Atrial fibrillation and frailty:

An observational cohort study using electronic healthcare records

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Intellectual property statement

The candidate confirms that the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Publications

Chapter 2 contains work based on the following publication, the abstract of which was presented at the British Geriatric Society Spring Meeting

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CW set the literature review question and the inclusion criteria, performed the search, sifted abstracts, selected papers for inclusion, extracted the relevant data, wrote the synthesis, and performed the meta-analysis.

Contribution of other authors: OT performed second review of the abstracts and full-text articles for inclusion, extracted data, and checked the meta-analysis results. MH, AC and CPG provided supervision and strategic direction. All authors contributed to the preparation of the manuscript and approved the final version. Diedre Andre, research librarian helped devise the search strategy.

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Attributable content to Chris Wilkinson: defined the question, undertook the coding, analysis, and drafted the abstract.

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Abstract

Atrial fibrillation is common in older people, and is associated with increased mortality and stroke. Patients with atrial fibrillation/flutter (AF) also commonly have frailty, which is associated with increased risk of a range of further adverse clinical outcomes. However, there is a lack of evidence on the burden and management of AF in people with frailty.

A study using the primary care electronic health records of 536,955 patients aged ≥65 years was conducted to investigate the burden of frailty and AF amongst older people, and their associations with clinical outcomes.

A systematic review and meta-analysis was completed to establish the current knowledge base, and to inform the quantitative analyses. Baseline characteristics were described and compared between those with and without AF as well as by frailty category according to the electronic frailty index. Rates of all-cause mortality, stroke, bleeding (intracranial and gastrointestinal), transient ischaemic attack (TIA), and falls were calculated per 1000 person-years, and compared with the non-AF patient population.

Cox proportional hazards modelling was used to determine unadjusted and adjusted risk for each clinical outcome and mortality, and presented as hazard ratios (HR) alongside 95% confidence intervals. The association between oral anticoagulation (OAC) prescription stratified by frailty category with clinical outcomes was investigated using Cox proportional hazards modelling.

At baseline, 61,177 (11.4%) patients had AF. People with AF had a higher burden of frailty than those without (89.5% vs. 55.3%) and had higher rates of mortality, stroke, TIA and bleeding. Of patients with AF and eligible for OAC, it was prescribed in 53.1% (41.7% in robust, mild frailty 53.2%, moderate 55.6%, severe 53.4%). OAC was associated with a 19% reduction in all-cause mortality (HR 0.81, 95%CI 0.77-0.85) and 22% reduction in stroke (HR 0.78, 0.67-0.92). There was no statistically significant difference in rates of bleeding between those prescribed and not prescribed OAC.

For the first time in a large representative cohort of older people, this study quantified the burden of AF and frailty, and their association with a range of clinical outcomes. This study found no evidence that OAC should be withheld on the basis of concomitant frailty.

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Abbreviations

/1000pys	per 1000 person-years
ADL	Activities of daily living
AF	Atrial fibrillation
BD	Twice daily
BGS	British Geriatric Society
BNF	British National formulary
CALIBER	Clinical research using lInked bespoke studies and electronic health Records
CCS	Charlson comorbidity score
CFS	Clinical frail scale
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CPRD	Clinical practice research datalink
CSV	Comma-separated values
CTV-3	Clinical terms version 3
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eFI	Electronic frailty index
EFS	Edmonton frail scale
EHR	Electronic health records
EMIS	Egton medical information systems
ESC	European society of cardiology
GARFIELD-AF	Global anticoagulant registry in the field - atrial fibrillation
GFI	Groningen frailty indicator
GFR	Glomerular filtration rate
GI	Gastrointestinal
GRASP-AF	Guidance on risk assessment in stroke prevention for atrial fibrillation
GUG&G	Get-up and go test
H/O	History of
HES	Hospital episode statistics
HR	Hazard ratio
IC	Intracranial

ICD-10 / 11	International statistical classification of diseases and related health problems 10^{th}/11^{th} revision
IMD	Indices of multiple deprivation
INR	International normalised ratio
IQR	Interquartile range
IRC	Integrated research campus
ISAR	Identification of seniors at risk
LIDA	Leeds Institute for data analytics
m/s	Metres per second
MINAP	Myocardial ischaemia national audit programme
MOOSE	Meta-analysis of observational studies in epidemiology
MPI	Multidimensional prognostic index
N/A	Not applicable
N/R	Not reported
NH	Nursing home
NHS	National health service
NICE	National institute for health and care excellence
NOS	Not otherwise specified
NSAID	Non-steroidal anti-inflammatory drug
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulation
OD	Once daily
ONS	Office for National statistics
OR	Odds ratio
PE	Pulmonary embolism
PPB	Physical performance battery
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
SNOMED	Systematized nomenclature of medicine reference terminology
SQL	Structured query language
TFI	Tilburg frailty indicator
THIN	The health improvement network
TIA	Transient ischaemic attack
TILDA	The Irish longitudinal study of ageing
TRUD	Technology Reference data Update Distribution
UK	United Kingdom

USA	United States of America
VRE	Virtual research environment
VTE	Venous thromboembolism
WHO	World health organisation

Chapter 1 – Frailty and the heart

Globally, there are 962 million people over the age of 60 years, which is anticipated to rise to 2.1 billion in the next thirty years.[2] This remarkable demographic shift is likely to have far-reaching cultural, social and economic consequences, and alongside these, a substantial burden of ill-health in the form of multiple long-term conditions.

A person with disability has a long-term restriction in their ability to perform an activity.[3] Disability-free life expectancy is the average number of years an individual is expected to live free of disability, assuming that current patterns of mortality and disability continue.[4] In the United Kingdom in 2016, disability-free life expectancy was 63 years, followed by 16 years with disability in men and 20 years in women.[5]

Multimorbidity is the coexistence of two or more long-term conditions in an individual.[6] Providing healthcare to a growing population of older people with multimorbidity and disability is a major challenge for healthcare systems, because there is the potential for substantial increases in the requirement for healthcare provision, and associated costs.[7] However, there is limited evidence that ‘more healthcare’ will necessarily improve outcomes.[8] There is a clear need to identify patients that are likely to benefit from medical interventions in order to maximise their utility. Chronological age alone is not an adequate, or equitable, metric for clinical decision making,[9] and so frailty has been proposed as a framework for a more individualised approach to patient management. Frailty is a condition in which there is a decline in biological reserves and deterioration in physiological mechanisms, which render the person vulnerable to a range of adverse outcomes.[10] Frailty provides an insight into biological age and is more useful than chronological age in predicting adverse events including death.[11]

In this thesis, I will investigate the implications of frailty on outcomes and thromboembolism prevention for older people with a common long-term cardiovascular condition, atrial fibrillation (AF). Within this chapter I will provide a broad overview of frailty, discuss frailty in the context of cardiovascular disease, and then specifically in AF. In Chapter 2, a systematic review of the literature will be reported, followed by a summary of the data sources that could be considered for use in the study. The methodology and results of the quantitative analysis will be detailed in Chapters 4 to 8, and these will be critically discussed in the context of the literature in Chapter 9.

1.1 Aims and objectives

This thesis will investigate the impact of frailty on clinical outcomes in older people with AF. The aims and objectives below have been informed by a systematic review of the literature reported in Chapter 2.

Aims

1. To establish the prevalence of AF and frailty in people aged 65 years and over
2. To describe the clinical characteristics of people with AF at different levels of frailty
3. To identify whether prescription of oral anticoagulation (OAC) differs by frailty category in people with AF
4. To determine whether frailty modifies the association between OAC use and clinical outcomes.

Research questions

1. What is the population prevalence of AF in older people with different levels of frailty?
2. What differences are there in the clinical characteristics of people with AF, compared to those without?
3. Is frailty associated with different OAC prescribing in patients with AF?
4. Is OAC prescription associated with similar efficacy and safety endpoints for older people with different levels of frailty?

Objectives

To use ResearchOne primary care electronic health record data to:

1. establish the population prevalence of atrial fibrillation, stratified by electronic frailty index categories.
2. report prescription rates of OAC in patients with AF by frailty category
3. estimate the association between frailty and OAC prescription.
4. report rates of clinical outcomes (stroke, death and major bleeding) by frailty category and OAC prescription status.
5. investigate the association between OAC and clinical outcomes (stroke, death and major bleeding), and whether the association is modified by frailty.

1.2 Frailty

Over time, damage accumulates at a cellular level as a part of the ageing process. This leads to a gradual deterioration in function, and a reduction in homeostatic mechanisms across a range of organ systems.[12] In health, there is considerable physiological redundancy to most body systems. For example, humans have substantially more renal nephrons than are required for survival, which compensates for age-related deterioration.[13] However, in people with frailty there is acceleration of the loss of biological reserves, leading to failure of homeostatic mechanisms and vulnerability to a range of adverse clinical outcomes as a result of stressor events.[10]

Physiological regulatory systems are dynamic and interconnected, and therefore the loss of adaptive capacity that characterises frailty tends to have effects across multiple organ systems.[10, 13] These changes have been described in skeletal muscle, the brain, and in the endocrine, immune, cardiovascular, respiratory and renal systems.[10]

Frailty may explain the differential vulnerability to adverse outcomes of people of the same chronological age.[11, 14-16] Frailty has important prognostic implications, as people with frailty are at a greater risk of nursing home admission and of all-cause mortality than those without frailty.[11, 17] However, frailty is considered to have greater reversibility than disability,[18-20] and there is now an increased focus on frailty prevention in mid-life,[3] and on identifying patients at risk of frailty through National Health Services (NHS) general practices with the aim of improved holistic patient care.[21, 22] In particular, more accurate prognostication may help with clinical decision making regarding therapies where risk is ‘up front’, and benefits are in the long term.[23] The British Geriatric Society (BGS) recommends routine assessment for frailty during all encounters with health and social care professionals.[24] Within primary care, NHS England have introduced a contractual obligation for general practices to identify patients with moderate or severe frailty under their General Medical Service contract.[25] This is in-keeping with an international consensus that patients aged over 70 years should be screened for frailty.[26]

1.2.1 Epidemiology of frailty

In community-dwelling adults aged 65 years or older, the overall weighted prevalence of frailty was 10.7% (95% confidence interval [95% CI] 10.5% to 10.9%) in a meta-analysis of 21 studies.[27] However, estimates ranged from 4.0% to 59.1%, as a result of variation between studies in the definition and measurement of frailty, and differences in the inclusion and exclusion criteria. Frailty was more common in women than men (9.6% compared with 5.2%, $p<0.001$).[27] Amongst hospital inpatients aged 65 years or older, the prevalence of frailty has increased over time, and is estimated to have reached 14% in 2013.[28] Given that this estimate included elective admissions, who may have a different frailty profile from non-elective admissions, this may be an underestimate of the true burden amongst inpatients.[29] The authors suggest that at least 4,000 patients with frailty are admitted per month to hospitals in England.[28]

Frailty is more common with increasing age. Just 3.2% of participants in the Cardiovascular Health Survey aged 65 to 70 years were identified as frail, compared with 25.7% of those aged 85 to 89 years.[30] In Europe, 25% of the population are aged 60 years or over, but this is projected to increase to 35% by 2050.[31] As the population ages, the overall burden of frailty is likely to increase substantially over coming years.

1.2.2 Models of frailty

There are two well established conceptual frameworks for frailty: the phenotype and the cumulative deficit models.[32] These will now be discussed, followed by an outline of the frailty measures that are in common clinical use.

1.2.2.1 Phenotype model

The phenotype model is based upon the premise that patients with frailty share a set of physical characteristics, and that these can be summarised.[14] It was developed in a secondary analysis of the Cardiovascular Health Study, which was a prospective, community based cohort study of 5,317 people aged 65

years or older.[33] The cardinal characteristics that defined the phenotype were identified through clinical consensus, and are listed in Table 1. Those with three or more factors were defined as frail, those with one or two as intermediate or 'pre-frail', and those with no factors as not frail.[30] In the original study 7% of participants were categorised as frail, 47% as pre-frail, and 46% as not frail.

Table 1: The five indicators included in the phenotype model

Indicator	Definition
Weight loss	Unintentional loss of ≥10 lbs or ≥5% of body weight in prior year
Poor endurance exhaustion	Self-reported "exhaustion"
Low activity	Males: <384 kilocalories per week; females: <270 kilocalories per week
Slow gait speed	Time to walk 15 feet, cut-off stratified by gender and height
Weak grip strength	Lowest 20% of the population, stratified by gender and body mass index.[30]

Patients in the frail group had worse clinical outcomes than the intermediate or non-frail groups. Compared with the non-frail group, frailty at baseline was associated with an 80% higher risk of falls (adjusted hazard ratio [HR] 1.8, 95%CI 1.5 to 2.2[a]), 40% increased risk of worsened mobility (HR 1.4, 1.2 to 1.6), 80% risk of worsened activities of daily living (ADL) disability (HR 1.8, 1.5 to 2.2), 30% increased risk of hospitalisation (HR 1.3, 1.1 to 1.5), and 60% increased risk of death (HR 1.6, 1.3 to 2.1) at 7 years.[30]

[a] Each HR adjusted for age, gender, indicator for minority cohort, income, smoking status, blood pressure, fasting glucose, albumin, creatinine, carotid stenosis, history of heart failure, cognitive function, major electrocardiographic abnormality, use of diuretics, problem with independent activities of daily living, self-report health measure, and depression measure.

The Cardiovascular Health Study was originally designed to investigate coronary heart disease and stroke. This gives rise to two key limitations in its use for developing a frailty model. Firstly, patients with Parkinson's disease, previous stroke, cognitive impairment or depression were excluded.[10] Secondly, the constituent parts of the phenotype model were contingent upon data that were collected in the original trial, for a purpose for which it was not designed, and did not include factors such as cognitive impairment.[10] Despite this, in an external validation study there was an independent association between each of slow gait speed, low physical activity and weight loss with the outcomes of chronic disability, long-term nursing home stay, injurious fall and death.[34] However, there was not an independent association between these outcomes and weak grip strength or self-reported exhaustion. Concerns have also been expressed over how to operationalise the phenotype model in primary care, due to the need for evaluation of muscle strength and gait speed, and also the existence of a 'ceiling effect' in the case of disabling conditions.[32]

1.2.2.2 Cumulative deficit model

The cumulative deficit model considers the 'building blocks' of frailty to be additive, and is based upon the idea that "the more things individuals have wrong with them, the higher the likelihood that they will be frail".[35] In the cumulative deficit model, deficits are considered to be abnormal signs, symptoms, laboratory values, disease states and disabilities. The number of deficits identified can be summed and expressed as a proportion of the total to create a frailty index. This reflects the view that the accumulation of deficits contribute to the likelihood of frailty.[10, 36] Three rules are used for the inclusion of variables in a frailty index: the variable must be biologically sensible; accumulate with age; and not saturate too early.[37]

The original frailty index consisted of 92 items from the cross-sectional and longitudinal components of the Canadian Study of Health and Ageing.[38] The statistical properties of the model were explored in detail in the original paper, and were consistent with probability models seen in complex systems with in-built redundancy, which is in-keeping with the concept of frailty as a condition with a reduction in homeostatic reserve.[10] Subsequent work, such as a study

using data from the National Population Health Survey of Canada, has shown that it is possible to reduce the number of potential deficits in the model from 92 to 36 variables whilst maintaining validity.[39] This lower number of variables is more practical for use in routine clinical practice, and the electronic frailty index (eFI) of 36 variables was subsequently developed for routine use within general practice computing systems.[11] The eFI will be discussed in detail in section 1.2.7.3.

Although the two models of frailty are not mutually exclusive, the cumulative deficit model has been shown to more precisely evaluate the probability of death than the phenotype model,[40] and allows a graded approach to evaluating frailty in a number of different clinical settings.[32]

1.2.3 Comprehensive geriatric assessment

In clinical practice, the identification and impact assessment of frailty is typically achieved using the evidence based holistic evaluation known as comprehensive geriatric assessment (CGA).[12] It is used in order to provide a tailored approach to care for patients with complex health and care needs, and should include medical, psychological, functional and social needs assessments. This is a multi-disciplinary process, typically making use of the expertise of a geriatrician, general practitioner, specialist nurse, nurse, physiotherapist, occupational therapist and a social worker.[12] Other specialists may also be involved, such as a pharmacist or other medical specialist.

This multi-dimensional evaluation aims to systematically formulate a list of problems, including identifying frailty. It is an important part of developing a management plan that addresses health and care needs, guided by patient-centred prioritisation.[14] Use of a CGA as part of inpatient care has been shown to be associated with improved outcomes for older people with frailty, including improved rates of independent survival and lower functional decline following hospital discharge.[12, 41] Some frailty measures, such as the multi-dimensional prognostic index or the Canadian Study of Health and Ageing Clinical Frailty Scale are only recommended for use following a CGA.[36, 41, 42]

1.2.4 Frailty instruments

A subjective label of 'frailty' from a clinician, even without using formal criteria, is associated with increased healthcare utilisation and a greater number of geriatric syndromes.[43] However, clinical assessment in the absence of a structured CGA lacks sensitivity in identifying individuals with frailty, with one study finding that general practitioner global judgement had a sensitivity of 0.67, and specificity of 0.77 compared with the phenotype model.[44] To improve diagnostic accuracy it is recommended that validated tools are used alongside clinical judgement to identify patients with frailty.[24, 61] However, there is no consensus on which tool should be used,[45] and a recent systematic review identified 67 frailty instruments to select from.[46]

The BGS recommend slow gait speed, the PRISMA 7 questionnaire, and the timed-up-and-go test as reasonable frailty assessments for general use, and the Edmonton Frail Scale when elective surgical intervention is under consideration.[24] Whilst these population-based frailty scores have limitations in the acute setting,[47] various tools have been used successfully in acute myocardial infarction,[48-50] and a hospital frailty risk score has been developed as a systematic screening tool for inpatients.[29] Some of the commonly used instruments are outlined below.

1.2.5 Multidimensional frailty assessment instruments

These instruments test components across different dimensions of a patient's health and care, as in the comprehensive geriatric assessment.

1.2.5.1 Edmonton Frail Scale

Ten domains are included to assess cognition, health (two domains), hospitalisation, social support, nutrition, mood, function, and continence. Mild frailty is diagnosed with a score of 8-9 of a possible 17.[51] Moderate frailty is defined as a score of 10-11, and severe as a score of 12 or more.[52] The scale was developed in a population of community dwelling people aged 65 years or over who were referred for specialist geriatric assessment. It was shown to have good correlation with the geriatrician's clinical impression of frailty formed following a one-hour comprehensive geriatric assessment. By comparison, the

Edmonton Frail Scale takes considerably less time, and does not require specialist training.[51]

1.2.5.2 PRISMA-7 questionnaire

This simple, seven-item, self-completed questionnaire is used to identify patients with moderate or severe disability.[53] The questions included are:

1. Are you more than 85 years old?
2. Are you male?
3. In general, do you have any health problems that require you to limit your activities?
4. Do you need someone to help you on a regular basis?
5. In general, do you have any health problems that require you to stay at home?
6. In case of need, can you count on someone close to you?
7. Do you regularly use a cane, a walker or a wheelchair to move about?

A score of three or more is the cut-off for significant disability, which has a sensitivity of 78%, and specificity of 75% compared with the Functional Autonomy Measurement system, which is a 29-item scale from which the PRISMA-7 questionnaire was derived.[54] Although it was originally developed to identify disability, PRISMA-7 is recommended by the British Geriatric Society for recognising frailty.[24, 41] Advantages include the simplicity of the test, and that patients can complete the questionnaire at home, without the need for a visit to a healthcare provider.[24]

1.2.6 Simple frailty instruments

These instruments rely on a single assessment, rather than spanning multiple dimensions of care. Three commonly used tests are briefly summarised.

1.2.6.1 Timed-up-and-go test

The original ‘get-up and go’ test was devised as an assessment of balance in the elderly.[55] Adding a timed element gave additional power to quantify functional mobility that could be used to evaluate change over time.[56] An

individual that takes more than 30 seconds to stand from a chair, walk 3 metres, turn around, walk back and be seated is considered to have mobility problems.

1.2.6.2 Gait speed

Various cut-off values for identifying frailty are used in the literature, which are associated with varying sensitivity and specificity values.[57] Compared with the phenotype model, a gait speed of less than 0.8 metres per second (m/s) had a sensitivity of 0.99 and specificity of 0.64 for identifying frailty.[44] There are also survival implications of a reduced gait speed, as it has been shown to be an independent predictor of all-cause mortality in older people.[58] In a recent meta-analysis, the HR for survival per each 0.1 m/s faster gait speed was 0.88 (95% CI 0.87 to 0.90).[57]

1.2.6.3 Grip strength

Low grip strength is predictive of functional decline and mortality in community-dwelling adults.[52] In a prospective cohort study of 142,861 patients, grip strength was inversely associated with all-cause mortality: a reduction of 5 kg in grip strength was associated with a 16% increase in all-cause mortality (HR 1.16, 95% CI 1.13 to 1.20).[59]

1.2.7 Using routinely collected data to identify frailty

These tools use routinely collected data to identify patients with frailty. They are not subject to the limitations of inter-operator reliability, and as they can be calculated automatically within existing data structures, their use tends to result in a low additional burden on the healthcare professional to calculate the score.[29]

1.2.7.1 QMortality

QMortality is a risk prediction algorithm to estimate short term risk of death and assess frailty.[25] The authors identified 180,132 deaths from 4.4 million person-years of observation. They combined the predicted one-year risks of unplanned hospital admission (QAdmission) and mortality to classify patients into frailty groups: 2.7% were classified as severely frail (these were either in the highest 2% in the cohort in predicted risk of death or in the top 2% at greatest risk of hospital admission in the next year), 9.4% as moderately frail (in the top 10% of

either risk of death or of hospital admission), 43.1% as mildly frail (in the top 50% of either risk of death or of hospital admission), and 44.8% as fit (the remainder).[25]

1.2.7.2 Hospital Frailty Risk score

The hospital frailty risk score is a recent addition to the available screening tools. It was developed in a cohort (n=22,139) of patients aged 75 years or older who had been discharged from hospital.[29] A cluster analysis was performed to identify cohorts of patients that had similar characteristics in terms of the clinical codes assigned during their admission, number of hospital bed-days, and the cost of their admission, alongside a set of candidate clinical codes for frailty that were defined *a priori*. The hospital frailty risk score was calculated using coefficients from a logistic regression model, where membership of the frail cluster was the binary dependent variable, and the set of clinical codes as binary predictor variables. These were weighted based upon their prevalence amongst patients in the cohort that were determined as frail, and the score was created. Patients were categorised into frailty risk groups by their score: low risk (score of less than 5), intermediate risk (score of 5-15), and high risk (score of greater than 15).

People with high frailty risk had a 70% higher adjusted risk of 30-day mortality than those in the low-risk group (OR 1.71, 95% CI 1.68 to 1.75). They had a six-fold higher adjusted odds of a long hospital stay (OR 6.03, 5.92 to 6.10) and 48% higher risk of emergency readmission within 30 days (1.48, 1.46 to 1.50).[29]

1.2.7.3 Electronic frailty index (eFI)

The eFI uses routinely available primary care electronic health record (EHR) data. It was developed using a cohort of 931,541 patients aged 65 to 95 years registered with a practice that was enrolled in ResearchOne or The Health Improvement Network (THIN) research databases. The authors used the cumulative deficit model as a theoretical framework.[11] 36 deficits were identified that met the three criteria of being biologically plausible, increased in prevalence with age, and did not saturate too early.[37] The included deficits are listed in Table 2. These deficits are identified within EHR by 2,171 Clinical Terms Version 3 (CTV-3) codes (discussed further in section 3.2.4.1).

Table 2: The 36 deficits included in the electronic frailty index

Disease state	**Symptoms/signs**
Arthritis	Dizziness
Asthma/COPD	Dyspnoea
Atrial fibrillation	Falls
Cerebrovascular disease	Memory/cognitive problems
Chronic kidney disease	Polypharmacy
Diabetes	Sleep disturbance
Foot problems	Weight loss and anorexia
Fragility fracture	Urinary incontinence
Heart failure	
Hypertension	Abnormal laboratory values
Hypotension/syncope	Anaemia and haematinic deficiency
Ischaemic heart disease	
Osteoporosis	**Disability**
Parkinsonism and tremor	Activity limitation
Peptic ulcer	Housebound
Peripheral vascular disease	Hearing impairment
Respiratory disease	Mobility/transfer problems
Skin ulcer	Requirement for care
Thyroid disease	Social vulnerability
Urinary system disease	Visual impairment [11, 60]

The deficits for each patient are summed and expressed as a proportion of the maximum possible. Population quartiles were used to categorise patients as being fit, or having mild frailty, moderate frailty or severe frailty, as shown in Table 3. The eFI showed good discrimination for outcomes of mortality and nursing home admission, and moderate discrimination for hospitalisation.
The research paper describing the development and validation of the eFI was published in 2016,[11] and has since been integrated into the electronic health record systems SystmOne, EMISWeb, and Vision EHR.[60] Use of the eFI is supported in National Institute for Health and Care Excellence (NICE) guidance.[61] The score can be calculated automatically from data within primary care records, and this integration into existing GP record systems allows wide-spread access to the tool. Real-life usage of the eFI to identify patients with frailty in primary care has been described as simple, quick, acceptable to staff, and useful.[62]

Table 3: Frailty categories using the eFI score. Also showing prevalence of frailty, and HR for all-cause mortality and nursing home (NH) admission.

Frailty category	eFI score	Description	Prevalence	One year adjusted HR for mortality (95%CI)	One year adjusted HR for NH admission (95%CI)
Fit	0 – 0.12	No, or few long-term conditions that are usually well controlled. Mainly independent in day-to-day living activities.	50%	REF	REF
Mild frailty	0.13 – 0.24	Slowing up in older age. May need help with personal activities of daily living such as finances, shopping, transportation.	35%	1.9 (1.8-2.0)	1.9 (1.6-2.2)
Moderate frailty	0.25 – 0.36	Difficulties with outdoor activities. May have mobility problems or require help with washing and dressing	12%	3.1 (2.9-3.3)	3.2 (2.7-3.7)
Severe frailty	>0.36	People who are often dependent for personal cares and have a range of long-term conditions/ multimorbidity. Some of this group may be medically stable. Others can be unstable and at risk of dying within 6 - 12 months.	3%	4.5 (4.2-4.9)	4.8 (3.9-5.8)

Adapted from Clegg and de Biase.[11, 60]

1.3 Frailty and cardiovascular disease

An increasing proportion of patients have co-existing cardiovascular disease and frailty. This is partly as a consequence of improvements in life expectancy, but also in improved treatments and survival following index cardiovascular presentations.[63] There is evidence that manifest or subclinical frailty is an important consideration across a range of cardiovascular conditions,[64] and it is possible that increased recognition of frailty may facilitate improved clinical decision making and clinical management of patients with increasingly complex health and care needs.[65, 66] A recent position paper by the Acute Cardiovascular Care Association called for an increased focus on defining the targeted utility of frailty measurement in patients with cardiovascular disease, which they identify as an area of unmet research need.[23] Below I will discuss the implications of age and frailty on cardiovascular disease in general in the context of the existing literature, followed by a more detailed section on AF, which will be the focus of the remainder of the thesis.

1.3.1 The ageing heart

Anatomical and physiological changes in the heart and vasculature that occur with ageing result in deterioration over time. Key age-related changes that have been observed include:

- Diastolic impairment secondary to myocyte loss and increased size of remaining cells
- Disruption of electrical conducting tissue and sclerosis of valves, due to calcification
- Hypertrophy as a result of collagen changes
- Reduced heart rate responsiveness to adrenergic stimulation
- Hypertension as a consequence of thickening or decreased compliance of arterial walls.[67]

The mechanisms driving these changes are complex. Key factors include oxidative stress, inflammation, non-enzymatic glycation, and genetic changes.[67] It is thought that these insults cumulatively result in molecular and cellular damage that ultimately reduce physiological reserve.[10]

1.3.2 Acute coronary syndrome

Older people account for an increasing proportion of acute coronary syndrome presentations: 12.9% of entries into the Myocardial Ischaemia National Audit Project (MINAP) are now for patients aged 85 years or older,[68] although the true number of admissions to hospital due to acute coronary syndrome is likely to be higher due to under-recording in the registry.[69-71]

A treatment paradox has emerged, whereby older people who are at highest risk of mortality are less likely to receive contemporary, evidence-based treatment and tend to have poorer clinical outcomes.[71-74] Frailty is common in patients with acute coronary syndrome, and is a risk factor for mortality.[48, 75-77] Trials are ongoing to establish the optimal care strategy in patients with frailty and acute coronary syndrome,[214, 215] who were under-represented in the evidence that underpins clinical guideline recommendations,[68, 78] and who may not be best served by single-organ orientated care strategies.[21]

1.3.3 Heart failure

In the UK, the mean age at first diagnosis of heart failure is 77.0 years (SD 12.9).[79] Three-quarters of patients with heart failure also meet diagnostic criteria for frailty, which is associated with increased functional decline, all-cause mortality, and hospital readmission in patients with heart failure.[80-87] As in acute coronary syndrome, patients with heart failure and frailty are underrepresented in clinical trials.[88]

Clinical decisions regarding therapy for long-term potential prognostic gain may be particularly challenging in patients with frailty. An example concerning patients with heart failure is when considering patients for cardioverter defibrillator implant. This device is designed to provide protection against sudden arrhythmic death. However, the prognostic benefit for patients with frailty may be attenuated by a relatively higher non-arrhythmic mortality,[89, 90] who also have higher complication and mortality rates following implantation.[91-93] In order to identify patients that are most likely to benefit, case selection is of key importance. Frailty could be a helpful addition to aid in this clinical decision making.[23]

Age should not necessarily be a barrier to defibrillator implant,[94] as rates of appropriate shocks are similar across age categories.[95] Instead, defibrillator specific risk scores alongside frailty assessment are advised,[90, 96-100] particularly when deciding between resynchronisation pacing, which is associated with symptomatic improvement and left ventricular remodelling in older people,[101] and a defibrillator alone, which does not improve symptoms.[216, 217] In younger people with advanced heart failure, there is evidence that frailty status can be improved with a left ventricular assist device implant or cardiac transplant.[102, 103]

1.3.4 Valvular heart disease

In Europe, valvular heart disease is predominantly degenerative and age-related.[67, 104] By way of example, aortic stenosis affects 9.8% of people over 80 years of age, many of whom are also frail.[105] Once patients are symptomatic of their aortic stenosis their prognosis without intervention is poor, however conventional surgery carries a high risk of major complications in older people.[106, 107] The advent of trans-catheter aortic valve intervention has provided a therapeutic option for patients that are deemed too high risk for conventional surgery, and is associated with good clinical outcomes.[108] Although the procedure is associated with an increased risk of post-procedural mortality and delirium in patients with frailty,[109] trans-catheter aortic valve intervention is often the only viable treatment option in this vulnerable group, and it is likely that percutaneous options will play an increasing role in patients with frailty and mitral valve disease in the future.[110, 111]

1.3.5 Stroke

There were 84,184 patients admitted to hospitals in England, Wales and Northern Ireland with stroke between 2015 and 2016.[112] Although over 80% of strokes occur in those aged 65 years or older, older people with stroke are less likely to receive effective treatment and have poorer outcomes,[113] suggesting that there may be a high burden of potentially avoidable morbidity and mortality. Pre-stroke health status has been shown to be a more important determinant of outcome than age,[114] raising the concept of frailty as an important consideration.[115] Frailty is independently associated with increased mortality and care home admission following stroke,[116, 117] and frailty status may be a greater determinant of clinical outcome than the currently available optimal

medical therapy for hyper-acute stroke.[118] Stroke in the context of AF is discussed in greater detail in section 1.4.5.

1.4 Atrial fibrillation

Atrial fibrillation is a condition characterised by disorganised electrical activity in the atria, causing irregularity of the pulse. It is the most common arrhythmia encountered clinically, with a lifetime risk of one in four for adults over the age of 40 years.[119]

1.4.1 Pathophysiology of atrial fibrillation

The pathogenesis of AF is understood to involve rapidly firing ectopic foci, usually within the pulmonary veins, that are propagated within abnormal atrial tissue which acts as a substrate for the arrhythmia.[120, 121] At a cellular level, AF is initiated and perpetuated by pro-arrhythmic mechanisms such as triggered activity, in addition to re-entry of electrical excitation.[122] At a macroscopic level, the organised contraction of sinus rhythm is replaced by a chaotic fibrillation. This leads to a loss of atrio-ventricular synchrony and reduction in efficiency, but also the possibility of stasis of blood that can allow thrombus formation. This often occurs within the left atrial appendage (Figure 1).[123] Subsequent thromboembolism may then cause cerebral infarction leading to a stroke, or infarction elsewhere.[123-125] Atrial flutter is a more ‘organised’ rhythm that commonly coexists with or precedes AF, and also carries an elevated stroke risk.[126]

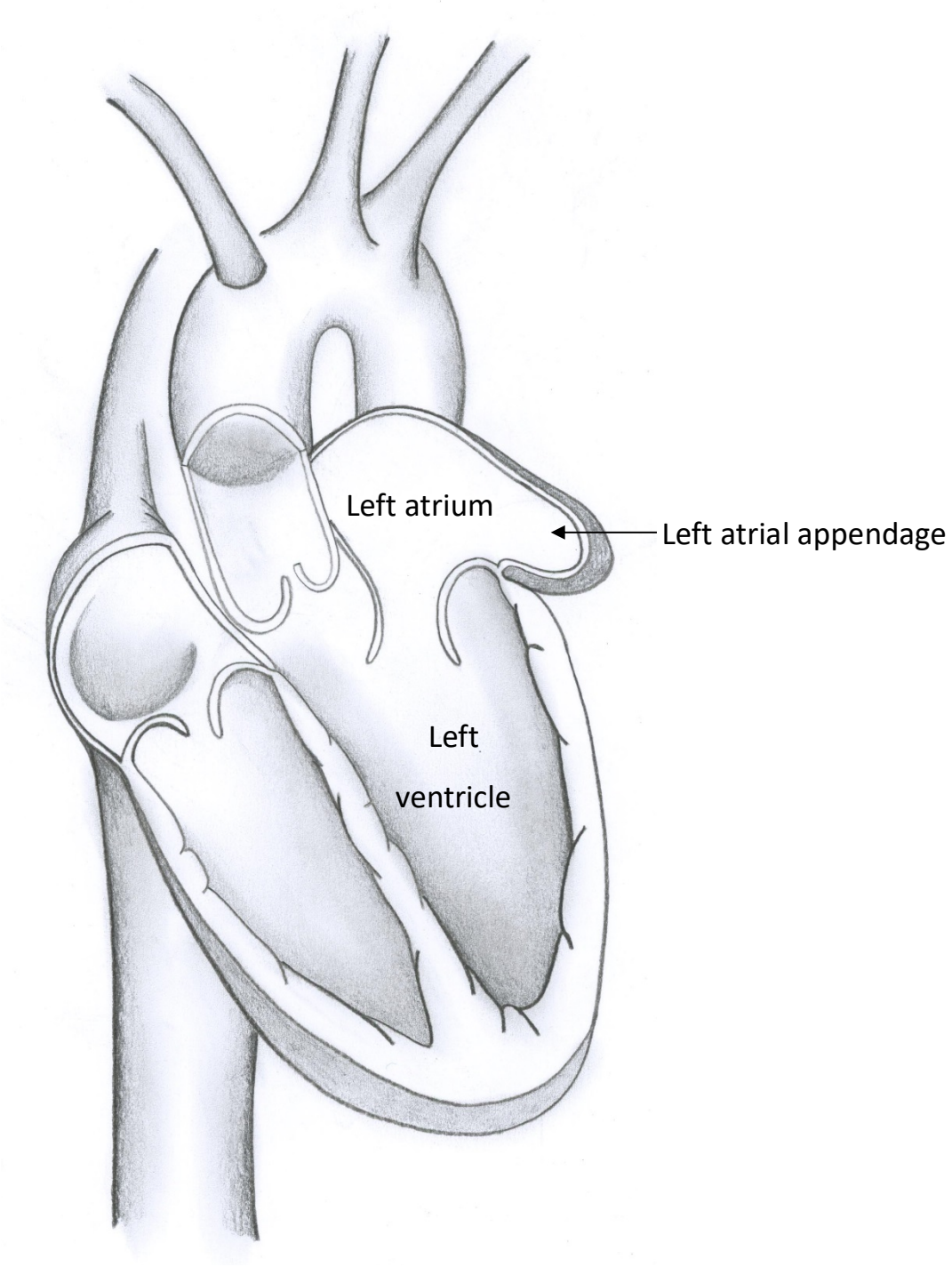


Figure 1: Diagram of the heart, showing the anatomical location of the left atrium and the left atrial appendage. Artist: Bryony Cousins

Over time, oxidative stress promotes remodelling of the electromechanical activity of the atria.[127, 128] The persistence of AF leads to further chamber dilatation and interstitial fibrosis, which in turn increases the burden of atrial substrate, thereby sustaining the arrhythmia.[127, 129]

1.4.2 Epidemiology of atrial fibrillation

Atrial fibrillation affects 2-3% of the population of Europe.[130] In the UK, age and sex standardised prevalence of AF was 3.3% (95% CI 3.27% to 3.32%) in 2016.[131] The incidence of AF appears to be increasing over time. In the UK, the age-adjusted incidence of AF per 1000 person-years was 1.11 (95% CI, 1.09 to 1.13) in 1998–2001, 1.33 (1.31 to 1.34) in 2002–2006, and 1.33 (1.31 to 1.35) in 2007–2010.[132] The incidence and prevalence of AF is higher with increasing age.[131, 132] The prevalence of the risk factors for developing AF are also increasing over time.[130] Considering these factors alongside population ageing, it is likely that the prevalence of AF will continue to increase. Indeed, AF has been described as an 'epidemic'.[130]

Globally, hypertension and increasing age are thought to be the most significant risk factors for AF.[133-135] Other risk factors for AF include heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus and chronic kidney disease.[126]

Atrial fibrillation is associated with a range of adverse outcomes, including stroke, heart failure, unplanned hospital admission and death.[126, 136, 137] For example, in a nationwide cohort study of patients admitted to hospital in Sweden, AF was associated with a greater risk of mortality compared with controls up to 14 years following admission.[136] In women, AF was associated with a two-fold increased risk of all-cause mortality compared with controls (adjusted HR 2.2, 95% CI 2.0 to 2.3) in patients aged under 65 years. There was a 70% increased risk in women with AF aged 65 to 74 years (HR 1.7, 1.67 to 1.78), and 40% (HR 1.4, 1.42 to 1.46) in women with AF aged 75 to 85 years. The mortality disadvantage associated with AF was lower for men than women (corresponding figures for men were 1.8 (1.69 to 1.84), 1.4 (1.33 to 1.40), and 1.2 (1.22 to 1.26) respectively).[136] In these data, there was a reduction in the mortality disadvantage associated with AF with increasing age.

1.4.3 Patterns of atrial fibrillation

Atrial fibrillation is commonly classified according to the pattern of arrhythmia:

- Paroxysmal – this describes episodes that last up to seven days, or required cardioversion treatment within that time to restore sinus rhythm.
- Persistent – episodes that last longer than seven days
- Long-standing persistent – continuous AF lasting for one year or more, where the intention is to restore sinus rhythm (a rhythm control strategy)
- Permanent – where a decision has been made to accept AF rather than attempt to restore sinus rhythm (a rate control strategy)[126]

However, patients often move between categories,[138] and the natural history of AF is that the disease pattern frequently progresses from paroxysmal to persistent to permanent over time.[139]

1.4.4 Diagnosis of atrial fibrillation

Common symptoms of AF include palpitations, fatigue, breathlessness, anxiety and depressed mood, symptoms which may prompt the patient to present to healthcare services.[130] Patients may also present with a complication of AF, such as heart failure or stroke, as it is possible to have AF with no associated symptoms.[130]

During a clinical examination, palpation of the pulse may reveal an irregularly irregular rhythm, which would raise the suspicion of AF.[140] The heart rhythm should then be evaluated with a 12-lead electrocardiogram (ECG), which would show irregular R-R intervals and absent discernible distinct P waves if the patient was in AF at the time.[126] If there is a suspicion of paroxysmal AF a more prolonged period of ECG monitoring may be required to detect an episode, such as an ambulatory ECG monitor (which records a prolonged surface ECG), an event recorder (which is activated by the patient when symptoms occur) or an implantable loop recorder, which is placed anteriorly to the pre-pectoral fascia through a small incision and makes recordings automatically when an arrhythmia is detected by the device or when it is activated by the patient.[126, 140]

As many episodes of AF are 'silent',[130] meaning that they occur without symptoms, the European Society of Cardiology (ESC) recommend opportunistic screening for AF in patients aged 65 years or older, in patients that present with a transient ischaemic attack or ischaemic stroke, and as part of the routine follow-up of pacemakers and implantable cardioverter defibrilators.[126] In England, NICE recommend investigating for AF as part of the assessment of a symptomatic patient.[140] There is currently no consensus on population-based screening for AF,[130] although this is a rapidly developing area. Watches are now being marketed that include technology that may identify episodes of AF,[141] although this function has not been approved in the UK as yet.

Management of AF centres upon two key considerations: the prevention of thromboembolic consequences such as stroke, and treatment of the arrhythmia itself.[126, 140] These will be discussed in sections 1.4.5 and 1.4.7 respectively.

1.4.5 Thromboembolism in atrial fibrillation

There is strong evidence that AF confers a state of blood stasis, endothelial dysfunction and clotting activation, thus fulfilling Virchow's triad of criteria for thrombus formation, Figure 2.[124, 125]

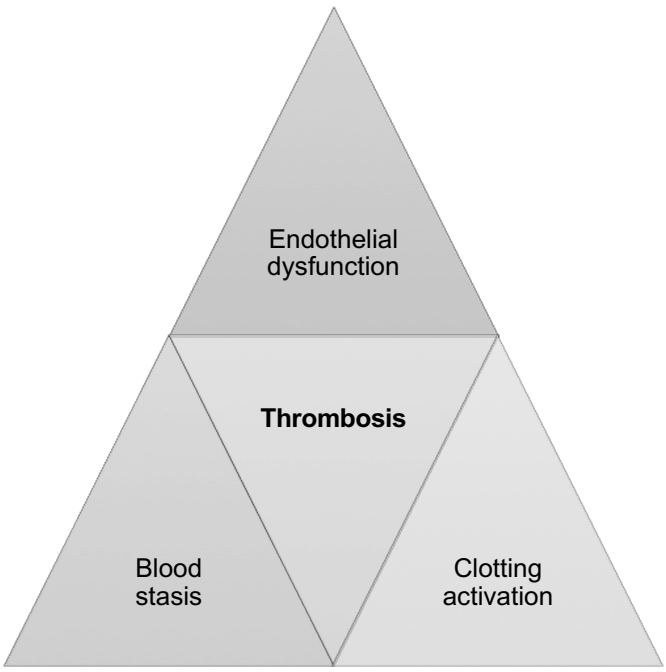


Figure 2: Virchow's triad of criteria for thrombus formation

The formation of thrombus in the fibrillating atria leads to the potential of embolism, which may occlude a distal blood vessel. In the brain, this causes cerebral ischaemia, and potentially infarction.[125, 142] If the symptoms and signs related to cerebral ischaemia resolve within 24 hours, this is known as a transient ischaemic attack (TIA).[143] However, if they persist for longer than 24 hours then the criteria for a diagnosis of stroke are met.[143]

Although the risk of stroke is elevated in patients with AF, appropriate use of oral anticoagulation (OAC) has been shown to reduce the risk of stroke by 64%.[144] Yet despite good evidence of the efficacy of OAC a recent study using UK primary care records showed that OAC was prescribed in just 55% of eligible patients.[145] Indeed, of 15,807 patients that were admitted to hospital with a stroke in the context of a known history of AF in England, Wales, and Northern Ireland in 2017/18, 42.4% of these were not prescribed OAC.[146] This suggests that there is a potential for reducing the population burden of stroke in patients with AF through appropriate use of OAC for stroke prophylaxis.[140] There is also the potential of significant cost savings to health and care services, as stroke disease has an annual estimated cost of £3.6 billion for the first five years following admission in England Wales and Northern Ireland, and a mean cost per patient of £46,039.[112]

1.4.6 Oral anticoagulation for stroke prophylaxis in atrial fibrillation

Until 2012, warfarin was the only commonly used OAC in the UK.[154] Warfarin has a narrow therapeutic window, and requires blood test monitoring to guide dose-adjustment.[147] The first direct oral anticoagulant (DOAC) medication came onto the formulary in the UK in 2012, and there are now four such agents available: apixaban, edoxaban, rivaroxaban and dabigatran.[148] Each has been shown to be non-inferior to warfarin in stroke reduction, Table 4.

Table 4: Rates of stroke or systemic embolism in patients with AF reported in the literature

Study, year (ref)	Warfarin, compared with:	Patients enrolled	Stroke or systemic embolism, rate per 100 person-years		
			Warfarin	DOAC	No OAC
ROCKET AF. 2011 [149]	Rivaroxaban 20mg OD	14,143	2.4	2.1	-
RE-LY. 2009 [150]	Dabigatran 150mg BD*	18,113	1.7	1.5	-
	Dabigatran 110mg BD			1.5	-
ENGAGE AF-TIMI 48. 2013 [151]	Edoxaban 60mg OD	21,105	1.5	1.2	-
ARISTOTLE. 2011 [152]	Apixaban 5mg BD	18,201	1.6	1.3	-

Abbreviations OAC: oral anticoagulation; DOAC: direct OAC; OD: once daily; BD: twice daily
* in renal impairment
Intention to treat analysis reported from the clinical trials.

The current guidance on when OAC should be considered for stroke prophylaxis in patients with AF will be discussed below.

1.4.6.1 Considerations in valvular atrial fibrillation

AF is traditionally dichotomised into valvular (usually considered as moderate/severe mitral stenosis or mechanical heart valves) and non-valvular AF.[126, 153] Valvular AF is associated with a particularly high stroke risk, requiring more intensive anticoagulation using warfarin.[154] This is in part because in mitral stenosis, AF-related endothelial damage and dilatation of the left atrium tends to be more pronounced than in a non-stenotic valve,[125] and left atrial dilatation is associated with further blood stasis and propensity to thrombosis.[155] None of the DOAC agents are currently licenced for use in valvular AF.[154] Where a patient has a prosthetic heart valve, there is clear guidance for OAC directed for the specific valuvlar indication.[156] Where a patient has AF and OAC is not indicated for the prosthetic valve, for example in the case of a bio-prosthetic aortic valve, then OAC should still be considered for AF thromboprophylaxis.

1.4.6.2 Assessment of stroke risk in non-valvular atrial fibrillation

Guidelines from NICE[140] and the ESC[126] recommend that the decision whether or not to commence OAC in people with non-valvular AF should be based upon an objective stroke-risk scoring system, specifically the CHA_2DS_2-VASc score.[157] There were four thromboembolic risk scoring systems identified in a recent meta-analysis.[158] These were the Framingham,[159] ABC,[160] $CHADS_2$,[161] and CHA_2DS_2-VASc scores.[157] Each will be summarised in turn.

