULES
80210979	DOXEPIN 50MG/5ML ORAL SOLUTION
62857020	DOXEPIN 75MG CAPSULES
96307998	DOXEPIN 75MG CAPSULES
98123998	DOXEPIN 75MG CAPSULES
88747998	DOXEPIN HYDROCHLORIDE
94795998	DOXEPIN HYDROCHLORIDE
96687992	IMIPRAMINE 100 MG TAB
59429020	IMIPRAMINE 10MG TABLETS
97112998	IMIPRAMINE 10MG TABLETS
99554990	IMIPRAMINE 10MG TABLETS
99555990	IMIPRAMINE 10MG TABLETS
49845020	IMIPRAMINE 10MG TABLETS
49841020	IMIPRAMINE 10MG TABLETS
68803020	IMIPRAMINE 10MG TABLETS
97091998	IMIPRAMINE 10MG TABS
95155992	IMIPRAMINE 25 MG CAP
49838020	IMIPRAMINE 25MG TABLET
59430020	IMIPRAMINE 25MG TABLETS
97112997	IMIPRAMINE 25MG TABLETS
98140997	IMIPRAMINE 25MG TABLETS
98149990	IMIPRAMINE 25MG TABLETS
99554989	IMIPRAMINE 25MG TABLETS
99555989	IMIPRAMINE 25MG TABLETS
99556989	IMIPRAMINE 25MG TABLETS
49846020	IMIPRAMINE 25MG TABLETS
49842020	IMIPRAMINE 25MG TABLETS
55369020	IMIPRAMINE 25MG TABLETS
96130998	IMIPRAMINE 25MG/5ML ORAL SOLUTION
62948979	IMIPRAMINE 25MG/5ML ORAL SOLUTION SUGAR FREE
82432998	IMIPRAMINE 25MG/5ML ORAL SOLUTION SUGAR FREE
97872020	IMIPRAMINE 25MG/5ML ORAL SOLUTION SUGAR FREE

95156992	IMIPRAMINE 50 MG TAB
95154992	IMIPRAMINE 75 MG TAB
98140998	IMIPRAMINE 10MG TABLETS
97593992	IMIPRAMINE 12.5 MG
98140996	IMIPRAMINE
85437998	IMIPRAMINE
64034020	LOFEPRAMINE 70MG TABLETS
95999998	LOFEPRAMINE 70MG TABLETS
96793990	LOFEPRAMINE 70MG TABLETS
96963990	LOFEPRAMINE 70MG TABLETS
97142990	LOFEPRAMINE 70MG TABLETS
97192990	LOFEPRAMINE 70MG TABLETS
97743990	LOFEPRAMINE 70MG TABLETS
97861990	LOFEPRAMINE 70MG TABLETS
98132998	LOFEPRAMINE 70MG TABLETS
59084020	LOFEPRAMINE 70MG TABLETS
57022020	LOFEPRAMINE 70MG TABLETS
56517020	LOFEPRAMINE 70MG TABLETS
60055020	LOFEPRAMINE 70MG TABLETS
67063979	LOFEPRAMINE 70MG
55646020	LOFEPRAMINE 70MG
64035020	LOFEPRAMINE 70MG
95999997	LOFEPRAMINE 70MG
98077990	LOFEPRAMINE 70MG
89205998	LOFEPRAMINE 70MG
94249992	NORTRIPTYLINE 10 MG ELI
94630998	NORTRIPTYLINE 10MG / FLUPHENAZINE 500MICROGRAM TABLETS
95695998	NORTRIPTYLINE 10MG CAPSULE
98154998	NORTRIPTYLINE 10MG CAPSULES
65153020	NORTRIPTYLINE 10MG TABLETS
95696998	NORTRIPTYLINE 10MG TABLETS

96248979	NORTRIPTYLINE 10MG TABLETS
98152998	NORTRIPTYLINE 10MG TABLETS
95695996	NORTRIPTYLINE 10MG/5ML LIQUID
98154996	NORTRIPTYLINE 10MG/5ML LIQUID
95695997	NORTRIPTYLINE 25MG CAPSULE
98154997	NORTRIPTYLINE 25MG CAPSULES
65154020	NORTRIPTYLINE 25MG TABLETS
95696997	NORTRIPTYLINE 25MG TABLETS
98152997	NORTRIPTYLINE 25MG TABLETS
77778020	NORTRIPTYLINE 25MG TABLETS
94630997	NORTRIPTYLINE 30MG / FLUPHENAZINE 1.5MG TABLETS
67280020	TRIMIPRAMINE 10MG TABLETS
93841990	TRIMIPRAMINE 10MG TABLETS
95107998	TRIMIPRAMINE 10MG TABLETS
98136998	TRIMIPRAMINE 10MG TABLETS
71733020	TRIMIPRAMINE 10MG TABLETS
67281020	TRIMIPRAMINE 25MG TABLETS
93840990	TRIMIPRAMINE 25MG TABLETS
95107997	TRIMIPRAMINE 25MG TABLETS
98136997	TRIMIPRAMINE 25MG TABLETS
71736020	TRIMIPRAMINE 25MG TABLETS
98212992	TRIMIPRAMINE 50 MG TAB
67282020	TRIMIPRAMINE 50MG CAPSULES
93839990	TRIMIPRAMINE 50MG CAPSULES
95107996	TRIMIPRAMINE 50MG CAPSULES
98136996	TRIMIPRAMINE 50MG CAPSULES
55440020	TRYPTIZOL 10MG TABLET
55450020	TRYPTIZOL 10MG/5ML SUGAR FREE ORAL SOLUTION
55445020	TRYPTIZOL 10MG/ML INJECTION
55441020	TRYPTIZOL 25MG TABLET
55442020	TRYPTIZOL 50MG TABLET
55446020	TRYPTIZOL MR 75MG MODIFIED-RELEASE CAPSULE

Monoamine oxidase inhibitors (MAOIs)	
96105998	ISOCARBOXAZID 10MG TABLETS
97169990	ISOCARBOXAZID 10MG TABLETS
99450998	ISOCARBOXAZID 10MG TABLETS
71994020	MANERIX 150MG TABLETS
71995020	MANERIX 300MG TABLETS
50286020	MARPLAN 10MG TABLET
93749998	MOCLOBEMIDE 150MG TABLETS
93759998	MOCLOBEMIDE 150MG TABLETS
96061990	MOCLOBEMIDE 150MG TABLETS
93749997	MOCLOBEMIDE 300MG TABLETS
93759997	MOCLOBEMIDE 300MG TABLETS
50620020	NARDIL 15MG TABLETS
51010020	PARNATE 10MG TABLET
51013020	PARSTELIN TABLET
65635020	PHENELZINE 15MG TABLETS
95560998	PHENELZINE 15MG TABLETS
99377998	PHENELZINE 15MG TABLETS
95144998	TRANYLCYPROMINE 10MG TABLETS
95665990	TRANYLCYPROMINE 10MG TABLETS
99281998	TRANYLCYPROMINE 10MG TABLETS
95143998	TRANYLCYPROMINE WITH TRIFLUOPERAZINE TABLET
94626998	TRIFLUOPERAZINE WITH TRANYLCYPROMINE 1MG + 10MG TABLET

Appendix 9-13.Pneumonia codes

A022200	SALMONELLA PNEUMONIA
A116.00	TUBERCULOUS PNEUMONIA
A203.00	PRIMARY PNEUMONIC PLAGUE
A204.00	SECONDARY PNEUMONIC PLAGUE
A205.00	PNEUMONIC PLAGUE, UNSPECIFIED
A380300	SEPTICAEMIA DUE TO STREPTOCOCCUS PNEUMONIAE
A3BXA00	MYCOPLASMA PNEUMONIAE
A3BXB00	KLEBSIELLA PNEUMONIAE
A54x400	HERPES SIMPLEX PNEUMONIA
A551.00	POST-MEASLES PNEUMONIA
A730.00	ORNITHOSIS WITH PNEUMONIA
A789300	HIV DISEASE RESULTING IN PNEUMOCYSTIS CARINII PNEUMONIA
A789311	HIV DISEASE RESULTING IN PNEUMOCYSTIS JIROVECII PNEUMONIA
A789900	HIV DISEASE RESULTING IN LYMPHOID INTERSTITIAL PNEUMONITIS
AB24.11	PNEUMONIA
AB40500	HISTOPLASMA CAPSULATUM WITH PNEUMONIA
AB41500	HISTOPLASMA DUBOISII WITH PNEUMONIA
AyuK900	MYCOPLASMA PNEUMONIAE
AyuKA00	KLEBSIELLA PNEUMONIAE/CAUSE/DISEASE CLASSIFIED /OTHER CHAPTERS
H060A00	ACUTE BRONCHITIS DUE TO MYCOPLASMA PNEUMONIA
H062.00	ACUTE LOWER RESPIRATORY TRACT INFECTION
H06z112	ACUTE LOWER RESPIRATORY TRACT INFECTION
H2...00	PNEUMONIA AND INFLUENZA
H20..00	VIRAL PNEUMONIA
H20..11	CHEST INFECTION - VIRAL PNEUMONIA