The Framingham score includes age, sex, systolic blood pressure, use of antihypertensives, evidence of left ventricular hypertrophy on ECG, prevalent cardiovascular disease, smoking status, current or previous AF, and diabetes.[159] These were combined in order to predict the probability of stroke at 10 years. The score was developed using stroke data collected in the 1960's and 1970's and has tended to over-estimate stroke risk in contemporary cohorts.[162] This prompted the development of the revised Framingham risk score in which left ventricular hypertrophy was removed, and other factors such as coronary artery calcium score, and blood markers including c-reactive protein were included.[163] A c-statistic gives an indication of model performance, where a value of 0.5 means that the model is no better than random chance and a value of 1 identifies a model that perfectly predicts patients that will experience an event.[164] In this case, the authors reported that the revision of the Framingham score resulted in a modest improvement in the c-statistic from 0.65 in the original, to 0.72 in the revised model.[163]

The ABC (age, biomarker, clinical history) stroke risk score includes age, N-terminal fragment B-type natriuretic peptide, high-sensitivity cardiac troponin, and prior history of stroke or TIA.[160] The score was developed using data from the ARISTOTLE trial,[152] and validated using data from the STABILITY trial.[165] The authors report a c-statistic of 0.68 in the derivation cohort, and 0.66 in the external validation cohort. Again, these c-statistics show only a modest model performance.

The components of the $CHADS_2$ score are congestive heart failure, hypertension, age 75 years or older, type 2 diabetes, and previous stroke or TIA

(for either of which two points are allocated).[161] The performance of the model was assessed in a meta-analysis of 14 studies, and a pooled c-statistic of 0.69 (95% CI 0.66 to 0.73) was reported.[158] One particular weakness of the $CHADS_2$ score was a tendency to misclassify patients as low risk, and so OAC prescription was not advised. For example, in the validation study the stroke rate in patients with a $CHADS_2$ score of zero was 1.9 (1.2 to 3.0) per 100 person-years.[161] The CHA_2DS_2-VASc score was developed, and includes the additional risk factors of vascular disease (defined as prior myocardial infarction, peripheral arterial disease or aortic plaque) and sex. As in $CHADS_2$, two points were allocated for previous thromboembolism. Older age was given additional weighting, with two points allocated for patients aged 75 years or older, Table 5.

Table 5: Assessment of stroke risk using CHA_2DS_2-VASc

Criteria	Value	Points
Age	<65 years old	0
	65-74 years old	+1
	≥ 75 years old	+2
Sex	Male	0
	Female	+1
Congestive heart failure history	Yes / no	+1
Hypertension history	Yes / no	+1
Stroke / TIA / thromboembolism history	Yes / no	+2
Vascular disease history	Yes / no	+1
Diabetes mellitus history	Yes / no	+1

Abbreviation TIA: transient ischaemic attack

In the validation study, no patients with a score of zero had a stroke. Stroke rates increased with increasing score up to 5.5 per 100 person-years (95% CI 0.91 to 27.0) in patients with a score of nine.[157] The authors went on to estimate what the stroke risk would have been in the absence of OAC, assuming that warfarin provides a 64% reduction in stroke risk.[144] In this model, a CHA_2DS_2-VASc score of 9 was associated with a stroke risk of 15.2 per 100 person-years, Table 6.[157]

Table 6: Stroke or Other Thromboembolism Events per Patient Year Based on the CHA_2DS_2-VASc Scoring System, adapted from Lip *et al*.[157]

CHA_2DS_2-VASc score	Adjusted annual stroke or thromboembolism events per 100 person-years*
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

* adjusted for warfarin use to give theoretical thromboembolism rates without therapy, assuming that warfarin provides a 64% reduction in risk.[144]

In a meta-analysis of 17 studies, the c-statistic for prediction of stroke using CHA_2DS_2-VASc was 0.67 (95% CI 0.64 to 0.70).[158] On the basis of their meta-analysis, the authors suggest that there is little difference between the four scores. At present, CHA_2DS_2-VASc is recommended in national and international guidelines,[126, 167, 168] and is widely used.[169] NICE guidelines state that OAC should be considered in men with a CHA_2DS_2-VASc score of one, and should be offered to men or women with a CHA_2DS_2-VASc of two or more.[140]

1.4.6.3 Assessment of bleeding risk in non-valvular atrial fibrillation

Both ESC and NICE guidelines recommend that bleeding risk should be assessed, and that risk factors for bleeding should be modified alongside a decision to commence OAC, but that a high bleeding risk should not generally result in withholding OAC.[126, 167] Four commonly used scores for estimating bleeding risk in patients taking warfarin and the evidence supporting their use are summarised in Table 7.[170]

Table 7: Risk scores for bleeding associated with warfarin use in patients with AF

Bleeding risk score	Components of score	Cohort	Risk thresholds	Definition of major bleeding
HAS-BLED[171]	1 point each for: Hypertension, abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition, labile INR, age >65 years, concomitant use of antiplatelet or NSAID, alcohol consumption.	Euro Heart Survey n= 3,978 35 ESC member countries	Low: 0–1 Intermediate: 2–3 High: ≥ 4	any bleed requiring hospitalization or causing a decrease in haemoglobin level of 2 g/L or requiring blood transfusion
HEMORR$_2$HAGES[172]	1 point each for: Hepatic or renal disease, alcohol abuse, malignancy, age >75 years, reduced platelet count or function, uncontrolled hypertension, anaemia, genetic factors (CYP 2C9 single-nucleotide polymorphisms), excessive fall risk, stroke. 2 points for: previous haemorrhage	National Registry of Atrial Fibrillation (NRAF), USA n= 3791	Low: 0 - 1 Intermediate: 2-3 High: ≥4	Hospital admission, any site of bleeding

Bleeding risk score	Components of score	Cohort	Risk thresholds	Definition of major bleeding
ORBIT[173] (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)	1 point for: Age ≥75 years; reduced haemoglobin, haematocrit or history of anaemia; bleeding history; renal impairment, and treatment with antiplatelet)	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation 176 sites in USA. n=7411	Low: 0 - 2 Intermediate: 3 High: ≥4:	International Society on Thrombosis and Haemostasis criteria.[218]
ATRIA[174]	Anaemia (3 points), severe renal disease (GFR <30 ml/min or dialysis-dependent, 3 points), age ≥75 years (2 points), prior bleeding (1 point), hypertension (1 point)	Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Northern California, USA n=9,186	Low: 0–3 Intermediate: 4 High: 5–10	Fatal; requiring transfusion of ≥2 units, into a critical anatomic site.

Abbreviations ESC: European Society of Cardiology; GFR: glomerular filtration rate; INR: international normalised ratio; NSAID: non-steroidal anti-inflammatory drug

There are few scores that have been validated in patients that are prescribed a DOAC. One example is the ABC-bleeding score, which was developed as part of a nested prospective biomarker study of 8,705 participants in the ENGAGE AF-TIMI 48, which was a multinational, randomized trial of the oral factor Xa inhibitor edoxaban in patients with AF and $CHADS_2$ score two or more. The score includes age, prior bleeding, haemoglobin, baseline high-sensitivity troponin T, and growth differentiation factor-15.[175] However, the biomarkers tested are not currently in routine clinical use for this purpose, and the score offered limited risk discrimination with a c-statistic of 0.65 in the validation study.[158]

NICE guidelines currently recommend the HAS-BLED score,[167] which was first published in 2010.[171] Two recent meta-analyses have concluded that HAS-BLED has the best evidence for predicting bleeding risk.[158, 176] However, the meta-analyses are limited by the fact that various classification systems for major bleeding were used in the included studies, leading to clinical heterogeneity.

In patients that are unable to take OAC because it contraindicated or not tolerated, a left atrial appendage occlusion device is a potential option, and was formally commissioned by NHS England in June 2018.[177] These devices physically block the connection between the appendage and the left atrium, preventing thrombus the appendage from entering the circulation.

1.4.7 Arrhythmia management in atrial fibrillation

There are two strategies for management of the AF itself. The first is rate control, whereby the presence of AF is ‘accepted’, and arrhythmia modifying drugs such as beta blockers, calcium channel blockers and digoxin are used to moderate the tendency to tachycardia. The second is rhythm control, where the aim is to restore sinus (‘normal’) rhythm.[126, 167] Initial therapies include pharmacological or electrical cardioversion, with the option of longer-term arrhythmia-modifying medication. Should these options be unsuccessful in maintaining sinus rhythm and the patient is symptomatic, more invasive therapy such as pulmonary vein isolation can be considered.[126, 167]

At present, guidelines from the ESC and NICE would suggest a rhythm control strategy only to improve symptoms where a rate control strategy has been unsuccessful.[126, 167] This is supported by evidence that generally there is no mortality advantage to a rhythm control strategy,[178] although there is recent trial evidence that an invasive rhythm control strategy carries a mortality advantage in the specific group of patients with AF and severe left ventricular systolic impairment.[179]

A recent meta-analysis has shown an improved quality of life in patients treated with a rhythm control strategy using the short-form 36-item health survey (SF-36) physical component summary score.[178, 180] However, all of the eight studies included were at high risk of bias, partly due to incomplete blinding.[178] There was no difference in stroke risk between the two groups, and there were more adverse treatment events in the rhythm control group than the rate control group.

1.5 Atrial fibrillation and frailty

This chapter has described the association between AF, mortality, and morbidity including stroke. Whilst OAC is effective in reducing the risk of stroke, it is not prescribed in 45% of patients with a CHA_2DS_2-VASc score of two or more, and would therefore be considered eligible for treatment.[145] Older people, who tend to have the highest baseline risk of stroke, are often not prescribed OAC.[145, 181-183] A possible factor in OAC decisions is frailty, which will form part of the literature review.

Frailty and AF are particularly common in older people, and the two conditions frequently co-exist.[11, 184] However, clinical guidelines tend to focus upon single-organ conditions, and take little account of frailty.[126, 140] Indeed, the absence of applicable guidance may reflect the existing uncertainty as to whether frailty should inform judgements in management of AF and OAC.[185] This uncertainty suggests that shared decision making has an important role. Shared decision making is characterised by a partnership between the patient and clinician, and joint deliberation of therapeutic options based on the knowledge and experience that each brings to the consultation.[186] As the prevalence of AF and of frailty are increasing,[131, 187] and each condition is associated with a substantial burden of

morbidity and mortality,[10, 136] effective management of patients with AF and frailty is of vital importance. This thesis will seek to help address the current lack of evidence in the epidemiology and management of patients with AF and frailty.

1.6 Summary

- Frailty is a condition characterised by decreased physiological reserves and a vulnerability to adverse outcomes from a relatively minor stressor event. It is considered using two main theoretical frameworks: the cumulative deficit and phenotype models.
- There are a range of different measures that can be used to identify frailty, including bedside assessments, scoring systems, and models derived from primary care records.
- Frailty is associated with adverse outcomes, including all-cause mortality and nursing home admission. This has been demonstrated in unselected populations, and also in a number of common cardiovascular conditions.
- Patients with frailty have a different risk and benefit profile for clinical interventions compared to patients without frailty, which should be considered when recommending treatment. How this applies to AF will be investigated in this thesis.
- AF is common and is associated with an increased risk of clinical outcomes including stroke. Guidelines suggest that stroke risk should be estimated using the CHA_2DS_2-VASc score to guide the appropriate prescription of OAC, which can substantially reduce stroke risk.

1.7 Conclusion

In this chapter I have provided a summary of frailty as a concept, and some of the ways that it may be operationalised clinically using frailty measures. The association between frailty and common cardiovascular conditions has been described, followed by a more in-depth exploration of AF. The existing evidence base on frailty and AF will be synthesised in a systematic review of the literature in the next chapter. In Chapter 3 the data sources will be summarised that are available to explore the association between frailty and AF, which will be the focus for the rest of the thesis.

Chapter 2 - Literature review

Atrial fibrillation and older people with frailty:
a systematic review and meta-analysis

2.1 Abstract

Background

Despite a large and growing population of older people with frailty and atrial fibrillation (AF), there is a lack of guidance on optimal AF management in this high-risk group.

Objective

To synthesise the existing evidence base on the association between frailty, AF and clinical outcomes.

Methods

A systematic review of studies examining the association between validated measures of frailty, AF, and clinical outcomes, and meta-analysis of the association between frailty and oral anticoagulation (OAC) prescription.

Results

20 studies (30,883 patients) were included, all observational. Fifteen were in hospital, four in the community, and one in nursing home care. Risk of bias was low to moderate. AF prevalence was between 3% and 38%, and frailty prevalence varied by setting from 6% in a community-based cohort to 100% of patients with AF in a nursing home. In people with AF, frailty was associated with increased stroke incidence, all-cause mortality, symptom severity, and length of hospital stay.

Meta-analysis of six studies showed that frailty was associated with decreased OAC prescription at hospital admission (pooled adjusted OR 0.45 [95%CI 0.22-0.93], 3 studies), but not at discharge (pooled adjusted OR 0.40 [95%CI 0.13-

1.23], 3 studies). A community-based study showed increased OAC prescription associated with frailty (OR 2.33 [95%CI 1.03-5.23]).

Conclusion

Frailty is common, and is associated with adverse clinical outcomes in patients with AF. There is evidence of an association between frailty status and OAC prescription, with a different direction of effect in community compared with hospital cohorts. Despite the majority of care for older people being provided in the community, there is a lack of evidence on the association between frailty, AF, anticoagulation and clinical outcomes to guide optimal care in this setting.

2.2 Introduction

As discussed in Chapter 1, it is increasingly recognised that frailty is a more useful approach to guide care in older people than chronological age,[10] and can help guide more individualised treatments with advancing multi-morbidity and polypharmacy.[219] The prevalence of patients with frailty and AF is growing,[187] making optimal management an important goal for older people, clinicians, health services and social care.[23, 26, 78] However, the optimal treatment strategy for people with AF and frailty is unclear. The objective of this review is to synthesise the existing evidence base on the association between frailty, atrial fibrillation and clinical outcomes, with a particular focus on OAC.

2.3 Methods

The review was conducted according to meta-analysis of observational studies in epidemiology (MOOSE) guidelines, and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[220, 221]

2.3.1.1 Protocol and registration

The review protocol was registered with the international prospective register of systematic reviews (PROSPERO), record number CRD42018092951.[222]

2.3.1.2 Eligibility criteria

Studies that used a measure that is reported within the published literature to identify frailty in populations with AF (permanent, paroxysmal or persistent) or atrial flutter were considered eligible. Reviews, case reports, case series and conference proceedings were excluded. Studies were limited to those in the English language.

2.3.1.3 Information sources

We searched CINAHL, Cochrane, Embase, Medline, and Web of Science from inception of each until October 2017. The search strategy was developed with Mrs Deidre Andre, Research Librarian at the University of Leeds, and is outlined in Table 8.

Table 8: Search strategy for Ovid Medline. Rows combined with 'OR', columns combined with 'AND'

atrial fibrillation/	frail elderly/
atrial fibrillation*.tw.	(frail* or sarcop?eni* or prefrailty).tw.
auricular fibrillation*.tw.	sarcopenia/
atrium fibrillation*.tw.	Geriatric Assessment/
catheter ablation/	"comprehensive geriatric assessment".tw.
atrial ablation*.tw.	(multimorbid* or multi-morbid*).tw.
(electric* adj2 ablation*).tw.	(multidisease? or multi-disease? or (multiple adj (ill* or disease? or condition? or syndrom* or disorder?))).tw.
catheter ablation*.tw.	geriatric syndrom*.tw.
(radiofrequency adj2 ablation*).tw.	cumulative deficit*.tw.
pulmonary vein isolation*.tw.	Phenotype model*.tw.
exp Anti-Arrhythmia Agents/	((Edmonton or Fried) adj5 (index* or indicator* or score* or scale* or tool* or test* or model* or phenotype* or criteri* or marker* or method* or instrument* or assess* or exam* or evaluat* or measure* or screen* or diagnos* or detect* or identif*)).tw.
Atrial Flutter/	(Gait speed* or walking speed* or grip strength*).tw.
atrial flutter.tw.	exp hand strength/
atrium flutter.tw.	("Timed up and go test*" or tugt or gug or "get up and go").tw.
Tachycardia, Ectopic Atrial/	frail elderly/
((atrial or atrium or auricular) adj2 (tachycardia* or tachyarrhythmia*)).tw.	(frail* or sarcop?eni* or prefrailty).tw.
antiarrhythmi*.tw.	sarcopenia/
anti-arrhythmi*.tw.	Geriatric Assessment/
exp Anticoagulants/	"comprehensive geriatric assessment".tw.
anticoagulant*.tw.	(multimorbid* or multi-morbid*).tw.
antithrombotic*.tw.	(multidisease? or multi-disease? or (multiple adj (ill* or disease? or condition? or syndrom* or disorder?))).tw.

Symbols: * = Truncation. This identifies variant endings for the stem word
? = Wildcard. This allows a different character (or no character) to identify variant spellings of words.

2.3.1.5 Study selection

Two independent reviewers (Dr Oliver Todd [OT] and I [CW]) screened titles and abstracts for potentially eligible studies, and assessed full text articles against the eligibility criteria. All disagreements were resolved through consensus. Reasons for exclusion of articles at the full-text review stage were collated using Covidence.[223]

2.3.1.6 Data extraction

Data from the included studies was extracted using a pro forma including author, year of publication, study period, study design, country, setting, patient characteristics (age, sex, prevalence of co-morbidities, ethnicity), frailty measure, AF prevalence and outcomes assessed. Where frailty status was dichotomised, the threshold used by the study author was used. Data for meta-analysis were extracted by two independent reviewers (CW and OT).

2.3.1.7 Outcomes

The primary outcome was OAC prescription by frailty status. Secondary outcomes included: ischaemic and haemorrhagic stroke; all-cause mortality; disability; care home admission; hospitalisation; and haemorrhagic events.

2.3.1.8 Risk of bias in individual studies

The Newcastle-Ottawa checklist was used by two authors (CW and OT) to independently assess risk of bias,[224, 225] with an adapted scale for cross-sectional studies.[226] Studies were assessed on the domains of selection, comparability, exposure and outcome. Studies rated as moderate or good were considered as having low risk of bias.

2.3.1.9 Synthesis of results

Two authors (CW and OT) extracted adjusted odds ratios (ORs) with 95% CIs for dichotomous data. OR for frail vs. non-frail were used; when the reverse was reported by the authors, then an inverse OR was calculated. We synthesised data for meta-analysis by generic inverse variance random-effects modelling summarised as an odds ratio using RevMan 5.3 software.[227] Random effects modelling was selected because we anticipated that the classification of frailty

status may be based on different instruments, and to allow for clinical heterogeneity. Adjusted data were prioritised because they account for confounding variables and are considered more reliable. Unadjusted ORs were not included in the meta-analysis.

2.4 Results

2.4.1 Study selection

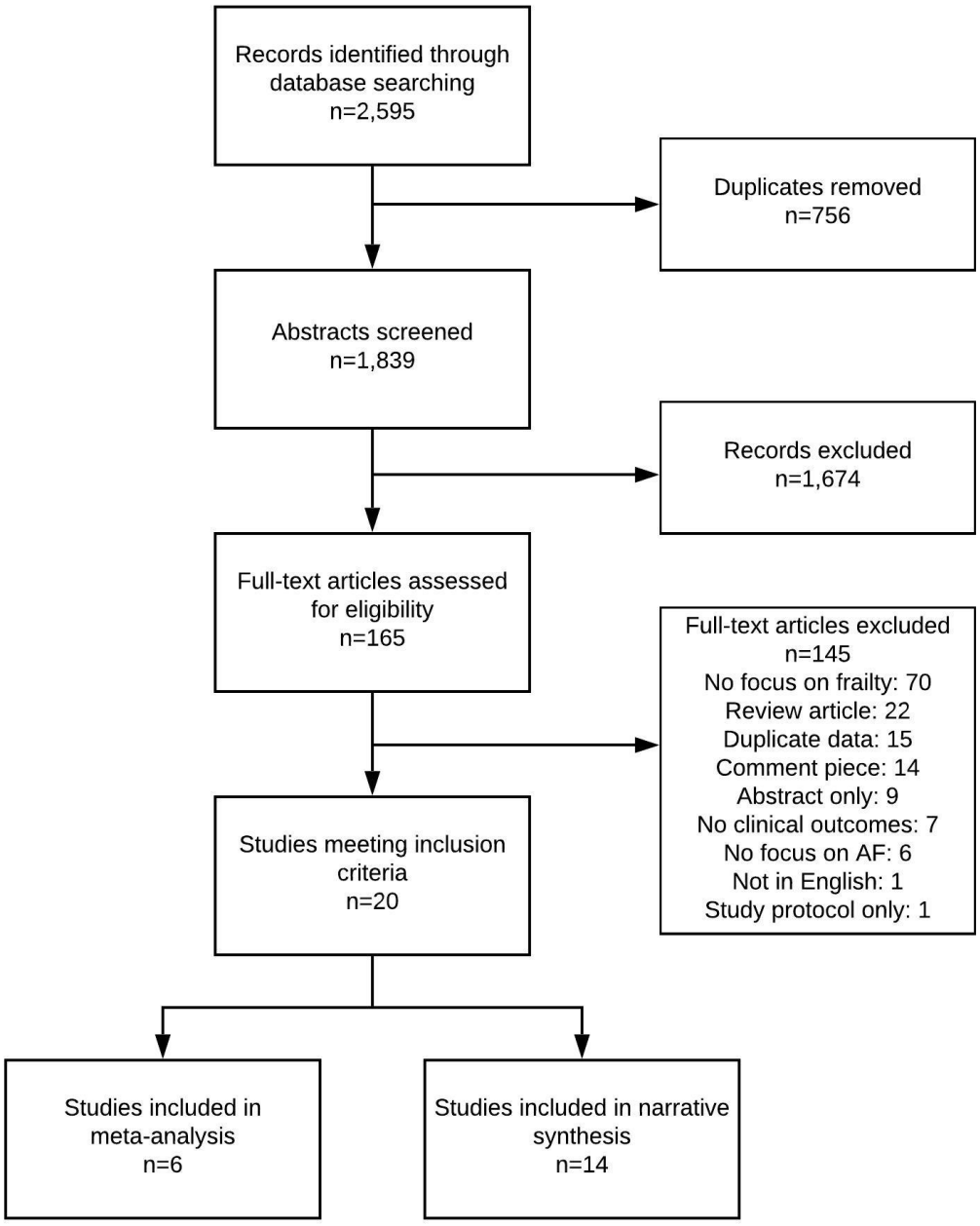


Figure 3: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of the included studies[228]

The review is summarised in Figure 3. The search identified 1,839 studies, of which 165 were retrieved for full-text review. A common reason for exclusion at the stage of full-text review was 'no focus on frailty', which includes studies that were identified because they used the word frailty, but in a different context such as 'shared frailty model', or included the term 'frail elderly' in the abstract, but did not investigate frailty as such. In total, 20 studies met the eligibility criteria and were included in this review; six within a meta-analysis,[181, 190, 193, 197, 210, 212] and fourteen in a narrative synthesis.[1, 189, 191, 194, 198-203, 206, 209, 211, 213] All were observational studies.

2.4.2 Study characteristics

Twelve cross-sectional [189, 190, 193, 197, 198, 200, 202, 203, 206, 209, 212, 213] and eight cohort studies were included,[1, 181, 191, 194, 199, 201, 210, 211] with a total of 30,883 participants, Table 9. 15 studies were based in hospital,[1, 181, 189-191, 193, 194, 197-200, 203, 209-211] and five were community-based,[201, 202, 206, 212, 213] one of which involved nursing home residents.[213] Thirteen studies were conducted in Europe,[1, 189, 191, 193, 194, 197-200, 206, 209, 212, 213] three in Australia,[210, 211, 213] three in North America,[190, 201, 202] and one in Taiwan.[203]

2.4.3 Risk of bias within studies

Overall, the included studies were moderate to low risk of bias, Table 10. The six studies included in the meta-analysis were judged at low risk of bias overall, with risk identified in two studies regarding ascertainment of outcome[181] and follow-up duration.[181, 210] However, these did not relate to the specific meta-analysis question of OAC and frailty associations.

Table 9: Summary of included studies

Study	Setting	Age criteria	Mean [median] age	Country	Measure of frailty	n
Prospective cross-sectional studies						
Bo, 2015 [193]	Hospital	≥65	81.7	Italy	GFI	513
Denoël, 2014 [200]	Hospital	≥75	NR	Belgium	ISAR	995
Donoghue, 2014 [206]	Community	≥50	70.7	Republic of Ireland	GU&G, Gait speed	4525
Frewen, 2013 [166]	Community	≥50	63.8	Republic of Ireland	Fried criteria	4890
Hess, 2013 [202]	Outpatients	≥18	[75]	USA	Fried criteria	10,096
Hung, 2013 [203]	Hospital	≥75	[75]	Taiwan	GU&G	401
Mlynarska, 2017 [209]	Hospital	none	72.7	Poland	TFI	132
O'Caoimh, 2017 [213]	Nursing home	none	[84]	Republic of Ireland	CFS	225
Polidoro, 2013 [198]	Hospital	none	79.3	Italy	Frailty index[37]	140
Retrospective cross-sectional studies						
Annoni, 2016 [189]	Hospital	≥65	84.6	Italy	Robinson criteria [192]	1619
Induruwa, 2017 [197]	Hospital	≥75	85.3	England	CFS	419
Lefebvre, 2016 [190]	Hospital	≥80	85.9	Canada	CFS	682
Prospective cohort studies						
Bo, 2017 [199]	Hospital	≥65	81.6	Italy	GFI	452
Doucet, 2008 [1]	Hospital	>65	84.7	France	GU&G	209
Gullón, 2017 [194]	Hospital	>75	85	Spain	FRAIL scale	804
Magnani, 2016 [201]	Community	70-79	N/A	USA	Health ABC battery	2753
Nguyen, 2016 [210]	Hospital	≥65	84.7	Australia	Reported EFS	302
Nguyen, 2016 [211]	Hospital	≥65	84.7	Australia	Reported EFS	302
Perera, 2009 [181]	Hospital	≥70	82.7	Australia	Modified EFS	207
Retrospective cohort study						
Pilotto, 2016 [191]	Community, previous hospitalisation	≥65	84.4	Italy	MPI	1287

Abbreviations EFS: Edmonton Frail Scale, GFI: Groningen frailty indicator, GU&G: get-up-and-go test, MPI: multidimensional prognostic index, MPI-SVaMA: MPI based on standardized multidimensional assessment schedule for adults and aged persons, NR: not reported, TFI: Tilburg Frailty Index. Further detail in Table 15, page 58.

Table 10: Risk of bias assessment

The Newcastle-Ottawa Scale was used for quality assessment, adapted for cross-sectional studies.[25, 26] A maximum of one star is awarded for each heading under selection and outcome, and two stars under comparability. The total possible is seven stars for cross-sectional studies. Good: ≥5; moderate: 3-4; poor ≤2. For cohort studies, the total possible is nine stars. Good: ≥7; moderate: 5-6; poor ≤4

Cross-sectional studies

	Selection			Comparability	Outcome		Total
	Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Controls and adjusted	Ascertainment of outcome	Statistical test	
Annoni, 2016 [189]	1	1	1	1	0	1	5
Bo, 2015 [193]	1	1	1	2	1	1	7
Denoël, 2014 [200]	1	1	1	2	0	1	6
Donoghue, 2014 [206]	1	1	1	2	1	1	7
Frewen, 2013 [166]	1	1	1	2	0	1	6
Hess, 2013 [202]	1	1	1	2	1	1	7
Hung, 2013 [203]	1	1	1	2	1	1	7
Induruwa, 2017 [197]	1	1	1	2	1	1	7
Lefebvre, 2016 [190]	1	1	1	2	1	1	7
Mlynarska, 2017 [12, 209]	1	1	1	1	1	1	6
O'Caoimh, 2017 [11, 17, 213]	1	1	1	1	0	1	5
Polidoro, 2013 [25, 198]	1	1	1	1	1	1	6

Cohort studies

	Selection			Comparability		Outcome			
	Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Controls and adjusted	Ascertainment of outcome	Was follow-up long enough	Adequate follow-up	Total
Bo 2017[199]	1	1	1	1	2	1	0	0	7
Doucet 2008[1]	1	1	1	1	1	1	0	0	6
Gullón, 2017[194]	1	0	1	1	2	1	1	1	8
Magnani 2016 [201]	1	1	1	1	2	1	1	0	8
Nguyen 2016 [210]	1	1	1	1	2	1	0	0	7
Nguyen 2016 [211]	1	1	1	1	2	1	0	0	7
Perera 2009 [181]	1	1	1	1	2	0	0	1	7
Pilotto 2016 [191]	1	0	1	1	2	1	1	1	8

2.4.4 Participant characteristics

Amongst patients with AF the mean age was 83.3 years (reported in 16 studies[1, 166, 181, 189-191, 193, 194, 197, 198, 203, 206, 209-211]), range 58 to 101 years (6 studies[194, 197, 198, 210, 211]), and 48.2% female (18 studies[1, 181, 189-191, 193, 194, 197-199, 202, 203, 206, 209-213]). Excluding a large registry of outpatients,[202] 56.8% of participants were female.

Eight studies also included patients without AF.[166, 189, 198, 200, 201, 203, 206, 213] The mean age of the whole cohort (those with AF and those without) was 68.5 years (reported in 6 studies[166, 189, 198, 201, 203, 206]), range 56 to 96 (2 studies[198, 206]). 50.3% were female (7 studies[166, 189, 198, 201, 203, 206, 213]), Table 11.

2.4.5 Assessment of frailty

Of the thirteen measures of frailty used, the timed-up-and-go test[56], clinical frailty scale[36], and Edmonton frail scale[51] were most common (3 studies each).

2.4.6 Prevalence of atrial fibrillation

AF prevalence was reported in six studies, but not stratified by frailty status.[189, 200, 203, 206, 212, 213] It varied by setting from 3% in community-dwellers,[206, 212] to 38% in nursing home residents.[213] In three studies of older patients admitted acutely to hospital, AF was identified in 14%,[200] 17%,[203] and 24%[189], Table 11.

Table 11: Summary of participant characteristics in the included studies

			Participants with AF					Whole cohort (those with and without AF)				
Study	Inclusion age	AF prevalence	n	Mean age [median]	SD [IQR]	Range	% female	n	Mean age [median]	SD [IQR]	Range	% female
Annoni [189]	≥65	24.3%	403	84.6	3.2	NR	59.6%	1619	84.1	6.7	NR	59.7%
Bo, 2015 [193]	≥65	-	631	81.7	6.8	NR	55.6%	-	-	-	-	-
Bo, 2017 [199]	≥65	-	513	81.6	6.6	NR	54.9%	-	-	-	-	-
Denoël [a] [200]	≥75	14%	142	NR	NR	NR	NR	995	NR	NR	NR	NR
Donoghue [206]	≥50	3.1%	112	70.7	8.6	NR	21.1%	4525	63.5	8.9	51-89	52.1%
Doucet [1]	≥65	-	228	84.7	7.0	65-100	60.8%	-	-	-	-	-
Frewen [166]	≥50	3%	118	63.8	9.8	NR	46%	4890	63.8	9.8	NR	46%
Gullón [194]	>75	-	804	85	5.1	75-101	53.9%	-	-	-	-	-
Hess[1] [202]	≥18	-	10,096	[75]	[67-82]	NR	42.6%	-	-	-	-	-
Hung [203]	≥75	16.5%	66	82.6	0.6	NR	26%	401	82.2	0.2	NR	24%
Induruwa[b] [197]	≥75	-	419	85.3	5.6	75-101	54.9%	-	-	-	-	-
Lefebvre [190]	≥80	-	682	85.9	4.4	NR	60.4%	-	-	-	-	-
Magnani [201]	70-79	-	N/A[c]	N/A	N/A	N/A	N/A	2753	73.6	2.9	NR	52%
Mlynarska [209]	None	-	132	72.7	6.73	NR	44.7%	-	-	-	-	-
Nguyen [210]	≥65	-	302	84.7	7.1	65-100	50%	-	-	-	-	-
Nguyen [211]	≥65	-	302	84.7	7.1	65-100	50%	-	-	-	-	-
O'Caoimh [213]	None	38%	86	[84]	[78-89]	NR	37%	225	[85]	[77-89]	NR	60%
Perera [181]	≥70	-	220	82.7	6.3	NR	54	-	-	-	-	-
Pilotto [191]	≥65	-	1827	84.4	7.1	NR	64.3%	-	-	-	-	-
Polidoro [198]	None	-	70	79.3	7.5	58-96	59%	140	79.2	7.4	56-96	59%

Abbreviations NR: not reported, N/A: not applicable. a: Author contacted for further information, but they did not respond; b: Author kindly provided additional information for completeness; c: Data reported are from baseline visit. The study reports incident AF.

2.4.7 Atrial fibrillation and frailty

Sixteen studies reported the prevalence of frailty in patients with AF.[181, 189-191, 193, 194, 197-200, 202, 203, 209-211, 213] This varied between populations, affecting 6% in a registry of outpatients aged ≥18,[202] and 100% in a nursing home population,[213] Table 12. In older people admitted to hospital, AF was strongly associated with being frail (adjusted OR 4.09, 95% CI 1.51 to 11.07, adjusted for age, sex, hypertension, diabetes, stroke, myocardial infarction and heart failure).[198]

Hung *et al* found that whilst there was no difference in frailty between those admitted to a geriatric unit with AF and without, AF was an independent risk factor for falls (adjusted OR 1.98 [95%CI 1.08 to 3.63], adjusted for benzodiazepine use, paroxysmal subgroup of AF, hypertension, polypharmacy and age).[203] However, the tendency to fall may have increased AF case-detection through use of ambulatory electrocardiography. Magnani *et al* showed that age-related decline in physical performance in community-dwellers was accelerated by approximately four years for those with AF compared to those without.[201]

Table 12: Reported prevalence and definitions of frailty in included studies

Study	Mean age [median], patients with AF	Frailty definition		Frailty prevalence	
		Measure	Cut-point	Whole cohort	Patients with AF
Annoni [189]	84.6	Robinson criteria [192]	≥4	NR	57.3%
Bo [193]	81.7	GFI	≥4	-	77.5%
Bo [199]	81.6	GFI	≥4	-	75.4%
Denoël [200]	NR	ISAR	≥2	NR	84%
Donoghue [206]	70.7	GU&G Gait speed	Comparison was made between groups with AF and without AF, no threshold was used		
Doucet [1]	84.7	GU&G	Comparison was made between those prescribed OAC and those that weren't.		
Frewen [166]	63.8	Fried criteria	≥1	NR	NR
Gullón [194]	85	FRAIL scale	≥3	-	50.3%
Hess [202]	[75]	Fried criteria	≥3	-	6.0%
Hung [203]	82.6	GU&G	>10 seconds	87%	83%
Induruwa [197]	85.3	CFS	5-8	-	67.3%
Lefebvre [190]	85.9	CFS	≥7	-	25.4%
Magnani [201]	N/A	Health ABC PPB	Scores were compared over time for the same individuals, and the effect of developing AF estimated		
Mlynarska [209]	72.7	TFI	≥5	-	60%
Nguyen [210]	84.7	Reported EFS	≥8	-	53.3%
Nguyen [211]	84.7	Reported EFS	≥8	-	53.3%
O'Caoimh [213]	[84]	CFS	≥5 ≥7*	- -	100% 85.8%
Perera [181]	82.7	Modified EFS	≥8	-	64%
Pilotto [191]	84.4	MPI	≥2	-	61.4%
Polidoro [198]	79.3	Frailty index[37]	0.25	77.9%	88.6%

* Threshold of 5 used by the authors. Results for a threshold of 7 also reported in this table for comparison purposes.

Abbreviations CFS: clinical frail scale, EFS: Edmonton frail scale, GFI: Groningen frailty indicator, GU&G: get up and go, ISAR: Identification of seniors at risk, MPI: multidimensional prognostic index, N/A: not-applicable, NR: not reported, PPB: physical performance battery, OAC: oral anticoagulant, TFI: Tilburg frailty indicator

Table 13: Studies reporting the association between frailty and OAC status

Study	Association: frailty and OAC prescription	Time of assessment	n=	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lefebvre, 2016 [190]	Less use	Hospital admission	682	0.45 (0.31-0.65)	0.29 (0.16-0.54)
Induruwa, 2017 [197]	Less use	Hospital admission	419	NR	0.77 (0.70–0.85)
Perera, 2009 [181]	Less use	Hospital admission	220	NR	0.34 (0.17-0.68)
		Hospital discharge	220	NR	0.12 (0.06-0.23)
Denoël, 2014 [200]	No difference	Hospital admission	142	OR 1.12 (0.50-2.96)	NR
Bo, 2015 [193]	No difference	Hospital discharge	430	NR	0.80 (0.41–1.57)
Nguyen, 2016 [210]	No difference	Hospital discharge	302	0.58 (0.36-0.93)	0.66 (0.40–1.10)
Doucet, 2008 [1]	No difference	Hospital discharge	209	NR	NR
Frewen, 2013 [212]	More use	Community sample	118	NR	2.33 (1.03-5.23)

Abbreviations: NR: not reported, OR: odds ratio. Adjustments are detailed in Table 14, page 57

2.4.8 Atrial fibrillation, frailty and anticoagulation

2.4.8.1 Hospital cohorts

Eight studies were in a hospitalised population with AF, Table 13.[1, 181, 190, 193, 197, 199, 200, 210] Five were methodologically similar, reported adjusted OR for the association between frailty and OAC, and were included in the meta-analysis, Figure 4.[181, 190, 193, 197, 210] Two studies reported OR at admission,[190, 197] and two at discharge.[193, 210] One study reported both.[181]

At hospital admission: Meta-analysis showed that people with frailty had lower odds of OAC prescription than those without frailty (pooled adjusted OR 0.45 [95%CI 0.22 to 0.93].[181, 190, 197] One study reported an unadjusted OR, and was not included in the meta-analysis. This showed no association between OAC prescription and frailty (unadjusted OR 1.12 [0.50 to 2.96].[200] The later was a small study using a brief screening tool with limited predictive validity (Identifying Seniors at Risk).[229]

At hospital discharge: Meta-analysis showed that frailty had no statistically significant association with OAC prescription (pooled adjusted OR 0.40 [95% CI 0.13 to 1.23]).[181, 193, 210] One study used propensity score analysis and whilst it was not included in the meta-analysis, it also found no association between frailty and OAC prescription after matching.[199]

2.4.8.2 Community cohorts

In contrast to the hospital cohorts, a study using a nationally representative community sample found that people with frailty had an increased odds of OAC prescription compared to people without frailty (adjusted OR 2.33 [95%CI 1.03 to 5.23], adjusted for age, sex and education).[166] In a study of nursing home residents with AF and frailty, 70% of participants were eligible for OAC according to a bespoke risk based decision support aid incorporating stroke and bleeding risk.[213] However, just 17% were prescribed OAC. A separate study found that advanced age, very short life expectancy, difficult/impossible management of therapy, fear of bleeding, and harm greater than benefit were commonly reported reasons for not prescribing OAC in older patients.[193]

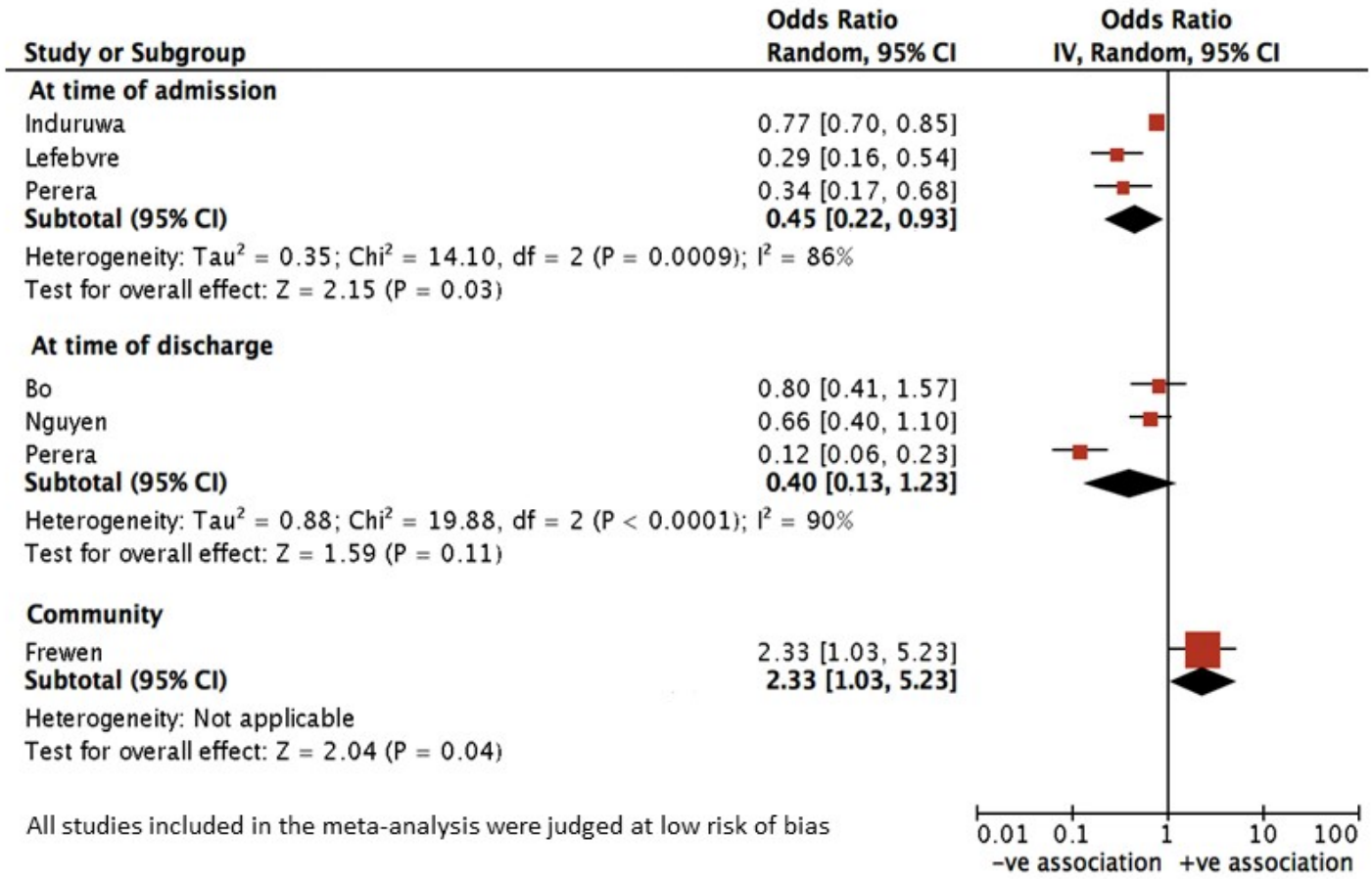


Figure 4: Forest plot to show the association between frailty and anticoagulation status at admission, at discharge, and in the community

2.4.9 Direct oral anticoagulation prescription

Across five studies, DOAC was prescribed in between 5.4% and 20.6% of those anticoagulated.[190, 193, 194, 197, 210] This was stratified by frailty status in one study, but it only included 11 patients on DOAC.[197]

2.4.10 Age, co-morbidity, and oral anticoagulation

Six studies reported the association between increasing age and OAC prescription,[166, 190, 193, 197, 210] five of which adjusted for other factors, Table 14.[166, 190, 193, 197, 210] Increased age was independently associated with reduced OAC prescription in four studies (adjusted OR range 0.71 [0.59 to 0.84] to 0.98 [0.97 to 0.98]),[190, 193, 197, 210] but not in the fifth (adjusted OR 1.02 [0.97 to 1.07]).[166] Finally, a study published in 2008 showed patients prescribed antiplatelet medications instead of OAC tended to be older (mean 86.5 vs 82.9 years, $p<0.01$).[1]

Two studies reported the association between Charlson co-morbidity score and OAC prescription. One showed that an increased adjusted score was independently associated with not being prescribed OAC.[193] The second showed no statistically significant difference in score between those prescribed OAC and those that were not.[200]

2.4.11 Oral anticoagulation and outcomes

One study noted a greater incidence of cardio-embolic stroke among individuals with frailty compared to those without frailty (12.3 vs. 3.9%, $p<0.05$). However, the incident cases of stroke were not stratified by OAC prescription due to a small number of events.[181] Patients with AF and frailty also had a higher six-month mortality compared to those with AF without frailty (unadjusted RR 2.8 [95%CI 1.2 to 6.5]).[181] Nguyen *et al* showed no difference in stroke or major bleeding by frailty status in patients with AF, which the authors suggest may be related to careful patient selection and OAC management.[210]

Doucet *et al* found no difference in clinical outcomes (stroke, death, major bleeding) at 3 months between patients with AF who were prescribed OAC compared with an antiplatelet.[1] The prevalence of falls post-discharge was

higher in the aspirin compared to the OAC group (18.6% vs. 7.5%, p<0.02) despite similar pre-admission falls history. This may suggest that clinicians were aware of an increased falls risk in these individuals that was not captured by the study. Physicians tended to overestimate the risk of bleeding, and underestimate the risk of thrombosis compared with objective scores.

2.4.12 Frailty and mortality in atrial fibrillation

Three studies report the association between frailty and mortality in patients with AF. However, the different representations of risk and durations of follow-up did not allow pooling for meta-analysis. Perera *et al* identified increased mortality in patients with AF and frailty compared to patients with AF but not frailty (unadjusted RR 2.8 [95%CI 1.2 to 6.5]).[181] Nguyen *et al* report increased six-month mortality associated with frailty, (adjusted HR 2.33 [95%CI 1.31 to 4.14], adjusted for age, gender, comorbidity, $CHAD_2DS_2$-VASc, HAS-BLED, delirium, OAC, digoxin or psychotropic medication) and that length of stay was 3.1 days longer in individuals with frailty compared to those without.[211] During a mean follow-up period of 301 days Bo *et al* found that in patients with AF, frailty was associated with an increased risk of mortality compared to non-frail patients (adjusted OR 2.77 [95% CI 1.44 to 5.33], adjusted for OAC, ADL dependence, serum albumin and readmission).[199] A further study found that functional status, but not frailty (FRAIL scale), was independently associated with inpatient mortality.[194]

2.5 Discussion

This systematic review included 20 research articles. Although the search period commenced at the inception of each included database, the articles that met the inclusion criteria were published between 2013 and 2017. Six studies were included in a meta-analysis of the association between frailty status and OAC prescription in patients with AF. At hospital admission frailty was associated with decreased OAC prescription, but there was no statistically significant association at discharge. A community-based study found that frailty was associated with increased OAC prescription.

We report evidence that in patients with AF, frailty is associated with increased stroke incidence,[181] medium-term mortality,[181, 211] symptom severity,[209] and length of hospital stay.[211] One study showed frailty was not associated with stroke or major bleeding.[210] Having AF was associated with a greater chance of being frail, [198] having falls,[203] and physical performance decline[201] compared to people without AF, suggesting that AF itself may be a marker of frailty. There was a lack of data on clinical outcomes stratified by both frailty and OAC status.[1, 181, 210]

The different association between frailty and OAC prescription among hospital and community cohorts was striking. The findings at hospital admission are reflective of prescribing patterns in the community, albeit in a subgroup who have been hospitalised, with potential for different characteristics. The absence of a statistically significant association between OAC prescription and frailty status at discharge may be because hospitalisation allowed more complete case ascertainment and prescription of therapy. However, survivorship bias is also a potential factor, whereby fitter patients are more likely to survive to discharge. Furthermore, hospitalisation in the context of frailty is a potential marker of nearing end of life, so de-prescribing decisions could be influenced accordingly.[230]

In a community study with a relatively young population and low AF prevalence, frailty was associated with an increased OAC prescription rate.[166] In contrast, in a nursing home population with a relatively high prevalence, just 25% of the eligible population were prescribed OAC.[213] Competing risks are likely to be influencing prescribing behaviour in this vulnerable population.