H200.00	PNEUMONIA DUE TO ADENOVIRUS
H201.00	PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS
H202.00	PNEUMONIA DUE TO PARAINFLUENZA VIRUS
H203.00	PNEUMONIA DUE TO HUMAN METAPNEUMOVIRUS
H20y.00	VIRAL PNEUMONIA
H20z.00	VIRAL PNEUMONIA
H21..00	LOBAR (PNEUMOCOCCAL) PNEUMONIA
H22..00	OTHER BACTERIAL PNEUMONIA
H22..11	CHEST INFECTION - OTHER BACTERIAL PNEUMONIA
H220.00	PNEUMONIA DUE TO KLEBSIELLA PNEUMONIA
H221.00	PNEUMONIA DUE TO PSEUDOMONAS
H222.00	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZA
H222.11	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZA
H223.00	PNEUMONIA DUE TO STREPTOCOCCUS
H223000	PNEUMONIA DUE TO STREPTOCOCCUS, GROUP B
H224.00	PNEUMONIA DUE TO STAPHYLOCOCCUS
H22y.00	PNEUMONIA DUE TO OTHER SPECIFIED BACTERIA
H22y000	PNEUMONIA DUE TO ESCHERICHIA COLI
H22y011	E. COLI PNEUMONIA
H22y100	PNEUMONIA DUE TO PROTEUS
H22y200	PNEUMONIA - LEGIONELLA
H22yX00	PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
H22yz00	PNEUMONIA DUE TO BACTERIA NOS
H22z.00	BACTERIAL PNEUMONIA NOS
H23..00	PNEUMONIA DUE TO OTHER SPECIFIED ORGANISMS
H23..11	CHEST INFECTION - PNEUMONIA ORGANISM
H230.00	PNEUMONIA DUE TO EATON'S AGENT
H231.00	PNEUMONIA DUE TO MYCOPLASMA PNEUMONIA
H232.00	PNEUMONIA DUE TO PLEUROPNEUMONIA LIKE ORGANISMS

H233.00	CHLAMYDIAL PNEUMONIA
H23z.00	PNEUMONIA DUE TO SPECIFIED ORGANISM NOS
H24..00	PNEUMONIA WITH INFECTIOUS DISEASES EC
H240.00	PNEUMONIA WITH MEASLES
H241.00	PNEUMONIA WITH CYTOMEGALIC INCLUSION DISEASE
H242.00	PNEUMONIA WITH ORNITHOSIS
H243.00	PNEUMONIA WITH WHOOPING COUGH
H243.11	PNEUMONIA WITH PERTUSSIS
H244.00	PNEUMONIA WITH TULARAEMIA
H246.00	PNEUMONIA WITH ASPERGILLOSIS
H247.00	PNEUMONIA WITH OTHER SYSTEMIC MYCOSES
H247000	PNEUMONIA WITH CANDIDIASIS
H247100	PNEUMONIA WITH COCCIDIOIDOMYCOSIS
H247z00	PNEUMONIA WITH SYSTEMIC MYCOSIS
H24y.00	PNEUMONIA WITH OTHER INFECTIOUS DISEASES EC
H24y000	PNEUMONIA WITH ACTINOMYCOSIS
H24y100	PNEUMONIA WITH NOCARDIOSIS
H24y200	PNEUMONIA WITH PNEUMOCYSTIS CARINII
H24y300	PNEUMONIA WITH Q-FEVER
H24y400	PNEUMONIA WITH SALMONELLOSIS
H24y500	PNEUMONIA WITH TOXOPLASMOSIS
H24y600	PNEUMONIA WITH TYPHOID FEVER
H24y700	PNEUMONIA WITH VARICELLA
H24yz00	PNEUMONIA WITH OTHER INFECTIOUS DISEASES EC NOS
H24z.00	PNEUMONIA WITH INFECTIOUS DISEASES EC NOS
H25..00	BRONCHOPNEUMONIA DUE TO UNSPECIFIED ORGANISM
H25..11	CHEST INFECTION - UNSPECIFIED BRONCHOPNEUMONIA
H26..00	PNEUMONIA DUE TO UNSPECIFIED ORGANISM

H26..11	CHEST INFECTION - PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H260.00	LOBAR PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H260000	LUNG CONSOLIDATION
H261.00	BASAL PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H262.00	POSTOPERATIVE PNEUMONIA
H270.00	INFLUENZA WITH PNEUMONIA
H270.11	CHEST INFECTION - INFLUENZA WITH PNEUMONIA
H270000	INFLUENZA WITH BRONCHOPNEUMONIA
H270100	INFLUENZA WITH PNEUMONIA, INFLUENZA VIRUS IDENTIFIED
H270z00	INFLUENZA WITH PNEUMONIA
H28..00	ATYPICAL PNEUMONIA
H2B..00	COMMUNITY-ACQUIRED PNEUMONIA
H2C..00	HOSPITAL ACQUIRED PNEUMONIA
H2y..00	OTHER SPECIFIED PNEUMONIA OR INFLUENZA
H2z..00	PNEUMONIA OR INFLUENZA
H47..00	PNEUMONITIS DUE TO INHALATION OF SOLIDS OR LIQUIDS
H47..11	ASPIRATION PNEUMONITIS
H470.00	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS
H470.11	ASPIRATION PNEUMONIA
H470000	PNEUMONITIS DUE TO INHALATION OF REGURGITATED FOOD
H470300	PNEUMONITIS DUE TO INHALATION OF VOMITUS
H470311	VOMIT INHALATION PNEUMONITIS
H470312	ASPIRATION PNEUMONIA DUE TO VOMIT
H470z00	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS

H471.00	PNEUMONITIS DUE TO INHALATION OF OIL OR ESSENCE
H510900	PNEUMOCOCCAL PLEURISY
H511000	PNEUMOCOCCAL PLEURISY WITH EFFUSION
H530200	GANGRENOUS PNEUMONIA
H530300	ABSCESS OF LUNG WITH PNEUMONIA
H540000	HYPOSTATIC PNEUMONIA
H540100	HYPOSTATIC BRONCHOPNEUMONIA
H564.00	BRONCHIOLITIS OBLITERANS ORGANISING PNEUMONIA
H56y100	INTERSTITIAL PNEUMONIA
H571.00	RHEUMATIC PNEUMONIA
Hyu0800	OTHER VIRAL PNEUMONIA
Hyu0900	PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
Hyu0A00	OTHER BACTERIAL PNEUMONIA
Hyu0B00	PNEUMONIA DUE TO OTHER SPECIFIED INFECTIOUS ORGANISMS
Hyu0C00	PNEUMONIA IN BACTERIAL DISEASES CLASSIFIED ELSEWHERE
Hyu0D00	PNEUMONIA IN VIRAL DISEASES CLASSIFIED ELSEWHERE
Hyu0G00	PNEUMONIA IN OTHER DISEASES CLASSIFIED ELSEWHERE
Hyu0H00	OTHER PNEUMONIA, ORGANISM UNSPECIFIED
SP13100	OTHER ASPIRATION PNEUMONIA AS A COMPLICATION OF CARE

Appendix 9-14. COPD exacerbation algorithm codes

Lower Respiratory tract infection	
H06z011	CHEST INFECTION
H060.00	ACUTE BRONCHITIS
H27..00	INFLUENZA
H061.00	ACUTE BRONCHIOLITIS
H060w00	ACUTE VIRAL BRONCHITIS UNSPECIFIED
H27z.11	FLU LIKE ILLNESS
H07..00	CHEST COLD
H06z000	CHEST INFECTION NOS
H06z100	LOWER RESPIRATORY TRACT INFECTION
H27z.12	INFLUENZA LIKE ILLNESS
H060.11	ACUTE WHEEZY BRONCHITIS
H062.00	ACUTE LOWER RESPIRATORY TRACT INFECTION
H061400	OBLITERATING FIBROUS BRONCHIOLITIS
16L..00	INFLUENZA-LIKE SYMPTOMS
H060600	ACUTE PNEUMOCOCCAL BRONCHITIS
H060300	ACUTE PURULENT BRONCHITIS
H27y100	INFLUENZA WITH GASTROINTESTINAL TRACT INVOLVEMENT
H271000	INFLUENZA WITH LARYNGITIS
H27z.00	INFLUENZA
H061200	ACUTE BRONCHIOLITIS WITH BRONCHOSPASM
H30..11	CHEST INFECTION - UNSPECIFIED BRONCHITIS
H061z00	ACUTE BRONCHIOLITIS
H061500	ACUTE BRONCHIOLITIS DUE TO RESPIRATORY SYNCYTIAL VIRUS
H060z00	ACUTE BRONCHITIS
H3y0.00	CHRONIC OBSTRUCT PULMONARY DIS WITH ACUTE LOWER RESPIRATORY INFECTION
H060400	ACUTE CROUPOUS BRONCHITIS
H060800	ACUTE HAEMOPHILUS INFLUENZAE BRONCHITIS