There are concerns that clinical guidelines tend to relate to single-organ pathology,[23, 219] and the trial evidence on which they are based frequently excludes people with frailty, including of DOACs.[149-152] Furthermore, CHA_2DS_2-VASc has not been validated for use in the oldest old or people with frailty.[231] In the absence of trial evidence, observational data can offer insights into current practice and patient outcomes. However, this review identified a lack of research in a community setting using validated frailty measures, despite growing evidence that a greater mortality risk is carried by measures of

biological than chronological age.[10, 11] There is therefore a limited evidence base to guide management in this high-risk population in whom bleeding complications may be more common and more problematic than in the general population.[232, 233] A risk-treatment paradox exists, whereby those at the highest risk of stroke are not more likely to receive anticoagulation.[183, 234] Whether frailty should influence OAC prescribing, including through incorporation into AF decision-support tools, is currently unknown.

2.5.1 Strengths of the review

To my knowledge, this is the first systematic review to summarise current evidence for the management of AF in older people with frailty. We have used a robust search strategy, risk of bias assessment and methods pre-specified in a published protocol. We were able to present pooled adjusted estimates of the association between OAC prescription and frailty, and included data on DOAC use, reflecting recent prescribing trends. However, the small proportion of patients that were taking DOAC in the included studies despite its increasing role reinforces the need for contemporary research.[235]

2.5.2 Limitations of the review

A range of frailty measures were used and frailty status was dichotomised as in the source studies. This may have introduced additional clinical heterogeneity in the meta-analysis. This, in combination with the relatively low number of participants in the included studies (ranging from 118 to 682 participants) as well as variation in the confounders used between the studies is likely to have contributed to the high measure of statistical heterogeneity (I^2 greater than 80%). Therefore, the estimates should be interpreted with a degree of caution. We have reported adjusted and unadjusted estimates where available, and importantly these show similar direction of associations.

Whilst we have reported OAC prescription at different time points, this was without access to individual patient data, so we cannot exclude misclassification error. Frailty was often diagnosed in an acute hospital setting, although guidance suggests frailty assessment is best performed in the community.[24] Most studies excluded patients with cognitive or major sensory impairment due

to the necessity for informed consent, and so may not be representative of the overall frail population. Some studies required participants to complete a physical task, which may exclude those with advanced frailty.

As with any meta-analysis of observational data there are risks of confounding by indication and other systemic biases that are incompletely accounted for. Further observational data in a community setting with complementary qualitative work would contribute to our understanding of current practice, but with susceptibility to bias. A randomised trial may ultimately be needed to help quantify efficacy and safety endpoints in a frail population.

2.6 Conclusion

At hospital admission frailty was associated with decreased OAC prescription. However, there was no statistically significant association at the time of discharge. A single study in a community setting showed that frailty was associated with increased OAC prescription. There is evidence that in patients with AF, frailty is associated with increased stroke incidence, mortality, symptom severity, and length of hospital stay. There was a lack of evidence with which to evaluate the impact of frailty on the association between OAC prescription and clinical outcomes.

Although anticoagulation is largely initiated and managed in primary care, there is a lack of evidence to guide optimal care in this setting for patients with AF and frailty. This may in part explain a gap between current guidelines and clinical practice in management of these patients, particularly in relation to OAC prescription.

Table 14: Adjustments in studies reporting association between frailty and OAC status

Study	Association: frailty and OAC use	Time of OAC	n=	Estimate (95% CI)	Adjustments
Lefebvre, 2016 [190]	Less use	Inpatient	682	OR 0.29 (0.16-0.54)	Falls history, $CHADS_2$ score, bleeding risk, age, length of hospital stay, use of antiplatelet agents or medication that increases bleeding risk)
Induruwa, 2017 [197]	Less use	Admission	419	OR 0.77 (0.70–0.85)	Age, sex, and the components of CHA_2DS_2-VASc and HAS-BLED
Perera, 2009 [4, 181]	Less use	Admission	220	OR 0.34 (0.17-0.68)	Age, CCS, Gender, herbal medications, admission ward, nutritional status number of medications, MMSE, Katz Daily Living Score, alcohol use, excessive falls risk, anaemia, previous adverse reaction to warfarin, previous adverse reaction to aspirin, previous haemorrhagic stroke, malignancy, reduced platelet count, previous major bleeding episode, uncontrolled hypertension, age > 75 years, diabetes mellitus, hypertension congestive heart failure, prior stroke
		Discharge	220	OR 0.12 (0.06-0.23)	
Denoël, 2014 [200]	No difference	Admission	142	OR 1.12 (0.50-2.96)	Unadjusted
Bo, 2015 [193]	No difference	Discharge	430	OR 0.80 (0.41–1.57)	Age, AF subtype, CHA_2DS_2-VASc, HAS-BLED, CCI, ADL dependence, cognitive impairment, depression, malnutrition, discharge to a facility
Bo, 2017 [199]	No difference	Discharge	452	N/A	Propensity score analysis using a 1:1 nearest-neighbour-matching algorithm
Nguyen, 2016 [210]	No difference	Discharge	302	OR 0.66 (0.40–1.10)	Age, history of bleeding/ predisposition to bleeding and abnormal renal function, congestive heart failure
Doucet, 2008 [1]	No difference	Discharge	209	N/A	Simple comparison between groups, no adjustment
Frewen, 2013 [10, 11, 13-16, 212]	More use	Community (TILDA)	118	OR 2.33 (1.03-5.23)	Age, sex and education

Abbreviations ADL: Activities of Daily Living, CCS: Charlson Comorbidity Score, CFS: Clinical Frail Scale, EFS: Edmonton Frail Scale, GFI: Groningen Frailty indicator, ISAR: Identification of Seniors at Risk, OAC: Oral Anticoagulant, OR: odds ratio, TILDA: The Irish longitudinal study on ageing.

Table 15: Summary of included studies

Study	Study type	Study population	Age criteria	Centres	Country	Frailty measure	n	Summary
Annoni 2016 [189]	Retrospective cross-sectional	Consecutive admissions to acute geriatric unit	≥65	1	Italy	Robinson criteria [192]	1619	AF prevalence 24.9%. 86% of those with AF were frail or pre-frail. Those with AF had more comorbidities and medications.
Bo 2015 [193]	Prospective cross-sectional	Admissions with AF to internal medicine	≥65	3	Italy	GFI	513	78% were frail. 49% were on OAC at discharge. Age and co-morbidities were independently associated with lack OAC; frailty was not. Common reasons for not anticoagulating: advanced age, life expectancy, difficult management of therapy, perceived fear of harm including bleeding.
Bo 2017 [199]	Prospective cohort	Discharges with AF	≥65	3	Italy	GFI	452	33% of patients died within mean follow-up of 301 days. OAC prescribed at discharge in 50%, and was associated with decreased mortality and ischaemic stroke. After propensity matching, frailty status was not associated with OAC use.
Denoël 2014 [200]	Prospective cross-sectional	Consecutive admissions to ED with AF.	≥75	1	Belgium	ISAR	995	AF prevalence 14%. OAC was guideline-recommended for 71%, and prescribed in 61%. OAC use not associated with $CHADS_2$ score or geriatric characteristics.
Donoghue 2014 [206]	Prospective cross-sectional	Mobile, community-dwelling participants in the TILDA study	≥50	N/A	Republic of Ireland	GU&G Gait speed	4525	AF prevalence 3.1% overall, 4.7% aged >70. AF independently associated with slower TUG and usual gait speed. Adults with AF at age 70 walked 3.8 cm/s more slowly than those without. The difference increased with age, and persisted after adjustment.

Doucet 2008 [1]	Prospective cohort	Consecutive admissions with AF	>65	2	France	GU&G	209	49% discharged on OAC, the rest on aspirin. Physicians overestimated bleeding and underestimated thrombosis risks. There was no difference in GU&G scores between the groups, or in stroke, haemorrhage or death at 3 months.
Frewen 2013 [166]	Prospective cross-sectional	Mobile, community-dwelling participants in the TILDA study	≥50	N/A	Republic of Ireland	Fried criteria	4890	AF prevalence 3%. 41% on OAC if CHA_2DS_2-VASc ≥2 OR for non-treatment with OAC associated with frailty 0.43 (95%CI 0.19-0.96).
Gullón 2017 [194]	Prospective cohort	Inpatients with NVAF	>75	64	Spain	5 item FRAIL scale	804	50% were frail. Frailty was not independently associated with mortality, but total dependency was – OR 4.73 (2.32-9.63) All-cause in-hospital mortality 10%.
Hess 2013 [202]	Prospective cohort	Outpatients in registry	≥18	174	USA	Health ABC physical performance battery	10,096	Frailty was significantly associated with not receiving evidence based therapy for co-morbidities, OR 0.75 (0.59-0.95).
Hung 2013 [203]	Prospective cross-sectional	Admissions to geriatric unit	≥75	1	Taiwan	GU&G	401	71.2% of patients with AF had a history of falls. AF was an independent risk factor for falls, OR 1.98 (1.08-3.63).
Induruwa 2017 [197]	Retrospective cross-sectional	General medical admissions with AF.	none	1	England	CFS	419	51% were not on OAC. Frailty was an independent predictor for non-use of OAC, OR 0.77 (0.70-0.85).

Study	Study type	Study population	Age criteria	Centres	Country	Frailty measure	n	Summary
Lefebvre 2016 [190]	Retrospective cross-sectional	Admissions with AF	≥80	3	Canada	CFS	682	70% on OAC, 20.6% of these with DOAC. Compared with severely frail patients, non-frail to moderately frail had adjusted OR for OAC 3.41 (1.84-6.33). $CHADS_2$ score was positively (and HAS-BLED negatively) correlated with OAC
Magnani 2016 [201]	Prospective cohort	Community based cohort receiving Medicare Two cities.	70-79	N/A	USA	Health ABC physical performanc e battery	2753	There was an accelerated progressive decline of physical performance in cohort participants with AF compared with those without. AF appears to be a marker of frailty that is associated with exacerbated decline.
Mlynarska 2017 [209]	Prospective cross-sectional	Inpatients with AF	none	1	Poland	TFI	132	60% were frail. Frailty was associated with a lower acceptance of AF diagnosis and a greater reported intensity of symptoms.
Nguyen 2016 [210]	Prospective cohort	Inpatients with AF	≥65	1	Australia	Reported EFS	302	53% were frail. 51% of whole cohort on OAC, but use not independently associated with frailty. Greater use of digoxin in frail people (34.7% vs 23% p0.03), but not in other anti-arrhythmic use. No difference in bleeding or stroke by frailty.
Nguyen 2016 [211]	Prospective cohort	Inpatients with AF	≥65	1	Australia	Reported EFS	302	Adjusted HR for mortality associated with frailty 2.33 (1.31-4.14). LOS longer in the frail, 14.1 vs 11 days, p0.002. No difference in readmissions by frailty.
O'Caoimh 2017 [213]	Prospective cross-sectional	Frail NH residents.	none	4	Republic of Ireland	CFS	225	AF prevalence 38%. All had CHA_2DS_2-VASc ≥2. 17% were anticoagulated, but a risk based decision support aid suggested that 70% should be.
Perera 2009 [10, 13, 181]	Prospective cohort	Inpatients with AF	≥70	1	Australia	Modified EFS	207	63% were frail, and this was negatively associated with OAC use. Increased likelihood of death or embolic stroke with in the frail, but not stratified by OAC status.

Pilotto 2016 [191]	Retrospective cohort	Community-dwelling adults with previous hospitalisation for AF	≥65	N/A	Italy	MPI	1287	44% on OAC. Tended to be younger, with better cognitive status and MPI-SVaMA. Overall mortality reduction with warfarin regardless of MPI-SVaMA group, HR 0.6 (0.6-0.7) over mean 2 year follow-up.
Polidoro 2013 [198]	Prospective cross-sectional	Consecutive admissions to geriatric unit.		1	Italy	Frailty index[37]	140	AF was associated with frailty status, OR 4.09 (95%CI 1.51-11.07). The authors suggest that AF could be a useful marker of frailty.

Abbreviations
AF: atrial fibrillation, DOAC: direct oral anticoagulant, ED: emergency department, EFS: Edmonton Frail Scale, GFI: Groningen frailty indicator, GU&G: get-up-and-go test, LOS: length of stay, MPI: multidimensional prognostic index, MPI-SVaMA: MPI based on standardized multidimensional assessment schedule for adults and aged persons, NH: nursing home, NVAF: non-valvular AF, OR: odds ratio, TFI: Tilburg Frailty Index, TILDA: the Irish longitudinal study on ageing

Chapter 3 - Potential electronic health record data sources

3.1 Introduction

Clinical record keeping is central to safe and effective patient care at an individual level, but the secondary use of these routinely collected data for research has the additional potential to improve patient care for the population.

The use of large observational datasets for research may significantly add to current understanding of the epidemiology and clinical outcomes of patients with a wide range of conditions. The large number of participants, long follow-up duration and broad inclusion criteria are advantages, and may complement knowledge gained from clinical trials, which tend to be more restricted in scale and in the participants that are included.[236] Observational data may allow researchers to evaluate 'real world' experience, generate hypotheses, and develop an understanding of the associations between exposures and outcomes.[237, 238] However, care must be taken to consider confounding and other forms of bias, and due regard given to governance and consent.[239] The increasing use of routinely collected health and social care data in observational research presents a particular opportunity for research involving older people, who tend to be under-represented in randomised controlled trials and other types of research.[240]

The quantitative analysis in this thesis will use routinely collected electronic health record (EHR) data from primary care, supplied by ResearchOne. This chapter will provide a summary of the EHR data sources with potential to address the research questions of the thesis, followed by a discussion of the definitions and code lists that are needed to make use of EHR for research purposes.

3.2 Electronic health records

Examples of EHR data sources that are available to researchers in the UK are shown in Figure 5.[241]

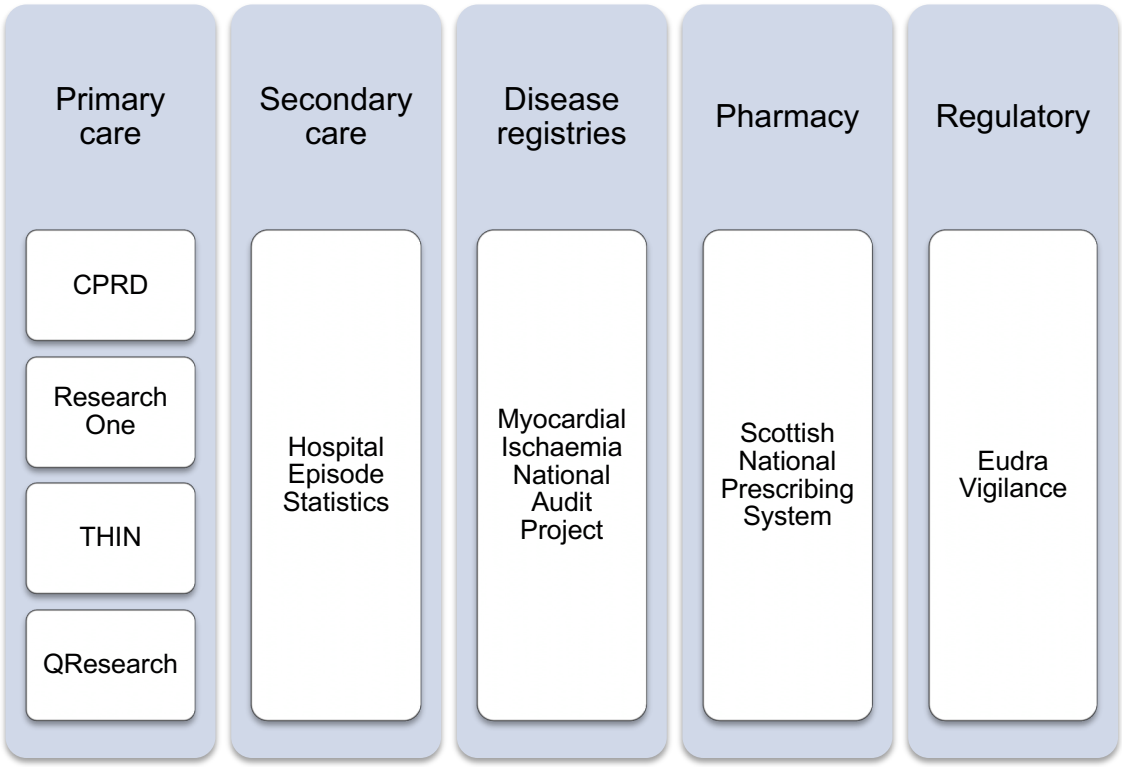


Figure 5: Examples of electronic health records available in the UK

Abbreviations CPRD: Clinical Practice Research Datalink; THIN: The Health Improvement Network.

Primary care databases have the advantage of holding relatively comprehensive longitudinal clinical data from a large, unselected population. The datasets are likely to be representative of the overall population, but in the absence of linkage to another source may under-represent secondary care diagnoses, and may lack data resolution.[242] Other data sources may hold high resolution data for a very specific and single-issue remit, such as EudraVigilance, which is the system for managing and analysing information relating to adverse drug reactions operated by the European Medicine Agency.[241]

Disease registries contain highly detailed information relevant to the particular condition of interest, but are not representative of the overall population that have not been diagnosed with that condition. As clinical data sources are

increasingly computerised, patient-level datasets are being linked across traditional boundaries of care services, which also allows more robust and comprehensive ascertainment of exposures and outcomes from across secondary care and some disease registries.[243]

Whilst the availability of EHR has benefits to researchers, concerns have been expressed by patients and clinicians regarding the governance and consent arrangements for this secondary use of EHR, and it has been suggested that these concerns may prove to be a barrier to further implementation.[239] In particular, there are risks of patient privacy violations associated with data breaches.[238, 244] However, the impact of these is mitigated in the research arena by the use of anonymised or pseudonymised datasets and stringent data security policies.[243, 245-247] In fact, it may be that the greater risk to confidentiality is from inappropriate access of identifiable patient records in the clinical environment,[248] rather than from research breaches. A summary of primary care, secondary care, and registry datasets will now follow.

3.2.1 Primary care datasets

There are over 300 million consultations annually in primary care in the UK,[249] and 96% of practices have been using EHR since 1996.[250, 251] The use of EHR has a range of advantages including improved quality of care, guideline adherence, and financial efficiencies.[244] This huge repository of data has also allowed a proliferation in research using EHR in recent years. Indeed, publications using three large primary care databases have increased at an annual rate of 18.7% over twenty years.[252]

Despite differences in the coding and structure of different primary care datasets, there is evidence that analyses can be externally validated across databases with differences in population characteristics, data definitions, recording, quality and completeness having only a minimal impact on findings.[253] Examples of international datasets include the Information System for the Development of Primary Care Research database, which includes records representing 80% of the Catalan population,[254] and the Snow Agent surveillance system for infectious diseases in Norway,[255] amongst others.[256] In

the UK, there are four key primary care datasets for research, and each will be briefly outlined below.

3.2.1.1 ResearchOne

This research database is derived from the TPP SystmOne clinical database.[257] SystmOne holds the health and care records of over 26 million patients, and these are made available within the ResearchOne database if healthcare providers 'opt-in' to making pseudonymised records available for research. Individual patients have the right to 'opt-out'. The eFI was developed using ResearchOne, and validated using the THIN database.[11] The ResearchOne database will be discussed in detail in section 4.4.

3.2.1.2 Clinical Practice Research Datalink (CPRD)

The research service CPRD is a governmental, not-for-profit organisation. They provide research access to two main primary care research databases, CPRD GOLD and CPRD Aurum.[243] The databases contain data from two different clinical computing systems, and are offered separately due to differences in the structure and coding of the data between the two. Both databases offer routine data linkage with Hospital Episode Statistics (HES), death registration data from the Office for National Statistics (ONS), Mental Health Dataset and deprivation scores. Access to patient-level datasets is provided for research following protocol approval from an independent scientific advisory committee.

The current iteration of CPRD built upon previous databases, the Value Added Medical Products dataset (established in 1987), and subsequently the General Practice Research Database (established in 1993), which expanded to become CPRD in 2012.[258] CPRD GOLD contains data contributed by 674 general practices in the UK that use Vision® software. In 2015, there were 4.4 million patients that were alive and registered in CPRD GOLD with records that meet their quality criteria (approximately 6.9% of the UK population).[258] CPRD Aurum contains data contributed by practices using EMIS Web® software. They provide anonymised primary care records from 738 general practices (10% of practices in England), with EHR from over 19 million patients. Of these, seven million are alive and currently contributing (13% of the population of England).[259]

3.2.1.2.1 Clinical research using LInked Bespoke studies and Electronic health Records (CALIBER)

The CALIBER programme was established in 2012, and provides linkage of CPRD data with multiple other EHR sources, including MINAP, secondary care data, and cause-specific mortality.[247] The programme are also developing links between datasets such as UK Biobank and MINAP to support bespoke investigator-led cohort studies. All projects must be approved by the CPRD Independent Scientific Advisory Committee. The CALIBER programme hold EHR of 10 million patients, but the specific numbers for each dataset are not published.

3.2.1.3 The Health Improvement Network (THIN)

Like CPRD GOLD, the THIN database collects data from practices that use Vision® software dating back to 1987 in some cases.[260] Patients may appear in either or both research database. In 2012, it was found that of 781 practices that were submitting data to CPRD or THIN, 41.9% (327) submitted data to both.[260] The THIN database contains anonymised primary care records from 562 general practices covering 6.5% of the UK population.[245] It currently holds the EHR of 11.1 million patients, of whom 3.7 million are active. Data from THIN are linked with postcode based socioeconomic and environmental indicators, and are increasingly being linked with secondary care datasets, but the proportion of records in which linked data are available is not reported.[260]

3.2.1.4 QResearch

QResearch was developed as a collaboration between the University of Nottingham and the primary care software company Egton Medical Information Systems (EMIS).[260] It is now a not-for-profit collaboration between the University of Oxford and EMIS. QResearch contains pseudonymised health records of over 30 million patients across 1500 general practices using the EMIS clinical computer system.[246] The entire database has been linked to cause of death data, cancer and hospital data at individual patient level, and data linkages extend back to 1993. Data are available to researchers following protocol approval by the data controller for QResearch and the linked datasets, supported by the advice from a Scientific Advisory Committee.[246]

3.2.2 Secondary care datasets

Historically, uptake of EHR in secondary care has lagged behind primary care. However, hospital records are increasingly being computerised.[250] As in primary care, the original purpose of data collection is often for another purpose such as clinical administration or audit, but datasets are increasingly available for research, and may be linked to general practice records.[247] Using secondary care datasets alone would miss patients that were not admitted to hospital.

3.2.2.1 Hospital Episode Statistics

Hospital Episode Statistics (HES) is a data warehouse containing data of all admissions, outpatient appointments and attendances at accident and emergency in NHS hospitals in England. Each HES record includes clinical, demographic, administrative and geographical information. The clinical information comprises of primary and secondary diagnoses, coded using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) by hospital coding departments.[261, 262] HES are collected predominantly to enable healthcare analysis for the NHS, government, statutory bodies, and providers. However, data extracts can be obtained for research use from the NHS Digital Secondary Use Service.

3.2.3 Clinical registry data

Clinical registries are often designed to collect data for the evaluation of disease-specific care and outcomes. Registry data tend to be prospectively acquired which has advantages in terms of reliability, and includes variables that are considered relevant to the particular condition of interest. However, registries are potentially subject to selection bias. For example, there is evidence that there is under-reporting of myocardial infarction in MINAP compared with general practice records from CPRD and HES,[242] and patients that are not included may be systematically different from those that are.[263]

A recent systematic review identified 15 registries of patients with AF, with a wide range of different designs, inclusion criteria and duration of follow-up.[264] One example is the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF), which is a large, industry-funded registry of patients with a

new diagnosis of non-valvular atrial fibrillation, and aims to evaluate the management and outcomes of those with an indication for OAC.[265] 57,262 patients from 1048 centres in 35 countries worldwide were recruited over five sequential cohorts between December 2009 and August 2016. Follow up is planned of between two- and eight-years following diagnosis.

The TuRkish Atrial Fibrillation cohort is a population-based, whole-country cohort of patients with AF, extracted from a health insurance database in Turkey.[266] It was the first cohort of its kind, and aims to study patterns, causes and impact of therapy on AF incidence and outcomes.

The Guidance on Risk Assessment in Stroke Prevention for Atrial Fibrillation (GRASP-AF) tool was developed by PRIMIS, which is a part of the School of Medicine at the University of Nottingham. It is incorporated into general practice computer systems to aid clinicians in case-finding and care management, in particular by identifying patients with possible or probable AF in whom it calculates an estimated stroke risk using CHA_2DS_2-VASc. The tool also identifies patients that are potentially eligible but not currently prescribed OAC, and estimates the number of strokes across the general practice list that may potentially be preventable by instigating OAC. The tool assists practices with providing evidence of compliance with the Quality Outcomes Framework, and data that is useful for comparison of performance between practices and clinical commissioning groups.[145, 267]

3.2.4 Data definitions in electronic health records

Information in EHR are commonly coded rather than kept as free-text. Coding offers greater consistency, and makes data storage and analysis more efficient. In clinical practice, free-text data may be available alongside the coded data, which provides additional context. However, in EHR research this ‘free text’ data is often not available, and if it is available then it is challenging to analyse at scale. Clinical coding structures tend to be based upon internationally accepted classifications, such as the World Health Organisation’s International Classification of Diseases, currently in version 11 (ICD-11),[262] which is commonly used for coding clinical data in secondary care. Clinical coding within primary care will now be discussed.

3.2.4.1 Read codes

In 1986, Dr James Read published his innovative system of using hierarchical four-byte codes for clinical coding.[268] Subsequent iterations were Clinical Term Versions 2, and then 3. In 2002, CTV-3 was merged with the College of American Pathologists' Systematized Nomenclature of Medicine Reference Terminology (SNOMED RT) to create SNOMED Clinical Terms (SNOMED CT), which has now replaced previous versions in much of the UK.[251, 268, 269]

The Read clinical classification was purchased by the UK Department of Health in 1990, which gave the opportunity for comprehensive and standardised clinical coding.[270] This has brought benefits for clinical care including by identifying patients with a particular condition for clinical review and enabling a concise summary of their past medical history. There are also population level benefits, such as estimating the burden of a particular disease in a local area, and clinical coding has also been used in establishing remuneration for clinical practice that is in line with NHS England objectives set out in the Quality Outcomes Framework.

Coded primary care records have also allowed a proliferation of research making secondary use of these data. Whilst researchers have often used clinical codes, advances in machine learning are allowing increasingly sophisticated uses to be made of data that were difficult to clean and utilise at scale for research, such as free text, in a rapidly advancing field of 'deep learning'.[271]

3.2.4.2 Code-lists

One challenge associated with clinical coding is the large number of potential codes for a phenotypically similar entity. For example, AF could be coded as G5730 - AF; Xa7nl - controlled AF; X202R - lone AF, among others. This has implications for the reproducibility of research, as there is the potential for large variation in the clinical codes that are included or excluded for any given diagnosis, investigation, result or observation.

Many publications that use EHR have published their code-lists, which is important for scrutiny and reproducibility of research. Open-access repositories

of code-lists have also been developed, including through CALIBER.[247] However, these are currently not available for CTV-3 codes, which is the coding structure used in ResearchOne. In the absence of a universally accepted set of codes that can be used to define a particular condition, there have been efforts made to increase the rigour of decision making processes using a rule-based phenotyping framework to develop and validate code-lists through consensus.[272]

Ultimately, research datasets are reliant on the coding practices at the source of the data, which can be suboptimal. For example, in a cross-sectional analysis, a large proportion of heart disease events recorded in EHR were coded used terms that did not distinguish between angina and myocardial infarction, and that the use of more non-specific codes appeared to be increasing over time.[273] This poses a challenge for researchers using EHR, where more specific clinical information is often required to reach meaningful conclusions. Using linked datasets has the potential to increase the sensitivity and specificity of primary care records, for example through linkage to a disease specific registry, death certificate information or hospital admissions data.[242]

Regardless of the source of the code-lists, it has been suggested that case definitions are reported transparently, and that researchers should consider undertaking a sensitivity analyses using different sets of clinical codes.[273] There is scope for an increased transparency of reporting of code-lists. In a representative sample of 450 papers published using EHR data, only 19 (5.1%) were accompanied by a full set of published clinical codes.[274]

3.3 Summary

- Primary care electronic health records allow for breadth of data across a large and representative population, but may under-report diagnoses made in secondary care.
- Datasets linked between primary and secondary care are increasingly available.
- There are four key primary care research databases available in the UK: ResearchOne, CPRD, THIN and QResearch.
- There are multiple different clinical coding structures. Within the coding structure, code-lists are required to define each condition, investigation, observation and test of interest. These are integral to the validity of the research, and there is an increasing focus on transparency of code-lists.
- At present, there is no code-repository for CTV-3 codes.

3.4 Conclusion

A range of data sources are available for EHR research in patients with AF. Registry data would have the advantage of high-resolution data that is highly specific to AF, but would have limited generalisability to the overall population. Secondary care data is limited to patients that have required hospital admission, and information about that admission. Importantly, neither of these sources include routine ascertainment of frailty status. Primary care data was selected for use in this thesis, as it is representative of the community-dwelling population, has breadth of data that enables estimation of frailty status using the eFI, and contains detailed information on repeat prescriptions. These three factors are integral to meeting the aims and objectives of this thesis, which were informed by the literature review.

Chapter 4 - Development of the research cohort data set

4.1 Chapter introduction

The quantitative analysis in this thesis was based upon an extract of patients aged 65 years or older from ResearchOne, a national, primary care based dataset. The aims were to establish the prevalence of AF and frailty; describe the clinical characteristics of people with AF at different levels of frailty; to identify whether prescription of OAC differs by frailty category in people with AF; and to determine whether frailty modifies the association between OAC use and clinical outcomes. The focus of this chapter will be the dataset, the extract that formed the analytical cohort, the selection of the variables that were studied, and data cleaning and coding. The analytical methods will be detailed in Chapter 5.

4.2 Chapter summary

The electronic health records of all patients aged 65 years or older on the 31st December 2015 who were in the ResearchOne database were included in this retrospective cohort study. The initial data extract consisted of 115.4 million rows of data, with clinical information mostly held in CTV-3 codes. Code-lists were developed to identify the clinical conditions of interest, and these were used to clean and code the dataset.

The key exposures included AF, frailty, and OAC, and the outcomes of interest were all-cause mortality, stroke, intracranial bleeding and gastrointestinal bleeding. A wide range of co-variates and baseline characteristics are also reported.

4.3 Study design

This was a retrospective cohort study of patients aged 65 or over on the 31st December 2015.

4.4 Data

Data used for the analysis were from ResearchOne, which is a health and care research database developed by The Phoenix Partnership (TPP) in collaboration with the University of Leeds and the UK Government's Technology Strategy Board. It is run on a not-for-profit basis, and includes de-identified clinical and administrative data derived from the EHR of patients in England who are registered at a practice that use the TPP SystmOne clinical system.[275] There are a number of clinical settings that use SystmOne outside general practice including some providers of child health, community health, palliative care, Accident & Emergency and acute hospital services. Whilst data may be included in ResearchOne from each of these settings, formal comprehensive linkage from other databases is not available.

As of 2016, there were 20.2 million patients registered in SystmOne, representing 35% of all patients in England.[276] There were 2,552 general practices represented, and 11,160 general practitioners. The median list size was 7,080 (interquartile range, IQR, 4,214 to 10,553) of whom 524 (IQR 256 to 895) were aged 75 years or older. Patients are included from all NHS England geographical regions in England (as of 2016) except for Lancashire, with coverage ranging from 5% of patients in Cheshire and Merseyside to 77% in the East of England.[276]

The transfer of EHR data from SystmOne to ResearchOne is subject to the general practice 'opting in' to the research database. If they are part of a ResearchOne practice, individual patients also have the right to 'opt out' of their EHR being used for research purposes.

ResearchOne was selected for this study because of the size and national coverage of the data set.[276] Other similar resources are available, as outlined in

Chapter 3, but these tend to be costly, and ResearchOne has additional benefits such as pre-existing collaborative links with University of Leeds,[275] and that it was used in the development of the eFI.[11]

4.5 Housing and security

Data were obtained following an application to TPP, which was reviewed internally by their research committee. Following approval, a data extract was prepared by a TPP analyst, and this was delivered through a secure data link. The flow of data is shown in Figure 6.

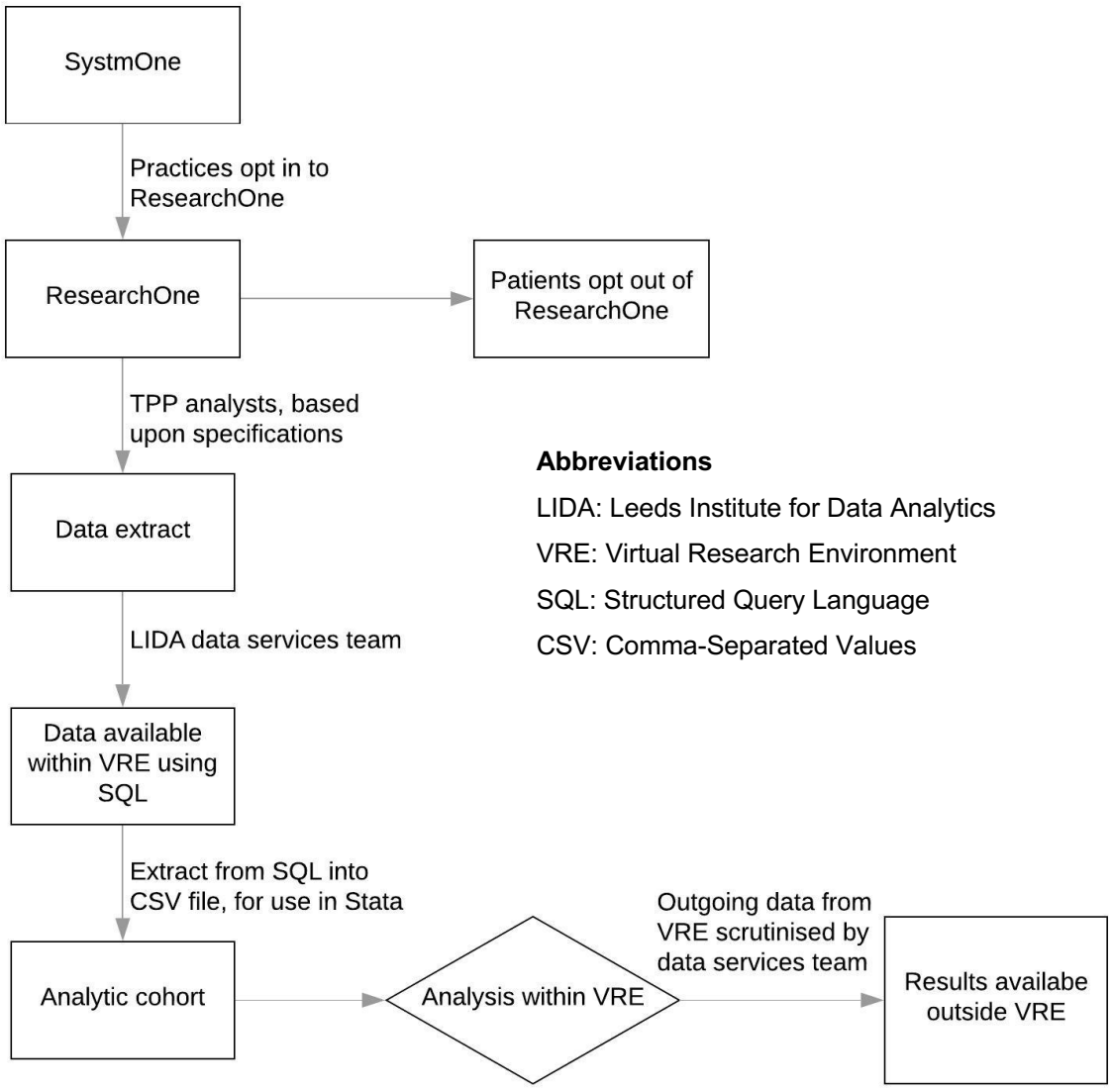


Figure 6: Chart to illustrate data flow

All data were housed within a secure Virtual Research Environment (VRE). This is a 'private cloud' with limited, secure access and strict protocols for transfer of data in and out. The VRE is managed by a team of data analysts who are responsible for disclosure control, information classification, security, and back-up arrangements. It is accredited to the international standard for information security management, ISO/IEC 27001:2013, and meets the requirements to store health data from NHS Digital, Public Health England and other NHS or social care organisations.[277] A data management protocol was completed with input from the data services team, and was approved by the information governance manager for the Leeds Institute for Data Analysis (LIDA). A brief summary of this will follow.

4.5.1 Extract from data management protocol

4.5.1.1 Data Collection

What data will you collect or create? Patient records will be extracted from the ResearchOne database. Long-term access will not be allowed, or required. Data will be accessible for up to 5 years.

How will the data be collected or created? Data are extracted electronically from routine primary care records. Data will be transferred electronically.

4.5.1.2 Documentation and Metadata

What documentation and metadata will accompany the data? Some of the data will be coded using controlled terminologies such as ICD, British National Formulary (BNF) and Read, and the appropriate version of these terminologies will be stored with the data.

4.5.1.3 Ethics and Legal Compliance

How will you manage any ethical issues? The data are de-identified. Routine clinical data will be used. This does not require specific ethical review, as the research is limited to secondary use of information previously collected in the

course of normal care without the intention to use it for research at the time of collection. Patients are not identifiable to the research team. The ResearchOne database has NHS Research Ethics Committee and National Information Governance Board approval. The data will be saved securely on the university Integrated Research Campus (IRC).

How will you manage copyright and Intellectual Property Rights issues? Research findings can be freely published without interference, regardless of the nature of the findings. Where the ResearchOne dataset contributes toward any publication or presentation the source must be acknowledged and a copy of any journal or conference publication submitted to the ResearchOne Project Committee.

4.5.1.4 Storage and Backup

How will the data be stored and backed up during the research? The University of Leeds IRC is a secure data management platform. The IRC handles a large volume and variety of data so that it can be used securely and efficiently in research.

Data will be stored on a project-specific VRE on the IRC. The VRE enables data analysis through remote access into a secure virtual desktop, ensuring the data stays within the secure environment. Researchers sign an IRC User Agreement and undertake any required information governance training before being given access to the data through the VRE. Data cannot leave the environment without approval and intervention by the IRC Data Services Team, who check for unauthorised disclosure. Researchers disseminate non-disclosive findings or consented information – and publish these open access where possible. Data is subjected to volume-level snapshots periodically throughout the day and is synchronously replicated to a secondary data centre on campus.

How will you manage access and security? IRC processes are based on international standards and legal requirements for the confidentiality, availability and integrity of data. Data handling procedures are determined by the IRC's

Information Security Management System which has gained accredited certification to ISO/IEC 27001:2013 and has been assessed as satisfactory against the NHS Information Governance Toolkit. The main risk to data security is re-identification of data subjects, either accidentally or intentionally. The use of a VRE on the IRC significantly reduces this risk. Researchers are not able to introduce additional data to the VRE to enable jigsaw attacks to attempt re-identification. Researchers are not able to download data from the VRE themselves, therefore preventing release of data that may be potentially identifiable. The platform itself has been designed to be secure in operation, has been penetration tested and undergoes regular patching and vulnerability scanning. Access control is strict and researchers can only access their own projects, and only in isolation from each other so they cannot leak data across projects.

Researchers accessing the IRC are bound by an IRC User Agreement which details their responsibilities. Researchers are also bound by the terms and conditions of their contract with the University of Leeds, and its requirement to be bound by the statutes, ordinances and policies of the institution. Any outputs of data from the VRE will be verified by the IRC Data Services Team as compliant with relevant legislation, contracts and agreements which the project is bound by, in particular to the Data Protection Act 1998. Researchers are also bound by the ResearchOne confidentiality agreement which contains clauses which confer duties upon the institution and individual in relation to confidentiality and data protection.

4.5.1.5 Selection and Preservation

Which data are of long-term value and should be retained, shared, and/or preserved? The data must be destroyed after five years by agreement with ResearchOne. The dataset is solely for use on projects that have approval from the ResearchOne Project Committee and relevant ethics and governance bodies.

What is the long-term preservation plan for the dataset? The data must be destroyed after five years by agreement with ResearchOne. The dataset is solely for use on projects that have approval from the ResearchOne Project Committee and relevant ethics and governance bodies.

4.5.1.6 Data Sharing

How will you share the data? This data must not be shared. Other researchers may apply to ResearchOne for the same data. The results of the research will be published in the academic literature, and will form an MD dissertation. The dataset is solely for use on projects that have approval from the ResearchOne Project Committee and relevant ethics and governance bodies.

4.5.1.7 Responsibilities and Resources

Who will be responsible for data management? The data will remain in the IRC, Leeds. Responsibility for good practice lies with each researcher using the dataset. The researchers are under the supervision of Professor Chris Gale, (Professor of Cardiovascular Medicine, University of Leeds and co-supervisor).

4.6 Ethics

This study was approved by the ResearchOne project committee under the terms of the National Research Ethics Service Research Ethics Committee North East approval of the research database (REC reference number 11/NE/0184, Appendix B). This study was based on the secondary use of pseudonymised patient level data previously collected in the course of normal care, therefore under the Health and Social Care Act 2012, further NHS or University research ethics committee approval was not required. This was confirmed by Dr Alice Temple (Research Ethics Training and Development Officer, University of Leeds). The study was conducted in compliance with the Declaration of Helsinki.[278]

4.7 Data extract

Data from the beginning of each patients' EHR up until the date of data extraction were requested from ResearchOne by Professor Andrew Clegg, (Professor of Geriatric Medicine, University of Leeds and co-supervisor) in May 2015. The study participants were all patients aged 65 years or older who were alive and registered at an included SystmOne practice on 31st December 2015. Variables requested by Prof Clegg were age, sex, socioeconomic status (Indices of Multiple Deprivation [IMD] score and Townsend quintile), eFI score, and all CTV-3 codes that identify a 'recorded diagnosis of cardiovascular disease, comorbidities, medications, systolic and diastolic blood pressure, smoking status, residence (home/care home), incident cardiovascular event and mortality.'

The dataset was extracted by Dr Chris Bates (Director of Research & Analytics, TPP) and his team of analysts, and arrived in February 2018. Following analysis of the dataset, it became apparent that the data that were supplied did not meet the requested specifications, as only CTV-3 codes for the past medical history required for the calculation of the patient's eFI were provided. An auxiliary data file was supplied in January 2019.

The initial extract consisted of 115.4 million rows of data, which were delivered in tables that were accessed through Microsoft SQL Management Studio 2017. An Open DataBase Connectivity (ODBC) link was used to bring data into Stata (StataCorp LP. 2015. Stata Statistical Software: MP version 14. College Station, TX) for coding, cleaning, and analysis. Data were in the form of seven relational tables, with a common identifier, which was a patient identification number (patient ID). Table 16 shows a summary of the contents of each data table.

Table 16: Summary of data tables that were supplied by ResearchOne

Table name	Contents	Rows of data
Patient details	One row per patient, containing date of birth, date of death, and gender	570,131
Address	The indices of multiple deprivation (IMD) rank and combined rurality indicator of the patient's address, along with the start and end date of residence at that address. One row for each new address.	1,353,172
Additional coded data	This table contained the clinical data. For each clinical encounter, multiple clinical codes could be recorded with each on a new row in the table. The CTV-3 code associated with a clinical entry, the textual definition of the CTV-3 code, and any numeric value (such as haemoglobin, with associated units and normal range) were reported in the same row, along with the date of the clinical entry and an event identification code.	66,619,796
Care home	The addresses of providers registered with the Care Quality Commission was used by ResearchOne staff to identify a list of nursing homes. Where a patient's address matched this database, the start and end date of their residence at a nursing home was recorded in this table.	90,975
Ethnicity	Ethnicity was recorded using a CTV-3 code with an associated date of recording and definition. There could be many recordings per patient.	1,001,341
GP registration history	The general practice that the patient was registered with was recorded with an anonymous practice identification number, with the dates the patient as registered at the practice.	723,330
Repeat medications	The name and dose of each drug that the patient as prescribed, with the start and end dates associated with that prescription. Repeat prescriptions frequently had a review date and/or a maximum number of allowed issues of the prescription.	44,998,666

4.8 Cleaning and coding

Extensive data cleaning and coding was required in order to make use of the dataset, and a brief summary of the approach taken for each data table will follow. Each row of data contained a unique patient identification number, which allowed data from across tables to be combined.

4.8.1 Patient details

This table contained key demographic data and was directly imported into Stata. It included date of birth, date of death. A variable was labelled 'Gender', was treated as biological sex, as a binary code for male/female was provided with a single entry for the duration of the patient's EHR.

4.8.2 Address

This table contained data on the IMD rank associated with a patient's postal address. IMD is a measure of relative deprivation at a neighbourhood level (lower-layer Super Output Areas with an average of 1,500 residents, based on 2011 census data).[279] The IMD is calculated using a weighted cumulative model based on seven domains of deprivation:

1. Income Deprivation
2. Employment Deprivation
3. Education, Skills and Training Deprivation
4. Health Deprivation and Disability
5. Crime
6. Barriers to Housing and Services
7. Living Environment Deprivation[279]

In some cases, multiple addresses were recorded for an individual over their EHR, with a range of different IMD ranks associated with them. This could have arisen from address changes over the course of a patient's records. Whilst deprivation at an individual level is a dynamic state with consequences across the life-course,[280] and there may be large variation between individuals in socio-

economic status within a neighbourhood, the last recorded IMD was chosen as a proxy for the patient's relative deprivation state.

4.8.3 Additional Coded Data

Coded data in the form of CTV-3 codes provide one row of data for every measurement, observation or diagnoses for every aspect of a GP visit for one person, Table 16. In the original data extract, this table was 66.6 million rows long, with hundreds of rows per patient. Much of this was not directly relevant to this research question. Therefore, the first step in cleaning was to identify CTV-3 codes that were of relevance, and only retain data associated with these.

The method for extracting relevant data out of this table was to firstly create a list of all relevant CTV-3 codes related to a particular diagnoses or clinical measurement, and secondly identify all patients with any occurrence of any of the CTV-3 codes and label them with the particular diagnoses or clinical measurement. An illustration of this process is provided in Figure 7, for the example of smoking status.