H271z00	INFLUENZA WITH RESPIRATORY MANIFESTATIONS NOS
H24..11	CHEST INFECTION WITH INFECTIOUS DISEASE EC
H060x00	ACUTE BACTERIAL BRONCHITIS UNSPECIFIED
H312300	BRONCHIOLITIS OBLITERANS
H060C00	ACUTE BRONCHITIS DUE TO PARAINFLUENZA VIRUS
H271100	INFLUENZA WITH PHARYNGITIS
H06..00	ACUTE BRONCHITIS AND BRONCHIOLITIS
H27yz00	INFLUENZA WITH OTHER MANIFESTATIONS NOS
H06z112	ACUTE LOWER RESPIRATORY TRACT INFECTION
H06z.00	ACUTE BRONCHITIS OR BRONCHIOLITIS NOS
H061100	ACUTE OBLITERATING BRONCHIOLITIS
H060700	ACUTE STREPTOCOCCAL BRONCHITIS
H271.00	INFLUENZA WITH OTHER RESPIRATORY MANIFESTATION
H27y000	INFLUENZA WITH ENCEPHALOPATHY
H27y.00	INFLUENZA WITH OTHER MANIFESTATIONS
H060D00	ACUTE BRONCHITIS DUE TO RESPIRATORY SYNCYTIAL VIRUS
H060900	ACUTE NEISSERIA CATARRHALIS BRONCHITIS
H061000	ACUTE CAPILLARY BRONCHIOLITIS
43jQ.00	AVIAN INFLUENZA VIRUS NUCLEIC ACID DETECTION
H060E00	ACUTE BRONCHITIS DUE TO RHINOVIRUS
H060F00	ACUTE BRONCHITIS DUE TO ECHOVIRUS
H061600	ACUTE BRONCHIOLITIS DUE TO OTHER SPECIFIED ORGANISMS
Hyu1.00	[X]OTHER ACUTE LOWER RESPIRATORY INFECTIONS
H061300	ACUTE EXUDATIVE BRONCHIOLITIS
H060200	ACUTE PSEUDOMEMBRANOUS BRONCHITIS
Hyu1000	[X]ACUTE BRONCHITIS DUE TO OTHER SPECIFIED ORGANISMS
43jz.00	PARAINFLUENZA TYPE 3 NUCLEIC ACID DETECTION

H060B00	ACUTE BRONCHITIS DUE TO COXSACKIEVIRUS
43jx.00	PARAINFLUENZA TYPE 1 NUCLEIC ACID DETECTION
43jy.00	PARAINFLUENZA TYPE 2 NUCLEIC ACID DETECTION
H29..00	AVIAN INFLUENZA
4JU5.00	INFLUENZA B VIRUS DETECTED
4JU2.00	INFLUENZA H3 VIRUS DETECTED
4JU0.00	INFLUENZA H1 VIRUS DETECTED
4JUF.00	HUMAN PARAINFLUENZA VIRUS DETECTED
4JU4.00	INFLUENZA A VIRUS, OTHER OR UNTYPED STRAIN DETECTED
Hyu0700	[X]INFLUENZA + OTHER MANIFESTATIONS, VIRUS NOT IDENTIFIED
Hyu0600	[X]INFLUENZA + OTHER RESPIRATORY MANIFESTATIONS, VIRUS NOT IDENTIFIED
Hyu0500	[X]INFLUENZA + OTHER MANIFESTATIONS, INFLUENZA VIRUS IDENTIFIED
H2A..11	INFLUENZA A (H1N1) SWINE FLU
1W0..00	POSSIBLE INFLUENZA A VIRUS H1N1 SUBTYPE
1J72.11	SUSPECTED SWINE INFLUENZA
1J72.00	SUSPECTED INFLUENZA A VIRUS SUBTYPE H1N1 INFECTION
H2A..00	INFLUENZA DUE TO INFLUENZA A VIRUS SUBTYPE H1N1
4J3L.00	INFLUENZA A VIRUS H1N1 SUBTYPE DETECTED
4JU3.00	INFLUENZA H5 VIRUS DETECTED
Hyu0400	[X]FLU + OTHER RESPIRATORY MANIFESTATIONS, ‘FLU VIRUS IDENTIFIED
Hyu1100	[X]ACUTE BRONCHIOLITIS DUE TO OTHER SPECIFIED ORGANISMS
H060100	ACUTE MEMBRANOUS BRONCHITIS
4JU1.00	INFLUENZA H2 VIRUS DETECTED
Acute exacerbation of COPD	

H312200	ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
H3y1.00	CHRON OBSTRUCT PULMONARY DISSEASE WITH ACUTE EXACERBATION, UNSPECIFIED
Antibiotics	
88556998	AMOXICILLIN CAPS 250MG
89177998	AMOXICILLIN CAPS 250MG
92456990	AMOXICILLIN CAPS 250MG
93372998	AMOXICILLIN CAPS 250MG
93377998	AMOXICILLIN CAPS 250MG
93407998	AMOXICILLIN CAPS 250MG
93465998	AMOXICILLIN CAPS 250MG
94074990	AMOXICILLIN CAPS 250MG
94699998	AMOXICILLIN CAPS 250MG
95225990	AMOXICILLIN CAPS 250MG
96239998	AMOXICILLIN CAPS 250MG
96307990	AMOXICILLIN CAPS 250MG
96313998	AMOXICILLIN CAPS 250MG
96383990	AMOXICILLIN CAPS 250MG
96931990	AMOXICILLIN CAPS 250MG
96990990	AMOXICILLIN CAPS 250MG
97050990	AMOXICILLIN CAPS 250MG
97131998	AMOXICILLIN CAPS 250MG
97133990	AMOXICILLIN CAPS 250MG
97790990	AMOXICILLIN CAPS 250MG
97808998	AMOXICILLIN CAPS 250MG
98803990	AMOXICILLIN CAPS 250MG
99836990	AMOXICILLIN CAPS 250MG
99837990	AMOXICILLIN CAPS 250MG
99838990	AMOXICILLIN CAPS 250MG
99839990	AMOXICILLIN CAPS 250MG
99841990	AMOXICILLIN CAPS 250MG

99842990	AMOXICILLIN CAPS 250MG
99843990	AMOXICILLIN CAPS 250MG
99844990	AMOXICILLIN CAPS 250MG
99845990	AMOXICILLIN CAPS 250MG
99848990	AMOXICILLIN CAPS 250MG
99849988	AMOXICILLIN CAPS 250MG
99962998	AMOXICILLIN CAPS 250MG
88556997	AMOXICILLIN CAPS 500MG
89177997	AMOXICILLIN CAPS 500MG
92455990	AMOXICILLIN CAPS 500MG
93372997	AMOXICILLIN CAPS 500MG
93377997	AMOXICILLIN CAPS 500MG
93407997	AMOXICILLIN CAPS 500MG
93465997	AMOXICILLIN CAPS 500MG
94073990	AMOXICILLIN CAPS 500MG
94699997	AMOXICILLIN CAPS 500MG
95224990	AMOXICILLIN CAPS 500MG
96239997	AMOXICILLIN CAPS 500MG
96307989	AMOXICILLIN CAPS 500MG
96313997	AMOXICILLIN CAPS 500MG
96383989	AMOXICILLIN CAPS 500MG
96931989	AMOXICILLIN CAPS 500MG
96990989	AMOXICILLIN CAPS 500MG
97050989	AMOXICILLIN CAPS 500MG
97131997	AMOXICILLIN CAPS 500MG
98334990	AMOXICILLIN CAPS 500MG
98803989	AMOXICILLIN CAPS 500MG
99836989	AMOXICILLIN CAPS 500MG
99837989	AMOXICILLIN CAPS 500MG
99838989	AMOXICILLIN CAPS 500MG
99839989	AMOXICILLIN CAPS 500MG
99840990	AMOXICILLIN CAPS 500MG

99841989	AMOXICILLIN CAPS 500MG
99842989	AMOXICILLIN CAPS 500MG
99843989	AMOXICILLIN CAPS 500MG
99844989	AMOXICILLIN CAPS 500MG
99845989	AMOXICILLIN CAPS 500MG
99846990	AMOXICILLIN CAPS 500MG
99848989	AMOXICILLIN CAPS 500MG
99962997	AMOXICILLIN CAPS 500MG
96944998	AMOXICILLIN TAB 500MG
99962996	AMOXICILLIN TAB 500MG
88557996	AMOXICILLIN SF ORAL SUSP 125MG/5ML
89889998	AMOXICILLIN SF ORAL SUSP 125MG/5ML
93041990	AMOXICILLIN SF ORAL SUSP 125MG/5ML
93372996	AMOXICILLIN SF ORAL SUSP 125MG/5ML
93377996	AMOXICILLIN SF ORAL SUSP 125MG/5ML
93407996	AMOXICILLIN SF ORAL SUSP 125MG/5ML
93592990	AMOXICILLIN SF ORAL SUSP 125MG/5ML
94792998	AMOXICILLIN SF ORAL SUSP 125MG/5ML
96928989	AMOXICILLIN SF ORAL SUSP 125MG/5ML
97133989	AMOXICILLIN SF ORAL SUSP 125MG/5ML
97790988	AMOXICILLIN SF ORAL SUSP 125MG/5ML
97868998	AMOXICILLIN SF ORAL SUSP 125MG/5ML
98334989	AMOXICILLIN SF ORAL SUSP 125MG/5ML
99831989	AMOXICILLIN SF ORAL SUSP 125MG/5ML
99832989	AMOXICILLIN SF ORAL SUSP 125MG/5ML
99838988	AMOXICILLIN SF ORAL SUSP 125MG/5ML
88382998	AMOXICILLIN SF ORAL SUSP 250MG/5ML
89889997	AMOXICILLIN SF ORAL SUSP 250MG/5ML
93040990	AMOXICILLIN SF ORAL SUSP 250MG/5ML
93375998	AMOXICILLIN SF ORAL SUSP 250MG/5ML
93404998	AMOXICILLIN SF ORAL SUSP 250MG/5ML
93446998	AMOXICILLIN SF ORAL SUSP 250MG/5ML