Un-coded/cleaned dataset

Patient ID	Event ID	Event Date	CTV3Code	CTV3 Term Test	Number Value	Units
A	1	01/01/1988	Ub1tI	Cigarette consumption	80	per day
A	2	03/07/1994	137R.	Smoker		
A	3	15/12/2006	1374.	Moderate cigarette smoker (10-19 cigs/day)		
A	4	12/03/2012	137G.	Trying to give up smoking		
A	5	07/05/2014	Ub0p3	Age at starting smoking	13	
A	6	03/06/2016	137C.	Keeps trying to stop smoking		
B	1	01/12/2014	Xa1bv	Ex-cigarette smoker		
B	2	31/11/2015	Xa1bv	Ex-cigarette smoker		
C	1	01/12/2001	Ub0oq	Non-smoker		
C	2	08/06/2015	Ub0oq	Non-smoker		

Coding the variables

A list of CTV-3 codes is compiled and used to categorise smoking history into:

1. current smoker,
2. ex-smoker, and
3. non-smoker

Date information is retained

Patient ID	Event ID	Event Date	CTV3Code	CTV3 Term Test	Number Value	Units	Smoker
A	1	01/01/1988	Ub1tI	Cigarette consumption	80	per day	1
A	2	03/07/1994	137R.	Smoker			1
A	3	15/12/2006	1374.	Moderate cigarette smoker (10-19 cigs/day)			1
A	4	12/03/2012	137G.	Trying to give up smoking			1
A	5	07/05/2014	Ub0p3	Age at starting smoking	13		1
A	6	03/06/2016	137C.	Keeps trying to stop smoking			1
B	1	01/12/2014	Xa1bv	Ex-cigarette smoker			2
B	2	31/11/2015	Xa1bv	Ex-cigarette smoker			2
C	1	01/12/2001	Ub0oq	Non-smoker			3
C	2	08/06/2015	Ub0oq	Non-smoker			3

Patient ID	Smoker
A	1
B	2
C	3

Figure 7: illustration of the effect of coding on a dummy dataset

For each variable of interest, code-lists were developed by searching online repositories and papers with published code lists.[273, 281] These were supplemented with codes identified from the Technology Reference data Update Distribution (TRUD). TRUD was searched using free-text, and subsequent review of the 'parents and children' of each identified code in the database browser software.[269,b] For example, pure sensory lacunar infarction is considered as a 'child' of lacunar infarction, which is in turn a 'child' of cerebral infarction within the CTV-3 coding structure, Figure 8. The specific variables that were used in the study will be detailed in section 4.10.

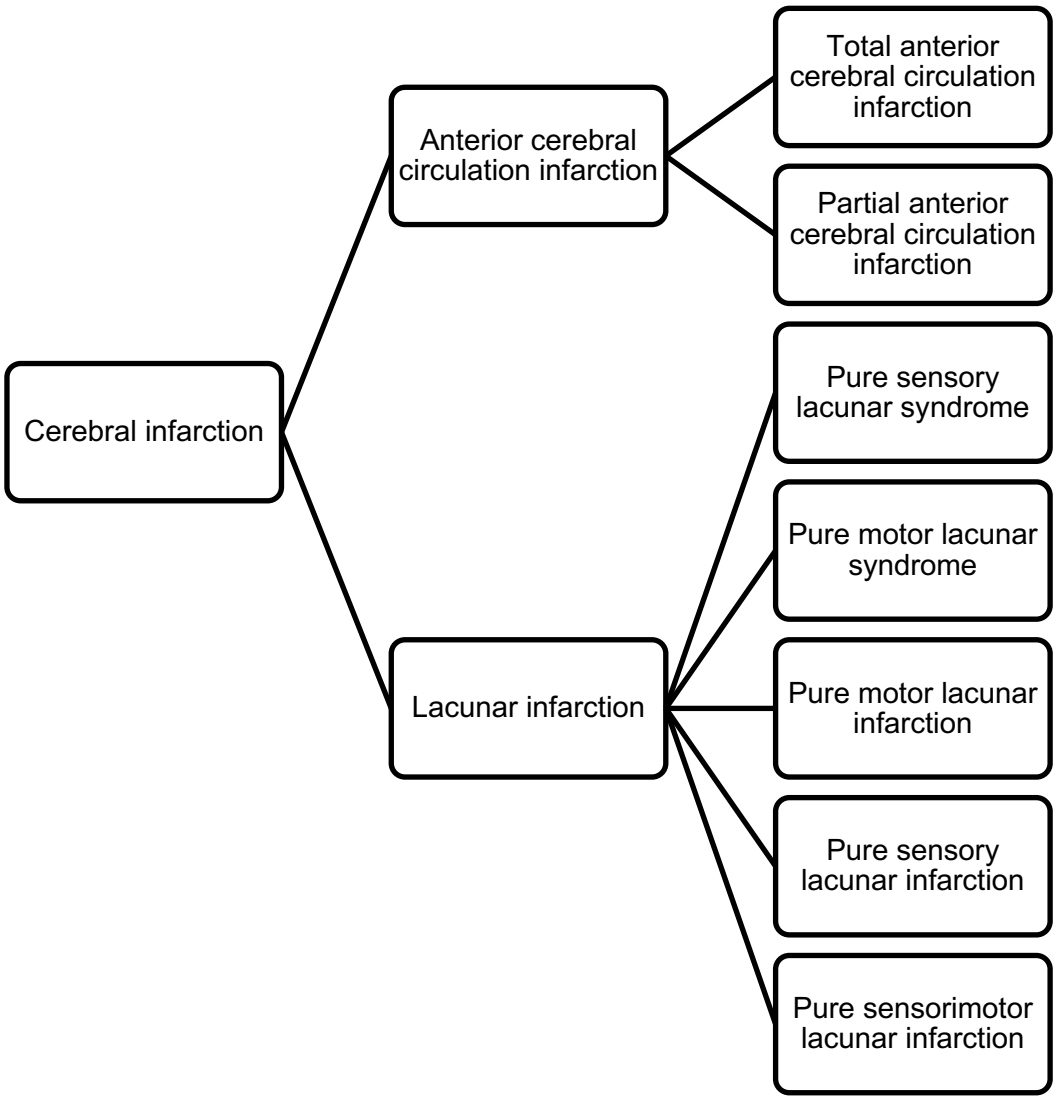


Figure 8: Example of the 'parent' and 'child' structure of CTV-3 codes

[b] Clinical Terminology Browser version 1.04. NHS Information Authority and NHS digital

The code lists that were used to define each condition of interest (and appeared in the dataset) are detailed in the appendix.

4.8.3.1 Care Home

The last entry recorded in this table for each patient was used to identify those that were recorded as being resident in a nursing home. This was identified by ResearchOne prior to the data extract. They identified nursing home residents through CTV-3 coded evidence of nursing home admission, or the patient's postcode matching a postcode on the Care Quality Commission list of registered UK nursing homes.[11]

4.8.3.2 Ethnicity

For each individual, multiple different recordings were made for ethnicity. Entries included classifications of race, but also included religions, or a person's status as a traveller. Where race data was available, this was summarised into top level ethnic category codes as defined by the NHS data dictionary, and detailed in Table 17.[282]

Table 17: Ethnic category codes

Ethnic category	Example
White	British, Irish
Mixed	White and black Caribbean, white and black African, white and Asian
Asian or Asian British	Indian, Pakistani, Bangladeshi
Black or black British	Caribbean, African
Other ethnic groups	Chinese

Where patients had multiple different categories recorded, the mode was used. As 'white' is the dominant category in the UK generally, it is possible that this is the default entry for individuals entering data. Therefore, where there were two equally commonly recorded categories, the non-white option was selected. This process has been previously developed for use with hospital episode statistics data, in which multiple ethnic categories occur per patient over the course of

their longitudinal healthcare records.[283] After applying these rules, recording of ethnicity data remained unreliable with multiple conflicting recordings for each patient, and this variable was not carried forward to the analysis.

4.8.3.3 General practice registration history

A unique code identified the general practice that each patient was registered at, which allowed adjustment by general practice (section 5.6). The start and end date associated with each general practice code was supplied. Where patients had been registered at multiple different practices, the most recent (i.e. current practice) was included as a co-variate, as this practice was responsible for the medical management of the patient during the study period.

The end date was also used to identify the end of the available follow-up data for that individual, which was used as the censorship date in survival analysis for patients that left the practice before the end of the study and had no recorded date of death. Censorship is discussed further in section 4.10.4.5.

4.8.3.4 Repeat Medications

Medication data were supplied in a table contained 45 million rows of data in free-text format, with no coded components. An anonymised extract from the medication table shows that the data input was inconsistent, with no coded elements, Table 18.

Table 18: Illustrative anonymised extract from the medications table

Medication	Start Date	End Date	Review Date	Dose	Quantity
Amlodipine 5mg tablets	09/12/13	02/03/14	-	Take one daily	28 tablet
Ticagrelor 90mg tablets	02/07/12	02/07/13	-	Take ONE tablet TWICE a day	1 pack of 56 tablet(s)
Fybogel 3.5g effervescent granules sachets plain SF (Reckitt Benckiser Healthcare (UK) Ltd)	17/07/13	19/09/14	-	ONE TO BE TAKEN TWICE A DAY, Orange	2*30 sachet – 3.5 grams/sachet
Doxazosin 4mg tablets	11/01/07	-	12/01/16	1 Twice Daily	56 tablets
Missing data represented with a dash (-)					

Non-medicinal prescriptions, such as diabetes testing strips and bandages were also included in the medications table. For the calculation of polypharmacy as an eFI deficit, it was necessary to exclude such non-pharmaceutical items. This required further cleaning steps to separate out these data into medications and other treatments. The calculation of the eFI is discussed further in section 4.10.1.

Medications that were considered to be relevant to the research question were identified through clinical expertise, discussion with supervisors, and review of the recent literature. Medications were identified in the table using either generic or trade names, and so a comprehensive list was collated of alternative ways of prescribing each medication using the BNF.[154] Where the intention was to report that a patient was taking a medication at the time of study entry, e.g.

calcium channel blocker, a binary entry was coded (on drug or not). For other drugs, such as OAC, more granularity was required and the coding incorporated date information in addition as detailed in section 4.10.3.

4.9 Participants

Patients who were in the ResearchOne database, and aged 65 years and over on 31st December 2015 were included. Patients who were identified as having AF, but without an associated date of that diagnosis were excluded from the analytical cohort. This is because they could not be classified as incident cases after study entry, or prevalent cases at study entry. Patients were categorised by whether they had a diagnosis of AF at the time of study entry or not.

NICE guidelines recommend that in patients with AF, clinicians should 'offer anticoagulation to people with a CHA_2DS_2-VASc score of two or above, taking bleeding risk into account.'[140] On this basis, patients with AF were further grouped into those with a CHA_2DS_2-VASc of two or above, and those with a score of below two. The groups available for analysis are shown in Figure 9.

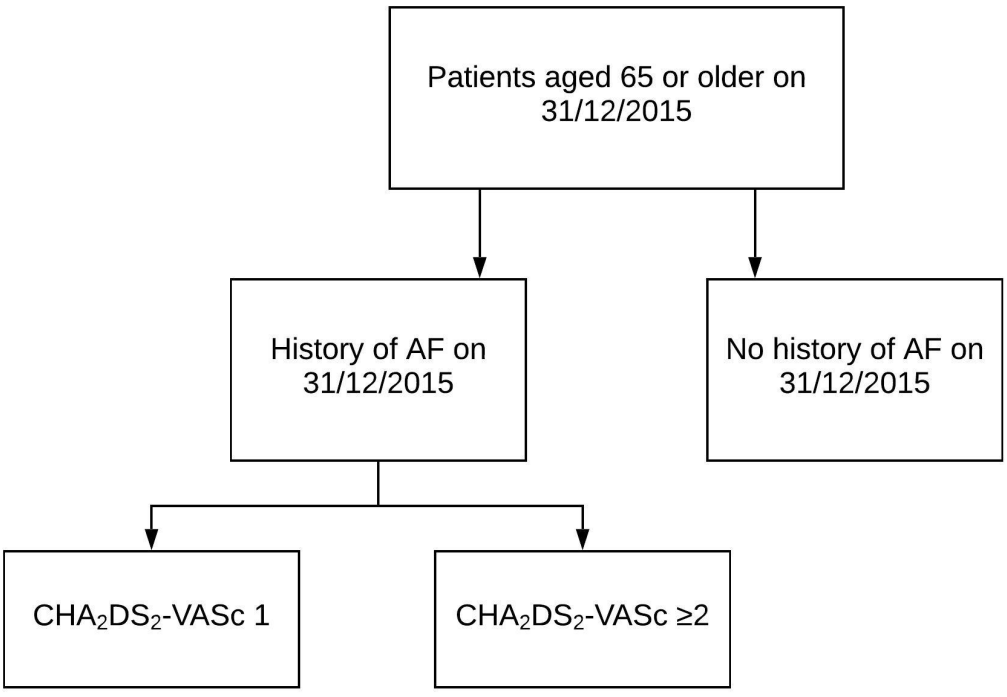


Figure 9: Categories of subgroups for analysis

As age is a component of CHA_2DS_2-VASc, patients aged 75 years or above have a minimum score of two points, and patients aged 65 to 75 years have a minimum score of one. Everyone in the cohort was 65 years or older, so a score of zero was not possible in this cohort.

The group with a CHA_2DS_2-VASc score of two or more was further divided into patients that were prescribed OAC, and those that were not.

4.10 Variables

ResearchOne is a positive recording dataset, whereby new diagnoses, observations, and results are added to the record. The assumption was made for this study that the absence of an entry means that the condition or observation is absent, or not yet identified.

4.10.1 Explanatory variable: frailty

Frailty was identified using the eFI, as it is based upon a robust theoretical framework (the cumulative deficit model). It has undergone independent external validation, has excellent predictive validity for clinically important outcomes, with good to moderate discrimination. The eFI has been nationally implemented, which provides a link for translation of the findings of the thesis into clinical practice. Furthermore the eFI was originally created and validated in the ResearchOne dataset, and the supervisory team have substantial experience of the eFI.[11]

A file of the CTV-3 codes used to define the deficits was obtained from Dr Clegg. The eFI score was calculated as recommended by the authors, as an equally weighted proportion of deficits present of the total possible.[11] There were no time constraints to individual deficits with the exception of polypharmacy, which was defined as 5 or more medications prescribed in the preceding 12 months using chapters 1–15 of the BNF.[154]

Dr Marlous Hall (Senior Epidemiologist in Cardiovascular Epidemiology, University of Leeds and lead supervisor) cleaned and de-duplicated the

medications table to exclude non-medicine prescriptions (e.g. bandages etc), and then calculated each patient's eFI using all patient records up until the date of study entry, 31/12/2015, within Microsoft SQL.

Frailty was then categorised as described in the original eFI validation publication: robust (0 to 0.12), mild (>0.12 to 0.24), moderate (>0.24 to 0.36) or severe (>0.36) frailty. The presence of AF as a component of the eFI and as part of the cohort definition, and of stroke as a component of the eFI and an outcome is potentially problematic due to mathematical coupling, which occurs when one variable is the whole or part of another.[284] A previous study examining the impact of frailty on the association between systolic blood pressure and all-cause mortality used a modified eFI that excluded hypertension.[285] However, the use of broad categories in the eFI is likely to mitigate any impact due to the need for multiple additional conditions to move from one frailty category to the next, and so the inclusion of AF in the eFI calculation is unlikely to have a large effect on the categorisation of frailty.[285]

4.10.2 Exposure: atrial fibrillation or atrial flutter

The AF cohort was defined by a list of 38 CTV-3 codes, Table 19. These were compiled using the process described in section 4.8.3. Patients were considered as having a history of AF if they had a recorded history of paroxysmal, persistent or permanent AF, or atrial flutter on or before the 31st December 2015. In the remainder of the thesis, AF will refer to both atrial fibrillation and atrial flutter as these frequently co-exist[126] which may not be well reflected in primary care coding; both carry an elevated stroke risk;[126] and the two have been previously grouped in a trial setting.[152]

Codes associated with resolved AF or flutter were also included in the cohort definition, as there is evidence of ongoing risk of increased risk of thromboembolic sequelae in the long-term, even in the absence of recurrent recorded arrhythmia.[286]

Table 19: CTV-3 codes used to define the AF cohort

CTV-3 code	Definition
G5730	Atrial fibrillation
XaeUP	Chronic atrial fibrillation
XaOft	Permanent atrial fibrillation
XaOfa	Persistent atrial fibrillation
Xa2E8	Paroxysmal atrial fibrillation
X202R	Lone atrial fibrillation
X202S	Non-rheumatic atrial fibrillation
Xa7nI	Controlled atrial fibrillation
XaEga	Rapid atrial fibrillation
G5731	Atrial flutter
XaeUR	Atypical atrial flutter
XaeUQ	Typical atrial flutter
XaaUH	Paroxysmal atrial flutter
G573.	Atrial fibrillation and flutter
G573z	Atrial fibrillation and flutter NOS
XaDv6	H/O: atrial fibrillation
Xafis	Atrial fibrillation detected
XaLFz	Atrial fibrillation resolved
XaIIT	Atrial fibrillation monitoring
XaMGD	Atrial fibrillation annual review
XaZdc	Atrial fibrillation care pathway
XaXrZ	Referral to atrial fibrillation clinic
XaMDG	Atrial fibrillation monitoring first letter
XaMDI	Atrial fibrillation monitoring third letter
XaMDH	Atrial fibrillation monitoring second letter
XaMDK	Atrial fibrillation monitoring verbal invite
XaMDF	Atrial fibrillation monitoring administration
XaMFn	Atrial fibrillation monitoring telephone invite
XE0Wk	(Atrial fibrillation) or (atrial flutter)
7936A	Implantation of intravenous pacemaker for atrial fibrillation
XaaaD	Provision of written information about atrial fibrillation
XaLFh	Exception reporting: atrial fibrillation quality indicators
XaLFi	Excepted from atrial fibrillation quality indicators: Patient unsuitable
XaLFj	Excepted from atrial fibrillation quality indicators: Informed dissent
XaNRA	History of atrial flutter
3272.	ECG: atrial fibrillation
2432.	O/E - pulse irregularly irreg.
3273.	ECG: atrial flutter

Abbreviations H/O: history of; NOS: not otherwise specified; ECG: electrocardiogram

4.10.3 Exposure: Oral anticoagulation

Prescription of OAC was identified from patient-level prescription data, using the process described in section 4.8.3.4. All OAC available for prescription in England and Wales at the time of the study were included:

- Vitamin K antagonists – warfarin, acenocoumarol, phenindione
- Direct inhibitors of activated factor X (factor Xa) – apixaban, edoxaban[c],[148] rivaroxaban
- Direct thrombin inhibitors – dabigatran etexilate

The terms used to search for OAC agents in the medications table are reported in Table 20.

Table 20: Search terms used to identify oral anticoagulants

Drug name	Search terms
Warfarin	warfarin
Apixaban	apixaban, eliquis
Edoxaban	edoxaban, lixiana
Rivaroxaban	rivaroxaban, xarelto
Dabigatran	dabigatran, pradaxa
Acenocoumarol	acenocoumarol, sinthrome
Phenindione	phenindione

Source: British National Formulary [287]

Parenteral anticoagulants were not included in this study, as this route is not routinely recommended in NICE guidance for prophylaxis of thromboembolism for patients with AF,[288] and only recommended in rare, short-term situations in the ESC guidelines (such as during pregnancy, as low-molecular weight heparins do not cross the placenta; and during perioperative management or procedures such as catheter ablation).[126, 289] As such, it is unlikely that patients in this cohort would have been taking parenteral OAC for a sustained period of

[c] Edoxaban was approved by NICE in England and Wales in September 2015.

time during the study period. It is possible that patients were prescribed OAC prior to their diagnosis of AF for an alternative indication, such as pulmonary embolism or mechanical heart valve. These patients were not excluded.

4.10.3.1 Doses

International Normalised Ratio (INR) results were not available in this study, and so a patient prescribed a vitamin K antagonist was considered to be anticoagulated. DOAC regimens were considered as likely to be of a sufficient therapeutic dose for prophylaxis of thromboembolic events for patients with AF in this study (and therefore the patient ‘anticoagulated’) if the prescribed DOAC dose was at least as high as that recommended in the BNF for this purpose, regardless of initial indication. These are detailed in Table 21. It was assumed that the prescribed dosage was correct and accounted for any necessary dose reductions. It was not possible to verify this assumption using the data available.

Table 21: DOAC dosing regimens that were considered as therapeutic for patients with AF, and alternative possible indications for each dose

Regimen	British national formulary indications[154]
Apixaban	
2.5mg BD	Stroke and systemic embolism prophylaxis in NVAF, in patients with 2 or more of: age ≥ 80 years, body-weight < 61 kg, or serum creatinine ≥ 133 mmol/L. Alternative indications: VTE prophylaxis following knee or hip replacement surgery; recurrent DVT or PE prophylaxis.
5mg BD	Stroke and systemic embolism prophylaxis in NVAF
Edoxaban	
30mg OD	Stroke and systemic embolism prophylaxis in NVAF in patients with body weight < 61kg Alternative indications: treatment or prophylaxis of DVT or PE in patients with body weight < 61kg.
60mg OD	Stroke and systemic embolism prophylaxis in NVAF Alternative indications: treatment or prophylaxis of DVT or PE
Rivaroxaban	
15mg OD	Stroke and systemic embolism prophylaxis in NVAF if creatinine clearance 15–49 mL/minute. Alternative indications: treatment of DVT or PE; prophylaxis of recurrent DVT or PE
20mg OD	Stroke and systemic embolism prophylaxis in NVAF Alternative indications: treatment or prophylaxis of DVT or PE
15mg BD	Initial treatment of DVT or PE
Dabigatran	
110mg BD	Stroke and systemic embolism prophylaxis in NVAF in patients aged ≥ 80 years, or in patients with moderate renal impairment, or increased risk of bleeding. Alternative indications: treatment of DVT or PE or prophylaxis of recurrent DVT or PE in patients aged ≥ 80 years, or in patients with moderate renal impairment, or increased risk of bleeding
150mg BD	Treatment of DVT or PE or prophylaxis of recurrent DVT or PE.

Abbreviations: DVT: deep vein thrombosis, NVAF: non-valvular AF, PE: pulmonary embolism, VTE: venous thromboembolism

4.10.3.2 Persistence and timings of exposure

Vitamin K antagonists exhibit a highly variable half-life and have a narrow therapeutic window. In contrast, DOACs have a relatively short half-life (7-11 hours for rivaroxaban, 9-11 hours for edoxaban, 10-14 hours for apixaban, 14-17 hours for dabigatran).[147] These characteristics mean that for both classes of OAC, rigorous concordance with therapy is needed to maximise efficacy and minimise treatment related harms.

A proxy for persistence is the issue of a prescription, with the assumption that a patient is taking the medication if they are requesting a further supply. Previous studies have considered an OAC as discontinued if there was a gap between prescriptions of 60 days or more,[290, 291] although most gaps between medication renewals were shorter than 30 days.[291] Johnson *et al* defined a 'discontinuation period' as being twice the median duration of a single prescription (60 days for dabigatran, and 56 days for apixaban, rivaroxaban and vitamin K antagonist).[195]

In this study, the association between OAC and clinical outcomes was initially modelled as 'intention to treat', with OAC status determined at the time of entry to the study (31/12/2015). A sensitivity analysis was completed that excluded patients that discontinued therapy during the study period, to emulate a 'per protocol' analysis. In this analysis, switching between OAC agents without a break of greater than 30 days was considered as persistent therapy, as used elsewhere.[205] OAC was considered to be persistent if there were no gaps in treatment of 30 days or more. Although this is a 'stricter' definition of persistence than used in some studies reported in the literature (Table 22), [195, 207] this has precedent in other recent studies,[196, 205] and represents a more rigorous approach using the maximum granularity that is possible within the limitations of the data.

Table 22: Examples of how persistence has been defined in the literature

Study	Setting	Design	Persistence definition	Analysis
Vinogradova, 2018[188]	UK primary care: CPRD and Q-research	Retrospective, new-users	Gap of less than 30 days between prescriptions.	Persistence not quantified – patients censored when OAC discontinued or changed.
Johnson, 2016[195]	UK primary care: CPRD	Retrospective, new-users	Gap of less than twice the median prescription duration between prescriptions.	Proportion of patients who were persistent over the course of follow-up. Cumulative incidence rates of persistence. Cox regression models to report time to non-persistence.
Beyer-Westendorf, 2015[3, 196]	Dresden, Germany: OAC registry[204]	Prospective, new users	Gap less than four weeks between prescriptions.	Discontinuation rates and time-to-event analysis for discontinuation.
Willey, 2015[6, 205]	USA: pharmacy claims data	Retrospective, new users	Gap less than 30 days between prescriptions. For warfarin gap between prescriptions of 60 days, and less than 42 days between INR tests.	Discontinuation rates and mean time to discontinuation.
Go, 2003[7, 207]	Northern California, USA, ATRIA cohort.[8-11, 208]	Prospective cohort study	Gap of less than 60 days between warfarin prescriptions, unless an intervening INR measurement every 42 days.	Multivariable Cox models, incorporated time-dependent warfarin use data.

Abbreviations ATRIA: The AnTicoagulation and Risk Factors In Atrial Fibrillation, INR: International Normalised Ratio, CPRD: Clinical Practice Research Datalink

4.10.4 Outcomes

It was shown in the introduction and literature review that AF is associated with an increased risk of stroke, and that this risk may be substantially reduced by the use of OAC.[144] However, OAC also increases the risk of clinically significant bleeding. These considerations informed the choice of outcomes for this study, and mirrors those in clinical trials of DOAC versus warfarin,[149-152] and in previous observational cohort work comparing the efficacy and safety of DOAC agents and warfarin.[188] Mortality was included as an endpoint as it is definitive, objective, likely to be well represented in the dataset, and highly relevant in a population of older people with frailty.[11] These endpoints are of importance to trialists and clinicians, but they are also key priorities for patients with AF. When 937 patients with AF were asked which attributes of OAC they ranked most highly, the highest priority was stroke prevention, followed by major bleeding risk.[292]

Only the first event of any outcome was considered per patient. This was to reduce bias caused by multiple recordings. By way of example – a GP may enter a code for stroke for a patient with a new hemiparesis and arrange hospital admission. The discharge letter may prompt a further stroke coded event, as would any subsequent follow-up clinic letter. In this scenario, the same index event could be coded on multiple occasions.

For every condition or exposure of interest in the remainder of this chapter, the CTV-3 code list was derived using the process described in section 4.8.3. The code lists are detailed in Appendix C, limited to the codes that actually featured in the ResearchOne dataset.

4.10.4.1 Mortality

The data for date of death was supplied as part of the dataset from ResearchOne. This was entered onto the GP record at the General Practice. Linked data from the Office for National Statistics (ONS) were not available.

In order to comply with Health Research Authority guidance for confidentiality, the dataset from ResearchOne was supplied with dates of birth and death rounded to the first day of the month. For example, '01 Mar 1963', '15 Mar 1963' and '31 Mar 1963' would all be presented as '01 Mar 1963'.[293]

4.10.4.2 Stroke

Strokes were classified into haemorrhagic, ischaemic, and unspecified using the codes reported in the appendix, and rates of each subtype were reported. For modelling, the unspecified and ischaemic stroke groups were combined, to enable comparison with recent clinical trials as 'efficacy' endpoints.[150, 152]

4.10.4.3 Bleeding

There is a substantial variation in the literature in the definitions of major bleeding. For example, in the ATRIA study the authors considered bleeding as significant if it was fatal, required transfusion of two units of blood or was into a critical anatomical site,[174] whereas in HEMORR$_2$HAGES, bleeding in any site requiring hospital admission was included.[172] In this study, it was not possible to quantify bleeding severity, whether a hospital admission was required, or any bleeding-related harms. Additionally, it is known that coding of inpatient bleeding events in primary care records is frequently incomplete.[294] The safety outcomes were selected were gastrointestinal and intra-cranial bleeding (intra-cerebral and sub-dural haemorrhage), as these were identified as being potentially life-threatening or life-changing.[295-298] These endpoints were used to derive and validate the QBleed scores in primary care, suggesting that recording in primary care is likely to be adequate.[297]

4.10.4.4 Secondary outcomes: falls and transient ischaemic attack

The rates of falls and TIA were studied as secondary endpoints. It has been reported that AF is an independent risk factor for falls.[203] A tendency to experience falls is associated with an increased risk of major bleeding in patients that are prescribed OAC,[233, 299] suggesting that this is a useful outcome to study in a secondary analysis. The occurrence of TIA may be as a consequence of AF and herald subsequent stroke,[300] and was included as a

secondary endpoint, with the caveat that diagnosis of a TIA in primary care has been shown to have limited correlation with the assessment of a specialist.[300, 301]

4.10.4.5 Censoring

For all participants, outcome data were right-censored, with the last death recorded in ResearchOne on 1st April 2017. The last recorded event in the data was on 10th April 2017. The date of censor was therefore set to 11th April 2017 for all outcomes. However, a patient record could be censored prior to this due to the occurrence of the event that is being investigated, death, or discontinuation of the medical record for another reason, such as moving away from a ResearchOne general practice.

Some possible patient journeys are shown Figure 10, where the outcome of mortality is being investigated. Patient 1 survives the duration of the study and is considered censored at the end of the follow-up period. Patient 2 dies during the follow-up period, and so experiences an event of interest. Patient 3 dies prior to study entry, so is not represented in the cohort.

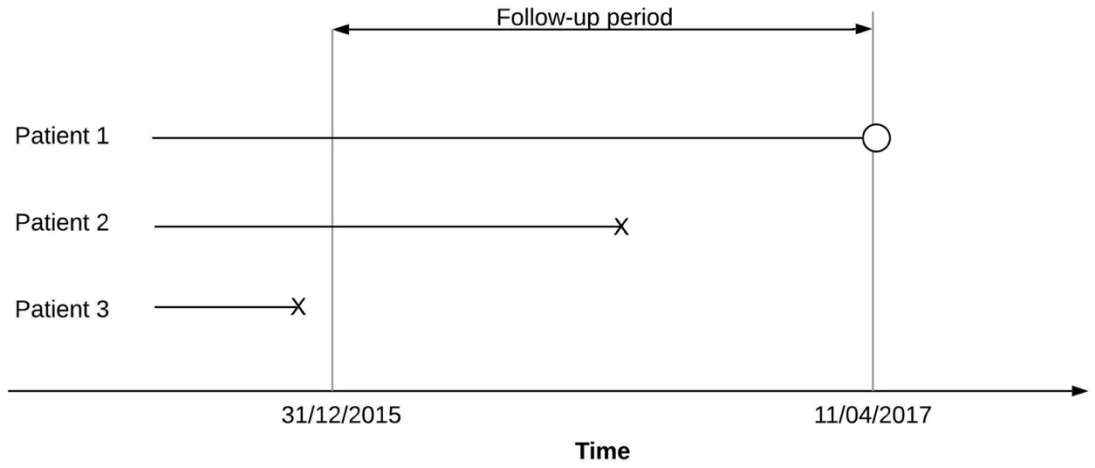


Figure 10: Illustration of censoring in survival analysis

4.10.5 Baseline characteristics and co-variates

Potential confounders were identified *a priori* on the basis of clinical understanding and relevant literature. These co-variates were included on the basis of the reported risk factors for AF,[302] those that may influence prescribing decision, or because they increase the risk of bleeding.[188, 297]

The list of baseline characteristics that are reported was intended to be inclusive, and therefore includes some variables that make up deficits in the eFI. However, only variables that were not part of the eFI were included in modelling as co-variates, to avoid collinearity.

4.10.5.1 Co-variates

The following variables were included for adjustment in all of the models, with the exception of cancer, which was only included as an additional adjustment for the outcome of death.

Age

Increasing age is associated with a higher hazard of death, and therefore a reduced probability of benefit from preventative or prophylactic therapy.[303] Age at study entry was calculated, and included as a co-variate as a continuous variable.

Sex

Women tend to have a higher life expectancy than men, and women also have a greater burden of disability and frailty.[7, 11] Sex is therefore an important confounder in this study.

Smoking status

Smoking is associated with a substantially increased death rate compared with people that have never smoked (HR 3.0; 99% CI 2.7 to 3.3 for women; 2.8, 2.4 to 3.1 for men),[304] and an increased risk of stroke.[304, 305] In this study, smoking was considered as a binary exposure, where patients were categorised as having never smoked, or as having a smoking history if they were a current or

ex-smoker. Ideally, the number of pack years would have been used to quantify the exposure with greater granularity, but these data tend to be recorded poorly in primary care.[306]

Socioeconomic status

Higher levels of deprivation are associated with an increased incidence (and severity) of stroke,[305] and all-cause mortality.[280] The most deprived small area in England has an IMD rank of 1, and the least deprived is ranked 32,844. For this study, IMD was considered in nationally derived quintiles. Further detail on IMD is provided in section 4.8.2.

General practice unique identification number

There may be unobserved determinants of outcome that may be shared between patients at the same general practice, such as clinical protocols or coding, but also in the local environment and therefore to account for possible confounding, a pseudonymised GP practice ID variable was included in the survival analyses (detailed in section 5.6.2).

Cancer

Cancer is a competing risk for death, and is also a contraindication for some OAC. [154] There are also a vast number of CTV-3 codes associated with cancer, many of which are historical diagnoses that have now potentially been cured. To approach this issue, codes associated with cancer was identified using the Quality and Outcomes Framework (QOF) code list.[307] These codes are likely to be well recorded in primary care, as remuneration of general practices is dependent on compliance with QOF, which has tended towards increased recording of incentivised conditions.[251, 308]

4.10.5.1.1 Risk scores

Stroke risk: CHA_2DS_2-VASC score

A list of CTV-3 codes for defining the components of the score is not publicly available in NICE guidance or in the original research papers. Following correspondence with the clinical team at SystmOne,[309] I was sent a list of CTV-3 parent codes that is used within SystmOne to calculation the CHA_2DS_2-VASc

score, and has been approved by Professor Gregory Lip, who devised the score. The codes are reported in Appendix A.

Bleeding risk; ATRIA score

The ATRIA score was used to assess bleeding risk.[310] Points are allocated on the basis of a past medical history of anaemia (3 points), severe renal disease (3 points), age ≥75 (2 points), previous diagnosis of haemorrhage (1 point), and hypertension (1 point). The scores are summed, then categorised as in Table 23.

Table 23: ATRIA risk score and risk of bleeding

ATRIA risk score	Risk category	Annual risk of haemorrhage
<4	Low	0.76%
4	Intermediate	2.6%
>4	High	5.8%

Alternatives such as HAS-BLED (hypertension, abnormal renal/liver function, previous stroke/TIA, bleeding history or predisposition, labile international normalized ratio [INR], elderly [age ≥65], drugs/alcohol concomitantly)[171] or HEMORR$_2$HAGES (Hepatic or renal disease, ethanol abuse, malignancy, older [aged ≥75 years], reduced platelet count or function, re-bleeding risk, uncontrolled hypertension, anaemia, genetic factors [cytochrome P450 2C9 single nucleotide polymorphism], excessive fall risk, and stroke)[172] were considered, and whilst there is evidence that HAS-BLED has been shown to have the best predictive and discriminative performance of the three,[311-313] components including labile INR, reduced platelet function and genetic factors were not part of the requested dataset. In this study, ATRIA was approximated based upon previously defined CTV-3 code lists. In particular, the codes for chronic kidney disease were used (rather than severe renal disease) and eFI codes for hypertension and anaemia were used.

4.10.5.1.2 Past medical history

Advanced liver disease – cirrhosis and varices

The liver has an important role in the synthesis and regulation of important factors of blood coagulation. Chronic liver disease, and in particular cirrhosis of the liver, is associated with a coagulopathy.[314] The portal hypertension associated with cirrhosis can lead to the development of oesophageal varices, which may bleed catastrophically, particularly in the presence of OAC.[315] This may be a consideration for clinicians when considering OAC prescription. Codes were identified using TRUD.

Alcohol excess

High intake of alcohol is of relevant to clinicians initiating OAC, due to concerns about medication adherence, pharmacological interaction and falls.[316] Alcohol excess may lead to decreased metabolism of warfarin through effects on the cytochrome P450 system, leading to an increased risk of haemorrhage, and there is a lack of data for concomitant alcohol excess and DOAC use.[316] Alcohol excess was identified through a GP recorded history of alcohol excess, rather than a quantification of alcohol intake. This is because a reported weekly intake is difficult to interpret in isolation. For example, it is not clear in ResearchOne whether a recorded value is ‘typical’ for an individual, and so may be misleading. A code selected by a clinician provides additional context. Text terms indicating chronic alcohol excess (e.g. alcohol abuse, alcoholism) or evidence of harm (e.g. alcohol-related coma, requirement for detoxification, or alcohol related organ damage) were searched in TRUD to identify patients with a history of alcohol excess.

Anaemia

Concomitant anaemia adds complexity when considering OAC. Anaemia may be the consequence of an occult bleeding process that may be worsened by OAC, and may be an adverse prognostic marker.[317] The code list used in the eFI to identify anaemia was used.

Bleeding disorder

The presence of a bleeding disorder affects anticoagulation decisions. Conditions were identified from the literature, and include von Willebrand's disease, thrombocytopenia, Bernard–Soulier syndrome, Glanzmann's disease, haemophilia, and factor deficiencies I, II, V, VII, X, XI, XII and XIII.[318] Any condition coded as a "child" of the term 'bleeding disorder' in the CTV-3 hierarchy within TRUD was also included.[154] Conditions were identified from the literature, and include von Willebrand's disease, Thrombocytopenia, Bernard–Soulier syndrome, hemorrhagiparous thrombocytic dystrophy, Glanzmann's disease, haemophilia, and factor deficiencies I, II, V, VII, X, XI, XII and XIII.[318] Any condition coded as a "child" of the term 'bleeding disorder' in the CTV-3 hierarchy within TRUD was also included.

Bleeding events

A previous history of bleeding events, such as a gastrointestinal (GI) or intracranial (IC) haemorrhage may be relative contraindications to OAC, depending on the aetiology. A history of haematuria or haemoptysis may also caution against anticoagulation. Code lists identifying these conditions were compiled using TRUD.

Chronic kidney disease

There is an independent, graded, inverse association between reduced estimated glomerular filtration rate and risk of death and cardiovascular events.[319] The code list for identifying CKD as part of the eFI was used.

Duration of atrial fibrillation

The median duration of time between first recorded diagnosis of AF in the EHR and study entry was calculated for each patient, and expressed as a median with IQR for each analytical group.

Falls

Frequent falls increase the potential for major injury, the consequences of which may be worse in an anticoagulated patient.[299] This may affect clinical decision-making. The eFI code list was used to identify a history of falls.[320]

Hypertension

Hypertension is a major risk factor for stroke and all-cause mortality.[321] As it is a component of the eFI, blood pressure was not included in the modelling, but was reported as an average over two years. Classifying hypertension using observational data presents challenges, as there is often a concertina effect whereby the most unwell patients have their blood pressure measured more frequently, leading to an effect of regression to the mean. Techniques such as regression dilution corrected measures seek to account for this.[322]

Hyperthyroidism

Hyperthyroidism is an established risk factor for AF,[323] and is reported for populations with and without AF using the code list from the eFI.

Ischaemic heart disease and myocardial infarction

Ischaemic heart disease is an important risk factor for AF,[126] and is also a potential indication for alternative antiplatelet or anticoagulant therapy, particularly following an acute coronary syndrome.[324] This may affect prescribing decisions regarding OAC for patients with concurrent AF.

Memory loss

Patients with cognitive impairment are less likely to be prescribed OAC, but benefits of therapy appear similar regardless of cognitive status.[325] The discrepancy in prescribing may be due to concerns over therapy concordance. Code lists were used from the eFI.

Nursing home

The proportion living in a nursing home was reported for each analytical group. The process that was used to identify a nursing home is described in section 4.8.3.1.

Obesity

Obesity is a risk factor for AF, stroke, and other cardiovascular diseases.[326] Codes were identified using TRUD.

Peptic ulcer

Peptic ulcers are responsible for 36% of acute upper GI bleeds, with an associated case mortality of 8.9% for a hospitalised event.[295] The presence of known peptic ulcer disease may impact on prescribing behaviour. Codes were identified using TRUD.

Stroke and TIA

A past history of ischaemic or unspecified stroke and TIA are reported. These are key components of stroke risk scores and will influence OAC decisions and risk of future stroke.[289, 327] Codes were identified from the eFI code list and TRUD.

Previous thromboembolic disease

A previous diagnosis of pulmonary embolism or deep vein thrombosis would be an alternative indication for OAC.[154]

Medications

Oral, dispersible and rectal preparations of medications were included as these are likely to have the highest systemic absorption. Eye drops, for example, were not included.

The medications groups that potentially increase bleeding risk or interact with anticoagulants were reported.[297] The selection and timing of their inclusion was considered on clinical grounds, as described below, and on the basis of precedent within the literature.[188]

4.10.5.1.3 Medications in recent use

A group of medications was compiled that may have been considered as a part of the decision-making process regarding OAC prescription,[188] that were either usually for short-term use, or could be stopped or exchanged for an alternative medicine prior to commencing OAC. Use of medication in these groups was reported for the year prior to study entry:

- Proton pump inhibitors
- Macrolide antibiotics
- Non-steroidal anti-inflammatory drugs (NSAID)
- Corticosteroids
- Statins

4.10.5.1.4 Medications in concurrent use

Concurrent prescription of an anti-platelet at the time of study entry was reported, as these independently act on the coagulation system, and are sometimes prescribed by clinicians according to an outdated perception that they are an alternative to OAC in thromboembolism prophylaxis for patients with AF.[145] The antiplatelets included were those in common current use in the UK:

- Aspirin
- Adenosine diphosphate (ADP) receptor antagonists: Clopidogrel, Ticagrelor, Prasugrel
- Adenosine re-uptake inhibitor: Dipyridamole

Concurrent use of the anti-epileptic medications phenytoin and carbamazepine were also reported, as these are not readily exchangeable for an alternative drug and may influence clinician choice of OAC. The search terms used to identify the medications of interest from the ResearchOne medications table are shown in Table 24.

Table 24: Search terms used to identify medications of interest

Drug class	Drug name	Search terms
Antiplatelet	Aspirin	aspirin, micropirin, nu-seals, danamep, disprin, mandaprin
	Clopidogrel	clopidogrel, plavix
	Ticagrelor	ticagrelor, brilique
	Prasugrel	prasugrel, efient
	Dipyridamole	dipyridamole, attia, ofcram pr, persantin retard, trolactin, persantin
Proton pump inhibitor	Omeprazole	omeprazole, losec, mepradec, mezzopram
	Esomeprazole	esomeprazole, emozul, ventra, nexium
	Pantoprazole	pantoprazole, pantoloc,
	Rabeprazole	rabeprazole, pariet
	Lansoprazole	lansoprazole, zoton fastab
Macrolide antibiotics	Azithromycin	azithromycin, zithromax, zedbac
	Clarithromycin	clarithromycin, klaricid, xetinin
	Erythromycin	erythromycin, erythrolar, erythrocin, erythroped
NSAID	Aceclofenac	aceclofenac, preservex
	Celecoxib	celecoxib, celebrex
	Dexibuprofen	dexibuprofen, seractil
	Dexketoprofen	dexketoprofen, keral
	Diclofenac	diclofenac , voltarol, dicloflex, econac, fenactol , volsaid, enstar, arthrotec, misofen, masidemen
	Etodolac	etodolac, etolyn, etopan, lodine, eccoxolac
	Etoricoxib	etoricoxib, arcoxia
	Fenoprofen	fenoprofen
	Flurbiprofen	flurbiprofen, strefen
	Ibuprofen	ibuprofen, brufen, brufen, anadin, feminax express, ibucalm, nurofen
	Indometacin	indomethacin, indocid, berlind
	Ketoprofen	ketoprofen, oruvail, tiloket cr, larafen cr, valket
	Mefenamic Acid	mefenamic acid, ponstan
	Meloxicam	meloxicam
	Nabumetone	nabumetone, relifex
	Naproxen	naproxen, feminax ultra, naprosyn ec, vimovo
	Dexketoprofen	dexketoprofen, skudexa
	Piroxicam	piroxicam, feldene
	Sulindac	sulindac
	Tenoxicam	tenoxicam, mobiflex
	Tiaprofenic Acid	tiaprofenic acid, surgam
	Tolfenamic Acid	tolfenamic acid, clotam rapid
Corticosteroid	Hydrocortisone	hydrocortisone, plenadren,
	Dexamethasone	dexamethasone, glensoludex, neofordex, dexsol, martapan
	Betamethasone	
Statin	Atorvastatin	atorvastatin, lipitor
	Fluvastatin	fluvastatin, dorisin xl, lescol xl, nandovar xl
	Pravastatin	pravastatin
	Rosuvastatin	rosuvastatin, crestor
	Simvastatin	simvastatin, simvador, zocor, inegy, cholib
Anti-epileptic	Phenytoin	phenytoin, epanutin
	Carbamazepine	carbamazepine, carbagen, tegretol

Abbreviation NSAID: non-steroidal anti-inflammatory drug
Source: British National Formulary[287]

4.11 Summary

- The quantitative analysis is a retrospective cohort study using an extract of patients aged 65 years or older from ResearchOne
- Code-lists were developed from existing sources and hand-searching to identify the clinical conditions of interest. These were used to clean and code the dataset.
- The key exposures were AF, frailty, and OAC
- The outcomes of interest were all-cause mortality, stroke, intracranial bleeding and gastrointestinal bleeding
- A range of other co-variates and medications were also included, and were selected on the basis of clinical expertise and precedent in the existing literature.

4.12 Conclusion

This chapter has detailed the dataset from ResearchOne and the variables of interest, with a justification for the inclusion of each. My role was in deciding upon the variables to include, and then to derive the code-lists required to define them. Subsequently, I cleaned and coded the dataset using the process that has been described within this chapter. These preparatory steps were necessary to make use of this large dataset. For transparency, the CTV-3 codes for each condition of interest are reported in Appendix C.

The analytical methods that were used to examine the associations between AF, frailty and OAC with these outcomes will be the subject of Chapter 5.

Chapter 5 - Analytical methods

5.1 Chapter introduction

The previous chapter included a summary of the dataset, and a discussion of the variables that were to be included in the analysis. This chapter will detail the approach that was taken to the analysis itself, with the aim of addressing the key objectives of this thesis. In brief, these were to establish the population prevalence of AF, and report prescription rates of OAC in patients with AF by eFI category. Next, to estimate the association between frailty and OAC prescription, and report the rates of clinical outcomes by eFI category and OAC status. Finally, to investigate the association between OAC and clinical outcomes (stroke, death and major bleeding), and whether the association is modified by frailty.

5.2 Chapter summary

This chapter sets out the methodological approach to the quantitative analysis of the thesis, building upon those described in Chapter 4. Baseline characteristics were reported for the whole cohort, and for patients with AF, and compared. Comparisons were also made by frailty category and OAC prescription status in patients with AF. The occurrence of clinical outcomes of interest by OAC status and frailty category were investigated and reported using standardised rates, and time to event analysis. Sensitivity analyses were completed to assess whether the findings were robust to a more specific definition of AF, and when accounting for persistence of OAC over the study period.

5.3 Descriptive statistics at study entry

As discussed in section 4.10, ResearchOne is a positive recording database, meaning that missing data is difficult to assess, and can only three items could realistically be checked. There was no missing data for sex or age. Data were missing for IMD in 32,336 (6%) of records. As missing data were minimal and in a variable that was not integral to the analysis, these data were not imputed.[328]

Two analytical groups were defined by the presence or absence of a recorded past medical history of AF at the time of study entry. This allowed AF prevalence in the whole cohort to be calculated. Prevalence of AF was then calculated by eFI category.

The baseline characteristics of the whole cohort was reported. This was then stratified by AF status, and baseline characteristics were reported and compared, and the difference in proportions between the groups plotted in a forrest plot. The number of eFI deficits and the eFI category were calculated and compared between the groups with and without AF, and presented graphically.

The cohort was then limited to just patients with AF. Risk scores (CHA_2DS_2-VASc and ATRIA) were calculated for each patient as described in section 4.10.5.1.1, and the group results were compared by eFI category. The prescription rates of medications of interest (section 4.10.5.1.3 and 4.10.5.1.4) and other baseline characteristics were compared by eFI category.

Baseline characteristics, risk scores, and prescription rates of medications of interest for patients with AF that were prescribed OAC were reported and compared with those of patients with AF that were not prescribed OAC. The cohort was then limited to patients with a CHA_2DS_2-VASc score of two or more, and these comparisons were repeated, between patients who were and were not prescribed OAC.

For all comparisons, data distribution was assessed using histograms, and normally distributed data were summarised using mean and standard deviation, and compared using Student's t-test. Non-parametric data were summarised using median and interquartile range and compared using the Mann–Whitney U-test. Categorical data were reported as a percentage, and proportions compared using Chi-square.

5.4 Rates of outcome events

Rates of the first event of each clinical outcome were reported (primary efficacy endpoints: all-cause mortality, stroke; primary safety endpoints; intracranial bleeding, gastrointestinal bleeding; secondary endpoints: TIA, falls).

Participants had differing periods of follow-up due to censorship (section 4.10.4.5). To account for this, the rate of each outcome event was reported per 1000 person years.

Rates were reported for each clinical outcome, and compared by:

- AF status
- Frailty category in patients with AF and without AF
- CHA_2DS_2-VASC score for patients with AF
- OAC prescription at baseline for patients with AF

To test the assumption that that age was an important confounder, rates were also reported by age category in patients with AF.

5.5 Prescription of oral anticoagulation in patients with AF

Prescription rates of OAC were reported at study entry and compared between each of the subgroups detailed above. Additionally, the odds ratio for prescription of OAC by frailty category was calculated using logistic regression, to estimate the association between frailty status and OAC prescription. The results from un-adjusted and adjusted models are presented as odds ratios with 95% confidence intervals.

The confounders included in the logistic regression model were identified through clinical consensus with the supervisory team. Adjustments were made for steroid, NSAID, macrolide antibiotic and PPI prescription in the previous year, concurrent antiplatelet prescription at time of study entry and GP practice. A further model was additionally adjusted for patient age, and past medical history of cancer, varices, GI bleed or IC bleed. An incremental model build was used in order to gain insight into the relative contribution of prescribed treatments and factors that relate to demographics and past medical history.

5.6 Survival models

The time to event was modelled for each outcome separately. Using survival analysis techniques gives the opportunity to incorporate time-to-failure and censorship information, which is not possible in other regression models. Survival analysis depends on two key concepts: the survivor function and the hazard function. The survivor function is the probability that the individual survives longer than a specified time, and the hazard function is the instantaneous potential for each unit of time for a failure event to occur, given survival up until that time point.[329]

5.6.1 Kaplan-Meier survival curves

Kaplan-Meier curves are used for a univariate nonparametric analysis of survival. Survival probabilities are estimated using a product limit formula, allowing curves to be drawn for each group (in this case frailty status), and compared with a log-rank test of the null hypothesis that there is a common survival curve between the two groups.[330]

5.6.2 Cox proportional hazard model

The Cox proportional hazard model is an example of a semiparametric model. These do not require assumptions about the distribution of failure times,[331] and in this dataset time-to-event is unlikely to be normally distributed. This is because risks of mortality and stroke increase with age. The model produces a hazard ratio between groups, where failure represents occurrence of the outcome of interest.

The results are presented as hazard ratios with 95% confidence intervals. Where possible these are displayed graphically using forest plots, for ease of interpretation. The unadjusted estimates are presented throughout. Additionally, adjustments were made in each case for age, sex, smoking status, IMD quintile and GP practice identifier, as these were identified as likely confounders. For the clinical outcome of all-cause mortality, a recorded past medical history of cancer was included as a confounder in addition, as this may be an important competing risk of death in older people.

5.6.2.1 Assumptions

The integral assumption within a Cox model is that the hazard for an individual is proportional to that of another individual, and that this proportionality is independent of time. This assumption is tested graphically, where the assumption is said to have been met if the lines do not cross between categories in a graph of the hazards. It is also tested numerically using a goodness of fit test, which gives p-value for evaluating the proportional hazards assumption.[332] Assumptions were tested for each outcome of interest.

5.6.2.2 Nesting, interaction and stratification

A multi-level approach was planned, using shared-frailty models to estimate and account for within-group correlation by general practice ID.[333] Whilst the intention was to use the general practice code as a frailty variable in every survival model, this is a computationally intense process that was not possible within the VRE. Instead, the general practice code was included as a variable in the Cox proportional hazard model, to account for differences between practices.

Frailty category was included as an interaction term in the Cox model, and results were stratified by frailty status.

5.7 Sensitivity analyses

5.7.1 Restricting the cohort to a more specific definition of AF

The CTV-3 codes that were used to define the AF cohort were critically reviewed for whether it was reasonable clinically to rely on them for a diagnosis of AF to be substantiated. This process was completed independently by two clinical researchers (myself, and Dr Oliver Todd). Disagreements were resolved through discussion.

Of the 37 codes that were included in the main analysis to identify AF, five were identified as insufficiently specific to be the sole determinant of an AF diagnosis:

- XaaaD: Provision of written information about atrial fibrillation
- XaLFh: Exception reporting: atrial fibrillation quality indicators
- XaLFi: Excepted from atrial fibrillation quality indicators: Patient unsuitable
- XaLFj: Excepted from atrial fibrillation quality indicators: Informed dissent
- 2432: O/E - pulse irregularly irreg.

The use of these codes within the dataset was summarised. Two sub-groups of patients were defined from the original analytical cohort of patients with AF. These were:

1. Excluded patients – these patients had AF identified only using one of the five codes listed above, and were excluded from the sensitivity analysis
2. Reduced analytical cohort – the remaining patients, who were included in the sensitivity analysis.

Baseline characteristics were reported and compared between the two subgroups. The rates of outcome events were calculated for each. The unadjusted and adjusted hazard ratios for each clinical outcome of interest were then reported for each subgroup to estimate the association between both frailty and OAC prescription.

5.7.2 Evaluating the intention to treat assumption

In the preceding analyses, the association between OAC and clinical outcomes was evaluated by OAC status at the start of the study (intention to treat). It is possible that patients may discontinue therapy during the study, and there may be systematic differences between those that remain on therapy throughout the study compared with those that discontinue (such as adverse clinical outcomes that may be associated with treatment, including bleeding events). A second sensitivity analysis was undertaken to investigate whether the findings of the main analysis were robust to an analysis that accounts for persistence on therapy.

The cohort of patients with AF was split into three:

1. Patients that were not prescribed OAC during the study
2. Patients that discontinued OAC during the study
3. Patients that persisted on OAC throughout the study

The baseline characteristics of patients in each group were described, and the rates of clinical outcome events reported in each. The association between OAC and clinical outcomes was evaluated separately for each of the three groups, and reported as hazard ratios with 95% confidence intervals.

5.8 Summary

- Baseline characteristics were reported and compared by AF status, frailty category, eligibility for OAC, and prescription of OAC.
- Rates of clinical outcomes were reported for each sub-group, standardised to 1000 person-years.
- Time to event analysis was used to estimate the association between frailty category and OAC status with clinical outcomes.
- A sensitivity analysis was performed to investigate whether the results of the main analysis were robust to a more specific definition of AF, and when accounting for persistence on OAC.

5.9 Conclusion

This chapter has detailed the analytical approach that was used in the quantitative component of the thesis. The results of these analyses will be presented over the next three chapters. The baseline characteristics and clinical outcomes for the whole analytical cohort will be reported in Chapter 6. The analytic cohort will then be restricted to patients with AF in Chapter 7, followed by a particular focus on the association between OAC prescription and clinical outcomes in patients with AF in Chapter 8.

Chapter 6 – Baseline characteristics and clinical outcomes for the whole cohort

6.1 Chapter introduction

This chapter will begin with a description of the derivation of the analytic cohort, followed by a summary of the baseline characteristics of the whole cohort, stratified by AF status. Clinical outcomes will be described using proportions, and rates standardised to 1000 person-years, and compared.

6.2 Chapter summary

In this cohort of 536,995 patients aged 65 years or older, 11.4% (61,177) had AF. The prevalence of AF was higher with increasing frailty category, and patients with AF had a greater burden of frailty and comorbidity than those without AF. Patients with AF experienced a higher incidence of adverse clinical outcomes during the follow-up period than those without AF, including all-cause mortality, stroke, and bleeding events.

6.3 Participants and data

6.3.1 Derivation of the analytic cohort

The analytical cohort of 536,955 patients was derived from the full patient table, which was used to assess the cohort eligibility criteria. There were 31,243 patients (5.5%) who were under the age of 65 years on the study entry date and were therefore excluded. Subsequently, the cohort was split into patients with a diagnosis of AF (n=61,177, 11.4%) and those without AF (n=475,778, 88.6%). Patients with AF recorded within their EHR, but without a date of AF diagnosis (n=96, 0.02%) were excluded from the cohort, Figure 11.[334]

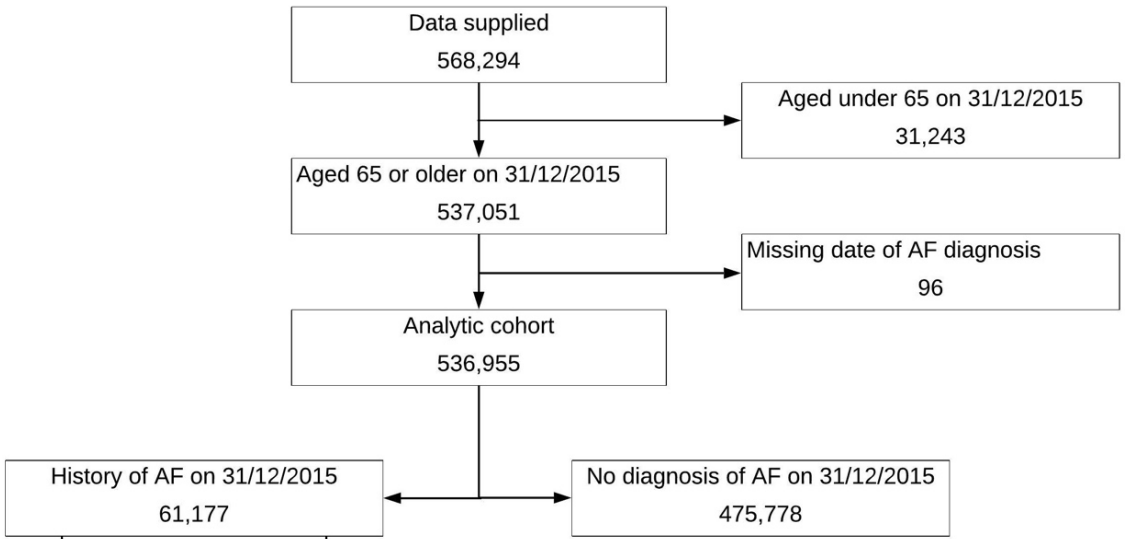


Figure 11: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram to show the derivation of the analytic cohort

6.3.2 Data available for analysis

Data were included from a total of 384 general practices. The number of patients registered at each practice ranged from a minimum of 16 to a maximum of 8,670 (median 1923, IQR 1244 to 2788). One practice reported no patients with AF. Of the remaining 383 practices, the minimum number of patients with AF at each practice was two, and the maximum was 1,016 (median 228, IQR 143 to 324). The minimum number of patients without AF at each practice was 13, and the maximum was 7,654 (median 1691, IQR 1089 to 2508).

In total, there were 671,135 person-years of follow-up. The minimum follow-up duration was 32 days, and maximum was 467 days. The mean follow-up duration was 15 months (456.5 days, SD 55.3). There were 74,238 person-years of follow-up for those with AF compared to 596,896 person-years for those without AF. The mean follow-up duration was 443.2 days (SD 81.8) in patients with AF, and 458.2 days (SD 50.6) in patients without AF. The range was 32 to 467 days for both groups.

Whilst it is not possible to summarise missing clinical data, due to the positive recording nature of ResearchOne, it was possible to identify missing data for patient demographics. Data were missing for IMD in 32,336 patients (6.0%). IMD rank was missing in 3,466 (5.7%) patients with AF, and in 28,870 (6.1%) patients without AF. There were no missing sex or age data.

6.3.3 Baseline characteristics

Overall, the median age was 73.8 years (interquartile range [IQR] 69.0 to 80.5). On average, patients with AF were older than those without (79.7, 73.3 to 85.5 years, compared with 73.1, 68.8 to 79.6 years). The difference in age distribution between patients with and without AF is shown in Figure 12.

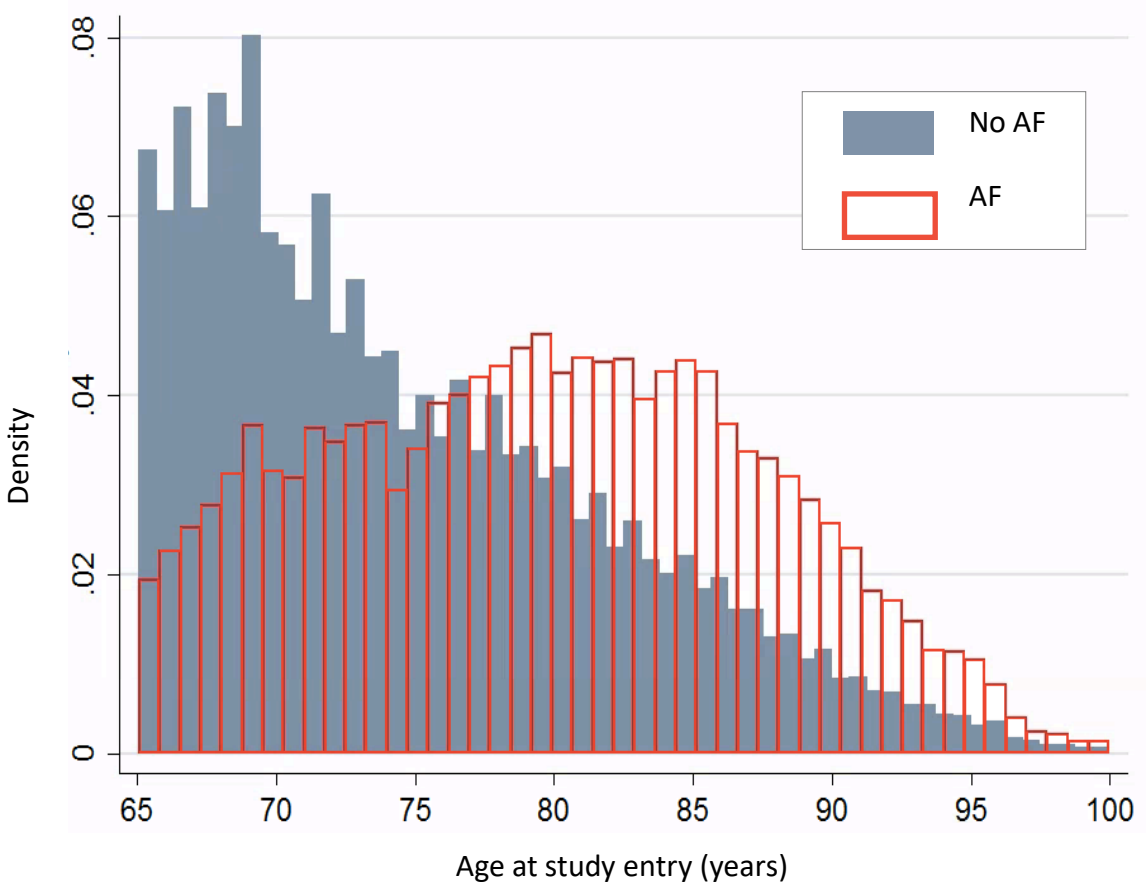


Figure 12: Histogram of age at study entry by AF status

Overall, 290,764 (54.2%) of the cohort were women. Women made up a greater proportion of the patients without AF than the group with AF (262,777, 55.2% of patients without AF compared to 27,987, 45.8% of patients with AF).

Postcode level deprivation as approximated by the IMD was similar for patients with AF and those without. In the AF group, 12.9% lived in the most deprived quintile, compared with 13.0% in the group without AF.

Of the complete cohort, 218,865 patients (41%) were in the robust category, 181,986 (34%) were classified as mildly frail, 91,411 (17%) as moderately frail, and 44,693 (8%) as severely frail, Figure 13.

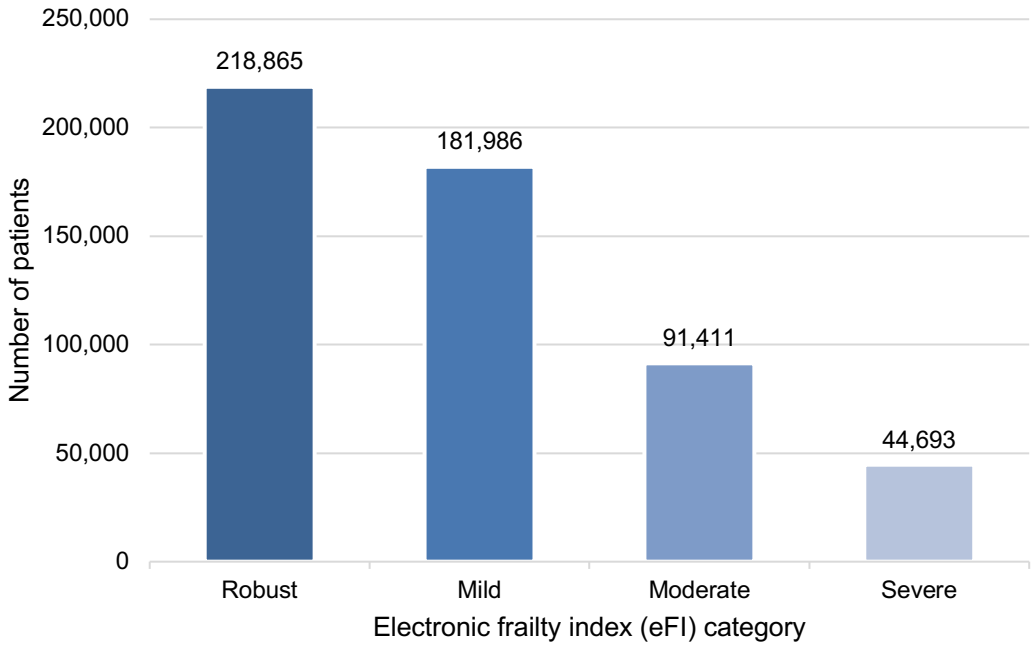


Figure 13: Histogram of frailty categories for the complete cohort, n=536,955

The prevalence of AF was higher with increasing frailty category, affecting 2.9% (6,443) of patients in the robust category, 11.2% (20,352) of those with mild frailty, 22.2% (20,315) moderate, and 31.5% (14,067) severe frailty, Figure 14.

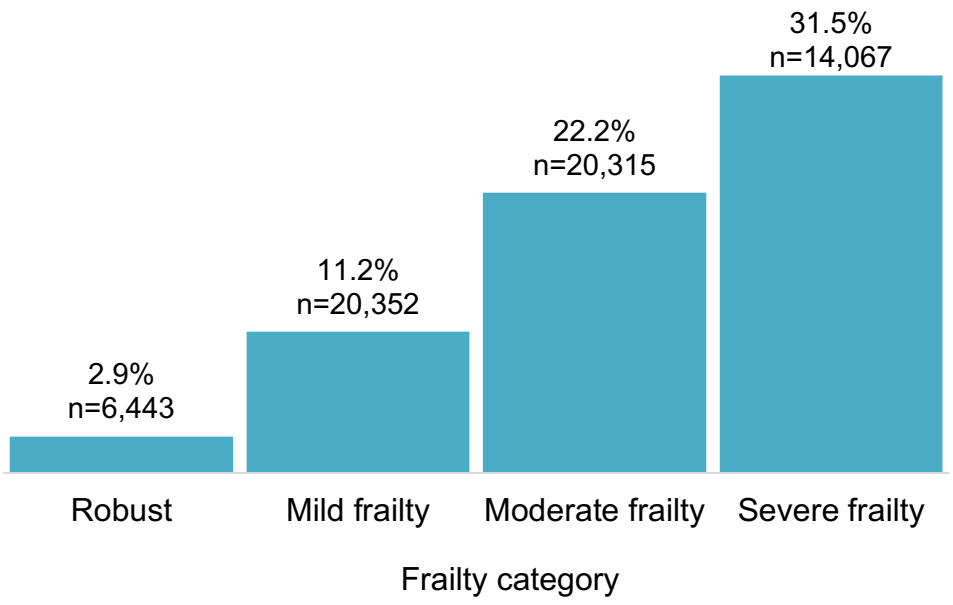


Figure 14: Bar chart to show the prevalence of AF by electronic frailty index category

The prevalence of AF was higher with increasing age, from 5% of patients aged 65 to 70 years to 24% of those aged 95 to 100, Table 25.

Table 25: Prevalence of atrial fibrillation by age category

Age category	n=	Patients with AF	AF prevalence, % (95% confidence interval)
≥65 to <70	169,357	8,391	5.0 (4.9 to 5.1)
≥70 to <75	127,409	10,463	8.2 (8.1 to 8.4)
≥75 to <80	98,257	12,721	13.0 (12.7 to 13.2)
≥80 to <85	72,305	13,215	18.3 (18.0 to 18.6)
≥85 to <90	45,144	10,194	22.6 (22.2 to 23.0)
≥90 to <95	19,693	5,046	25.6 (25.0 to 26.2)
≥95 to <100	4,790	1,147	23.9 (22.7 to 25.2)
Total	536,955	61,177	11.4 (11.3 to 11.5)

The group with AF had a higher burden of frailty than the group without AF. Of patients with AF, 89% (54,734) had mild, moderate or severe frailty, compared to 55% (263,356) of patients without AF. In patients with AF, 56% had moderate or severe frailty, compared with 21% of those without AF, Table 26.

Table 26: Electronic frailty index category by AF status

Frailty category	Complete cohort n=536,955	No history of AF n=475,778	AF n=61,177
Robust	218,865 (40.8%)	212,422 (44.7%)	6,443 (10.5%)
Mild	181,986 (33.9%)	161,634 (34.0%)	20,352 (33.3%)
Moderate	91,411 (17.0%)	71,096 (14.9%)	20,315 (33.2%)
Severe	44,693 (8.3%)	30,626 (6.4%)	14,067 (23.0%)

Overall, the median number of eFI deficits was 5 (IQR 3 to 8). Patients with AF had a median of 9 deficits (6 to 12) compared with 5 deficits (3 to 8) in patients without AF, Figure 15.

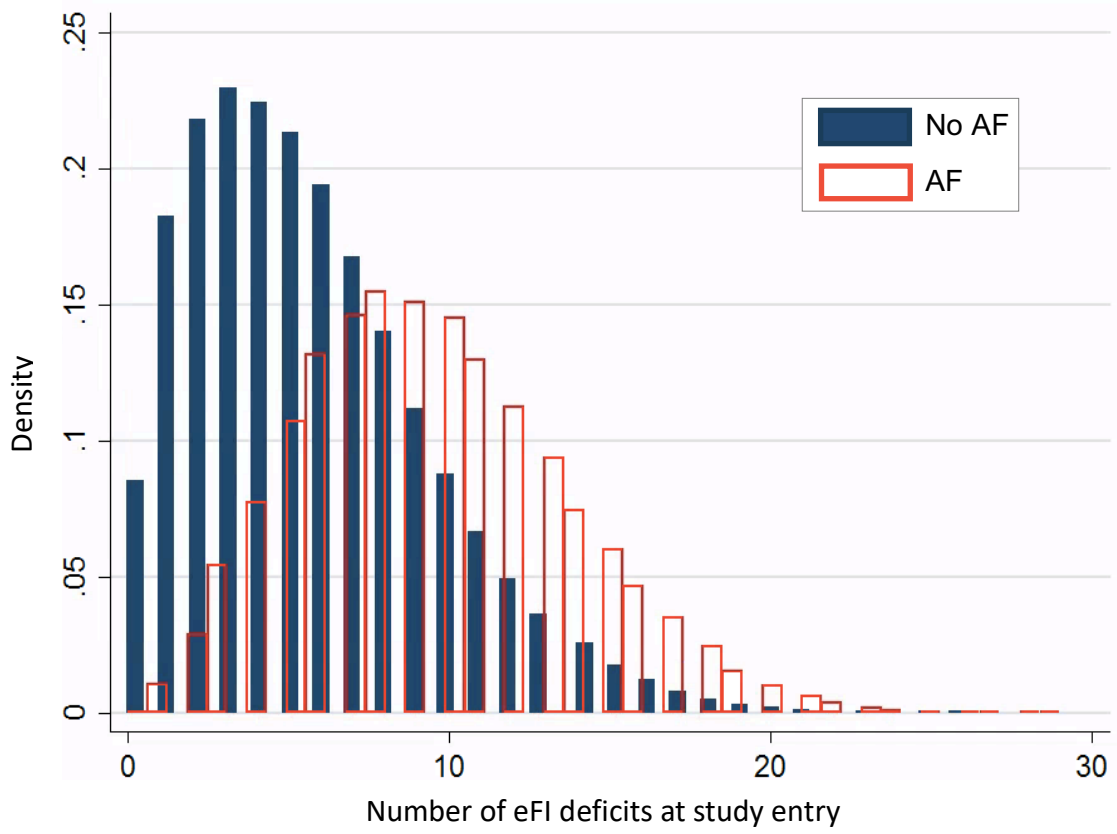


Figure 15: Number of electronic frailty index deficits by AF status at the time of study entry

The proportion of patients with a prior recorded history of every condition of interest was higher in patients with AF than those without ($p<0.001$ for each, Table 27). The greatest difference was in a recorded history of ischaemic heart disease, which was higher in patients with AF than those without (18.4% difference, 95% CI 18.0 to 18.8%, Figure 16). The next greatest difference was in history of heart failure (17.6% difference between those with AF and those without AF, 17.3 to 17.9%); hypertension (16.7%, 16.3 to 17.1%); and chronic kidney disease (15.9%, 15.6 to 16.3%). Each of the conditions mentioned above are also eFI deficits (shown in *italics* in Table 27). Valvular heart disease (11.3% difference, 95% CI 11.0 to 11.6%) and a history of stroke (8%, 7.8 to 8.3%) were more common in patients with AF than those without, and are not conditions that form part of the eFI.

Table 27: Baseline characteristics of the cohort by AF status

	All n=536,955	No history of AF n=475,778	History of AF n=61,177	p-value for difference between AF and non AF cohort
Age. Median (IQR)	73.8 (69.0-80.5)	73.1 (68.8-79.6)	79.7 (73.3–85.5)	<0.001
Female. n (%)	290,764 (54.2)	262,777 (55.2)	27,987 (45.8)	<0.001
IMD. n (%)				
Most deprived quintile	65,337 (13.0)	57,898 (13.0)	7,439 (12.9)	
Least deprived quintile	122,726 (24.3)	109,281 (24.5)	13,445 (23.3)	
Number of eFI deficits, median (IQR)	5 (3-8)	5* (3-8)	9 (6-12)	<0.001
Frailty category. n (%)				
Robust	218,865 (40.8)	212,422 (44.7)	6,443 (10.5)	<0.001
Mild	181,986 (33.9)	161,634 (34.0)	20,352 (33.3)	
Moderate	91,411 (17.0)	71,096 (14.9)	20,315 (33.2)	
Severe	44,693 (8.3)	30,626 (6.4)	14,067 (23.0)	
Past medical history				
Cancer	71,418 (13.3)	61,193 (12.9)	10,225 (16.7)	<0.001
Chronic kidney disease	102,529 (19.1)	82,204 (17.3)	20,325 (33.2)	<0.001
Diabetes	92,146 (17.2)	77,915 (16.4)	14,231 (23.3)	<0.001
Heart failure	25,553 (4.8)	13,103 (2.8)	12,450 (20.4)	<0.001
Hypertension	283,517 (52.8)	242,177 (51.0)	41,340 (67.6)	<0.001
Hyperthyroid	10,875 (2.0)	8,873 (1.9)	2,002 (3.3)	<0.001
Ischaemic heart disease	84,237 (15.7)	64,651 (13.6)	19,586 (32.0)	<0.001
Myocardial infarction	32,802 (6.1)	25,383 (5.3)	7,419 (12.1)	<0.001
Pulmonary embolism	9,597 (1.8)	7,718 (1.6)	1,879 (3.1)	<0.001
Stroke┼	25,412 (4.7)	18,173 (3.8)	7,239 (11.8)	<0.001
Infarct	10,593 (2.0)	7,414 (1.6)	3,179 (5.2)	<0.001
Unspecified	17,982 (3.4)	12,939 (2.7)	5,043 (8.2)	<0.001
Falls	56,407 (12.2)	53,649 (11.3)	11,758 (19.2)	<0.001
Valvular heart disease	23,003 (4.3)	14,263 (3.0)	8,740 (14.3)	<0.001
History of smoking	378,646 (70.7)	333,270 (70.3)	45,376 (74.3)	<0.001

┼ History of infarct or unspecified stroke. Not sum of each, but history of either. Conditions in *italics* are also deficits in the eFI.
Abbreviations eFI: electronic frailty index; IQR: interquartile range

Condition	Difference, % (95% CI)
Ischaemic heart disease	18.4 (18.0-18.8)
Heart failure	17.6 (17.3-17.9)
Hypertension	16.7 (16.3-17.1)
Chronic kidney disease	15.9 (15.6-16.3)
Valvular heart disease	11.3 (11.0-11.6)
Stroke	8.0 (7.8-8.3)
Infarct	3.6 (3.5-3.8)
Unspecified	5.5 (5.3-5.7)
Falls	7.9 (7.6-8.3)
Diabetes	6.9 (6.5-6.5)
Myocardial infarction	6.8 (6.5-7.1)
History of smoking	4.1 (3.8-4.5)
Cancer	3.9 (3.5-4.2)
Pulmonary embolism	1.4 (1.3-1.6)
Hyperthyroid	1.4 (1.3-1.6)

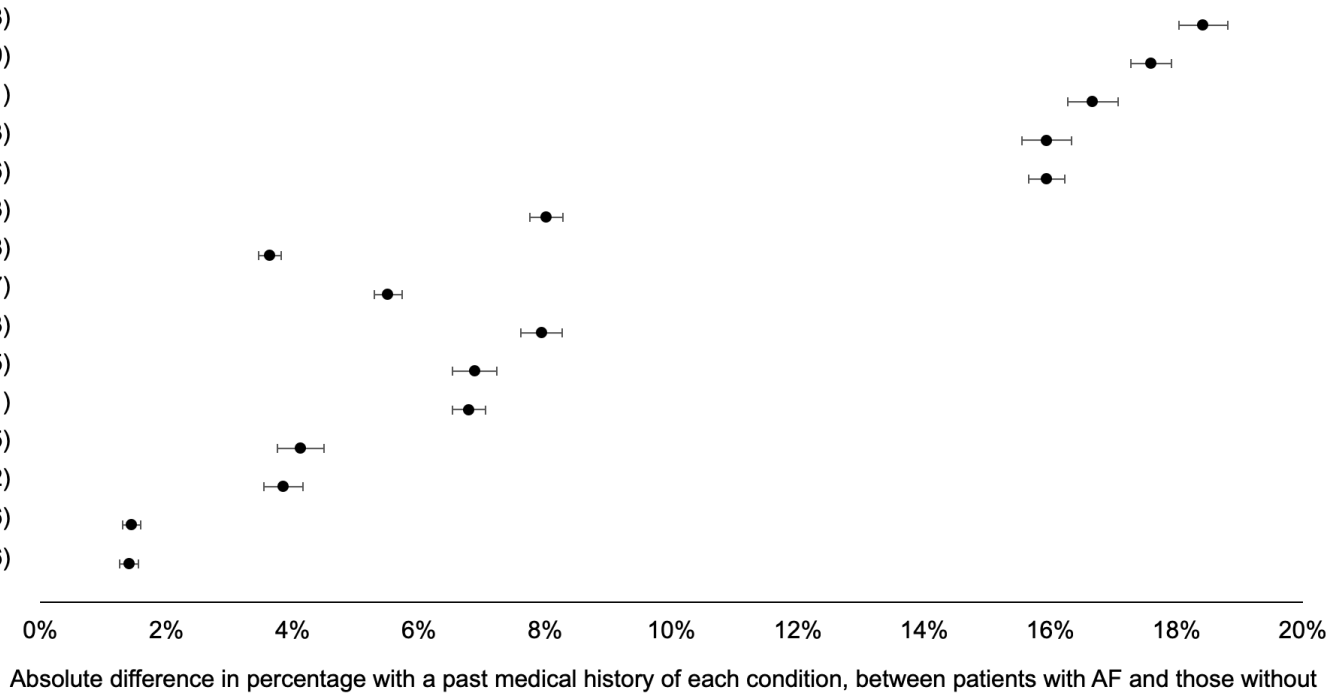
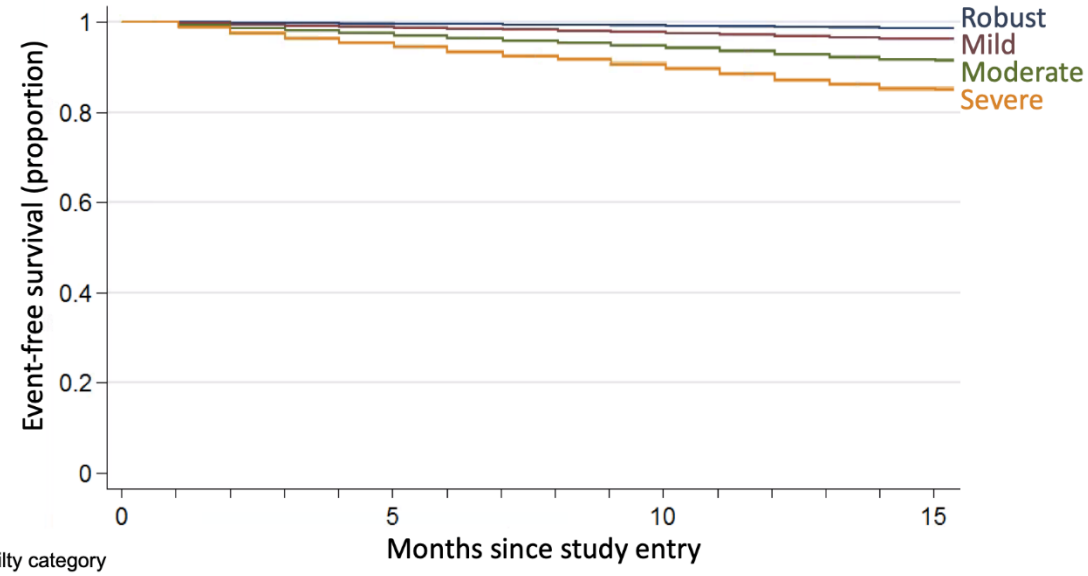


Figure 16: Difference in recorded past medical history between those with and without AF

6.4 Clinical outcomes

6.4.1 All-cause mortality

Over the duration of follow-up, 24,254 deaths (4.5%) were recorded in the complete cohort. The all-cause mortality rate was 36.1 (95% CI 35.7 to 36.6) per 1000 person-years (/1000pys).



Frailty category				
Robust	218,865	218,114	217,158	215,930
Mild	181,986	180,105	177,952	175,218
Moderate	914,111	89,124	86,665	83,744
Severe	44,693	42,601	38,086	38,086

Figure 17: Kaplan-Meier graph showing all-cause mortality by frailty category, with 95% confidence interval. n=536,955

The all-cause mortality rate was higher with increased frailty category (Figure 17), with a rate of 10.7 (95% CI 10.3 to 11.1) per 1000 person-years (/1000pys) in the robust group; 30.0 (29.3 to 30.7) /1000pys in the mild frailty group; 69.3 (67.8 to 70.9) /1000pys in the moderate frailty group and 126.4 (123.4 to 129.5) /1000pys in the group with severe frailty.

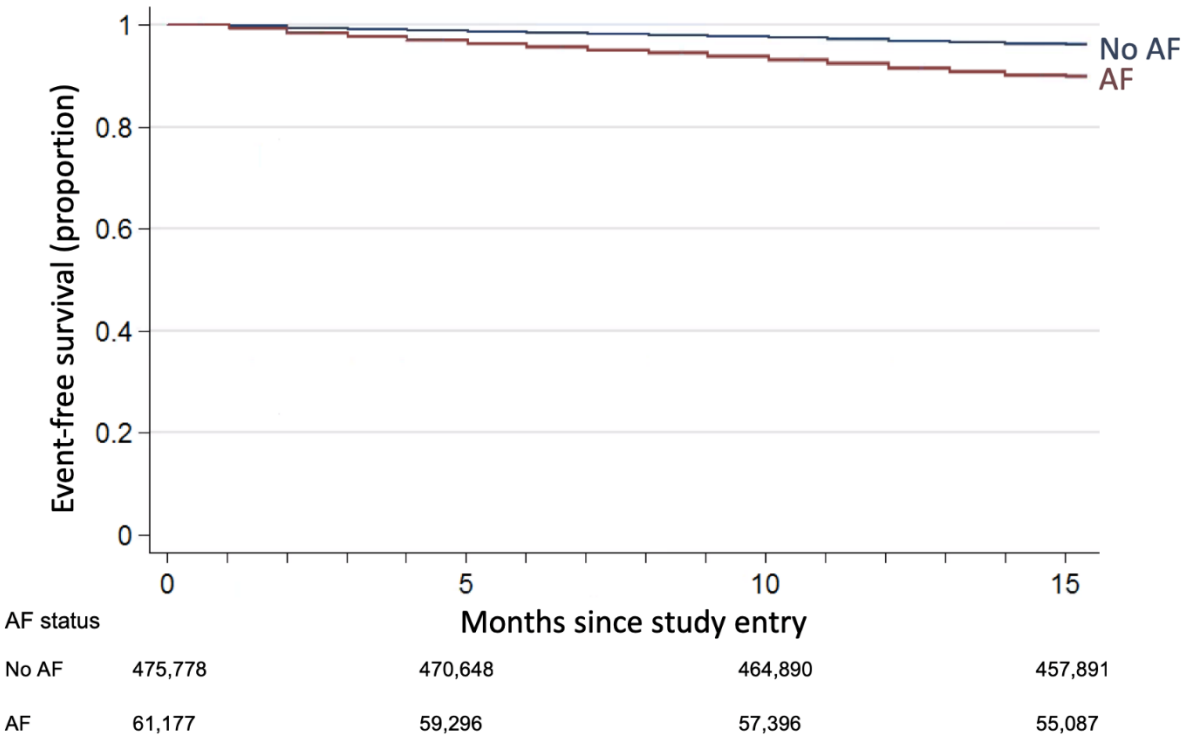


Figure 18: Kaplan-Meier graph showing all-cause mortality by AF status, with 95% confidence interval. n=536,955

All-cause mortality was also higher in patients with AF than in those without (Figure 18). In patients with AF there were 6,143 deaths (10.0%), conferring an all-cause mortality rate of 83.8 (81.7 to 85.9) /1000pys. In the group without AF there were 18,111 deaths (3.8%), with an all-cause mortality rate of 30.3 (29.9 to 30.8) /1000pys. The difference in mortality rate observed in patients with AF compared to those without AF was statistically significant (p <0.001), Table 28.

There was a 2.7-fold increased risk of death for those with AF compared to those without AF (HR 2.7, 95% CI 2.6 to 2.8). After adjustment for age, sex, IMD quintile and GP practice, the HR was 1.6 (1.55 to 1.64). Further adjustment for electronic frailty index category reduced the HR to 1.2 (1.18 to 1.26), suggesting that AF is associated with an increased risk of death, independent of baseline characteristics and frailty status.

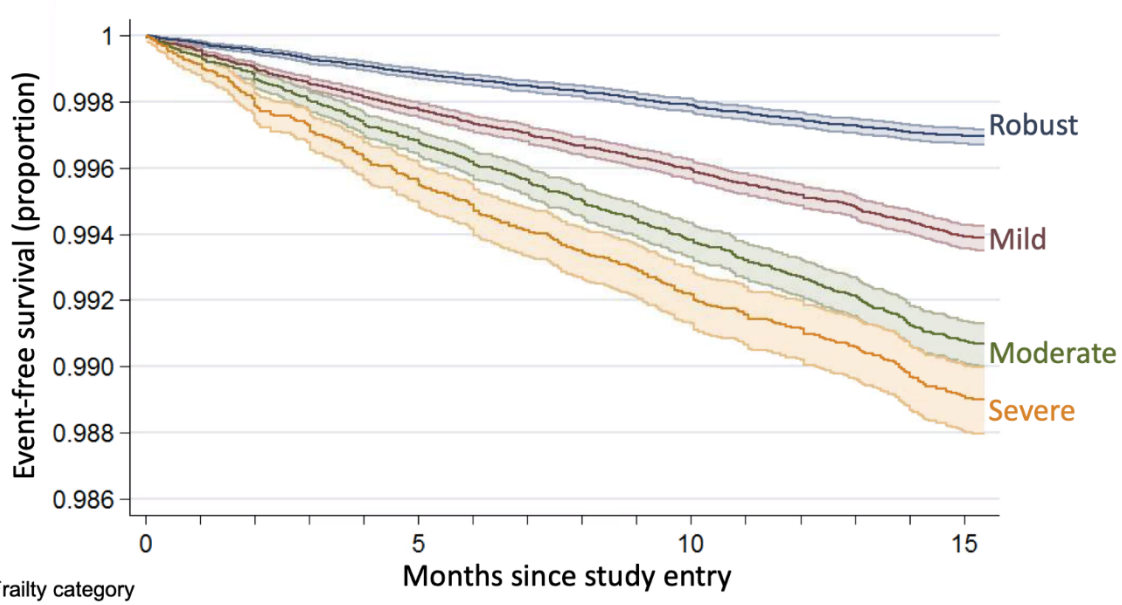
Table 28: Rates of outcome events by AF status

	Patients without AF, n=475,778		**Patients with AF**, n=61,177		Difference in proportions (95%CI) between patients with and without AF	p value for difference in proportions between patients with and without AF
	Events, n	Rate, /1000pys	Events, n	Rate, /1000pys		
Death	18,111	30.3 (29.9, 30.8)	6,143	83.8 (81.7, 85.9)	0.053 (0.051, 0.055)	<0.001
Stroke	2,418	4.1 (3.9, 4.2)	617	8.5 (7.8, 9.1)	0.004 (0.004, 0.005	<0.001
Ischaemic	1,117	1.9 (1.8, 2.0)	279	3.8 (3.4, 4.3)	0.002 (0.001, 0.002)	<0.001
Unspecified	1,301	2.2 (2.1, 2.3)	338	4.6 (4.2, 5.1)	0.002 (0.002, 0.003)	<0.001
GI bleed	2,653	4.5 (4.3, 4.6)	583	8.0 (7.4, 8.7)	0.004 (0.003, 0.004)	<0.001
IC bleed	493	0.8 (0.8, 0.9)	136	1.9 (1.6, 2.2)	0.001 (0.0007,0.0013)	<0.001
Falls	11,149	18.9 (18.5, 19.3)	2,707	37.7 (36.3, 39.2)	0.018 (0.016, 0.020)	<0.001
TIA	1,992	3.3 (3.2, 3.5)	372	5.1 (4.6, 5.6)	0.002 (0.001, 0.002)	<0.001

Abbreviations GI: gastrointestinal; IC: intracranial; TIA: transient ischaemic attack

6.4.2 Stroke

There were 1,396 patients (0.26%) with an episode of ischaemic stroke, and 1,639 (0.31%) with an episode of an unspecified stroke recorded during the follow-up period. After combining ischaemic and unspecified stroke categories, 3,035 patients (0.57%) had a recorded stroke event over the follow-up period, with a stroke rate for the whole cohort of 4.5 (4.4 to 4.7) /1000pys.



Frailty category				
Robust	218,863	217,872	216,726	215,329
Mild	181,983	179,740	177,305	174,277
Moderate	91,407	88,872	86,213	83,092
Severe	44,691	42,437	40,241	37,749

Figure 19:Kaplan-Meier graph showing incidence of first stroke event by frailty category, with 95% confidence interval. n=536,955

Stroke rates were higher with increasing frailty category (Figure 19). In the robust group the rate was 2.4 (2.2 to 2.6) /1000pys; in the mild frailty group 4.8 (4.5 to 5.1) /1000pys; in the moderate frailty group 7.3 (6.9 to 7.9) /1000pys, and in the severe frailty group 8.7 (8.0 to 9.6) /1000pys.

The recorded stroke incidence was higher in patients with AF than in those without AF (Figure 20). In patients with AF, 617 (1.0%) patients had a recorded stroke event (279 ischaemic and 338 unspecified). The rate of unspecified or

ischaemic stroke was 8.5 (7.8 to 9.1) /1000pys. In patients without AF, there were 2,418 (0.51%) patients with a stroke event recorded (1,117 ischaemic and 1,301 unspecified). The rate of unspecified or ischaemic stroke was 4.1 (3.9 to 4.2) /1000pys.