93591990	AMOXICILLIN SF ORAL SUSP 250MG/5ML
94792997	AMOXICILLIN SF ORAL SUSP 250MG/5ML
96928988	AMOXICILLIN SF ORAL SUSP 250MG/5ML
97133988	AMOXICILLIN SF ORAL SUSP 250MG/5ML
97789990	AMOXICILLIN SF ORAL SUSP 250MG/5ML
97868997	AMOXICILLIN SF ORAL SUSP 250MG/5ML
98334988	AMOXICILLIN SF ORAL SUSP 250MG/5ML
99828990	AMOXICILLIN SF ORAL SUSP 250MG/5ML
99831988	AMOXICILLIN SF ORAL SUSP 250MG/5ML
99832988	AMOXICILLIN SF ORAL SUSP 250MG/5ML
95086996	AMOXICILLIN SF POWDER 125MG
99830988	AMOXICILLIN SF POWDER 125MG
96156990	AMOXICILLIN SF POWDER 3G
96943998	AMOXICILLIN SF POWDER 3G
97790989	AMOXICILLIN SF POWDER 3G
97956990	AMOXICILLIN SF POWDER 3G
98673998	AMOXICILLIN SF POWDER 3G
99830989	AMOXICILLIN SF POWDER 3G
96944996	AMOXICILLIN SF POWDER 750MG
97868996	AMOXICILLIN SF POWDER 750MG
95077998	AMOXICILLIN SOL TAB 375MG
95086998	AMOXICILLIN SOL TAB 375MG
95077997	AMOXICILLIN SOL TAB 750MG
95086997	AMOXICILLIN SOL TAB 750MG
88557998	AMOXICILLIN SYRUP 125MG/5ML
93465996	AMOXICILLIN SYRUP 125MG/5ML
94071990	AMOXICILLIN SYRUP 125MG/5ML
94699996	AMOXICILLIN SYRUP 125MG/5ML
94794998	AMOXICILLIN SYRUP 125MG/5ML
96239996	AMOXICILLIN SYRUP 125MG/5ML
96307988	AMOXICILLIN SYRUP 125MG/5ML
96313996	AMOXICILLIN SYRUP 125MG/5ML

96383988	AMOXICILLIN SYRUP 125MG/5ML
96931988	AMOXICILLIN SYRUP 125MG/5ML
97808997	AMOXICILLIN SYRUP 125MG/5ML
98803988	AMOXICILLIN SYRUP 125MG/5ML
99836988	AMOXICILLIN SYRUP 125MG/5ML
99837988	AMOXICILLIN SYRUP 125MG/5ML
99839988	AMOXICILLIN SYRUP 125MG/5ML
99840989	AMOXICILLIN SYRUP 125MG/5ML
99841988	AMOXICILLIN SYRUP 125MG/5ML
99842988	AMOXICILLIN SYRUP 125MG/5ML
99843988	AMOXICILLIN SYRUP 125MG/5ML
99844988	AMOXICILLIN SYRUP 125MG/5ML
99845988	AMOXICILLIN SYRUP 125MG/5ML
99846989	AMOXICILLIN SYRUP 125MG/5ML
99848988	AMOXICILLIN SYRUP 125MG/5ML
99849990	AMOXICILLIN SYRUP 125MG/5ML
88557997	AMOXICILLIN SYRUP 250MG/5ML
93466998	AMOXICILLIN SYRUP 250MG/5ML
94070990	AMOXICILLIN SYRUP 250MG/5ML
94698998	AMOXICILLIN SYRUP 250MG/5ML
94794997	AMOXICILLIN SYRUP 250MG/5ML
96255998	AMOXICILLIN SYRUP 250MG/5ML
96306990	AMOXICILLIN SYRUP 250MG/5ML
96365998	AMOXICILLIN SYRUP 250MG/5ML
96377990	AMOXICILLIN SYRUP 250MG/5ML
96928990	AMOXICILLIN SYRUP 250MG/5ML
96965990	AMOXICILLIN SYRUP 250MG/5ML
98779990	AMOXICILLIN SYRUP 250MG/5ML
99827990	AMOXICILLIN SYRUP 250MG/5ML
99829990	AMOXICILLIN SYRUP 250MG/5ML
99830990	AMOXICILLIN SYRUP 250MG/5ML
99831990	AMOXICILLIN SYRUP 250MG/5ML

99832990	AMOXICILLIN SYRUP 250MG/5ML
99833990	AMOXICILLIN SYRUP 250MG/5ML
99834990	AMOXICILLIN SYRUP 250MG/5ML
99840988	AMOXICILLIN SYRUP 250MG/5ML
99846988	AMOXICILLIN SYRUP 250MG/5ML
99847990	AMOXICILLIN SYRUP 250MG/5ML
99849989	AMOXICILLIN SYRUP 250MG/5ML
96092992	AMOXYCILLIN FIZTAB 125 MG TAB
96822992	AMOXYCILLIN FIZTAB 250 MG TAB
88245998	CEFACLOR CAPS 250MG
89452998	CEFACLOR CAPS 250MG
94648990	CEFACLOR CAPS 250MG
96856998	CEFACLOR CAPS 250MG
96925990	CEFACLOR CAPS 250MG
97035988	CEFACLOR CAPS 250MG
97694990	CEFACLOR CAPS 250MG
97696990	CEFACLOR CAPS 250MG
97840990	CEFACLOR CAPS 250MG
99741998	CEFACLOR CAPS 250MG
85949998	CEFACLOR CAPS 500MG
88245997	CEFACLOR CAPS 500MG
89452997	CEFACLOR CAPS 500MG
94647990	CEFACLOR CAPS 500MG
94870998	CEFACLOR CAPS 500MG
94873998	CEFACLOR CAPS 500MG
96925989	CEFACLOR CAPS 500MG
97038990	CEFACLOR CAPS 500MG
97694989	CEFACLOR CAPS 500MG
97696989	CEFACLOR CAPS 500MG
97840989	CEFACLOR CAPS 500MG
85952998	CEFACLOR TAB 375MG
90961998	CEFACLOR TAB 375MG

93901997	CEFACLOR TAB 375MG
94791998	CEFACLOR TAB 375MG
96639990	CEFACLOR TAB 375MG
96923989	CEFACLOR TAB 375MG
93901998	CEFACLOR TAB 500MG
94791997	CEFACLOR TAB 500MG
89452996	CEFACLOR SF SUSP 125MG/5ML
94301990	CEFACLOR SF SUSP 125MG/5ML
94873997	CEFACLOR SF SUSP 125MG/5ML
96925988	CEFACLOR SF SUSP 125MG/5ML
97035989	CEFACLOR SF SUSP 125MG/5ML
97696988	CEFACLOR SF SUSP 125MG/5ML
88818998	CEFACLOR SF SUSP 250MG/5ML
94300990	CEFACLOR SF SUSP 250MG/5ML
94873996	CEFACLOR SF SUSP 250MG/5ML
96923990	CEFACLOR SF SUSP 250MG/5ML
97035990	CEFACLOR SF SUSP 250MG/5ML
97542990	CEFACLOR SF SUSP 250MG/5ML
85951998	CEFACLOR SUSP 125MG/5ML
88245996	CEFACLOR SUSP 125MG/5ML
96224990	CEFACLOR SUSP 125MG/5ML
96856997	CEFACLOR SUSP 125MG/5ML
97328998	CEFACLOR SUSP 125MG/5ML
97694988	CEFACLOR SUSP 125MG/5ML
97840988	CEFACLOR SUSP 125MG/5ML
99741997	CEFACLOR SUSP 125MG/5ML
85950998	CEFACLOR SUSP 250MG/5ML
88222998	CEFACLOR SUSP 250MG/5ML
96215990	CEFACLOR SUSP 250MG/5ML
96856996	CEFACLOR SUSP 250MG/5ML
97328997	CEFACLOR SUSP 250MG/5ML
97535990	CEFACLOR SUSP 250MG/5ML

97839990	CEFACLOR SUSP 250MG/5ML
99741996	CEFACLOR SUSP 250MG/5ML
82664998	CEFALEXIN CAPS 250MG
85946998	CEFALEXIN CAPS 250MG
90029998	CEFALEXIN CAPS 250MG
92076996	CEFALEXIN CAPS 250MG
93529998	CEFALEXIN CAPS 250MG
94174990	CEFALEXIN CAPS 250MG
94646990	CEFALEXIN CAPS 250MG
94730996	CEFALEXIN CAPS 250MG
96433989	CEFALEXIN CAPS 250MG
96911988	CEFALEXIN CAPS 250MG
97171990	CEFALEXIN CAPS 250MG
97859989	CEFALEXIN CAPS 250MG
97888996	CEFALEXIN CAPS 250MG
97991988	CEFALEXIN CAPS 250MG
98015989	CEFALEXIN CAPS 250MG
98195990	CEFALEXIN CAPS 250MG
98638990	CEFALEXIN CAPS 250MG
99699990	CEFALEXIN CAPS 250MG
99700990	CEFALEXIN CAPS 250MG
99701988	CEFALEXIN CAPS 250MG
82663998	CEFALEXIN CAPS 500MG
85945998	CEFALEXIN CAPS 500MG
90029997	CEFALEXIN CAPS 500MG
92077998	CEFALEXIN CAPS 500MG
93529997	CEFALEXIN CAPS 500MG
94173990	CEFALEXIN CAPS 500MG
94645990	CEFALEXIN CAPS 500MG
94729998	CEFALEXIN CAPS 500MG
96433988	CEFALEXIN CAPS 500MG
96909990	CEFALEXIN CAPS 500MG