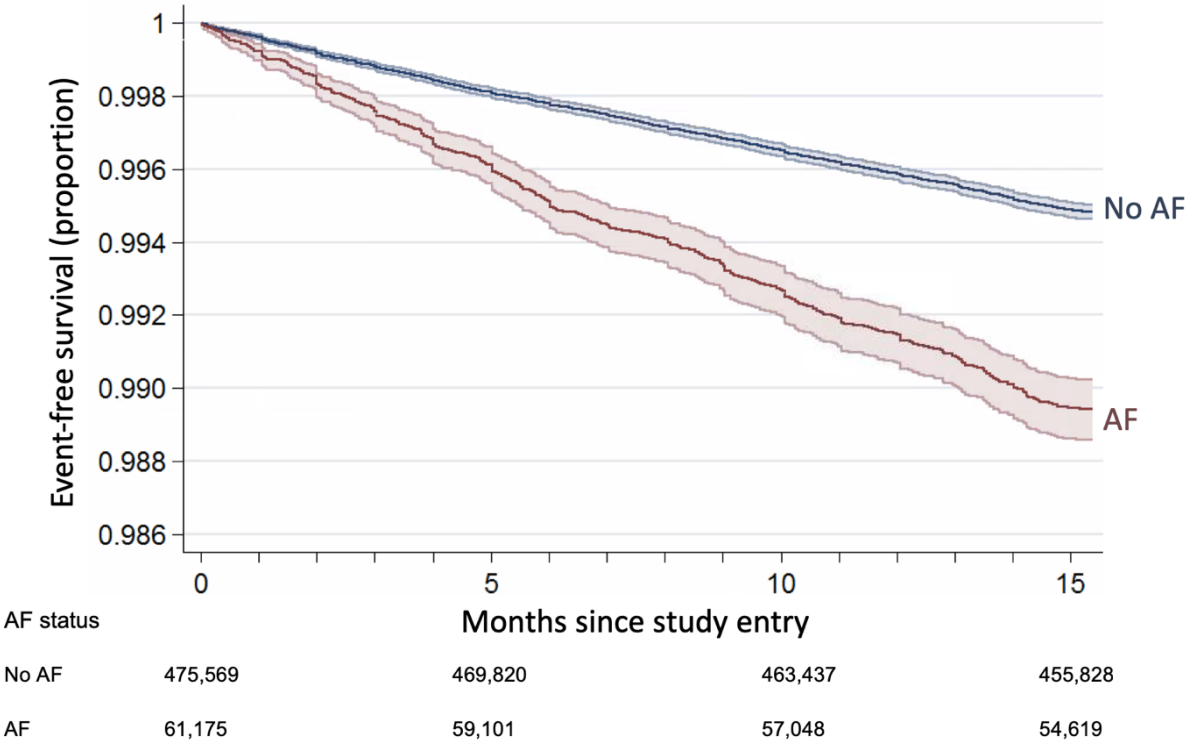
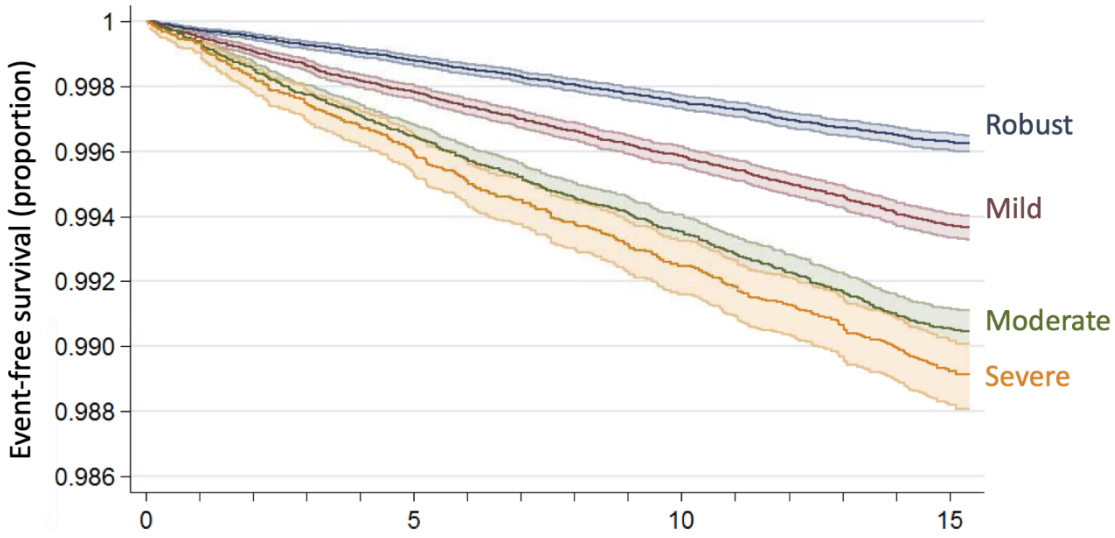


Figure 20: Kaplan-Meier graph showing first stroke event by AF status, with 95% confidence interval. n=536,955

The unadjusted hazard ratio for stroke in patients with AF compared to those without AF was 2.1 (95% CI 1.9 to 2.2). After adjustment for sex, smoking status, IMD quintile, age and GP practice, the HR was 1.5 (1.4 to 1.6). Further adjustment for eFI category reduced the estimate further to 1.3 (1.2 to 1.4). This suggests that differences in baseline characteristics explain some of the variation in stroke outcome between patients with AF and those without, and that eFI further accounts for some of the difference. This also suggests that AF is associated with stroke, independently of eFI category and baseline characteristics.

6.4.3 Bleeding

Overall, there were 3,236 (0.6%) patients with a recorded episode of GI bleed, conferring a rate of 4.8 (95% CI 4.7 to 5.0) /1000pys for first GI bleed events. The incidence of GI bleeding was higher with increased frailty category (Figure 21), from a rate of 2.9 (2.7 to 3.2) /1000pys in the robust group; 5.0 (4.7 to 5.3) /1000pys in the mild frailty group, 7.5 (7.0 to 8.0) /1000pys in the moderate frailty group to 8.6 (7.8 to 9.4) /1000pys in the severe frailty group.



Frailty category				
Robust	218,864	217,836	216,596	215,099
Mild	819,980	179,672	177,150	174,041
Moderate	91,407	88,757	86,006	82,828
Severe	44,691	42,370	40,134	37,575

Figure 21: Kaplan-Meier graph showing incidence of first gastrointestinal bleeding event by frailty category, with 95% confidence interval. n=536,955

The incidence of GI bleeds was higher in patients with AF than those without, (Figure 22) affecting 583 (1%) patients from the AF group, and 2,653 (0.6%) of the group without AF, The standardised rates were 8.0 (7.4 to 8.7) /1000pys in patients with AF, and 4.5 (4.3 to 4.6) /1000pys in patients without AF, p<0.001.

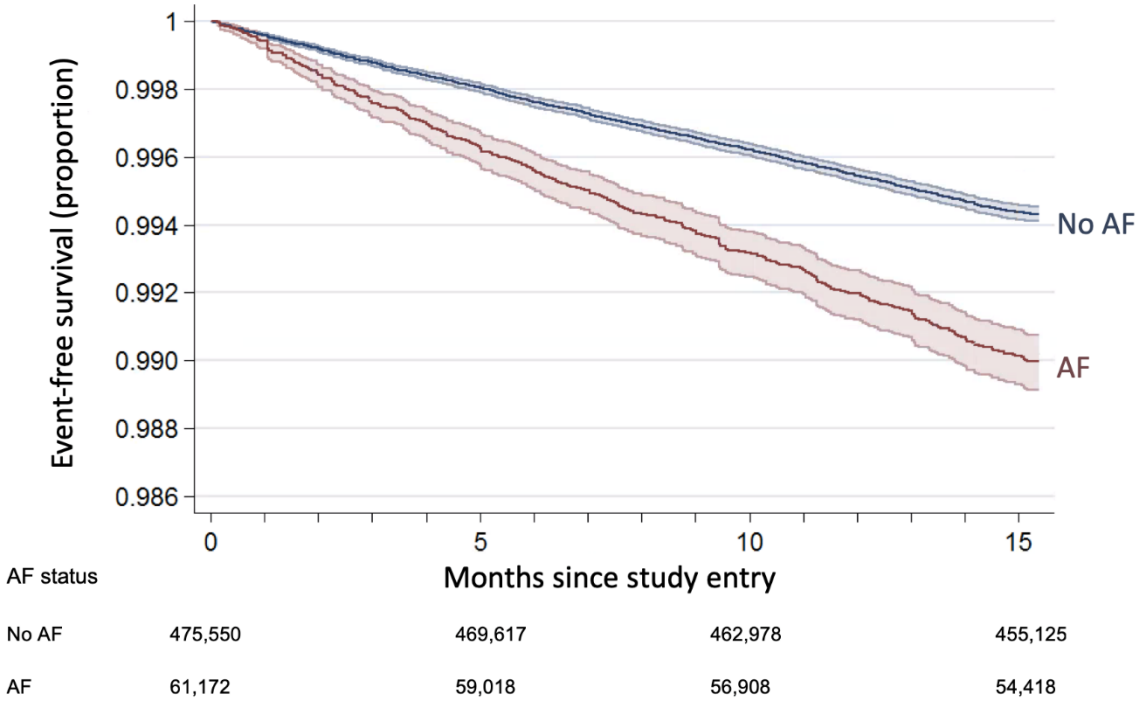
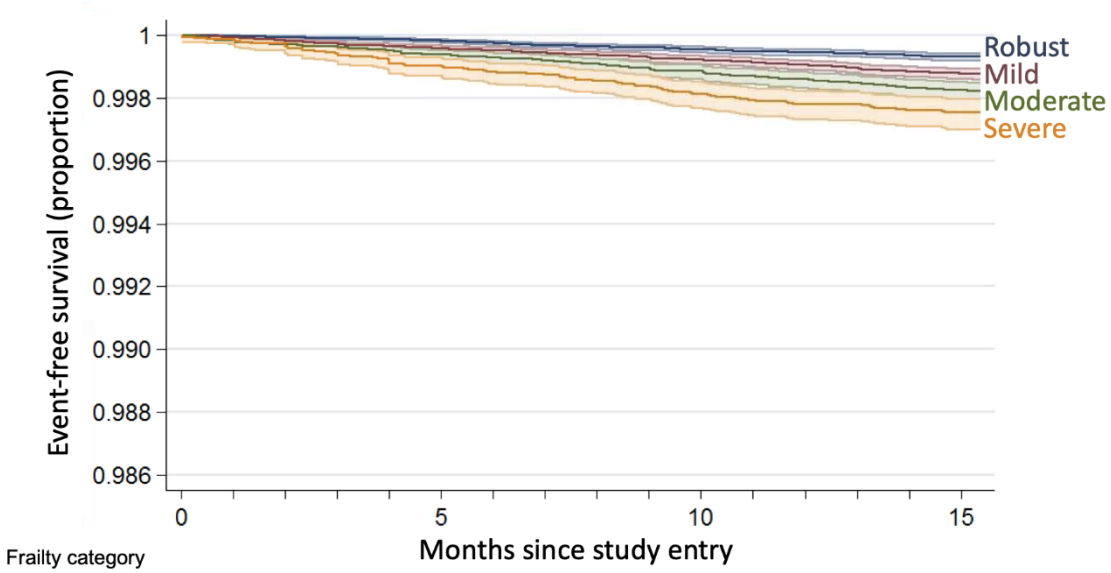


Figure 22: Kaplan-Meier graph showing first gastrointestinal bleeding event by AF status, with 95% confidence interval. n=536,955

Intracranial (IC) bleeds were comparatively rare: 629 patients (0.1%) had a recorded event in the overall cohort, with a rate of first IC bleeding event of 0.94 (0.9 to 1.0) /1000pys. The rate increased by frailty category (Figure 23), from 0.53 (0.46 to 0.63) /1000pys in the robust group to 0.96 (0.84 to 1.10) /1000pys in the group with mild frailty; 1.4 (1.2 to 1.6) /1000pys in the moderate frailty group and 2.0 (1.6 to 2.4) /1000pys in the group with severe frailty.



Frailty category				
Robust	218,864	218,059	217,032	215,747
Mild	181,985	180,018	177,784	174,956
Moderate	91,410	89,039	86,535	83,556
Severe	44,692	42,549	40,397	37,953

Figure 23: Kaplan-Meier graph showing incidence of first intracranial bleeding event by frailty category, with 95% confidence interval. n=536,955

Intracranial bleeds occurred more frequently in the group with AF than in those without AF (Figure 24). There were 136 (0.22%) patients with a recorded episode of IC bleed in the AF group, and 493 (0.10%) in the group without AF. Rates of IC bleeding were 0.8 (0.76 to 0.90) /1000pys in patients without AF, and 1.9 (1.6 to 2.2) /1000pys in patients with AF, $p<0.001$.

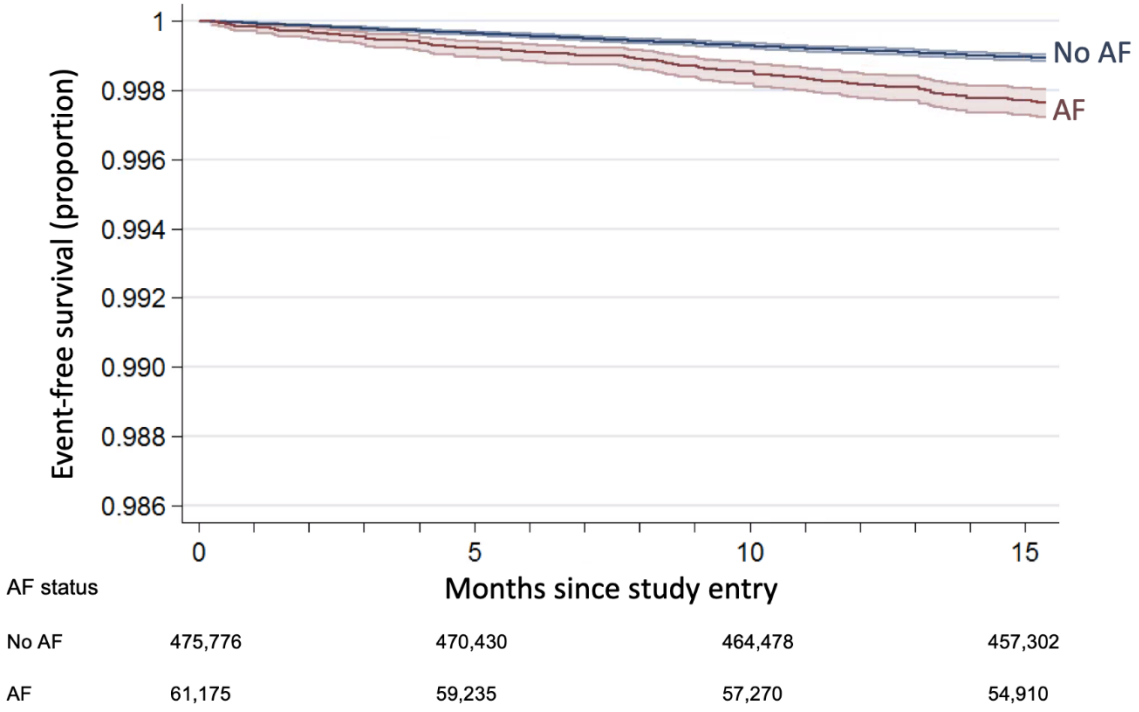


Figure 24: Kaplan-Meier graph showing first intracranial bleeding event by AF status, with 95% confidence interval. n=536,955

6.4.4 Falls

Overall, 13,856 (2.6%) patients had a recorded fall during the follow-up period. The overall rate was 20.9 (95% CI 20.6 to 21.3) /1000pys, although this increased with increasing frailty category, and was 6.0 (5.7 to 6.3) /1000pys in the robust group, 18.4 (17.9 to 19.0) /1000pys in the group with mild frailty, 42.4 (41.2 to 43.6) /1000pys in the group with moderate frailty and 67.1 (64.8 to 69.4) /1000pys in the group with severe frailty.

There were 2,707 (4.4%) patients with a recorded history of falls in the AF group, and 11,149 (2.3%) in the group without AF. Rates of falls was higher in patients with AF than those without: 37.72 (36.32 to 39.16) /1000pys in patients with AF, and 18.90 (18.5 to 19.25) /1000pys in patients without AF, p<0.001.

6.4.5 Transient ischaemic attack

There were 372 (0.61%) patients with a recorded history of TIA in the AF group, and 1,992 (0.42%) in the group without AF. Overall, the first TIA event rate was 3.5 (95% CI 3.4 to 3.7) /1000pys. Incidence of first TIA event was higher with increased frailty category, from 2.2 (2.0 to 2.3) /1000pys in the robust group; 3.5 (3.3 to 3.8) /1000pys in the mild frailty group, 5.6 (5.2 to 6.1) /1000pys in the moderate frailty group to 6.5 (5.8 to 7.2) /1000pys in the severe frailty group.

Rates of TIA was higher in patients with AF than those without: 5.09 (4.60 to 5.63) /1000pys in patients with AF, and 3.34 (3.20 to 3.49) /1000pys in patients without AF, $p<0.001$ (Table 28).

6.5 Summary of key findings

- In this primary care cohort of 536,995 patients aged 65 years or older, the prevalence of AF was 11.4%. The prevalence was higher with increased eFI category, from 2.9% in the robust group to 31.5% of those with severe frailty.
- The prevalence of AF was also higher with increased with age, from 5% of patients aged 65 to 70 years, to 24% of those aged 95 to 100
- Patients with AF tended to be older, and with a higher burden of frailty than patients without AF.
- A past medical history of every condition of interest was recorded more frequently in patients with AF than in those without AF. The difference was greater than 10% in the recorded history of ischaemic heart disease, heart failure, hypertension, chronic kidney disease and valvular heart disease.
- AF was associated with higher all-cause mortality, incident stroke, gastrointestinal bleeding, intracranial bleeding, falls and transient ischaemic attack compared to people without AF.
- AF was associated with an increased risk of mortality and stroke, independent of baseline characteristics and frailty status.

6.6 Conclusion

In this cohort, the prevalence of AF at study entry was 11.4%. The prevalence was higher with increased electronic frailty index category and increased age. Patients with AF had a higher burden of frailty than those without AF, and AF was associated with adverse outcomes including all-cause mortality, stroke, bleeding events, falls and transient ischaemic attack compared to patients without AF. In Chapter 7, the analysis will be restricted to patients with AF to examine the characteristics of this group in greater detail, and evaluate the association between frailty and clinical outcomes.

Chapter 7 - Baseline characteristics, frailty status and clinical outcomes of patients with atrial fibrillation

7.1 Chapter introduction

This chapter will describe the clinical characteristics and frailty status of patients who had a diagnosis of AF at study entry. Risk scores for stroke and bleeding, and prescription rates of key medications will be reported. Standardised rates of mortality, stroke, bleeding events, falls, and transient ischaemic attack will be reported by electronic frailty index category. The association between each clinical outcome and frailty category will be estimated using a univariate and then multivariate Cox proportional hazards model, and survival differences shown using Kaplan-Meier curves.

7.2 Chapter summary

Among 61,177 patients with AF, patients in higher frailty categories tended to be older, with a higher proportion of women, a longer history of AF, a greater proportion living in a nursing home and higher levels of deprivation.

Compared to the robust group, patients with AF and frailty had a significantly greater proportion with a past medical history of ischaemic heart disease, chronic kidney disease, hypertension, falls, and diabetes. Patients with frailty tended to have a greater risk score estimates for both bleeding and stroke, and were more frequently prescribed medications including statins, corticosteroids, non-steroidal anti-inflammatory drugs, macrolide antibiotics and proton pump inhibitors prior to study entry. Patients with frailty were also more commonly prescribed oral anticoagulation at the time of study entry.

Frailty and increased age were associated with higher rates of each clinical outcome of interest, including mortality, stroke, intracranial bleeding and gastrointestinal bleeding. The association between frailty and clinical outcomes was statistically significant for each frailty category compared to patients in the robust category for the outcome of mortality. For stroke and gastrointestinal bleeding, the relationship was only statistically significant for moderate and severe frailty. For intracranial bleeding, the difference between the robust category was only statistically significant for patients with severe frailty.

Following adjustment, the difference in clinical outcome between different frailty categories was eliminated for stroke, but a difference between the robust group and the moderate and severe groups persisted for GI bleeding. Patients with severe frailty had a significantly higher risk of IC bleeding than the robust group after adjustment. Compared to the robust group, adjusted mortality risk was higher with every frailty category.

7.3 Participants

The analyses in this chapter are based on a cohort of patients with a diagnosis of AF documented in their EHR at the start of the study (n=61,177). Of these 6,443 (10.5%) were in the robust category, 20,352 (33.3%) mild frailty, 20,315 (33.2%) moderate frailty and 14,067 (23.0%) severe frailty.

In total, there were 74,238 person-years of follow-up. The minimum follow-up duration was 32 days, and maximum was 467 days. The mean follow-up duration was 14.6 months (443 days, SD 82).

According to frailty category, the mean follow-up duration was 15.2 months (461 days, SD 41) in the robust group; 15.0 months (456 days, SD 57) in the group with mild frailty; 14.5 months (443 days, SD 83) in the group with moderate frailty; and 13.7 months (418 days, SD 113) in the group with severe frailty.

7.3.1 Baseline characteristics of patients with AF by frailty status

There were differences in baseline characteristics at the time of study entry across the frailty categories. With increasing frailty category, patients tended to be older, with a higher proportion of women, a greater proportion living in a nursing home, and a higher measure of postcode level deprivation, Table 29. The duration of AF since the time of diagnosis was higher with increasing frailty category. The median age of patients with AF was 79.7 (IQR 73.3 to 85.5) years, and was higher with increasing frailty category, at 72.7 (68.8 to 78.2) years in the robust group, 77.1 (71.6 to 82.7) years in those with mild frailty, 81.0 (75.4 to 86.2) years in those with moderate frailty, and 84.3 (79.1 to 89.0) years in those with severe frailty.

Overall, 45.8% (n=27,987) of patients with AF were women. The proportion of women was greater with increasing frailty category. In the robust group, 35.6% (95% CI 34.4 to 36.8%, n=2,293) were women, increasing to 41.1% (40.4 to 41.7%, n=8,355) of the group with mild frailty, 47.1% (46.4 to 47.8%, n=9,569) of the group with moderate frailty, and 55.2% (54.4 to 56.1%, n=7,770) of the group with severe frailty. In patients with AF, 8.6% (95% CI 8.4 to 8.8%, n=5,276) lived in a nursing home at study entry. The proportion living in a nursing home increased with frailty category, from 1.0% (0.8 to 1.3%, n=66) of patients in the robust category to 19.3% (18.7 to 20.0%, n=2,718) of patients in the severely frail category.

Patients tended to have a longer history of AF with increasing frailty category. The median time from a diagnosis of AF to entry into the study was 4.8 (IQR 2.1 to 9.4) years, but this ranged from 3.9 (1.8 to 7.7) years in the group with mild frailty to 5.8 (2.6 to 10.7) years in those with severe frailty. Neighbourhood level deprivation was higher in patients with increased frailty category. Overall, 12.9% (95% CI 12.6 to 13.2%, n=7,439) of patients with AF lived in the most deprived IMD quintile, and this increased from 8.8% (8.1 to 9.6%, n=532) in the robust group to 10.8% (10.3 to 11.2%, n=2,064) in those with mild frailty, 13.6% (13.2 to 14.1%, n=2,619) in those with moderate frailty and 16.7% (16.0 to 17.3%, n=2,751) in the group with severe frailty, Table 29.

Table 29: Baseline characteristics of patients with AF by frailty status

Variable	All n=61,177	Robust n=6,443	Mild frailty n=20,352	Moderate frailty n=20,315	Severe frailty n=14,067	p value for difference across categories	p value for trend across categories [c]
Demographics							
Age. Median (IQR)	79.7 (73.3-85.5)	72.7 (68.8-78.2)	77.1 (71.6-82.7)	81.0 (75.4-86.2)	84.3 (79.1-89.0)	<0.001[a]	<0.001
Female	27,987 (45.8)	2,293 (35.6)	8,355 (41.1)	9,569 (47.1)	7,770 (55.2)	<0.001	<0.001
Most deprived quintile	7,439 (12.9)	532 (8.8)	2,064 (10.8)	2,619 (13.6)	2,224 (16.7)	<0.001	<0.001
Least deprived quintile	13,445 (23.3)	1,620 (26.9)	4,672 (24.4)	4,402 (22.9)	2,751 (20.6)		
Living in a nursing home	5,276 (8.6)	66 (1.0)	729 (3.6)	1,763 (8.7)	2,718 (19.3)	<0.001	<0.001
Duration of AF, years prior to study start Median (IQR)	4.8 (2.1-9.4)	3.9 (1.8-7.7)	4.2 (1.9-8.6)	4.9 (2.2-9.7)	5.8 (2.6-10.7)	<0.001[a]	
Risk scores							
CHA_2DS_2-Vasc Mean (SD)	3.8 (1.5)	2.2 (0.98)	3.2 (1.2)	4.0 (1.3)	5.0 (1.4)	<0.001[b]	<0.001
ATRIA Median (IQR)	3 (2-6)	1 (0-2)	3 (1-5)	4 (3-6)	6 (4-8)	<0.001[a]	<0.001
Past medical history, n (%)							
Alcohol excess	1,855 (3.0)	163 (2.5)	649 (3.2)	616 (3.0)	427 (3.0)	0.065	0.404
Anaemia	12,145 (19.9)	193 (3.0)	2,018 (9.9)	4,552 (22.4)	5,382 (38.3)	<0.001	<0.001
Bleeding disorder	945 (1.5)	50 (0.8)	256 (1.3)	329 (1.6)	310 (2.2)	<0.001	<0.001
Cancer	10,225 (16.7)	695 (10.8)	3,071 (15.1)	3,656 (18.0)	2,803 (19.9)	<0.001	<0.001
Cirrhosis	261 (0.43)	16 (0.25)	73 (0.36)	75 (0.37)	97 (0.69)	<0.001	<0.001
Chronic kidney disease	20,325 (33.2)	318 (4.9)	4,334 (21.3)	7,888 (38.8)	7,785 (55.3)	<0.001	<0.001
Diabetes mellitus	14,231 (23.3)	127 (2.0)	2,661 (13.1)	5,536 (27.3)	5,907 (42.0)	<0.001	<0.001
Falls	11,758 (19.2)	109 (1.7)	1,489 (7.3)	3,928 (19.3)	6,262 (44.3)	<0.001	<0.001
Gastrointestinal bleed							
Upper	918 (1.5)	16 (0.25)	179 (0.88)	334 (1.6)	389 (2.8)	<0.001	<0.001
Lower	6,222 (10.2)	366 (5.7)	1,548 (7.6)	2,205 (10.9)	2,103 (15.0)	<0.001	<0.001
Unspecified	537 (0.88)	13 (0.20)	92 (0.45)	188 (0.93)	244 (1.7)	<0.001	<0.001

Variable	All n=61,177	Robust n=6,443	Mild frailty n=20,352	Moderate frailty n=20,315	Severe frailty n=14,067	p value for difference across categories	p value for trend across categories [c]
Haematuria	7,535 (12.3)	357 (5.5)	2,082 (10.2)	2,738 (13.5)	2,358 (16.8)	<0.001	<0.001
Haemoptysis	1,772 (2.9)	69 (1.1)	346 (1.7)	660 (3.3)	697 (5.0)	<0.001	<0.001
Heart failure	12,450 (20.4)	230 (3.6)	2,155 (10.6)	4,623 (22.8)	5,442 (38.7)	<0.001	<0.001
Hypertension	41,340 (67.6)	2,253 (35.0)	12,745 (62.6)	14,931 (73.5)	11,411 (81.1)	<0.001	<0.001
Hyperthyroidism	2,002 (3.3)	82 (1.3)	522 (2.6)	703 (3.5)	695 (4.9)	<0.001	<0.001
Intracranial bleeding	982 (1.6)	33 (0.51)	224 (1.1)	330 (1.6)	395 (2.8)	<0.001	<0.001
Ischaemic heart disease	19,586 (32.0)	312 (4.8)	3,932 (19.3)	7,425 (36.6)	7,917 (56.3)	<0.001	<0.001
Memory loss	7,880 (12.9)	79 (1.2)	1,095 (5.4)	2,679 (13.2)	4,030 (28.7)	<0.001	<0.001
Myocardial infarction	7,419 (12.1)	78 (1.2)	1,229 (6.0)	2,759 (13.6)	3,353 (23.8)	<0.001	<0.001
Obesity		828 (1.4)	28 (0.4)	168 (0.83)	309 (1.5)	323 (2.3)	<0.001
Peptic ulcer	3,676 (6.0)	83 (1.3)	709 (3.5)	1,315 (6.5)	1,569 (11.2)	<0.001	<0.001
Varices	86 (0.14)	<10 (<1)	<25 (0.11)	29 (0.14)	32 (0.23)	0.004	<0.001
Stroke	7,239 (11.8)	180 (2.8)	1,599 (7.7)	2,570 (12.7)	2,890 (20.5)	<0.001	<0.001
Ischaemic	3,179 (5.2)	111 (1.7)	760 (3.7)	1,157 (5.7)	1,151 (8.2)	<0.001	<0.001
Unspecified	5,043 (8.2)	76 (1.2)	1,024 (5.0)	1,754 (8.6)	2,189 (15.6)	<0.001	<0.001
TIA	6,019 (9.8)	133 (2.1)	1,247 (6.1)	2,192 (10.8)	2,447 (17.4)	<0.001	<0.001
Pulmonary embolism	1,879 (3.1)	65 (1.0)	385 (1.9)	717 (3.5)	712 (5.1)	<0.001	<0.001
Deep vein thrombosis	2,335 (3.8)	107 (1.7)	553 (2.7)	844 (4.2)	831 (5.9)	<0.001	<0.001

a=Kruskal-Walis; b=ANOVA; c=non-parametric test for trend (extension of Wilcoxon rank-sum test). All others: Chi-square
Conditions in *italics* are also deficits in the eFI.
Abbreviations eFI: electronic frailty index; IQR: interquartile range; SD: standard deviation; TIA: transient ischaemic attack

7.3.2 Risk scores

For the cohort of patients with AF, the mean CHA_2DS_2-Vasc was 3.8 (SD 1.5). The average score was higher with increased frailty category, from 2.2 (0.98) in the robust group to 3.2 (1.2) in the group with mild frailty, 4.0 (1.3) in moderate frailty and 5.0 (1.4) in the group with severe frailty. The upper and lower adjacent values, the 25th and 75th percentile, and the median are shown visually in Figure 25. Of the patients with AF, 95.1% (n=58,204) had a CHA_2DS_2-Vasc score of 2 or more.

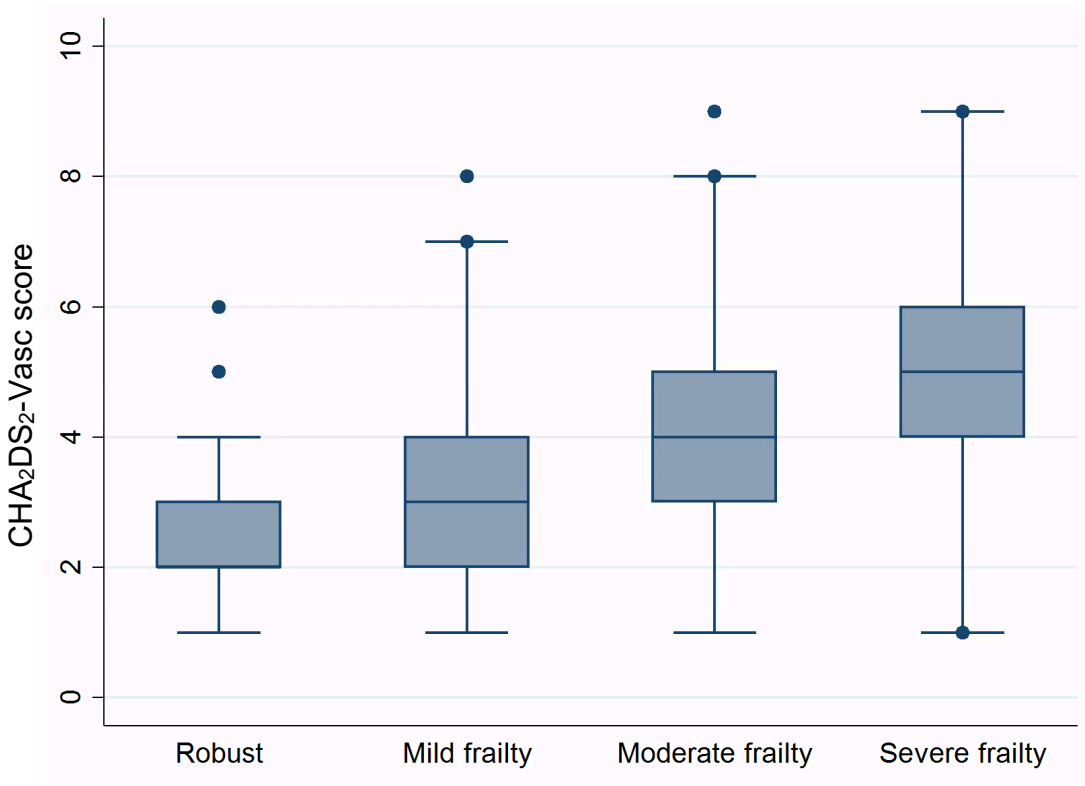


Figure 25: Box plot showing CHA_2DS_2-Vasc score at study entry by electronic frailty index category

The median ATRIA bleeding score was 3 (IQR 2 to 6). The median score increased with higher frailty categories, from 1 (0 to 2) in the robust group to 3 (1 to 5) in the group with mild frailty, 4 (3 to 6) in moderate frailty and 6 (4 to 8) in the group with severe frailty, Figure 26.

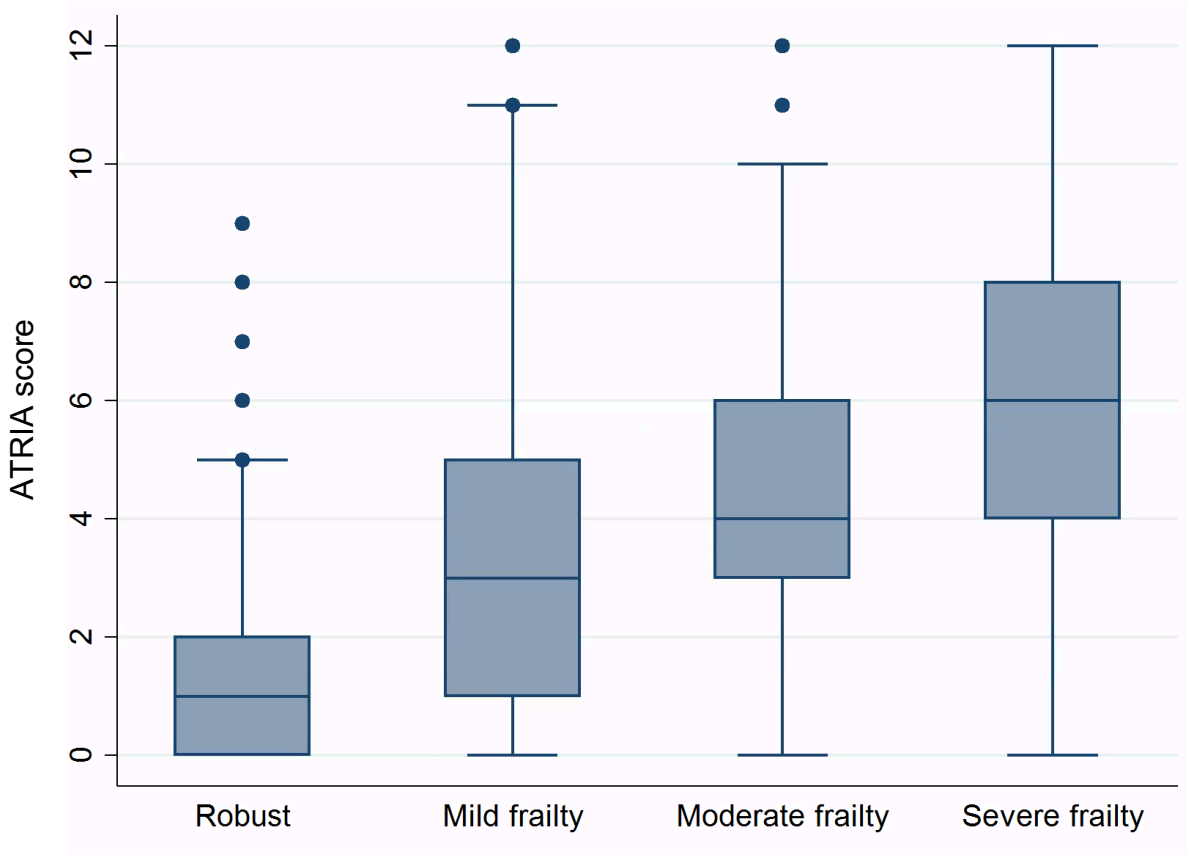


Figure 26: Box plot showing ATRIA score at study entry by electronic frailty index category

7.3.3 Past medical history

There was a stepwise positive association between frailty category and a recorded history of each condition of interest except alcohol excess. The most common co-morbidity was hypertension, which was recorded in 67.6% (95% CI 67.2 to 67.9%, n=41,340) of patients.

Five conditions had a difference in prevalence between the robust group and the group with severe frailty of 40% or more. These were ischaemic heart disease (difference 51.4%, 95% CI 50.5 to 52.4%), chronic kidney disease (50.4%, 49.4 to 51.4%), hypertension (46.2%, 44.8 to 47.5%), falls (42.8%, 41.9 to 43.7%), and diabetes (40.0%, 39.1 to 40.9%). These conditions were included in the eFI, but a similar pattern is seen in conditions outside the eFI, such as myocardial infarction (difference 22.6%, 95% CI 21.9 to 23.4%), transient ischaemic attack (15.3%, 14.6 to 16.4%), stroke (17.8%, 17.0 to

18.5%), haematuria (11.2%, 10.4 to 12.1%), peptic ulcer (9.9%, 9.3 to 10.5%) and cancer (9.1% 8.1 to 10.1%), Figure 27.

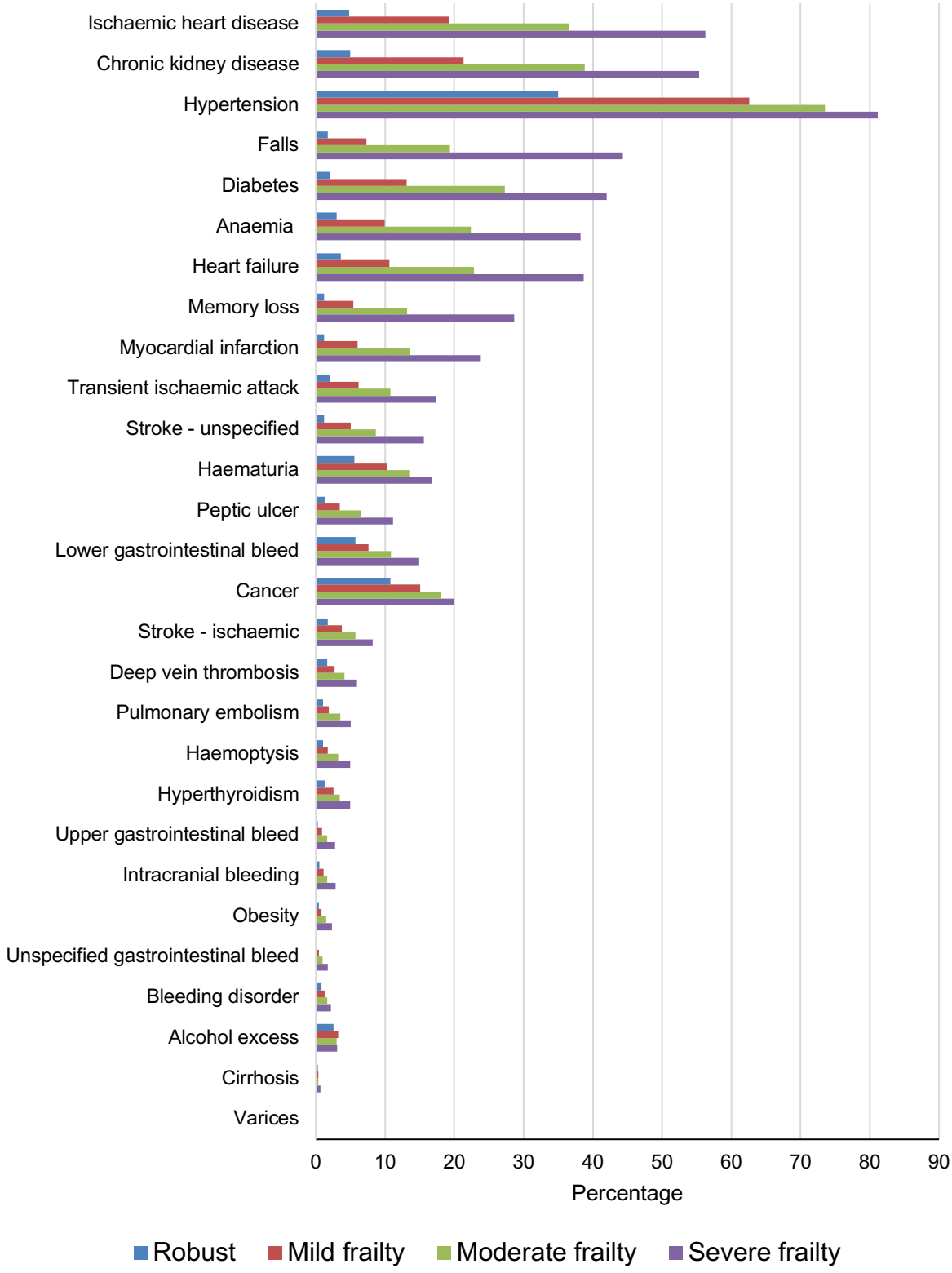


Figure 27: Chart showing percentage of patients with past medical history recorded of each condition of interest, by frailty category

7.3.4 Medications

Of the medications studied, statins were the most commonly prescribed among patients with AF. In the year prior to study entry, 59.7% (95% CI 59.3 to 60.0%, n=36,498) of patients had been prescribed a statin. Statins were prescribed more commonly with increasing frailty category from 37.4% (36.2 to 38.6%, n=2,410) of those in the robust category to 67.5% (66.7 to 68.3%, n=9,494) of the group with severe frailty, Figure 28 and Table 30.

The proportion of patients prescribed a proton pump inhibitor (PPI) exhibited the greatest difference in prescription rate by frailty categories. A PPI was prescribed in the year prior to study entry in 16.4% (95% CI 15.5 to 17.3%, n=1,057) of patients in the robust category, 32.8% (32.2 to 33.5%, n=6,677) in mild, 43.7% (43.1 to 44.4%, n=8,885) in moderate, and 56% (55.3 to 56.9%, n=7,892) in the category of severe frailty.

Each of the other drugs in the study showed a positive stepwise association between prescription rates and increased frailty status, including macrolide antibiotic, non-steroidal anti-inflammatory drugs (NSAID), corticosteroid, and statin in the year prior to study entry showed a positive stepwise association with increased frailty status, as did the prescription of anti-epileptic and anti-platelet medication at study entry, Figure 28 and Table 30.

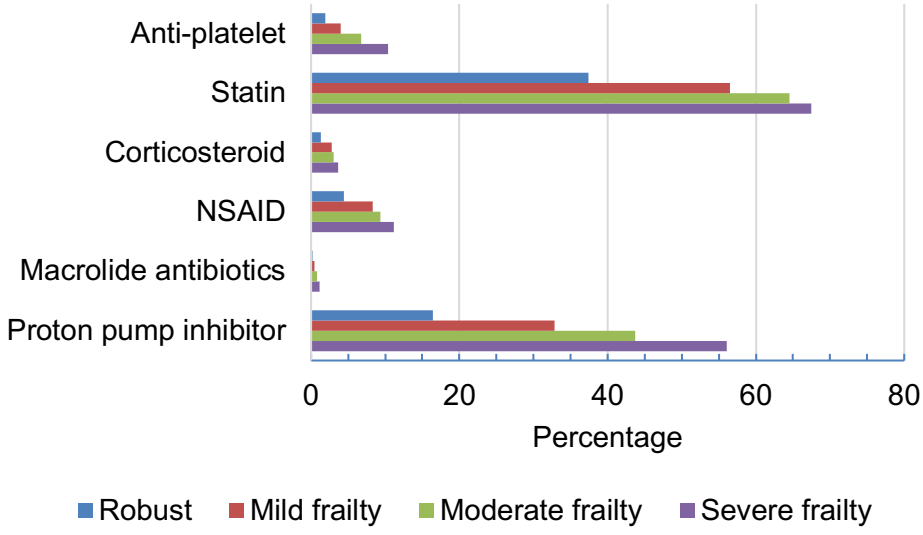


Figure 28: Bar chart showing proportion of patients prescribed key medications of interest, by frailty status

Oral anticoagulation was prescribed in 52.4% (95% CI 52.0 to 52.8%, n=32,079) of patients with AF. OAC was more commonly prescribed with increasing frailty category. This will be discussed in greater detail in Chapter 8, as will the association between OAC use and clinical outcomes.

DOAC were prescribed in sub-therapeutic doses (as defined by the BNF and described in section 4.10.3) in 85 patients (0.14%, 95% CI 0.11 to 0.17%). The proportion prescribed sub-therapeutic doses of DOAC was highest in patients with severe frailty (0.23%, 95% CI 0.15 to 0.31, n=32, Chi-square p=0.015, non-parametric test for trend p=0.017), Table 30.

Table 30: Medication history of patients with AF, by frailty status

Variable	All n=61,177	Robust n=6,443	Mild frailty n=20,352	Moderate frailty n=20,315	Severe frailty n=14,067	p value for difference across categories	p value for trend across categories [a]
Medications in the previous year, n (%)							
Proton pump inhibitor	24,511 (40.1)	1,057 (16.4)	6,677 (32.8)	8,885 (43.7)	7,892 (56.1)	<0.001	<0.001
Macrolide antibiotics	427 (0.70)	10 (0.16)	90 (0.44)	167 (0.82)	160 (1.1)	<0.001	<0.001
NSAID	5,453 (8.9)	284 (4.4)	1,697 (8.3)	1,903 (9.4)	1,569 (11.2)	<0.001	<0.001
Corticosteroid	1,777 (2.9)	87 (1.4)	566 (2.8)	613 (3.0)	511 (3.6)	<0.001	<0.001
Statin	36,498 (59.7)	2,410 (37.4)	11,492 (56.5)	13,102 (64.5)	9,494 (67.5)	<0.001	<0.001
Anti-epileptic							
Carbemazepine	235 (0.38)	11 (0.17)	56 (0.28)	87 (0.43)	81 (0.58)	<0.001	<0.001
Phenytoin	180 (0.29)	6 (0.09)	47 (0.23)	67 (0.33)	60 (0.43)		
Medications at the time of study entry, n (%)							
OAC at study entry	32,079 (52.4)	2,574 (40.0)	10,730 (52.7)	11,264 (55.5)	7,511 (53.4)	<0.001	<0.001
Any anti-platelet at study entry	3,767 (6.2)	123 (1.9)	812 (4.0)	1,377 (6.8)	1,455 (10.3)	<0.001	<0.001
DOAC at sub-therapeutic dose	85 (0.14)	7 (0.11)	24 (0.12)	22 (0.11)	32 (0.23)	0.015	0.017

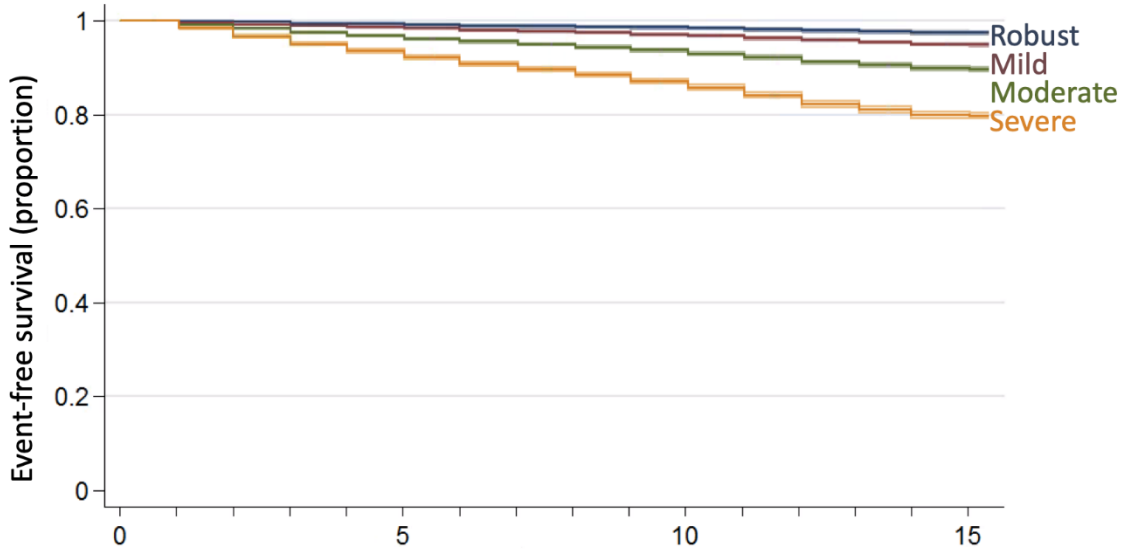
a=non-parametric test for trend (extension of Wilcoxon rank-sum test). All others: Chi-square
Abbreviations DOAC: direct oral anticoagulants; NSAID: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulation

7.4 Frailty and clinical outcomes in patients with AF

7.4.1 All-cause mortality

Overall, 6,143 (10.0%) patients died during the follow-up period, conferring a mortality rate of 83.8 (95% CI 81.7 to 85.9) /1000pys.

Mortality rates were higher with increased frailty category, Figure 29. In the robust group, 2.6% (164) of patients died during the follow-up period. In the group with mild frailty, 5.1% (1,042) died, with moderate frailty 10.3% (2,096), and severe frailty 20.2% (2,841). All-cause mortality rates, standardised to 1000 person-years were 20.3 (17.5 to 23.7); 41.5 (39.0 to 44.1); 86.2 (82.6 to 89.9); 179.5 (173.0 to 186.2) /1000pys for robust, mild, moderate and severe frailty categories respectively.



Frailty category				
Robust	6,443	6,397	6,352	6,280
Mild	20,352	20,069	19,760	19,319
Moderate	20,315	19,671	19,034	18,242
Severe	14,067	13,159	12,250	11,246

Figure 29: Kaplan-Meier graph showing all-cause mortality by frailty category in patients with AF, with 95% confidence interval. n=61,177

Mortality rates were positively correlated with age at study entry. For patients aged 65 to 70 years at study entry, the mortality rate was 23.3 (20.5 to 26.4) /1000pys, which increased by age category to a rate of 344.4 (312.3 to 379.7) /1000pys in the oldest category, 95 to 100 years of age. The steep rise in mortality rate with increasing age category is shown in Figure 30, and the rates of clinical outcomes by age category are reported in Table 31.

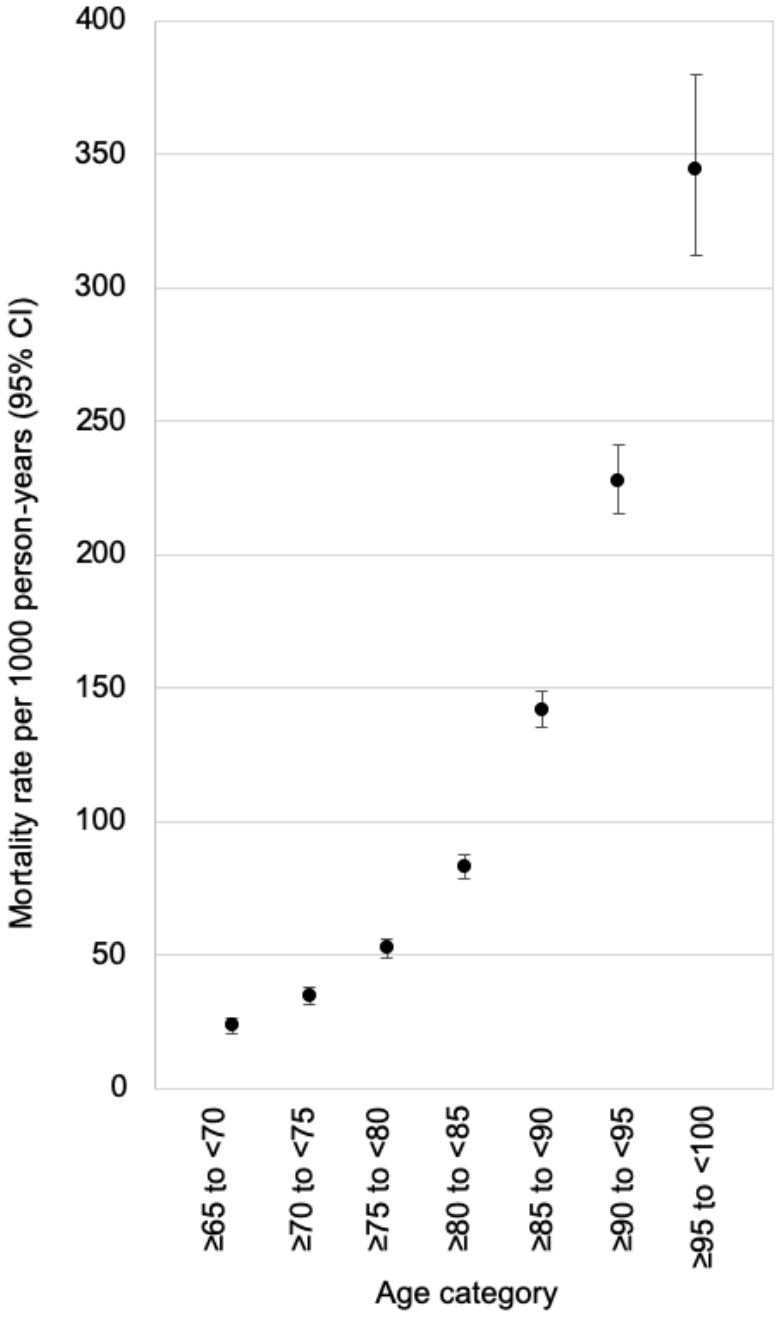


Figure 30: Mortality rates /1000pys by age category in patients with AF, n=61,177

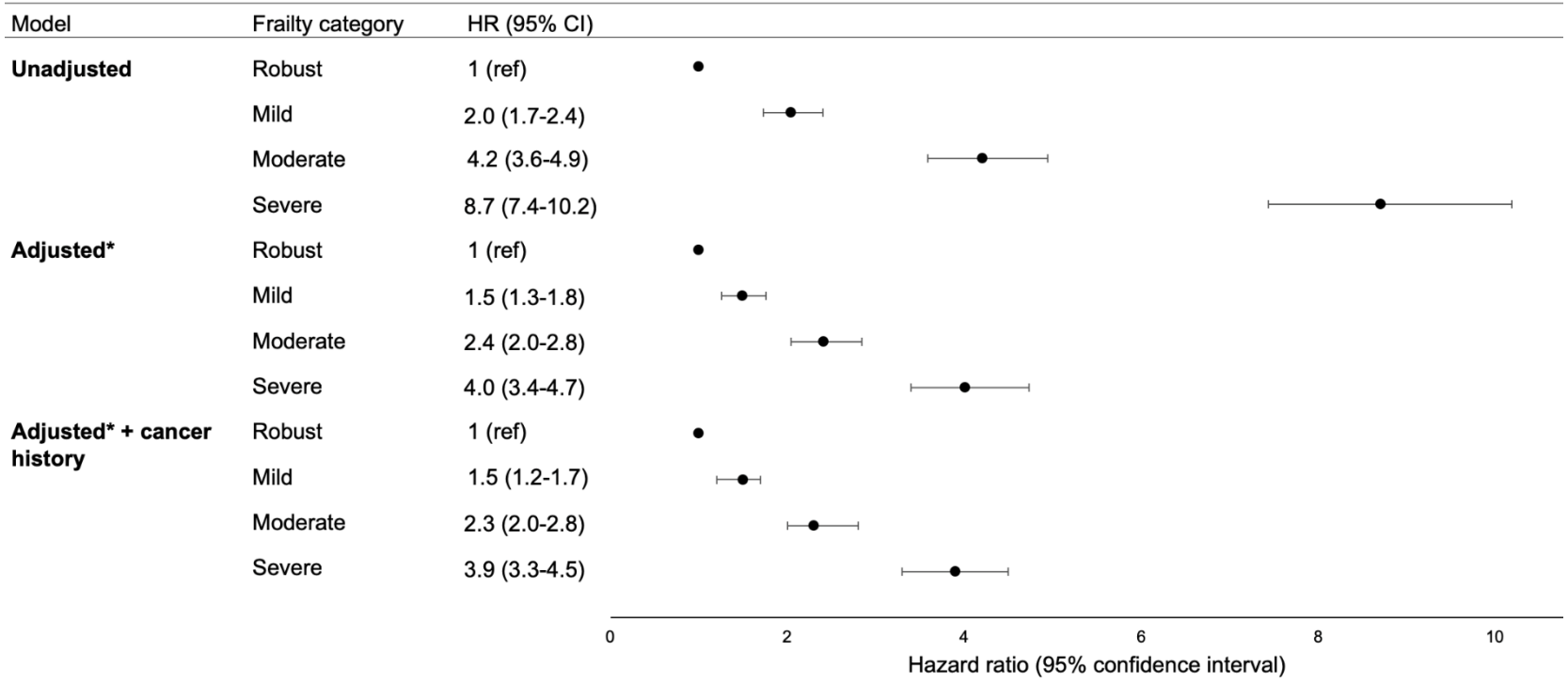
Table 31: Outcomes by frailty status, all patients with AF stratified by age category. Rates per 1000 patient years

		All n=61,177	Robust n=6,443	Mild n=20,352	Moderate n=20,315	Severe n=14,067
	Events, n	Rate	Rate	Rate	Rate	Rate
Death						
All ages	6,143	83.8 (81.7-85.9)	20.3 (17.5-23.7)	41.5 (39.0-44.1)	86.2 (82.6-89.9)	179.5 (173.0-186.2)
65-<70	244	23.3 (20.5-26.4)	10.5 (7.3-15.2)	16.4 (13.1-20.4)	34.6 (27.8-43.2)	80.6 (62.5-104.1)
70-<75	447	34.4 (31.4-37.8)	15.3 (11.1-24.2)	20.2 (16.8-24.3)	48.5 (41.9-56.2)	88.0 (73.6-105.4)
75-<80	817	52.4 (48.9-56.1)	18.6 (12.8-26.9)	31.0 (26.8-35.8)	55.3 (49.4-62.0)	111.0 (99.3-124.1)
80-<85	1317	83.0 (78.6-89.6)	26.9 (18.2-39.8)	49.4 (43.5-56.1)	75.3 (68.7-82.6)	147.8 (136.4-160.2)
85-<90	1668	141.7 (135.1-148.7)	71.9 (49.9-103.4)	81.3 (71.4-92.5)	128.4 (118.3-139.2)	206.4 (192.8-221.0)
90-<95	1248	227.8 (215.5-240.8)	131.3 (77.7-221.6)	154.2 (132.0-180.2)	185.5 (167.5-205.4)	300.0 (278.7-323.0)
95-<100	402	344.4 (312.3-379.7)	150.7 (48.6-467.3)	238.1 (175.3-323.4)	328.8 (227.4-389.8)	394.2 (345.9-449.2)
Ischaemic or unspecified stroke						
All	617	8.5 (7.8-9.1)	5.4 (4.0-7.2)	7.2 (6.2-8.3)	9.3 (8.2-10.6)	10.7 (9.2-12.5)
65-<70	48	4.6 (3.5-6.1)	1.1 (0.4-3.4)	5.5 (3.8-8.1)	5.7 (3.3-9.9)	8.2 (3.7-18.3)
70-<75	83	6.4 (5.2-8.0)	5.6 (3.2-9.6)	4.5 (3.0-6.6)	8.2 (3.3-9.9)	11.2 (6.8-18.6)
75-<80	111	7.2 (5.9-8.6)	8.0 (4.6-14.1)	6.3 (4.5-8.6)	7.7 (5.7-10.4)	7.6 (5.0-11.7)
80-<85	119	7.5 (6.3-9.0)	8.7 (4.3-17.3)	7.2 (5.2-10.1)	8.2 (6.2-10.8)	6.7 (4.6-9.8)
85-<90	152	13.0 (11.1-15.2)	12.4 (5.2-29.9)	12.5 (9.0-12.4)	12.2 (9.3-15.9)	14.3 (11.0-18.6)
90-<95	77	14.1 (11.3-15.2)	9.4 (1.3-66.8)	16.7 (10.4-26.9)	13.1 (8.9-19.2)	14.1 (10.0-19.9)
95-<100	27	23.3 (16.0-33.9)	51.3 (7.2-360.0)	29.1 (12.1-69.8)	27.4 (15.2-49.5)	17.6 (9.5-32.7)
Gastrointestinal bleed						
All ages	583	8.0 (7.4-8.7)	4.5 (3.2-6.2)	5.8 (4.9-6.8)	9.0 (7.9-10.3)	11.8 (10.2-13.6)
65-<70	69	6.6 (5.2-8.4)	2.6 (1.2-5.4)	7.0 (5.0-9.9)	7.9 (5.0-12.6)	15.3 (8.4-27.5)
70-<75	87	6.7 (5.5-8.3)	5.6 (3.2-9.6)	4.7 (3.2-6.9)	10.7 (7.9-14.6)	6.7 (3.5-12.9)
75-<80	123	7.9 (6.7-9.5)	4.7 (2.2-9.8)	5.2 (3.7-7.4)	10.5 (8.1-13.7)	10.6 (7.3-15.2)
80-<85	135	8.6 (7.2-10.1)	6.5 (2.9-14.4)	6.2 (4.3-8.9)	7.7 (5.7-10.2)	13.3 (10.1-17.4)
85-<90	103	8.8 (7.3-10.7)	5.0 (1.2-19.9)	6.1 (3.8-9.8)	8.9 (6.5-12.1)	11.1 (8.3-14.9)
90-<95	52	9.6 (7.3-12.6)	9.5 (1.3-67.7)	7.8 (3.9415.7)	7.6 (4.6-12.6)	12.0 (8.3-17.4)
95-<100	14	12.1 (7.2-20.4)	0	0	7.48 (2.4-23.2)	19.5 (10.8-35.2)

		All n=61,177	Robust n=6,443	Mild n=20,352	Moderate n=20,315	Severe n=14,067
	Events, n	Rate	Rate	Rate	Rate	Rate
Intracranial bleed						
All ages	136	1.9 (1.6-2.2)	1.2 (0.7-2.3)	1.2 (0.9-1.8)	1.9 (1.4-2.5)	3.1 (2.4-4.1)
65-<70	<5	0.3 (0.1-0.9)	0.4 (0.1-2.6)	0.4 (0.1-1.7)	0	0
70-<75	11	0.9 (0.5-1.5)	0.9 (0.2-3.4)	0.9 (0.4-2.2)	1.1 (0.4-2.9)	0
75-<80	33	2.1 (1.5-3.0)	2.0 (0.6-6.2)	1.2 (0.6-2.5)	2.6 (1.6-4.4)	3.3 (1.7-6.3)
80-<85	36	2.3 (1.6-3.2)	3.2 (1.0-10.0)	2.1 (1.1-3.4)	1.7 (0.9-3.1)	3.2 (1.9-5.6)
85-<90	32	2.7 (1.9-3.9)	2.5 (0.4-18.0)	1.4 (0.5-3.8)	2.9 (1.7-4.9)	3.5 (2.1-5.9)
90-<95	17	3.1 (1.9-5.0)	0	2.0 (0.5-7.8)	2.0 (0.8-5.4)	4.7 (2.6-8.5)
95-<100	<5	3.4 (1.3-9.1)	0	5.8 (0.8-41.0)	2.5 (0.4-18.0)	3.5 (0.9-14.0)
Fall						
All ages	2,707	37.1 (36.3-39.1)	6.1 (4.6-8.1)	20.2 (18.5-22.0)	40.1 (36.7-42.8)	79.5 (75.2-84.2)
65-<70	74	7.1 (5.6-8.9)	3.3 (1.7-6.3)	5.8 (3.9-8.4)	9.7 (6.4-14.7)	22.1 (13.6-36.1)
70-<75	187	14.5 (12.6-16.8)	3.9 (2.0-7.4)	8.8 (6.7-11.7)	18.9 (14.9-23.9)	45.5 (35.4-58.6)
75-<80	411	26.8 (24.3-29.5)	6.0 (3.1-11.5)	16.7 (13.7-20.3)	27.3 (23.2-32.5)	59.7 (51.1-69.7)
80-<85	660	42.6 (39.5-46.0)	8.7 (4.3-17.3)	26.4 (22.1-31.4)	40.8 (36.0-46.3)	73.7 (65.7-82.7)
85-<90	758	66.9 (62.3-71.8)	22.6 (11.8-43.4)	59.9 (53.1-67.6)	59.9 (53.1-67.6)	96.5 (87.1-106.9)
90-<95	487	93.6 (85.6-102.3)	28.7 (9.3-88.9)	93.8 (81.0-108.6)	93.8 (81.0-108.6)	105.1 (92.4-119.5)
95-<100	130	118.6 (99.9-140.8)	105.8 (26.5-423.2)	96.4 (69.8-133.0)	97.0 (69.8-133.0)	158.0 (127.4-196.0)
Transient ischaemic attack						
All ages	372	5.1 (4.6-5.6)	3.2 (2.2-4.8)	3.71 (3.0-4.6)	5.5 (4.7-6.6)	7.6 (6.3-9.0)
65-<70	31	3.0 (2.1-4.2)	2.6 (1.2-5.4)	3.0 (1.8-5.0)	3.5 (1.8-7.1)	2.7 (0.7-11.0)
70-<75	57	4.4 (3.4-5.7)	2.6 (1.2-5.7)	4.0 (2.6-6.0)	6.3 (4.2-9.4)	4.5 (2.0-9.9)
75-<80	65	4.2 (3.3-5.3)	2.0 (0.6-6.2)	4.1 (2.7-6.0)	3.6 (2.6-5.6)	6.9 (4.4-10.8)
80-<85	95	6.0 (4.9-7.4)	6.5 (2.9-14.5)	3.1 (1.9-5.1)	7.0 (5.2-9.5)	8.0 (5.6-11.3)
85-<90	78	6.7 (5.3-8.3)	5.0 (1.2-19.9)	4.6 (2.7-8.0)	5.5 (3.7-8.2)	9.5 (6.9-10.1)
90-<95	34	6.2 (4.5-8.7)	19.1 (4.8-76.2)	2.9 (1.0-9.1)	6.0 (3.4-10.6)	7.3 (4.5-11.7)
95-<100	12	10.3 (5.9-18.2)	0	11.7 (2.9-46.8)	12.5 (5.2-29.9)	8.8 (3.7-21.1)

The association between frailty category and all-cause mortality was modelled using a Cox regression, and a positive, stepwise association between frailty status and all-cause mortality was demonstrated. Compared with the robust group, those in the mild, moderate and severe frailty groups had a HR for mortality of 2.0 (95% CI 1.7 to 2.4), 4.2 (3.6 to 4.9), and 8.7 (7.4 to 10.2) respectively, Figure 31.

Adjustment for age, sex, smoking status, IMD quintile and GP practice identifier reduced the magnitude of the association, as did further adjustment for a past medical history of cancer. This indicates that the adjustment factors explain some of the difference between groups, but that a statistically significant difference in mortality by frailty category remained, Figure 31.



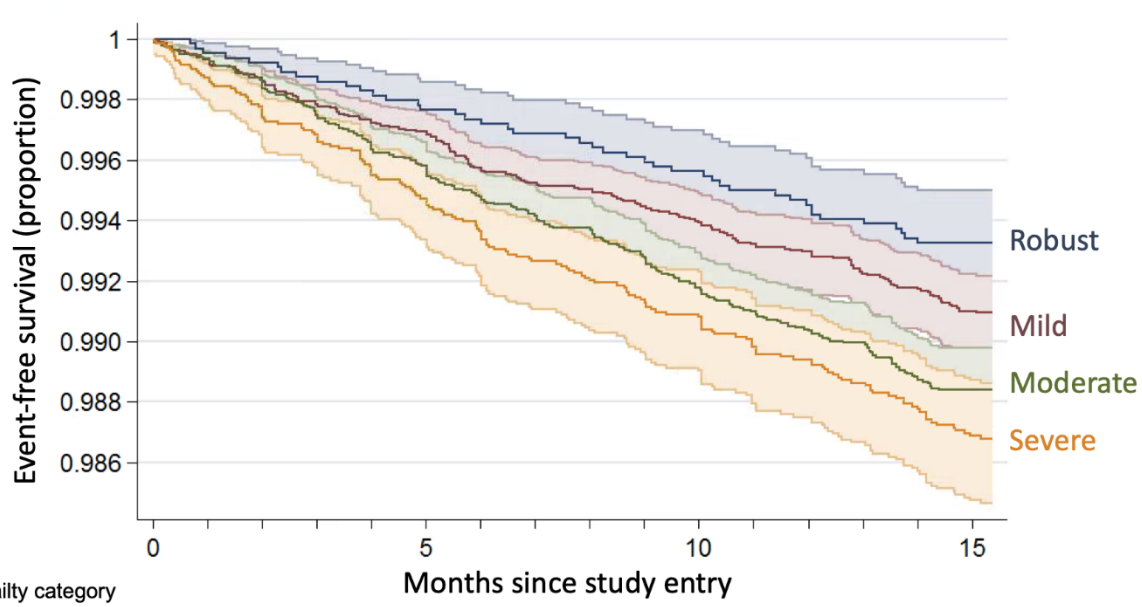
* Adjusted for age, sex, smoking status, IMD quintile, and GP practice ID

Figure 31: Association between frailty status and all-cause mortality in patients with AF, n=61,177

7.4.2 Ischaemic or unspecified stroke

Overall, 617 patients (1.0%, 95% CI 0.9 to 1.1%) had a stroke during the follow-up period, with a rate of first stroke event of 8.5 (95% CI 7.8 to 9.1) /1000pys. Of these, 45% (n=279) had an ischaemic stroke, and 55% (n=338) an unspecified stroke.

The rate of first stroke event increased with increased frailty category. The standardised rates for the robust, mild, moderate and severe frailty groups were 5.4 (4.0 to 7.2); 7.2 (6.2 to 8.3); 9.3 (8.2 to 10.6) and 10.7 (9.2 to 12.5) /1000pys respectively. There was overlap in the 95% confidence intervals between adjacent frailty categories, but a statistically significant difference between the robust and moderate category and severe category, Figure 32.



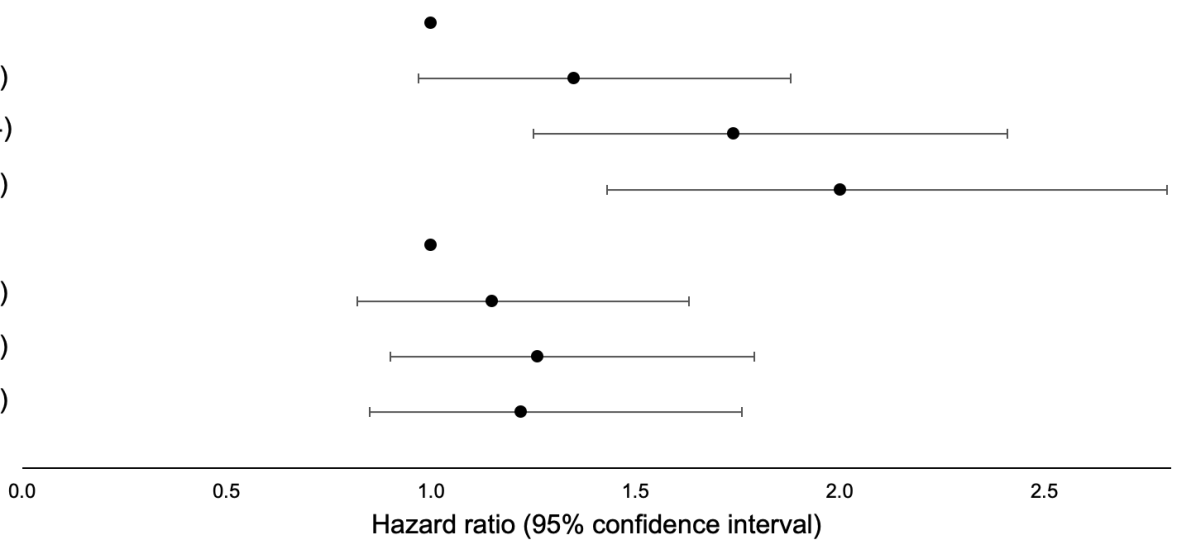
Frailty category				
Robust	6,442	6,382	6,325	6,241
Mild	20,352	20,016	19,654	19,173
Moderate	30,314	19,600	18,910	18,076
Severe	14,067	13,103	12,159	11,129

Figure 32: First stroke event by frailty category. Patients with AF, n=61,177

Stroke rates were positively correlated with age, with a rate of 4.6 (3.5 to 6.1) /1000pys in those aged 65 to 69.9 years, and 23.3 (16.0 to 33.9) /1000pys in those aged 95-100.

There was a stepwise increase in the unadjusted HR for stroke associated with increased frailty category (compared with the robust group), Figure 33. There was no statistically significant difference in HR between adjacent groups, but the HR for stroke was statistically different from the robust group in the moderate and severe frailty categories. However, this difference did not persist following adjustment, suggesting that the adjustment factors accounted for the difference in stroke rates between the groups.

Model	Frailty category	HR (95% CI)
Unadjusted	Robust	1 (ref)
	Mild	1.4 (1.0-1.9)
	Moderate	1.7 (1.3-2.4)
	Severe	2.0 (1.4-2.8)
Adjusted*	Robust	1 (ref)
	Mild	1.2 (0.8-1.6)
	Moderate	1.3 (0.9-1.8)
	Severe	1.2 (0.9-1.8)

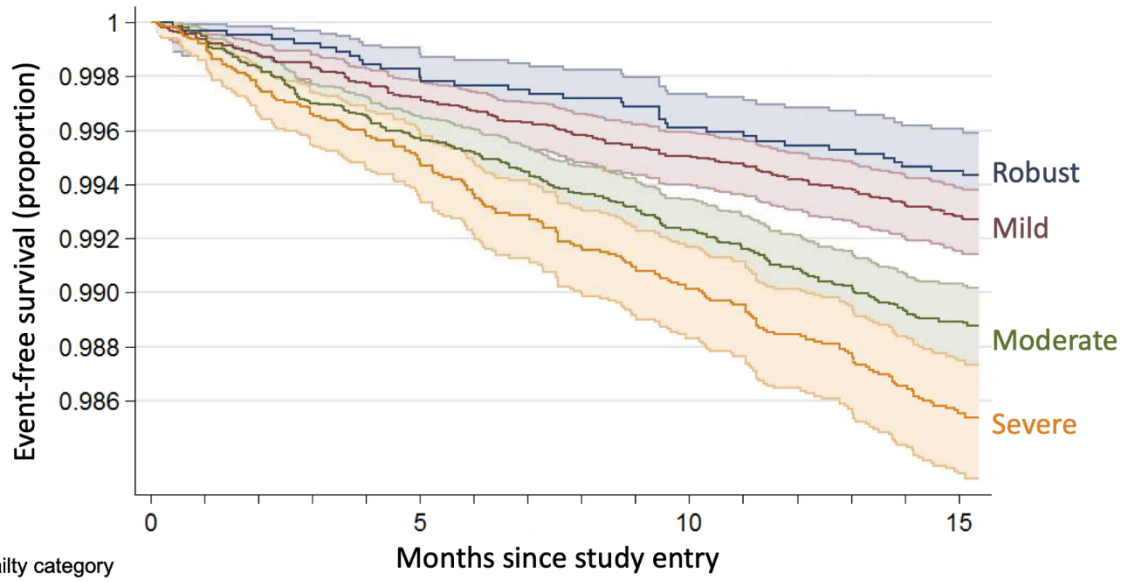


* Adjusted for age, sex, smoking status, IMD quintile, and GP practice ID

Figure 33: Association between frailty status and ischaemic or unspecified stroke in patients with AF, n=61,177

7.4.3 Gastrointestinal bleeding event

Overall, 583 patients (1.0%, 95% CI 0.88 to 1.04) had an GI bleeding event during the follow-up period. The rate was 8.0 (7.4 to 8.7) /1000pys, but increased by frailty category, with rates in the robust, mild, moderate and severe frailty categories of 4.5 (3.2 to 6.2); 5.8 (4.9 to 6.8); 9.0 (7.9 to 10.3); and 11.8 (10.2 to 13.6) /1000pys respectively. The lines separate by frailty category in the Kaplan-Meier plot, Figure 34.



Frailty category				
Robust	6,443	6,380	6,322	6,242
Mild	20,350	20,004	19,647	19,150
Moderate	20,312	19,567	18,847	17,988
Severe	14,067	13,067	12,092	11,038

Figure 34: First gastrointestinal bleeding event by frailty category. Patients with AF, n=61,177

Again, there was a positive association between frailty category and GI bleeding event, but the confidence intervals overlap between adjacent categories. Adjustment had only a minimal impact on the point estimate for the HR, which indicates that the adjustment factors explain little of the variance between groups in addition to frailty category, although there may be unmeasured confounding.

There was no significant difference between the robust group and those with mild frailty in terms of GI bleed outcomes (unadjusted HR 1.29, 0.90 to 1.86). This effect remained consistent after adjustment for age, sex, smoking status, IMD quintile and GP practice ID (HR 1.32, 0.90 to 1.94). There was a significant difference between the robust group and the group with moderate frailty (unadjusted HR 2.00, 1.40 to 2.84, adjusted HR 2.02, 1.38 to 2.94) and between the robust group and the group with severe frailty (unadjusted HR 2.60, 1.82 to 3.71; adjusted HR 2.71, 1.84 to 4.01), Figure 35.

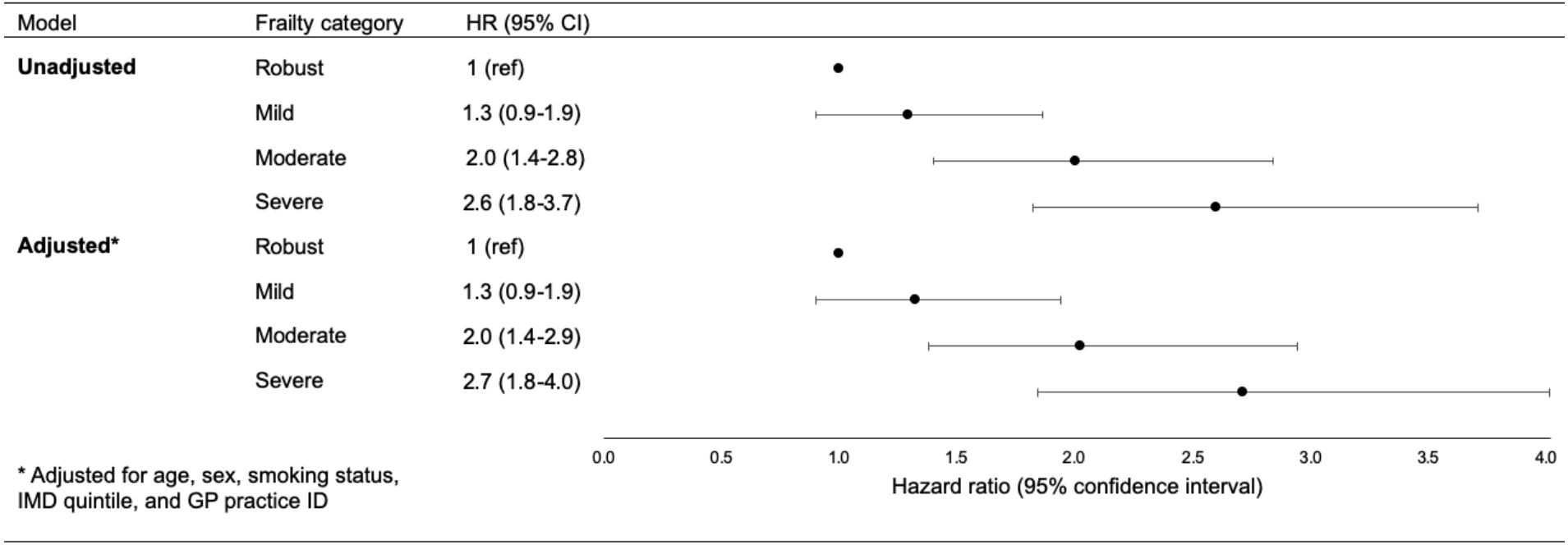
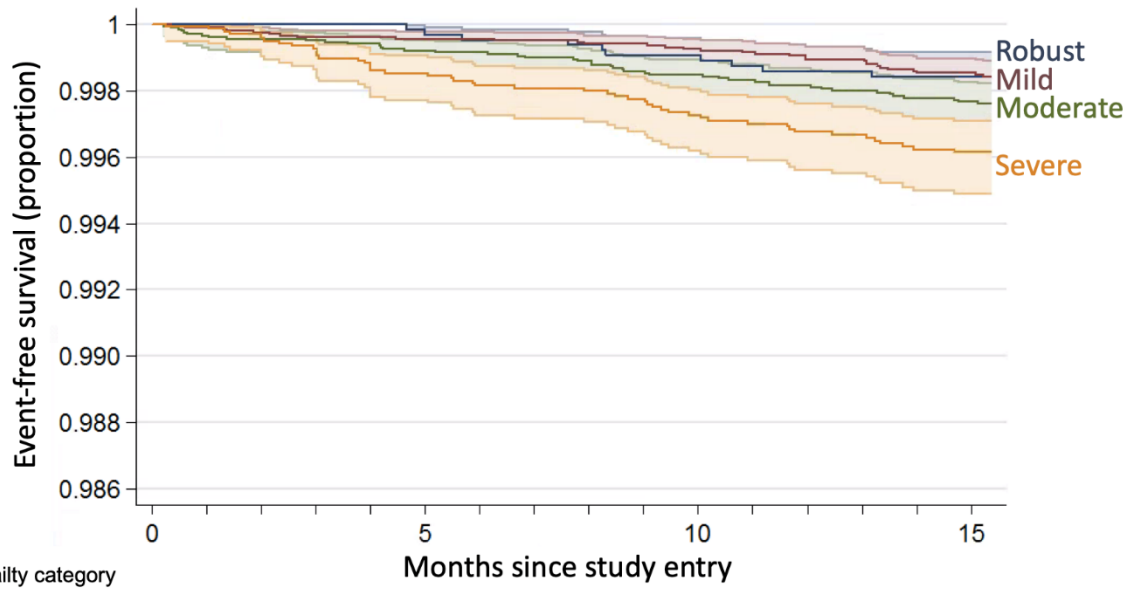


Figure 35: Association between frailty status and gastrointestinal bleeding event in patients with AF, n=61,177

7.4.4 Intracranial bleeding event

There were comparatively few patients with a recorded IC bleeding event during the follow-up period: 0.2% (95% CI 0.19 to 0.26%, n=136) of the patients with AF, with a standardised rate of 1.9 (1.6 to 2.2) /1000pys. This ranged from 0.3 (0.1 to 0.9) /1000pys in the group aged 65 to 70 years to 3.4 (1.3 to 9.1) per 1000-person years in the group aged between 95 and 100 years.

IC bleeding events were more common in patients with moderate or severe frailty. Rates /1000pys were 1.2 (0.7 to 2.3) in the robust group, 1.2 (0.9 to 1.8) in the group with mild frailty, 1.9 (1.4 to 2.5) in the group with moderate frailty, and 3.1 (2.4 to 4.1) in the group with severe frailty, Figure 36.



Frailty category				
Robust	6,443	6,395	6,344	6,267
Mild	20,351	20,054	19,727	19,266
Moderate	20,315	19,648	18,996	18,187
Severe	14,066	13,138	12,203	11,190

Figure 36: First intracranial bleeding event by frailty category. Patients with AF, n=61,177

Compared to the robust group, there was no statistically significant difference in IC bleeding events in the group with mild or moderate frailty. There was a statistically significant difference for the severe frailty category compared with the robust group, with a HR of 2.5 (95% CI 1.3 to 4.9), although this was eliminated following adjustment (HR 1.5, 0.8 to 3.5), suggesting that the adjustment factors explained the difference between frailty categories, Figure 37.

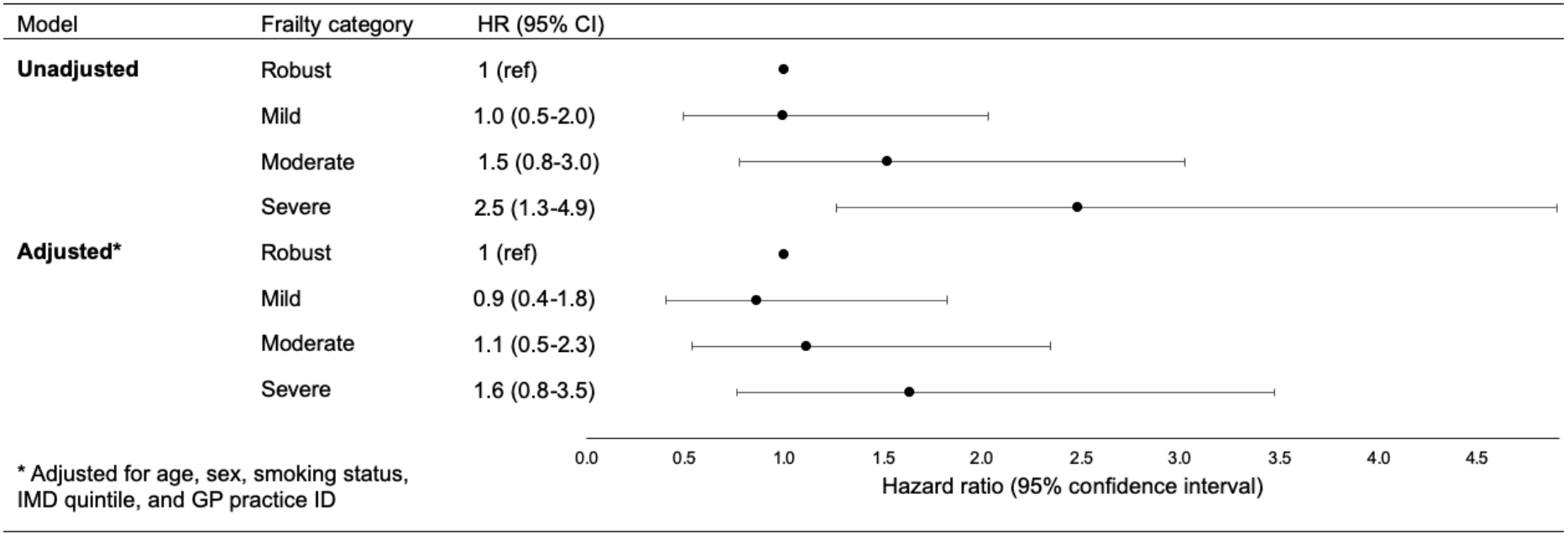


Figure 37: Association between frailty status and intracranial bleeding event in patients with AF, n=61,177

7.4.5 Falls

There were 2,707 participants that experienced a fall (4.4%, 95% CI 4.3 to 4.6%), with a rate of 37.1 (95% CI 36.3 to 39.1) /1000pys. This increased with age, from 7.1 (5.6 to 8.9) /1000pys in patients aged 65 to 70 years to 118.6 (99.9 to 140.8) /1000pys in patients aged 95 to 100 years. The rates were higher with increasing age, but the difference by age category was less than for other outcomes described. In patients aged 65 to 70, the rate was 5.1 (4.6 to 5.6), compared with 10.3 (5.9 to 18.2) in those aged 95 to 100.

Compared with the robust group, the HR for falls in mild frailty was 3.3 (95% CI 2.5 to 4.4), adjusted 2.7 (1.9 to 3.6); moderate frailty 6.6 (4.9 to 8.7), adjusted 4.1 (3.0 to 5.7); severe frailty 12.9 (9.7 to 17.2), adjusted 6.5 (4.8 to 8.8).

7.4.6 Transient ischaemic attack

Overall, 0.61% of participants had a TIA during the follow-up period (0.55 to 0.67%, n=372). The rate in the oldest category was substantially higher than in the youngest category (3.0, 2.1 to 4.2/1000pys in those aged 65 to 70, and 10.3, 5.9 to 18.2 1000pys in those aged 95 to 100).

Compared with the robust group, the HR for TIA in mild frailty 1.15 (0.74 to 1.77), adjusted 1.0 (0.7 to 1.6); moderate frailty 1.7 (1.1 to 2.6), adjusted 1.5 (0.9 to 2.3); 2.3 (1.5 to 3.5), adjusted 1.8 (1.1 to 2.8).

7.4.7 Summary of the association between frailty category and clinical outcomes, in patients with AF and without AF

To demonstrate the differential association between frailty category and clinical outcomes, the hazard ratios that have been presented and discussed above are displayed in single plot for unadjusted estimates in Figure 38, and adjusted estimates in Figure 39.

Outcome	Frailty category	HR (95% CI)
Death	Robust	1 (ref)
	Mild	2.0 (1.7-2.4)
	Moderate	4.2 (3.6-4.9)
	Severe	8.7 (7.4-10.2)
Stroke	Robust	1 (ref)
	Mild	1.4 (1.0-1.9)
	Moderate	1.7 (1.3-2.4)
	Severe	2.0 (1.4-2.8)
GI bleed	Robust	1 (ref)
	Mild	1.3 (0.9-1.9)
	Moderate	2.0 (1.4-2.8)
	Severe	2.6 (1.8-3.7)
IC bleed	Robust	1 (ref)
	Mild	1.0 (0.5-2.0)
	Moderate	1.5 (0.8-3.0)
	Severe	2.5 (1.3-4.9)

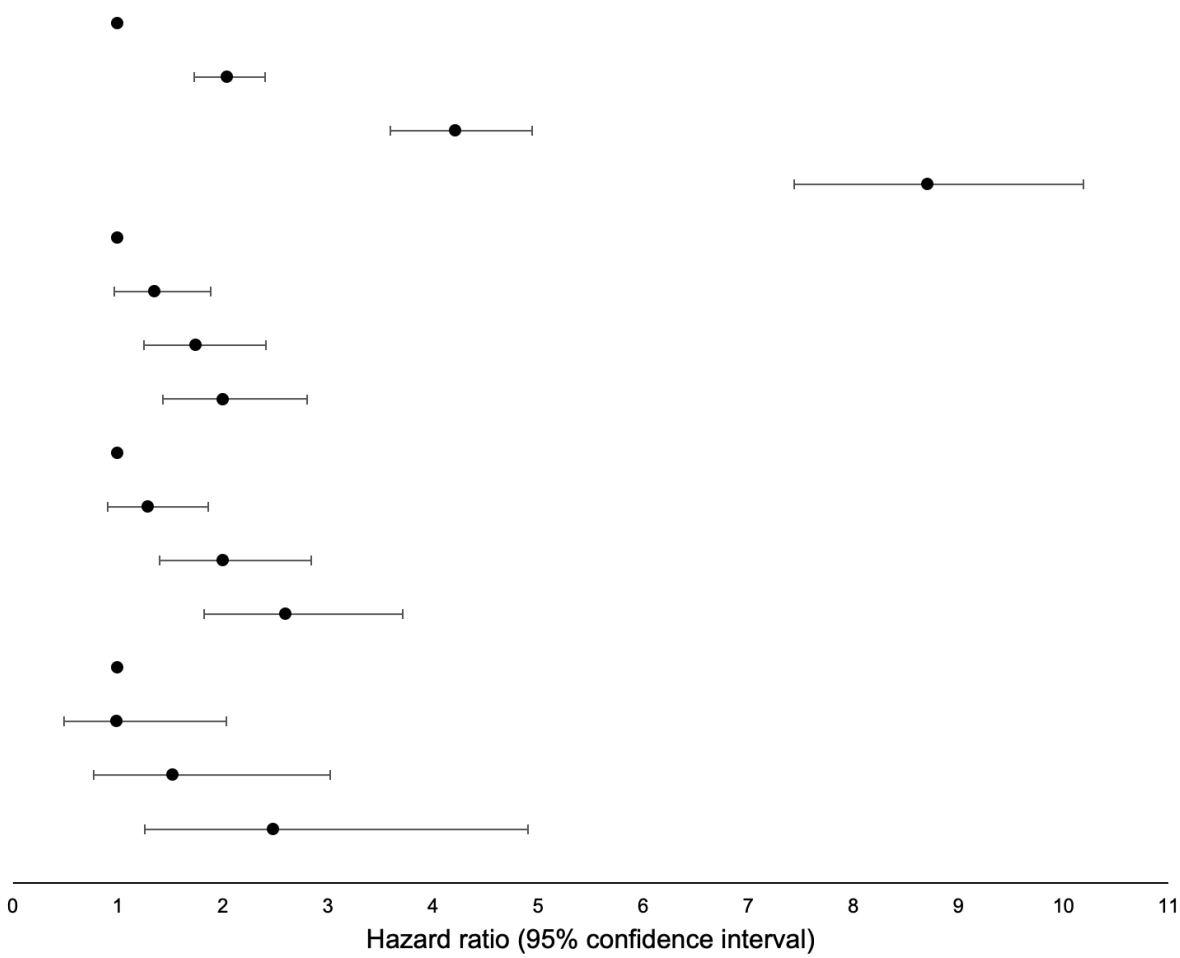
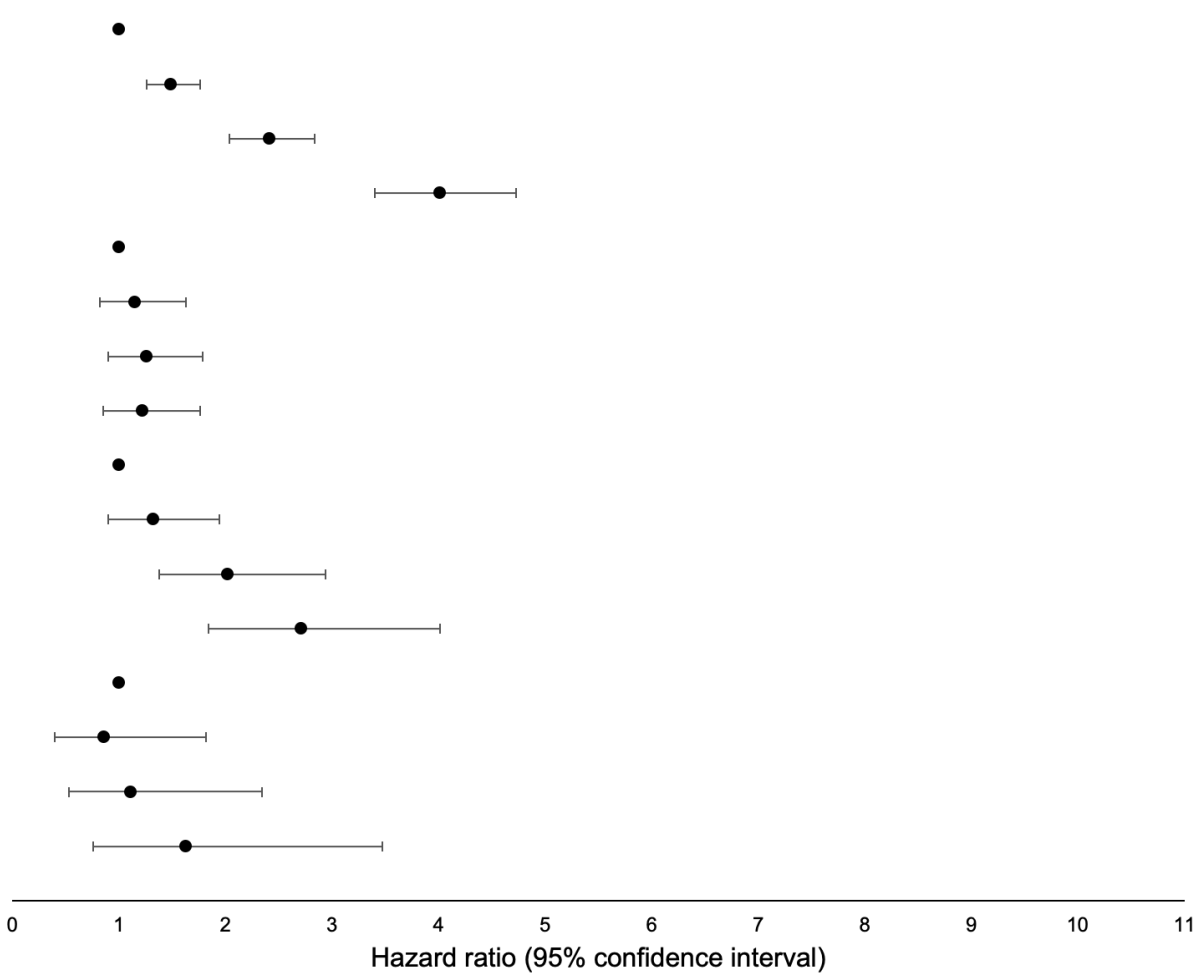


Figure 38: Association between frailty status and clinical outcomes, unadjusted, in patients with AF. n=61,177

Outcome	Frailty category	HR (95% CI)
Death	Robust	1 (ref)
	Mild	1.5 (1.3-1.8)
	Moderate	2.4 (2.0-2.8)
	Severe	4.0 (3.4-4.7)
Stroke	Robust	1 (ref)
	Mild	1.2 (0.8-1.6)
	Moderate	1.3 (0.9-1.8)
	Severe	1.2 (0.9-1.8)
GI bleed	Robust	1 (ref)
	Mild	1.3 (0.9-1.9)
	Moderate	2.0 (1.4-2.9)
	Severe	2.7 (1.8-4.0)
IC bleed	Robust	1 (ref)
	Mild	0.9 (0.4-1.8)
	Moderate	1.1 (0.5-2.3)
	Severe	1.6 (0.8-3.5)



Adjusted for age, sex, smoking status, IMD quintile, and GP practice ID

Figure 39: Association between frailty status and clinical outcomes, adjusted, in patients with AF. n=61,177

Finally, for comparison, plots showing the association between frailty status and clinical outcomes for the cohort of patients without AF are shown in Figure 40 and Figure 41. These show the same direction of association as in the group without AF, and a stepwise increase in the HR for each outcome associated with frailty status. The unadjusted HR for mortality associated with frailty is higher in the group without AF than in the group with AF (unadjusted HR for mortality in the severe frailty category compared to robust: HR 10.0, 95% CI 9.5 to 10.5 in patients without AF, and 8.7, 7.4 to 10.2 in patients with AF). After adjustment, the HR for mortality is similar, suggesting that the different association is explained by differences in the adjustment factors, age, sex, smoking, IMD, and GP practice (adjusted HR for mortality in the severe frailty category compared to robust: 4.3, 4.1 to 4.6 in patients without AF and 4.0, 3.4 to 4.7 in patients with AF).