97171989	CEFALEXIN CAPS 500MG
97859988	CEFALEXIN CAPS 500MG
97887998	CEFALEXIN CAPS 500MG
97990990	CEFALEXIN CAPS 500MG
98195989	CEFALEXIN CAPS 500MG
98638989	CEFALEXIN CAPS 500MG
99255990	CEFALEXIN CAPS 500MG
99699989	CEFALEXIN CAPS 500MG
99700989	CEFALEXIN CAPS 500MG
94728998	CEFALEXIN CHEWABLE TAB 250MG
96837996	CEFALEXIN CHEWABLE TAB 250MG
82662998	CEFALEXIN ORAL SUSP 125MG/5ML
85944998	CEFALEXIN ORAL SUSP 125MG/5ML
90028998	CEFALEXIN ORAL SUSP 125MG/5ML
92077997	CEFALEXIN ORAL SUSP 125MG/5ML
93104990	CEFALEXIN ORAL SUSP 125MG/5ML
94644990	CEFALEXIN ORAL SUSP 125MG/5ML
94729997	CEFALEXIN ORAL SUSP 125MG/5ML
96435988	CEFALEXIN ORAL SUSP 125MG/5ML
96836998	CEFALEXIN ORAL SUSP 125MG/5ML
96909989	CEFALEXIN ORAL SUSP 125MG/5ML
97171988	CEFALEXIN ORAL SUSP 125MG/5ML
97778989	CEFALEXIN ORAL SUSP 125MG/5ML
97886997	CEFALEXIN ORAL SUSP 125MG/5ML
97887997	CEFALEXIN ORAL SUSP 125MG/5ML
97990989	CEFALEXIN ORAL SUSP 125MG/5ML
98635989	CEFALEXIN ORAL SUSP 125MG/5ML
99698989	CEFALEXIN ORAL SUSP 125MG/5ML
82661998	CEFALEXIN ORAL SUSP 250MG/5ML
85943998	CEFALEXIN ORAL SUSP 250MG/5ML
90028997	CEFALEXIN ORAL SUSP 250MG/5ML
92077996	CEFALEXIN ORAL SUSP 250MG/5ML

93103990	CEFALEXIN ORAL SUSP 250MG/5ML
94643990	CEFALEXIN ORAL SUSP 250MG/5ML
94729996	CEFALEXIN ORAL SUSP 250MG/5ML
96277990	CEFALEXIN ORAL SUSP 250MG/5ML
96433990	CEFALEXIN ORAL SUSP 250MG/5ML
96836997	CEFALEXIN ORAL SUSP 250MG/5ML
96909988	CEFALEXIN ORAL SUSP 250MG/5ML
97778988	CEFALEXIN ORAL SUSP 250MG/5ML
97886996	CEFALEXIN ORAL SUSP 250MG/5ML
97887996	CEFALEXIN ORAL SUSP 250MG/5ML
97990988	CEFALEXIN ORAL SUSP 250MG/5ML
98195988	CEFALEXIN ORAL SUSP 250MG/5ML
98635988	CEFALEXIN ORAL SUSP 250MG/5ML
99698988	CEFALEXIN ORAL SUSP 250MG/5ML
82660998	CEFALEXIN ORAL SUSP 500MG/5ML
96836996	CEFALEXIN ORAL SUSP 500MG/5ML
97886998	CEFALEXIN ORAL SUSP 500MG/5ML
87657998	CEFALEXIN SF ORAL SUSP 125MG/5ML
97237990	CEFALEXIN SF ORAL SUSP 125MG/5ML
87658998	CEFALEXIN SF ORAL SUSP 250MG/5ML
97237989	CEFALEXIN SF ORAL SUSP 250MG/5ML
96835998	CEFALEXIN SUSP 125MG/5ML
96835997	CEFALEXIN SUSP 250MG/5ML
93533998	CEFALEXIN TABS 1G
93534998	CEFALEXIN TABS 1G
82666998	CEFALEXIN TABS 250MG
85948998	CEFALEXIN TABS 250MG
92076998	CEFALEXIN TABS 250MG
93102990	CEFALEXIN TABS 250MG
94642990	CEFALEXIN TABS 250MG
94730998	CEFALEXIN TABS 250MG
96275990	CEFALEXIN TABS 250MG

96435990	CEFALEXIN TABS 250MG
96837998	CEFALEXIN TABS 250MG
96911990	CEFALEXIN TABS 250MG
97859990	CEFALEXIN TABS 250MG
97888998	CEFALEXIN TABS 250MG
97991990	CEFALEXIN TABS 250MG
98010990	CEFALEXIN TABS 250MG
98015990	CEFALEXIN TABS 250MG
98141990	CEFALEXIN TABS 250MG
98638988	CEFALEXIN TABS 250MG
99699988	CEFALEXIN TABS 250MG
99701990	CEFALEXIN TABS 250MG
82665998	CEFALEXIN TABS 500MG
85947998	CEFALEXIN TABS 500MG
90029996	CEFALEXIN TABS 500MG
92076997	CEFALEXIN TABS 500MG
93101990	CEFALEXIN TABS 500MG
94622990	CEFALEXIN TABS 500MG
94641990	CEFALEXIN TABS 500MG
94730997	CEFALEXIN TABS 500MG
96435989	CEFALEXIN TABS 500MG
96837997	CEFALEXIN TABS 500MG
96911989	CEFALEXIN TABS 500MG
97778990	CEFALEXIN TABS 500MG
97888997	CEFALEXIN TABS 500MG
97991989	CEFALEXIN TABS 500MG
98635990	CEFALEXIN TABS 500MG
99698990	CEFALEXIN TABS 500MG
99700988	CEFALEXIN TABS 500MG
99701989	CEFALEXIN TABS 500MG
96681998	CHLORTETRACYCLINE CAPS 250MG
99923998	CHLORTETRACYCLINE CAPS 250MG

95828992	CHLORTETRACYCLINE HCL SYR
84350998	CIPROFLOXACIN ORAL LIQUID
93079996	CIPROFLOXACIN SUSP 250MG/5ML
93080996	CIPROFLOXACIN SUSP 250MG/5ML
93079997	CIPROFLOXACIN TABS 100MG
93080997	CIPROFLOXACIN TABS 100MG
94268990	CIPROFLOXACIN TABS 100MG
95686990	CIPROFLOXACIN TABS 100MG
95804990	CIPROFLOXACIN TABS 100MG
95824990	CIPROFLOXACIN TABS 100MG
95949990	CIPROFLOXACIN TABS 100MG
96033990	CIPROFLOXACIN TABS 100MG
96045990	CIPROFLOXACIN TABS 100MG
93830990	CIPROFLOXACIN TABS 250MG
94024990	CIPROFLOXACIN TABS 250MG
94607990	CIPROFLOXACIN TABS 250MG
94692990	CIPROFLOXACIN TABS 250MG
94912998	CIPROFLOXACIN TABS 250MG
94913998	CIPROFLOXACIN TABS 250MG
95212990	CIPROFLOXACIN TABS 250MG
95430990	CIPROFLOXACIN TABS 250MG
95629990	CIPROFLOXACIN TABS 250MG
95823990	CIPROFLOXACIN TABS 250MG
95867990	CIPROFLOXACIN TABS 250MG
95948990	CIPROFLOXACIN TABS 250MG
96024990	CIPROFLOXACIN TABS 250MG
96032990	CIPROFLOXACIN TABS 250MG
96044990	CIPROFLOXACIN TABS 250MG
96049990	CIPROFLOXACIN TABS 250MG
96052990	CIPROFLOXACIN TABS 250MG
96058990	CIPROFLOXACIN TABS 250MG
96067990	CIPROFLOXACIN TABS 250MG

94023990	CIPROFLOXACIN TABS 500MG
94606990	CIPROFLOXACIN TABS 500MG
94691990	CIPROFLOXACIN TABS 500MG
94912996	CIPROFLOXACIN TABS 500MG
94913996	CIPROFLOXACIN TABS 500MG
95131990	CIPROFLOXACIN TABS 500MG
95211990	CIPROFLOXACIN TABS 500MG
95429990	CIPROFLOXACIN TABS 500MG
95628990	CIPROFLOXACIN TABS 500MG
95822990	CIPROFLOXACIN TABS 500MG
95866990	CIPROFLOXACIN TABS 500MG
95947990	CIPROFLOXACIN TABS 500MG
96023990	CIPROFLOXACIN TABS 500MG
96031990	CIPROFLOXACIN TABS 500MG
96043990	CIPROFLOXACIN TABS 500MG
96048990	CIPROFLOXACIN TABS 500MG
96051990	CIPROFLOXACIN TABS 500MG
96057990	CIPROFLOXACIN TABS 500MG
96066990	CIPROFLOXACIN TABS 500MG
93079998	CIPROFLOXACIN TABS 750MG
93080998	CIPROFLOXACIN TABS 750MG
94267990	CIPROFLOXACIN TABS 750MG
94653990	CIPROFLOXACIN TABS 750MG
95132990	CIPROFLOXACIN TABS 750MG
95181990	CIPROFLOXACIN TABS 750MG
95210990	CIPROFLOXACIN TABS 750MG
95627990	CIPROFLOXACIN TABS 750MG
95821990	CIPROFLOXACIN TABS 750MG
95865990	CIPROFLOXACIN TABS 750MG
95946990	CIPROFLOXACIN TABS 750MG
96022990	CIPROFLOXACIN TABS 750MG
96030990	CIPROFLOXACIN TABS 750MG

96042990	CIPROFLOXACIN TABS 750MG
96047990	CIPROFLOXACIN TABS 750MG
96050990	CIPROFLOXACIN TABS 750MG
96056990	CIPROFLOXACIN TABS 750MG
88378998	CLARITHROMYCIN GRANS FOR SUSP 250MG/SACHET
92495997	CLARITHROMYCIN GRANS FOR SUSP 250MG/SACHET
89246998	CLARITHROMYCIN TAB 500MG
92495998	CLARITHROMYCIN TAB 500MG
86475998	CLARITHROMYCIN ORAL SUSP GRANULES 125MG/STRAW
86478998	CLARITHROMYCIN ORAL SUSP GRANULES 125MG/STRAW
86474998	CLARITHROMYCIN ORAL SUSP GRANULES 187.5MG/STRAW
86477998	CLARITHROMYCIN ORAL SUSP GRANULES 187.5MG/STRAW
86473998	CLARITHROMYCIN ORAL SUSP GRANULES 250MG/STRAW
86476998	CLARITHROMYCIN ORAL SUSP GRANULES 250MG/STRAW
92632990	CLARITHROMYCIN TABS 250MG
94185990	CLARITHROMYCIN TABS 250MG
94505990	CLARITHROMYCIN TABS 250MG
94530990	CLARITHROMYCIN TABS 250MG
94530998	CLARITHROMYCIN TABS 250MG
94531998	CLARITHROMYCIN TABS 250MG
94542990	CLARITHROMYCIN TABS 250MG
94551990	CLARITHROMYCIN TABS 250MG
92631990	CLARITHROMYCIN TABS 500MG
94370990	CLARITHROMYCIN TABS 500MG
94504990	CLARITHROMYCIN TABS 500MG
94529990	CLARITHROMYCIN TABS 500MG

94530996	CLARITHROMYCIN TABS 500MG
94531996	CLARITHROMYCIN TABS 500MG
94541990	CLARITHROMYCIN TABS 500MG
94550990	CLARITHROMYCIN TABS 500MG
96660997	CLAVULANIC ACID + AMOXICILLIN TAB
86034998	CLAVULANIC ACID + AMOXICILLIN ORAL SUSP 31MG + 125
86036998	CLAVULANIC ACID + AMOXICILLIN ORAL SUSP 62MG + 250
96660996	CLAVULANIC ACID + AMOXICILLIN SF SUSP 31MG + 125MG
97708996	CLAVULANIC ACID + AMOXICILLIN SF SUSP 57MG + 400MG
97708998	CLAVULANIC ACID + AMOXICILLIN SF SUSP 62MG + 250MG
95076998	CLAVULANIC ACID + AMOXICILLIN SUSP 62MG + 125MG/5M
96660998	CLAVULANIC ACID + AMOXICILLIN TABS 125MG + 250MG
97708997	CLAVULANIC ACID + AMOXICILLIN TABS 125MG+500MG
96635998	CLOMOCYCLINE CAPS 170MG
96636998	CLOMOCYCLINE CAPS 170MG
93225997	CO-AMOXICLAV TAB 250MG+125MG
99927997	CO-AMOXICLAV TAB 250MG+125MG
86055998	CO-AMOXICLAV ORAL SUSP 125MG + 31MG/5ML
95315990	CO-AMOXICLAV ORAL SUSP 125MG + 31MG/5ML
86056998	CO-AMOXICLAV ORAL SUSP 250MG + 62MG/5ML
95314990	CO-AMOXICLAV ORAL SUSP 250MG + 62MG/5ML
92340996	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
92396990	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
93225996	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML

94026990	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
95040990	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
96539988	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
96731989	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
96975988	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
97010988	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
98363998	CO-AMOXICLAV SF SUSP 125MG + 31MG/5ML
92339998	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
92395990	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
93224998	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
94025990	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
95039990	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
95586990	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
96538990	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
96731988	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
96974990	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
97009990	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
98364998	CO-AMOXICLAV SF SUSP 250MG + 62MG/5ML
91014998	CO-AMOXICLAV SF SUSP 400MG + 57MG/5ML
92125990	CO-AMOXICLAV SF SUSP 400MG + 57MG/5ML
93224996	CO-AMOXICLAV SF SUSP 400MG + 57MG/5ML
88536998	CO-AMOXICLAV TABS 250MG+125MG
92340998	CO-AMOXICLAV TABS 250MG+125MG
93225998	CO-AMOXICLAV TABS 250MG+125MG
94027990	CO-AMOXICLAV TABS 250MG+125MG
95872990	CO-AMOXICLAV TABS 250MG+125MG
96137990	CO-AMOXICLAV TABS 250MG+125MG
96189990	CO-AMOXICLAV TABS 250MG+125MG
96343990	CO-AMOXICLAV TABS 250MG+125MG
96539990	CO-AMOXICLAV TABS 250MG+125MG
96637990	CO-AMOXICLAV TABS 250MG+125MG
96731990	CO-AMOXICLAV TABS 250MG+125MG

96975990	CO-AMOXICLAV TABS 250MG+125MG
97010990	CO-AMOXICLAV TABS 250MG+125MG
99927998	CO-AMOXICLAV TABS 250MG+125MG
92340997	CO-AMOXICLAV TABS 500MG+125MG
93224997	CO-AMOXICLAV TABS 500MG+125MG
95070990	CO-AMOXICLAV TABS 500MG+125MG
95585990	CO-AMOXICLAV TABS 500MG+125MG
95618990	CO-AMOXICLAV TABS 500MG+125MG
96391990	CO-AMOXICLAV TABS 500MG+125MG
96539989	CO-AMOXICLAV TABS 500MG+125MG
96637989	CO-AMOXICLAV TABS 500MG+125MG
96975989	CO-AMOXICLAV TABS 500MG+125MG
97010989	CO-AMOXICLAV TABS 500MG+125MG
99110998	CO-AMOXICLAV TABS 500MG+125MG
93484992	CYCLODOX CAP 100 MG
96447998	DEMECLOCYCLINE + CHLORTETRACYCLINE & TETRACYCLINE
97246992	DEMIX 100 MG CAP
88431998	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
92362998	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
92775990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
92856998	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
93923998	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
96089990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
96305997	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
96354990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
97051990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
97121990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
97209989	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
97711998	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
97761989	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
98044990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG

98352990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
98601989	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
98969998	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
99101998	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
99613990	DOXYCYCLINE (AS HYCLATE) CAPS 100MG
92556998	DOXYCYCLINE (AS HYCLATE) CAPS 20MG
96304997	DOXYCYCLINE (AS HYCLATE) CAPS 20MG
92613998	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
92774990	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
92856997	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
96202990	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
97121989	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
97209990	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
97247990	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
97753998	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
97761990	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
98352989	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
98601990	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
99101997	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
99613989	DOXYCYCLINE (AS HYCLATE) CAPS 50MG
96305998	DOXYCYCLINE (AS HYCLATE) TAB 100MG
84948998	DOXYCYCLINE (AS HYCLATE) ORAL LIQUID
96304998	DOXYCYCLINE (AS HYCLATE) SYRUP 50MG/5ML
98969996	DOXYCYCLINE (AS HYCLATE) SYRUP 50MG/5ML
96282990	DOXYCYCLINE (AS HYCLATE) TABS 100MG
96305996	DOXYCYCLINE (AS HYCLATE) TABS 100MG
97913998	DOXYCYCLINE (AS HYCLATE) TABS 100MG
89467998	DOXYCYCLINE (AS HYCLATE) TABS 20MG
90801998	DOXYCYCLINE (AS HYCLATE) TABS 20MG
91630998	DOXYCYCLINE MONOHYDRATE TAB 100MG
98231998	DOXYCYCLINE MONOHYDRATE TAB 100MG
98969997	DOXYCYCLINE MONOHYDRATE TAB 100MG

82730998	DOXYCYCLINE MONOHYDRATE CAP 40MG
82732998	DOXYCYCLINE MONOHYDRATE CAP 40MG
94457992	ERYCEN 125 MG SUS
94153992	ERYCEN 250 MG SUS
94977992	ERYMAX 500 MG CAP
93003992	ERYMIN 250 MG/5ML SUS
96230992	ERYTHROCIN 100 MG SYR
97379992	ERYTHROCIN 125 MG SYR
97380992	ERYTHROCIN 250 250 MG TAB
97378992	ERYTHROCIN A 1 GM TAB
97381992	ERYTHROCIN B-PACK 10 FILMTABS 500 MG TAB
96229992	ERYTHROMYCIN 100 MG SYR
96648992	ERYTHROMYCIN 12 MG SYR
97375992	ERYTHROMYCIN 250 MG MIX
94980992	ERYTHROMYCIN 500 MG CAP
87506998	ERYTHROMYCIN CAPS 250MG
90844998	ERYTHROMYCIN CAPS 250MG
92104998	ERYTHROMYCIN CAPS 250MG
95920990	ERYTHROMYCIN CAPS 250MG
95965990	ERYTHROMYCIN CAPS 250MG
97118996	ERYTHROMYCIN CAPS 250MG
97932998	ERYTHROMYCIN CAPS 250MG
93914990	ERYTHROMYCIN TAB 250MG
94358990	ERYTHROMYCIN TAB 250MG
94426990	ERYTHROMYCIN TAB 250MG
95305990	ERYTHROMYCIN TAB 250MG
96352990	ERYTHROMYCIN TAB 250MG
96373990	ERYTHROMYCIN TAB 250MG
96786998	ERYTHROMYCIN TAB 250MG
97096998	ERYTHROMYCIN TAB 250MG
97118998	ERYTHROMYCIN TAB 250MG
97759990	ERYTHROMYCIN TAB 250MG

98166988	ERYTHROMYCIN TAB 250MG
98353988	ERYTHROMYCIN TAB 250MG
98559988	ERYTHROMYCIN TAB 250MG
99103997	ERYTHROMYCIN TAB 250MG
99435990	ERYTHROMYCIN TAB 250MG
99540998	ERYTHROMYCIN TAB 250MG
99604988	ERYTHROMYCIN TAB 250MG
99605988	ERYTHROMYCIN TAB 250MG
99607988	ERYTHROMYCIN TAB 250MG
99681998	ERYTHROMYCIN TAB 250MG
99683998	ERYTHROMYCIN TAB 250MG
96786997	ERYTHROMYCIN TAB 500MG
97118997	ERYTHROMYCIN TAB 500MG
98166989	ERYTHROMYCIN TAB 500MG
98345990	ERYTHROMYCIN TAB 500MG
98558990	ERYTHROMYCIN TAB 500MG
98752998	ERYTHROMYCIN TAB 500MG
99103996	ERYTHROMYCIN TAB 500MG
99210990	ERYTHROMYCIN TAB 500MG
99433990	ERYTHROMYCIN TAB 500MG
99434990	ERYTHROMYCIN TAB 500MG
99435989	ERYTHROMYCIN TAB 500MG
99542997	ERYTHROMYCIN TAB 500MG
99683997	ERYTHROMYCIN TAB 500MG
96785998	ERYTHROMYCIN ESTOLATE CAPS 250MG
97757990	ERYTHROMYCIN ESTOLATE CAPS 250MG
99542998	ERYTHROMYCIN ESTOLATE CAPS 250MG
96785996	ERYTHROMYCIN ESTOLATE SUSP 125MG/5ML
99542996	ERYTHROMYCIN ESTOLATE SUSP 125MG/5ML
98846998	ERYTHROMYCIN ESTOLATE SUSP 250MG/5ML
99541998	ERYTHROMYCIN ESTOLATE SUSP 250MG/5ML
96785997	ERYTHROMYCIN ESTOLATE TABS 500MG

89421998	ERYTHROMYCIN ETHYLSUCCINATE (COATED) SF ORAL SUSP
89423998	ERYTHROMYCIN ETHYLSUCCINATE (COATED) SF ORAL SUSP
93147998	ERYTHROMYCIN ETHYLSUCCINATE 125MG
99679997	ERYTHROMYCIN ETHYLSUCCINATE 125MG
94819998	ERYTHROMYCIN ETHYLSUCCINATE
94820998	ERYTHROMYCIN ETHYLSUCCINATE
93147997	ERYTHROMYCIN ETHYLSUCCINATE 250MG
99680997	ERYTHROMYCIN ETHYLSUCCINATE 250MG
94820996	ERYTHROMYCIN ETHYLSUCCINATE 500MG
98751997	ERYTHROMYCIN ETHYLSUCCINATE 500MG
93316992	ERYTHROMYCIN ETHYLSUCCINATE SF 125 MG/5ML SUS
96783998	ERYTHROMYCIN ETHYLSUCCINATE SF GRANS 250MG
97519998	ERYTHROMYCIN ETHYLSUCCINATE SF GRANS 250MG
83061998	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
90499998	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
92765990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
94217990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
94694990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
96352989	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
96721988	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
96783997	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML

97947989	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
98353989	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
99103998	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
99679996	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 125MG/5ML
83063998	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
90499997	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
92764990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
94216990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
94693990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
96352988	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
96721990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
96783996	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
97947988	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
98353990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
99680996	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 250MG/5ML
83062998	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML

90499996	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
90567998	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
92763990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
94215990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
96250990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
96721989	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
97898990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
98166990	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
98345989	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
98751996	ERYTHROMYCIN ETHYLSUCCINATE SF SUSP 500MG/5ML
88231998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
89630998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
94220990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
96177990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
96374990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
96784998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
97095998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
97119990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
97759989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
98557989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
98559990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
99604990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML

99605990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
99606990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
99607990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
99679998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 125MG/5ML
88231997	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
89630997	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
94219990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
96176990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
96374989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
96784997	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
97095997	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
97119989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
97360998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
97759988	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
98557990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
98559989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
99604989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
99605989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
99606989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
99607989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
99680998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 250MG/5ML
89630996	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
94218990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
96175990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
96374988	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
96784996	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
97095996	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
97119988	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
97757989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
97947990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
98557988	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
98751998	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML

99210989	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
99212990	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
99606988	ERYTHROMYCIN ETHYLSUCCINATE SUSP 500MG/5ML
83064998	ERYTHROMYCIN ETHYLSUCCINATE TABS 500MG
94819997	ERYTHROMYCIN ETHYLSUCCINATE TABS 500MG
94820997	ERYTHROMYCIN ETHYLSUCCINATE TABS 500MG
93317992	ERYTHROMYCIN SF 250 MG
94495998	ERYTHROMYCIN SPRINKLE CAPS 125MG
94496998	ERYTHROMYCIN SPRINKLE CAPS 125MG
83066998	ERYTHROMYCIN STEARATE TABS 250MG
96781998	ERYTHROMYCIN STEARATE TABS 250MG
97361998	ERYTHROMYCIN STEARATE TABS 250MG
99682998	ERYTHROMYCIN STEARATE TABS 250MG
83065998	ERYTHROMYCIN STEARATE TABS 500MG
96781997	ERYTHROMYCIN STEARATE TABS 500MG
97361997	ERYTHROMYCIN STEARATE TABS 500MG
98754998	ERYTHROMYCIN STEARATE TABS 500MG
97117998	ERYTHROMYCIN SUSP 125MG/5ML
97117997	ERYTHROMYCIN SUSP 250MG/5ML
97117996	ERYTHROMYCIN SUSP 500MG/5ML
94984992	ERYTHROPED 250 MG TAB
94208992	KEFLEX-C 125 MG TAB
94484992	KEFLEX-C 250 MG TAB
88261998	LEVOFLOXACIN FC TAB 250MG
88267998	LEVOFLOXACIN FC TAB 250MG
88261997	LEVOFLOXACIN FC TAB 500MG
88267997	LEVOFLOXACIN FC TAB 500MG
89356998	MOXIFLOXACIN TABS 400MG
89361998	MOXIFLOXACIN TABS 400MG
96367992	NOVOBIOCIN/TETRACYCLINE 125 MG CAP
97815992	NOVOBIOCIN/TETRACYCLINE 62.5 MG MIX
95680998	NYSTATIN + TETRACYCLINE HCL CAPS

95680996	NYSTATIN + TETRACYCLINE HCL SYRUP
95680997	NYSTATIN + TETRACYCLINE HCL TABS
91262998	OXYTETRACYCLINE + BROMHEXINE HCL CAPS 250MG + 8MG
99884998	OXYTETRACYCLINE + BROMHEXINE HCL CAPS 250MG + 8MG
97843992	OXYTETRACYCLINE 100 MG TAB
97842992	OXYTETRACYCLINE 250 MG SYR
95369992	OXYTETRACYCLINE 500 MG TAB
95644998	OXYTETRACYCLINE CAPS 250MG
97143998	OXYTETRACYCLINE CAPS 250MG
99060997	OXYTETRACYCLINE CAPS 250MG
83942998	OXYTETRACYCLINE ORAL LIQUID
95640998	OXYTETRACYCLINE SYRUP 125MG/5ML
95644997	OXYTETRACYCLINE SYRUP 125MG/5ML
93938998	OXYTETRACYCLINE TABS 250MG
94398990	OXYTETRACYCLINE TABS 250MG
94446990	OXYTETRACYCLINE TABS 250MG
94750990	OXYTETRACYCLINE TABS 250MG
97144998	OXYTETRACYCLINE TABS 250MG
97145998	OXYTETRACYCLINE TABS 250MG
97146998	OXYTETRACYCLINE TABS 250MG
97154998	OXYTETRACYCLINE TABS 250MG
97732990	OXYTETRACYCLINE TABS 250MG
98456998	OXYTETRACYCLINE TABS 250MG
98462990	OXYTETRACYCLINE TABS 250MG
98463990	OXYTETRACYCLINE TABS 250MG
98464990	OXYTETRACYCLINE TABS 250MG
99060998	OXYTETRACYCLINE TABS 250MG
99478990	OXYTETRACYCLINE TABS 250MG
99479990	OXYTETRACYCLINE TABS 250MG
99480990	OXYTETRACYCLINE TABS 250MG

99895998	OXYTETRACYCLINE TABS 250MG
96779992	TERRAMYCIN SYR
96826992	TETRACHEL 200 MG TAB
95190998	TETRACYCLINE + AMPHOTERACIN SYRUP
98795998	TETRACYCLINE + AMPHOTERACIN SYRUP
92481998	TETRACYCLINE + CHLORTETRACYCLINE & DEMECLOCYCLINE
95192998	TETRACYCLINE + CHLORTETRACYCLINE & DEMECLOCYCLINE
99767998	TETRACYCLINE + CHLORTETRACYCLINE & DEMECLOCYCLINE
95191997	TETRACYCLINE + NYSTATIN CAPS
99382998	TETRACYCLINE + NYSTATIN CAPS
96781992	TETRACYCLINE 500 MG CAP
96485992	TETRACYCLINE 500 MG TAB
93837998	TETRACYCLINE CAPS 250MG
95193998	TETRACYCLINE CAPS 250MG
95196997	TETRACYCLINE CAPS 250MG
97142998	TETRACYCLINE CAPS 250MG
98323998	TETRACYCLINE CAPS 250MG
98341997	TETRACYCLINE CAPS 250MG
98612990	TETRACYCLINE CAPS 250MG
99053998	TETRACYCLINE CAPS 250MG
99055997	TETRACYCLINE CAPS 250MG
99056998	TETRACYCLINE CAPS 250MG
95194998	TETRACYCLINE CAP 250MG
97892998	TETRACYCLINE CAP 250MG
95196996	TETRACYCLINE
98341996	TETRACYCLINE
93837997	TETRACYCLINE SYRUP 125MG/5ML
95196998	TETRACYCLINE SYRUP 125MG/5ML
97153997	TETRACYCLINE SYRUP 125MG/5ML

98323997	TETRACYCLINE SYRUP 125MG/5ML
96989990	TETRACYCLINE TABS 250MG
97142997	TETRACYCLINE TABS 250MG
97153998	TETRACYCLINE TABS 250MG
98341998	TETRACYCLINE TABS 250MG
98405990	TETRACYCLINE TABS 250MG
99043990	TETRACYCLINE TABS 250MG
99055998	TETRACYCLINE TABS 250MG
99354990	TETRACYCLINE TABS 250MG
99355990	TETRACYCLINE TABS 250MG
99356990	TETRACYCLINE TABS 250MG
Oral Corticosteroids (OCS)	
95492992	PREDNISOLONE 10 MG TAB
88912979	PREDNISOLONE 10MG/5ML ORAL SOLUTION
96411992	PREDNISOLONE 15 MG TAB
88905979	PREDNISOLONE 15MG/5ML ORAL SUSPENSION
97155998	PREDNISOLONE 1MG TABLETS
98456988	PREDNISOLONE 1MG TABLETS
99425990	PREDNISOLONE 1MG TABLETS
99228998	PREDNISOLONE 1MG TABLETS
99423990	PREDNISOLONE 1MG TABLETS
98514998	PREDNISOLONE 1MG TABLETS
99100990	PREDNISOLONE 1MG TABLETS
96361990	PREDNISOLONE 1MG TABLETS
95594990	PREDNISOLONE 1MG TABLETS
95493992	PREDNISOLONE 2 MG TAB
98562998	PREDNISOLONE 2.5MG E/C TABLETS
93912998	PREDNISOLONE 2.5MG GASTRO-RESISTANT TABLETS
99423988	PREDNISOLONE 2.5MG GASTRO-RESISTANT TABLETS
97726990	PREDNISOLONE 2.5MG GASTRO-RESISTANT TABLETS
99099990	PREDNISOLONE 2.5MG GASTRO-RESISTANT TABLETS
97101990	PREDNISOLONE 2.5MG GASTRO-RESISTANT TABLETS

91648990	PREDNISOLONE 2.5MG GASTRO-RESISTANT TABLETS
95417998	PREDNISOLONE 2.5MG TABLET
66092979	PREDNISOLONE 2.5MG/5ML ORAL SUSPENSION
66090979	PREDNISOLONE 20MG/5ML ORAL SOLUTION
66088979	PREDNISOLONE 20MG/5ML ORAL SUSPENSION
95417997	PREDNISOLONE 25MG TABLETS
97436998	PREDNISOLONE 25MG TABLETS
95912990	PREDNISOLONE 25MG TABLETS
66084979	PREDNISOLONE 25MG/5ML ORAL SUSPENSION
96744992	PREDNISOLONE 4 MG TAB
93912997	PREDNISOLONE 5 MG GASTRO-RESISTANT TABLET
96409992	PREDNISOLONE 50 MG TAB
93912996	PREDNISOLONE 50MG TABLETS
98562997	PREDNISOLONE 5MG E/C TABLETS
83565978	PREDNISOLONE 5MG E/C TABLETS
95417996	PREDNISOLONE 5MG GASTRO-RESISTANT TABLETS
98455990	PREDNISOLONE 5MG GASTRO-RESISTANT TABLETS
99425988	PREDNISOLONE 5MG GASTRO-RESISTANT TABLETS
99099989	PREDNISOLONE 5MG GASTRO-RESISTANT TABLETS
97101989	PREDNISOLONE 5MG GASTRO-RESISTANT TABLETS
98456989	PREDNISOLONE 5MG GASTRO-RESISTANT TABLETS
99226998	PREDNISOLONE 5MG SOL TABLETS
95487992	PREDNISOLONE 5MG SOL TABLETS
93075998	PREDNISOLONE 5MG SOLUBLE TABLETS
96577990	PREDNISOLONE 5MG SOLUBLE TABLETS
91788990	PREDNISOLONE 5MG SOLUBLE TABLETS
97155997	PREDNISOLONE 5MG TABLETS
99228997	PREDNISOLONE 5MG TABLETS
98107990	PREDNISOLONE 5MG TABLETS
99425989	PREDNISOLONE 5MG TABLETS
99423989	PREDNISOLONE 5MG TABLETS
99137998	PREDNISOLONE 5MG TABLETS

99100989	PREDNISOLONE 5MG TABLETS
95593990	PREDNISOLONE 5MG TABLETS
99424989	PREDNISOLONE 5MG TABLETS
97929990	PREDNISOLONE 5MG TABLETS
96361989	PREDNISOLONE 5MG TABLETS
98514997	PREDNISOLONE 5MG TABLETS
99099988	PREDNISOLONE 5MG TABLETS
65924979	PREDNISOLONE 5MG/5ML ORAL SOLUTION
95484992	PREDNISOLONE E/C 1 MG TAB
Cough and Sputum	
171..00	COUGH
1719.00	CHESTY COUGH
1719.11	BRONCHIAL COUGH
R062.00	[D]COUGH
1716.00	PRODUCTIVE COUGH NOS
171..11	C/O - COUGH
1717.00	NIGHT COUGH PRESENT
1716.11	COUGHING UP PHLEGM
171C.00	MORNING COUGH
173B.00	NOCTURNAL COUGH / WHEEZE
1712.00	DRY COUGH
1713.00	PRODUCTIVE COUGH -CLEAR SPUTUM
171Z.00	COUGH SYMPTOM NOS
1715.00	PRODUCTIVE COUGH-YELLOW SPUTUM
1714.00	PRODUCTIVE COUGH -GREEN SPUTUM
R063000	[D]COUGH WITH HAEMORRHAGE
171F.00	COUGH WITH FEVER
171H.00	DIFFICULTY IN COUGHING UP SPUTUM
171D.00	EVENING COUGH
1D87.00	COUGH AGGRAVATES SYMPTOM
4I2G.00	COUGH SWAB
R064.00	[D]ABNORMAL SPUTUM

4JF5.00	SPUTUM SENT FOR C/S
41D4.00	SPUTUM SAMPLE OBTAINED
R153100	[D]POSITIVE CULTURE FINDINGS IN SPUTUM
171..12	SPUTUM - SYMPTOM
H060300	ACUTE PURULENT BRONCHITIS
4E4..00	SPUTUM CULTURE
4E3..00	SPUTUM MICROSCOPY
4E2A.00	SPUTUM APPEARANCE
4E3Z.12	SPUTUM APPEARS INFECTED
R064100	[D]SPUTUM ABNORMAL - COLOUR
4E13.00	SPUTUM EXAMINATION: ABNORMAL
Z691.11	SPUTUM CLEARANCE
R064000	[D]SPUTUM ABNORMAL - AMOUNT
4E3Z.00	SPUTUM MICROSCOPY NOS
R064z00	[D]ABNORMAL SPUTUM NOS
4E23.00	SPUTUM: MUCOPURULENT
4E28.00	YELLOW SPUTUM
4E11.00	SPUTUM SENT FOR EXAMINATION
R064300	[D]ABNORMAL SPUTUM - TENACIOUS
4E29.00	GREEN SPUTUM
4E3Z.11	SPUTUM EVIDENCE OF INFECTION
Breathlessness	
R060D00	[D]BREATHLESSNESS
R060800	[D]SHORTNESS OF BREATH
173..00	BREATHLESSNESS
R060600	[D]RESPIRATORY DISTRESS
173C.00	SHORT OF BREATH ON EXERTION
Q30..00	RESPIRATORY DISTRESS SYNDROME
1738.00	DIFFICULTY BREATHING
R060A00	[D]DYSPNOEA
1739.00	SHORTNESS OF BREATH
173..11	BREATHLESSNESS SYMPTOM

173..13	SHORTNESS OF BREATH SYMPTOM
173..12	DYSPNOEA - SYMPTOM
1732.00	BREATHLESS - MODERATE EXERTION
1736.00	PAROXYSMAL NOCTURNAL DYSPNOEA
2322.00	O/E - DYSPNOEA
2324.00	O/E - RESPIRATORY DISTRESS
1735.00	BREATHLESS - LYING FLAT
1733.00	BREATHLESS - MILD EXERTION
R060700	[D]RESPIRATORY INSUFFICIENCY
173D.00	NOCTURNAL DYSPNOEA
173Z.00	BREATHLESSNESS NOS
173F.00	SHORT OF BREATH DRESSING/UNDRESSING
173G.00	BREATHLESS - STRENUOUS EXERTION
1734.00	BREATHLESS - AT REST