There was no increased adjusted risk of stroke for patients with AF who were severely frail compared with robust patients (HR 1.2, 95% CI 0.9 to 1.8), however, for those without AF, severe frailty was associated with a 2.2-fold increased risk of stroke compared with those who were robust (HR 2.2, 1.9 to 2.6). It was shown in the previous chapter that even after adjusting for differences in baseline characteristics and frailty category, AF was associated with an increased risk of stroke, HR 1.3 (1.2 to 1.4). This suggests that AF itself may confer a greater relative risk than frailty category.

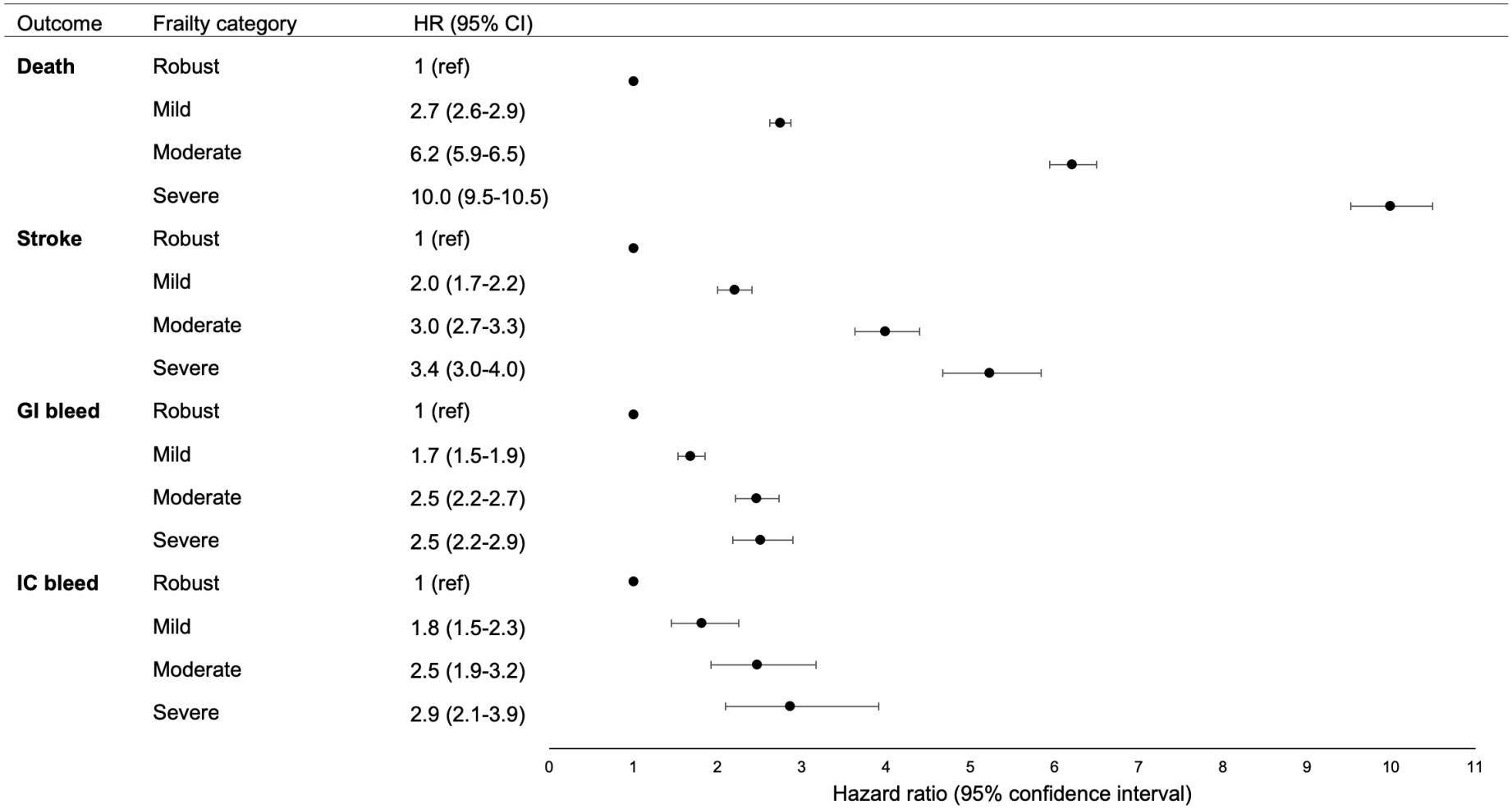


Figure 40: Association between frailty status and clinical outcomes, unadjusted, in patients without AF. n=475,778

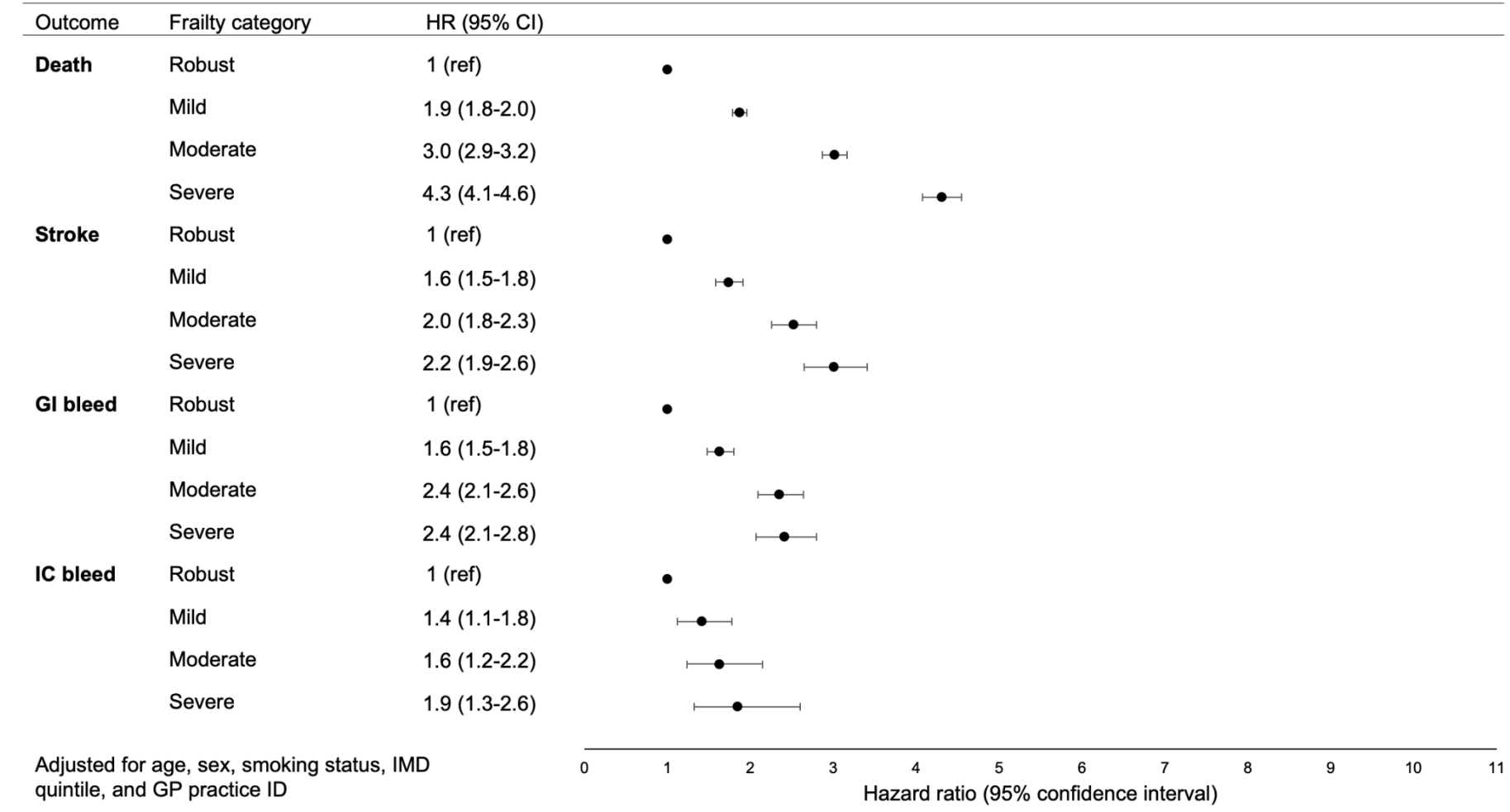


Figure 41: Association between frailty status and clinical outcomes, adjusted, in patients without AF. n=475,778

7.5 Summary of key findings

- Patients with AF and frailty tend to be older, have a longer history of AF, a greater proportion of women, higher levels of deprivation, and are more likely to live in a nursing home than patients who are robust.
- Patients with AF had higher estimated risk of stroke (CHA_2DS_2-VASc) and bleeding (ATRIA) if they also had frailty.
- Patients with frailty were more commonly prescribed a range of medications than those without frailty, including oral anticoagulation and anti-platelet medication at the time of study entry.
- Frailty and increased age were associated with higher rates of each clinical outcome of interest, including mortality, stroke, intracranial bleeding and gastrointestinal bleeding. However, in a survival analysis, the adjusted estimates were only significantly different by frailty category for the outcomes of death and GI bleed.
- There was a statistically significant difference in the association between each frailty category and mortality. This persisted despite adjustment for baseline characteristics.

7.6 Conclusion

Patients with AF and frailty tended to be older, with a longer history of AF. Frailty is associated with adverse clinical outcomes in patients with AF, including a higher risk of all-cause mortality, stroke, gastrointestinal and intracranial bleeding.

In Chapter 8, the association between oral anticoagulation and clinical outcomes in patients with atrial fibrillation will be investigated.

Chapter 8 - Oral anticoagulation and clinical outcomes in patients with AF

8.1 Chapter introduction

In this chapter, the cohort of patients with AF will be divided into those that were anticoagulated and those that were not, and the baseline characteristics described and compared. The cohort will then be restricted to patients with a CHA_2DS_2-Vasc score of two or more. The association between OAC and clinical outcomes will be estimated, by frailty category. Finally, sensitivity analyses will be carried out in order to test some of the assumptions that have been made in this thesis, including the code-list used to define AF and stroke, and to account for persistence on OAC therapy.

8.2 Chapter summary

Of the patients with AF, there were 58,204 patients (95.1%) with a CHA_2DS_2-Vasc score of two or more. Of these, 53.1% (n=30,916) were prescribed an OAC at study entry. Patients that were prescribed OAC tended to be younger, were more often male, with a longer duration of AF than patients that were not prescribed OAC. They were also less commonly taking an anti-platelet medication than patients that were prescribed OAC. Patients with frailty were more likely to be prescribed OAC than the robust group. DOAC accounted for 24% of OAC prescriptions.

OAC prescription was associated with a lower rate of all-cause mortality and stroke, but there was no statistically significant difference in the outcomes of GI bleed or IC bleeding event. OAC prescription was associated with a lower mortality rate in patients in each eFI category. When stratified by frailty status, OAC was associated with a decreased point estimate for the outcome of stroke,

but the confidence intervals were wide and crossed one in each category except moderate frailty.

8.3 Participants

The analytic cohort for this chapter consists of patients who were over the age of 65, with a history of atrial fibrillation at study entry, Figure 42.

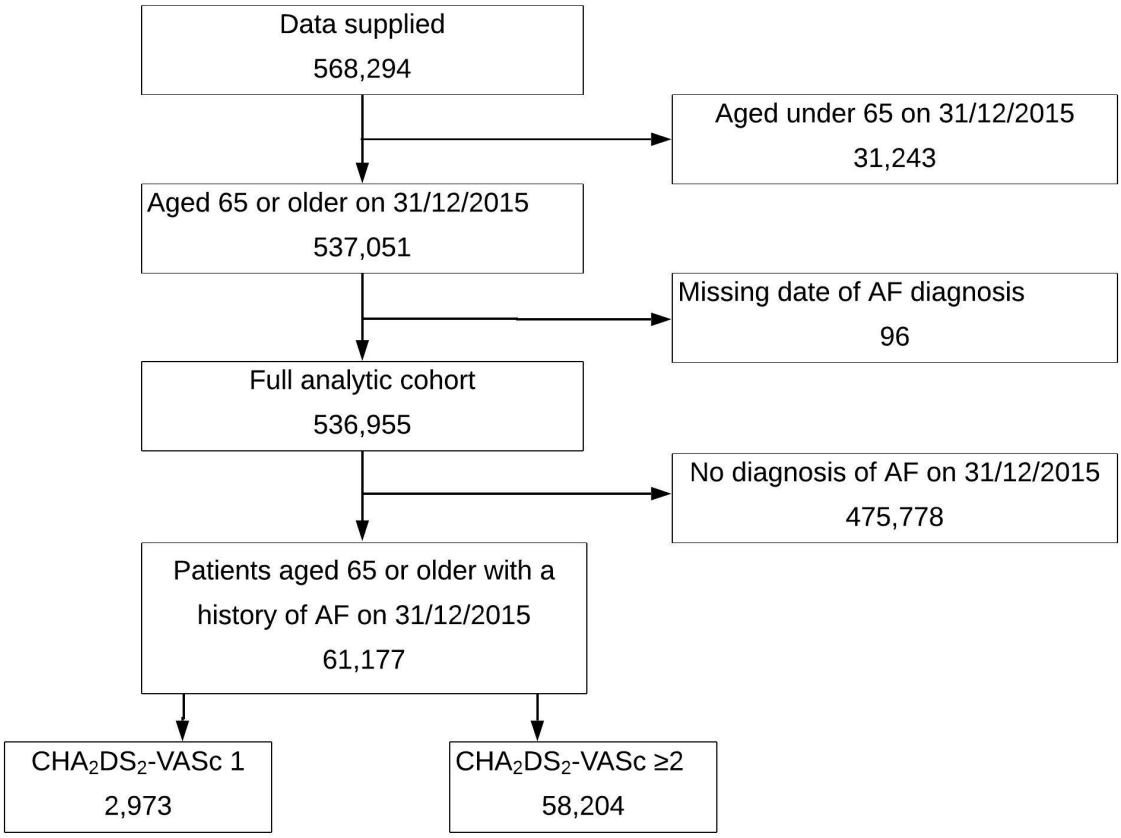


Figure 42: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram to show the derivation of the analytic cohort of patients with atrial fibrillation

There was a history of AF at study entry in 61,177 patients (11.4%). Of these, 32,079 (52.4%) were prescribed OAC at study entry.

8.3.1 Baseline characteristics of patients with AF by OAC status

Of the patients with AF, 95.1% (n=58,204) had a CHA_2DS_2-Vasc score of two or more, and were considered 'eligible' for OAC.[140] OAC was prescribed at study entry in 30,916 (53.1%) of patients with AF and a CHA_2DS_2-Vasc score of two or more.

The median age of patients with AF was 79.7 (IQR 73.3 to 85.5) years. In patients with a CHA_2DS_2-Vasc score of 2 or more, the median age was 80.2 (74.3 to 85.7) years, and among this group, patients prescribed OAC were on average 5 months younger than those not prescribed an OAC (80.1, IQR 74.6 to 85.2 years compared with 80.5, 74.0 to 86.6 years, p<0.001).

Of the patients with AF, 27,987 (45.8%) were women. Being female and over 65 years of age confers two CHA_2DS_2-Vasc points, therefore there was no difference in the number of women after restricting the cohort to patients with AF and CHA_2DS_2-Vasc score of two or more, but the proportion of women increased to 48.1% due to the removal of 2,973 men from the cohort. In patients with AF and a CHA_2DS_2-Vasc score of two or more, 46.2% of those prescribed OAC were women, compared with 50.2% of those not prescribed OAC, p<0.001). Those prescribed OAC tended to be less deprived by IMD rank than those not prescribed OAC (12.5% in the most deprived quintile in those prescribed OAC compared with 13.7% of those not prescribed OAC).

Of patients with AF and a CHA_2DS_2-Vasc score of two or more, 5,246 (9.0%) lived in a nursing home. The proportion living in a nursing home was lower in patients that were prescribed OAC than those that were not prescribed OAC (n=3,236 11.9% compared with n=2,010 6.5%, p<0.001). Patients that were prescribed OAC tended to have a longer duration of AF prior to study entry than those that were not prescribed OAC (5.4, IQR 2.4 to 10.1 years compared with 4.1, 1.9 to 8.4 years, p<0.001), Table 32.

Table 32: Baseline characteristics of patients with AF, by OAC status

	All patients with AF				Patients with AF and CHA_2DS_2-Vasc score of 2 or more			
	Total n=61,177	**Prescribed OAC n=32,079**	**Not prescribed OAC n=29,098**	**p-value***	**Total n=58,204**	**Prescribed OAC n=30,916**	**Not prescribed OAC n=27,288**	**p-value***
Demographics								
Age, Median (IQR)	79.7 (73.3-85.5)	79.7 (73.8-85.0)	79.7 (72.8-86.1)	0.087[a]	80.2 (74.3-85.7)	80.1 (74.6-85.2)	80.5 (74.0-86.6)	<0.001[a]
Female, n (%)	27,987 (45.8)	14,285 (44.5)	13,702 (47.1)	<0.001	27,987 (48.1)	14,285 (46.2)	13,702 (50.2)	<0.001
Number of eFI deficits, median (IQR)	9 (6-12)	9 (7-12)	9 (6-12)	<0.001	9 (7-12)	10 (7-12)	9 (6-12)	<0.001
IMD rank, n (%)								
Most deprived quintile	7,439 (12.4)	3,756 (12.4)	3,683 (13.5)	<0.001	7,188 (13.1)	3,654 (12.5)	3,534 (13.7)	<0.001
Least deprived quintile	13,445 (23.3)	7,343 (24.2)	6,102 (22.3)		12,696 (23.1)	7,060 (24.2)	5,636 (21.9)	
Living in a nursing home eFI, n (%)	5,276 (8.6)	2,021 (6.3)	3,255 (11.2)	<0.001	5,246 (9.0)	2,010 (6.5)	3,236 (11.9)	<0.001
Robust	6,443 (10.5)	2,574 (8.0)	3,869 (13.3)	<0.001	4,863 (8.4)	2,028 (6.6)	2,835 (10.4)	<0.001
Mild	20,352 (33.3)	10,730 (33.5)	9,622 (33.1)		19,198 (33.0)	10,221 (33.1)	8,977 (32.9)	
Moderate	20,315 (33.2)	11,264 (35.1)	9,051 (31.1)		20,099 (34.5)	11,167 (36.1)	8,932 (32,7)	
Severe	14,067 (23.0)	7,511 (23.4)	6,556 (22.5)		14,044 (24.1)	7,500 (24.3)	6,544 (24.0)	
Duration of AF, years prior to study start, Median (IQR)	4.8 (2.1-9.4)	5.4 (2.4-10.1)	4.1 (1.9-8.4)	<0.001	4.8 (2.2-9.4)	5.4 (2.4-10.1)	4.1 (1.9-8.4)	<0.001[a]
Risk scores								
CHA_2DS_2-Vasc, Mean (SD)	3.8 (1.5)	3.9 (1.5)	3.6 (1.5)	<0.001[b]	3.9 (1.4)	4.0 (1.4)	3.8 (1.4)	<0.001[b]
ATRIA, Median (IQR)	3 (2-6)	3 (2-6)	3 (2-6)	<0.001[a]	3 (2-6)	4 (2-6)	3 (2-6)	<0.001[a]
Past medical history, n (%)								
Alcohol excess	1,855 (3.0)	836 (2.6)	1,019 (3.5)	<0.001	1,695 (2.9)	789 (2.6)	906 (3.3)	<0.001
Anaemia	12,145 (19.9)	6,024 (18.8)	6,121 (21.0)	<0.001	11,974 (20.6)	5,959 (19.7)	6,015 (22.0)	<0.001
Bleeding disorder	945 (1.5)	466 (1.5)	497 (1.7)	0.053	913 (1.6)	453 (1.5)	460 (1.7)	0.033
Cancer	10,225 (16.7)	5,187 (16.2)	5,038 (17.3)	<0.001	9,862 (16.9)	5,045 (16.3)	4,817 (17.7)	<0.001

	All patients with AF				Patients with AF and CHA_2DS_2-Vasc score of 2 or more			
	Total n=61,177	**Prescribed OAC n=32,079**	**Not prescribed OAC n=29,098**	**p-value***	**Total n=58,204**	**Prescribed OAC n=30,916**	**Not prescribed OAC n=27,288**	**p-value***
Cirrhosis	261 (0.43)	112 (0.4)	149 (0.51)	0.002	253 (0.43)	111 (0.36)	142 (0.52)	0.003
CKD	20,325 (33.2)	11,528 (35.9)	8,797 (30.2)	<0.001	20,153 (34.6)	11,435 (37.0)	8,718 (32.0)	<0.001
Falls	11,758 (19.2)	5,893 (18.4)	5,865 (20.2)	<0.001	11,637 (20.0)	5,843 (18.9)	5,794 (21.2)	<0.001
GI bleed								
Upper	918 (1.5)	416 (1.3)	502 (1.7)	<0.001	890 (1.5)	403 (1.3)	487 (1.8)	<0.001
Lower	6,222 (10.2)	3,185 (9.9)	3,037 (10.4)	0.038	5,940 (10.2)	3,075 (10.0)	2,865 (10.5)	0.028
Unspecified	537 (0.88)	232 (0.7)	305 (1.1)	<0.001	524 (0.90)	228 (0.74)	296(1.1)	<0.001
Haematuria	7,535 (12.3)	4,228 (13.2)	3,307 (11.4)	<0.001	7,245 (12.5)	4,116 (13.3)	3,129 (11.5)	<0.001
Haemoptysis	1,772 (2.9)	1,042 (3.3)	730 (2.5)	<0.001	1,705 (2.9)	999 (3.2)	706 (2.6)	<0.001
Heart failure	12,450 (20.4)	8,102 (25.3)	4,348 (14.9)	<0.001	12,320 (21.2)	8,016 (25.9)	4,304 (15.8)	<0.001
Hypertension	41,340 (67.6)	22,259 (69.4)	19,081 (65.6)	<0.001	41,146 (70.7)	22,173 (71.7)	18,991 (69.6)	<0.001
Hyperthyroidism	2,002 (3.3)	1,068 (3.3)	934 (3.2)	0.407	1,944 (3.3)	1,046 (3.4)	898 (3.3)	0.535
Intracranial bleeding	982 (1.6)	304 (0.95)	678 (2.3)	<0.001	972 (1.7)	303 (0.98)	669 (2.5)	<0.001
Ischaemic heart disease	19,586 (32.0)	10,939 (34.1)	8,647 (29.7)	<0.001	19,158 (32.9)	10,741 (34.7)	8,417 (30.9)	<0.001
Memory loss	7,880 (12.9)	3,513 (11.0)	4,367 (15.0)	<0.001	7,782 (13.4)	3,474 (11.2)	4,308 (15.8)	<0.001
Myocardial infarction	7,419 (12.1)	3,946 (12.3)	3,473 (11.9)	0.167	7,400 (12.7)	3,939 (12.7)	3,461 (12.7)	0.835
Obesity	828 (1.4)	484 (1.5)	344 (1.2)	<0.001	818 (1.4)	481 (1.6)	337 (1.2)	0.001
Peptic ulcer	3,676 (6.0)	1,767 (5.5)	1,909 (6.6)	<0.001	3,555 (6.1)	1,723 (5.6)	1,832 (6.7)	<0.001
Varices	86 (0.14)	29 (0.09)	57 (0.20)	0.001	82 (0.14)	28 (0.09)	54 (0.20)	0.001
Stroke	7,239 (11.8)	4,375 (13.6)	2,864 (9.8)	<0.001	7,239 (12.4)	4,375 (14.2)	2,864 (10.5)	<0.001
Ischaemic	3,179 (5.2)	1,983 (6.2)	1,196 (4.1)	<0.001	3,179 (5.5)	1,983 (6.4)	1,196 (4.4)	<0.001
Unspecified	3,752 (6.1)	2,266 (7.1)	1,486 (5.1)	<0.001	5,043 (8.7)	3,003 (9.7)	2,040 (7.5)	<0.001
Transient ischaemic attack	6,019 (9.8)	3,624 (11.3)	2,395 (8.2)	<0.001	6,019 (10.3)	3,624 (11.7)	2,395 (8.8)	<0.001
Pulmonary embolism	1,879 (3.1)	1,348 (4.2)	531 (1.8)	<0.001	1,820 (3.1)	1,312 (4.2)	508 (1.9)	<0.001
Deep vein thrombosis	2,335 (3.8)	1,453 (4.5)	882 (3.0)	<0.001	2,264 (3.9)	1,413 (4.6)	851 (3.1)	<0.001
	Missing IMD data: 3,466 (5.7%)				Missing IMD data: 3,252 (5.6%).			

* p value for difference between groups prescribed and not prescribed OAC. a=Mann Whitney; b=T-test. All others: Chi-square
Conditions in *italics* are also deficits in the eFI.
Abbreviations eFI: electronic frailty index; IMD: index of multiple deprivation; IQR: interquartile range; SD: standard deviation

8.3.2 Risk scores

In patients with AF and CHA_2DS_2-Vasc score of two or more, the estimated risk of stroke was, on average, higher in patients that were prescribed OAC than in those that were not prescribed OAC (mean CHA_2DS_2-VASc score 3.8, SD 1.4; and 4.0, SD 1.4 respectively, p<0.001). The risk of bleeding was also higher - the median ATRIA score in the group that were prescribed OAC was 4 (IQR 2 to 6), and in the group that was not prescribed OAC the median was 3 (2 to 6), p<0.001, Figure 43.

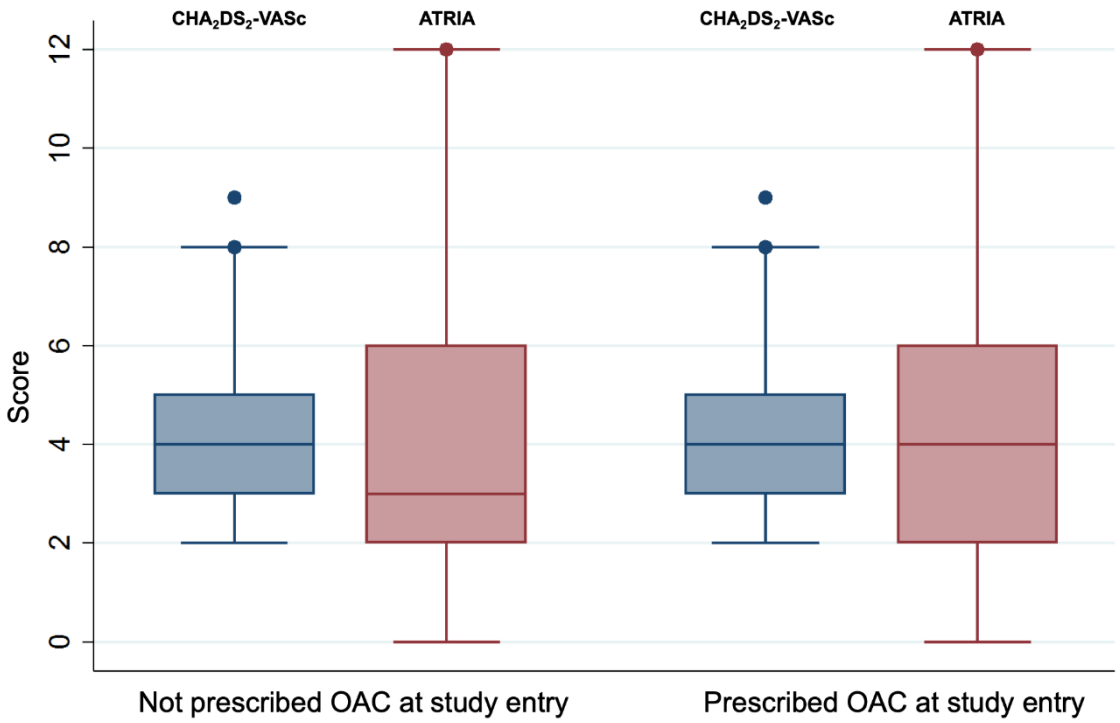


Figure 43: Stroke and bleeding risk (CHA_2DS_2-VASc and ATRIA) scores by oral anticoagulation prescription status, in patients with CHA_2DS_2-VASc score of two or more, n=58,204

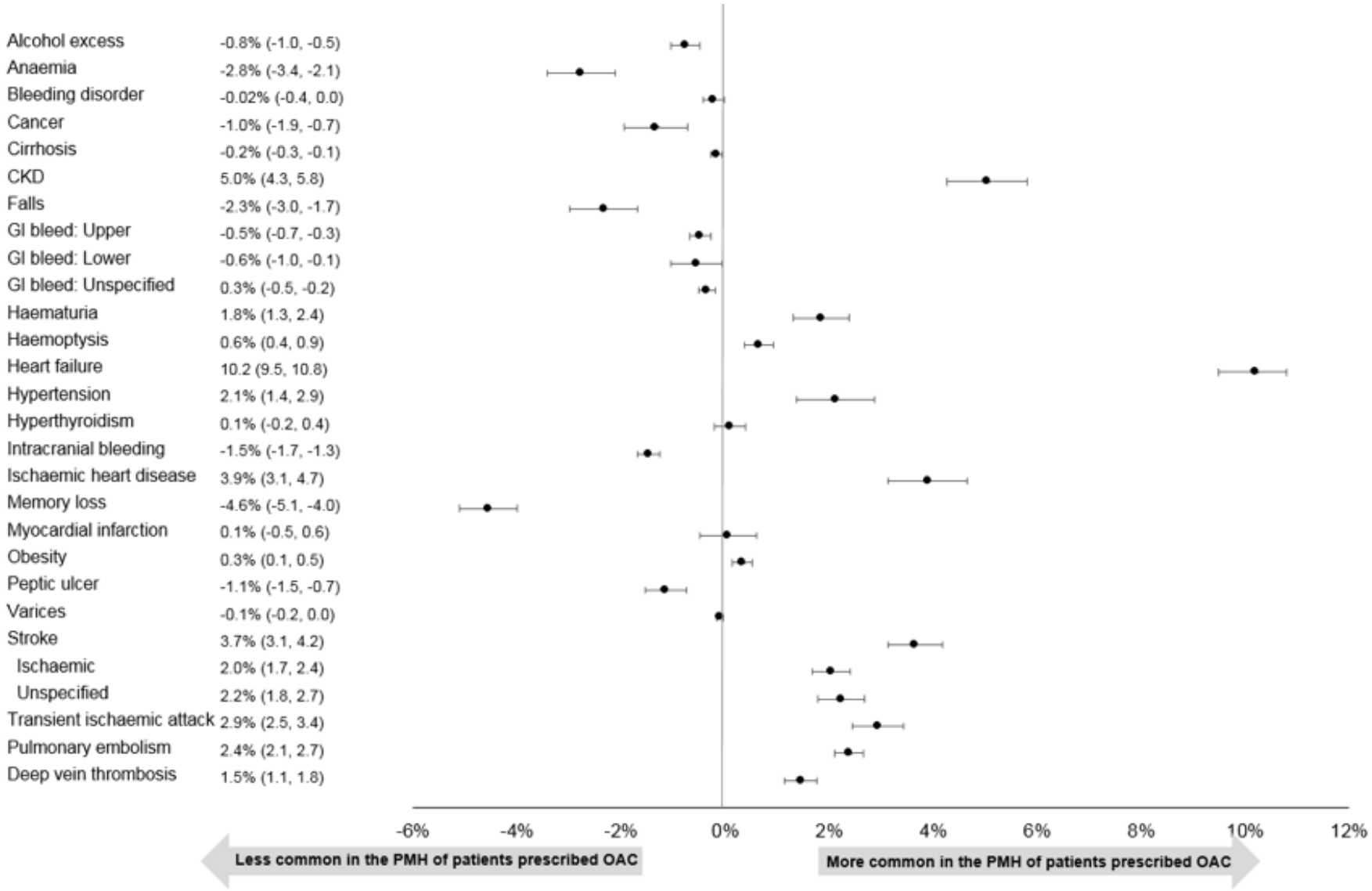


Figure 44: Forest plot showing the difference in proportion (%) with recorded past medical history (PMH) between those prescribed and not prescribed OAC. Patients with AF and CHA2DS2-VASc score of two or more, n=58,204.

8.3.3 Past medical history

Patients with AF and a CHA_2DS_2-VASc score of two or more less commonly had a recorded past medical history of memory loss if they were prescribed OAC at study entry (4.6% absolute difference between group prescribed OAC and not prescribed OAC, 95% CI 4.0 to 5.1%). They were also less likely to have a recorded history of peptic ulcer disease (difference of 1.1%, 0.7 to 1.5%), anaemia (2.8%, 2.1 to 3.4%), cancer (1.0%, 0.7 to 1.9%), falls (2.3%, 1.7 to 3.0%) and intra-cranial bleeding (1.5%, 1.3 to 1.7%), Figure 44.

Patients with AF and a CHA_2DS_2-VASc score of two or more who were prescribed OAC at study entry more commonly had a recorded past medical history of chronic kidney disease (4.0% absolute difference, 95% CI 4.3 to 5.8%), ischaemic heart disease (3.9%, 3.1 to 4.7%), stroke (3.7%, 3.1 to 4.2%), and transient ischaemic attack (2.9%, 2.5 to 3.4%). They also more commonly had a second indication for OAC prescription: in patients prescribed OAC, 4.2% (n=1,312) had a history of pulmonary embolism compared with 1.9% (n=508) of those that were not prescribed OAC ($p<0.001$). A history of deep vein thrombosis was recorded in 4.6% (n=1,413) of those prescribed an OAC, compared with 3.1% (n=851) of those that were not prescribed an OAC ($p<0.001$).

8.3.4 Medication

Patients with AF and a CHA_2DS_2-VASc score of two or more who were prescribed OAC were more commonly prescribed a statin in the year prior to study entry than those that were not prescribed OAC (64.6% compared with 55.9%, $p<0.001$). Patients that were prescribed an OAC were less commonly prescribed proton pump inhibitors (38.3% of those prescribed OAC compared with 43.4% of those not prescribed OAC, $p<0.001$) or non-steroidal anti-inflammatory medications (7.4% compared with 10.7%, $p<0.001$) in the year prior to study entry.

At study entry, 2.1% (n=664) of patients that were prescribed an OAC were also prescribed an anti-platelet agent, compared with 11.2% (n=3,044) of patients

that were not prescribed an OAC (p<0.001). There was no statistically significant difference between the groups in the prescription rates of macrolide antibiotics, corticosteroids, carbamazepine or phenytoin in the year prior to study entry, Table 33.

Table 33: Medication history by oral anticoagulation prescription at study entry status. Patients with AF and CHA_2DS_2-VASc score of two or more, n=58,204

Variable	Total n=58,204	Prescribed OAC n=30,916	Not prescribed OAC n=27,288	p-value*
Medications in the previous year, n (%)				
Proton pump inhibitor	23,695 (40.7)	11,852 (38.3)	11,843 (43.4)	<0.001
Macrolide antibiotics	402 (0.69)	196 (0.63)	206 (0.75)	0.079
NSAID	5,209 (9.0)	2,288 (7.4)	2,921 (10.7)	<0.001
Corticosteroid	1,684 (2.9)	901 (2.9)	783 (2.9)	0.747
Statin	35,236 (60.5)	19,972 (64.6)	15,264 (55.9)	<0.001
Anti-epileptic				
Carbemazepine	224 (0.38)	111 (0.36)	113 (0.41)	0.369
Phenytoin	176 (0.30)	85 (0.27)	91 (0.33)	
Medication at study entry, n (%)				
Any anti-platelet	3,688 (6.3)	644 (2.1)	3,044 (11.2)	<0.001

* p-value for the difference between group prescribed OAC and not prescribed OAC, Chi-square.
Abbreviation OAC: oral anticoagulation

8.3.5 Oral anticoagulation at study entry by frailty category

Of patients with AF and a CHA_2DS_2-VASc score of two or more, 53.1% (n=30,916) were prescribed an OAC at study entry. This varied by electronic frailty index category: 41.7% (n=2,028) were prescribed OAC in the robust category; 53.2% (n=10,221) in the mild frailty category; 55.6% (n=11,167) in the moderate frailty category and 53.4% (n=7,500) in the severe frailty category, Figure 45.

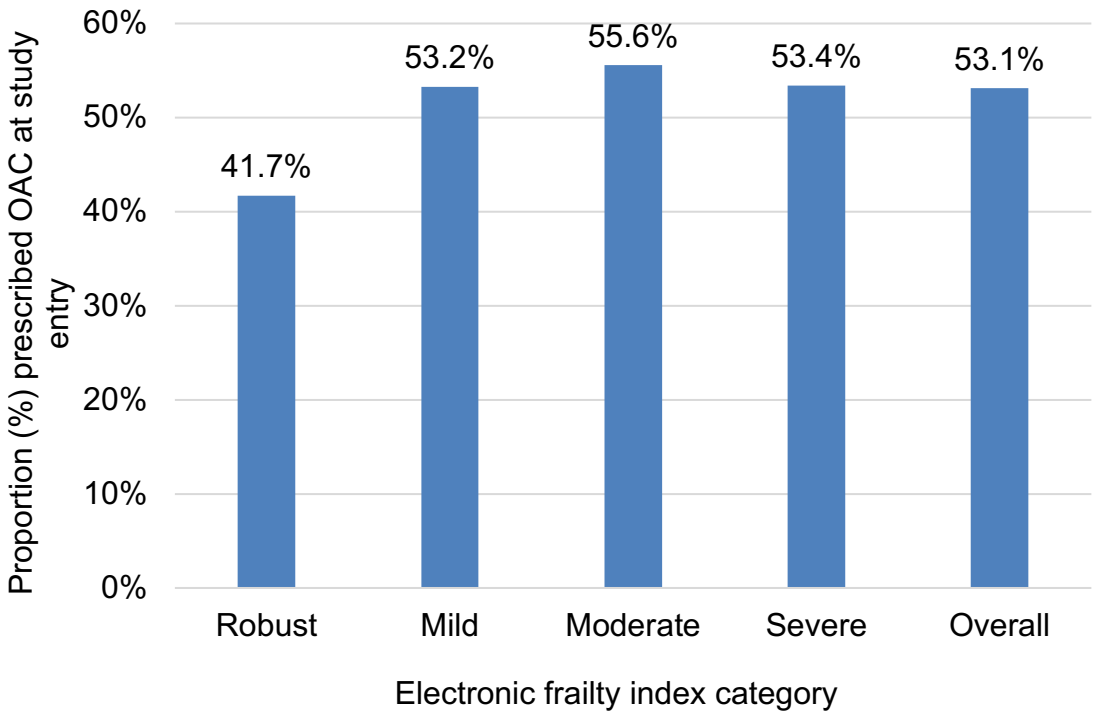
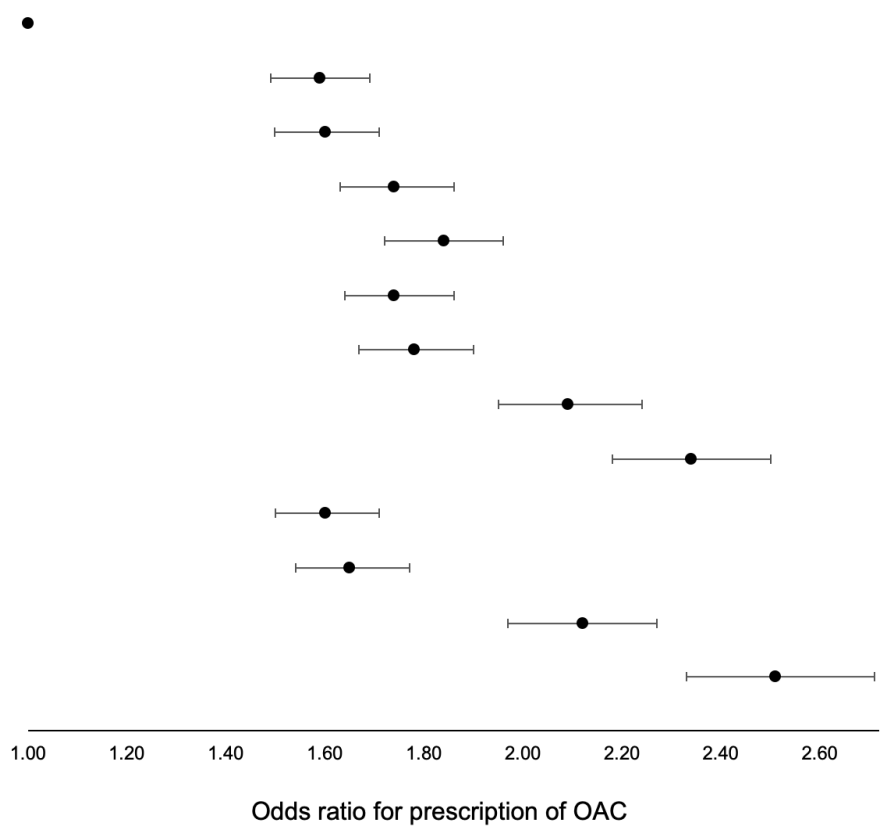


Figure 45: Proportion of patients with AF and a CHA_2DS_2-VASc score of two or more that were prescribed OAC at study entry by electronic frailty index category, n=58,204

The association between OAC status and frailty category was quantified using a logistic regression model, with OAC as the outcome and frailty category as the exposure. In comparison to the robust category, frailty was associated with higher odds of OAC prescription: mild frailty OR 1.6 (95% CI 1.5 to 1.7); moderate frailty OR 1.8 (1.6 to 1.9); severe frailty OR 1.6 (1.5 to 1.7).

Adjustment for sex and IMD had a minimal effect on the estimates (OR associated with mild frailty 1.6, 95% CI 1.5 to 1.7; moderate frailty: 1.8, 1.7 to 1.9; severe frailty: 1.7, 1.5 to 1.8. Further adjustment for concurrent medications increased the magnitude of the association between frailty and OAC prescription (OR associated with mild frailty: 1.7, 1.6 to 1.9; moderate frailty: 2.1, 2.0 to 2.2; severe frailty: 2.1, 2.0 to 2.3). Additional adjustment for age, history of cancer, varices and previous GI or intra-cranial bleeding increased the magnitude of the association further (OR associated with mild frailty 1.8, 1.7 to 2.0, moderate frailty: 2.3, 2.2 to 2.5, severe frailty: 2.5, 2.3 to 2.7), Figure 46.

Frailty category		OR (95% CI)
Robust		1 (ref)
Mild frailty	Unadjusted	1.6 (1.5-1.7)
	Adjusted for sex and IMD	1.6 (1.5-1.7)
	Adjusted for sex, IMD, and medications[a]	1.7 (1.6-1.9)
	Adjusted for sex, IMD, medications and PMH[b]	1.8 (1.7-2.0)
Moderate frailty	Unadjusted	1.7 (1.6-1.9)
	Adjusted for sex and IMD	1.8 (1.7-1.9)
	Adjusted for sex, IMD, and medications[a]	2.1 (2.0-2.2)
	Adjusted for sex, IMD, medications and PMH[b]	2.3 (2.2-2.5)
Severe frailty	Unadjusted	1.6 (1.5-1.7)
	Adjusted for sex and IMD	1.7 (1.5-1.8)
	Adjusted for sex, IMD, and medications[a]	2.1 (2.0-2.3)
	Adjusted for sex, IMD, medications and PMH[b]	2.5 (2.3-2.7)



[a] Adjusted for steroid, NSAID, macrolide antibiotic and PPI prescription in the previous year, concurrent antiplatelet prescription at time of study entry, GP practice ID

[b] Additionally adjusted for past medical history (PMH) of history of cancer, varices, GI bleed or ICH, and age at study entry

Figure 46: Association between eFI category and OAC prescription at study entry in patients with AF and CHA_2DS_2-VASc score of two or more. n=58,204

Table 34: Prescription rates of each OAC, of those prescribed OAC at study entry

Agent		Robust n=2,028	Mild n=10,220	Moderate n=11,166	Severe n=7,496	Total n=30,910
Warfarin		1,586 (78.2%)	8,059 (78.9%)	8,596 (77.0%)	5,261 (70.2%)	23,502 (76.0%)
DOAC		438 (21.6%)	2,136 (20.9%)	2,541 (22.8%)	2,214 (29.5%)	7,329 (23.7%)
Apixaban	2.5mg BD	63 (3.1%)	399 (3.9%)	681 (6.1%)	687 (9.2%)	1,830 (5.9%)
	5mg BD	<5 (0.1%)	<5 (0.0%)	<5 (0.0%)	<5 (0.0%)	7 (0.0%)
Edoxaban	30mg OD	<5 (0.0%)	8 (0.1%)	15 (0.1%)	13 (0.2%)	37 (0.1%)
	60mg OD	<5 (0.1%)	15 (0.1%)	15 (0.1%)	<5 (0.1%)	38 (0.1%)
Rivaraoxaban	15mg OD	38 (1.9%)	348 (3.4%)	588 (5.3%)	743 (9.9%)	1,717 (5.6%)
	20mg OD	328 (16.2%)	1,358 (13.3%)	1,231 (11.0%)	760 (10.1%)	3,677 (11.9%)
	15mg BD	0 (0.0%)	<5 (0.0%)	0 (0.0%)	0 (0.0%)	<5 (0.0%)
Dabigatran	110mg BD	<5 (0.1%)	<5 (0.0%)	5 (0.0%)	<5 (0.0%)	14 (0.0%)
	150mg BD	<5 (0.1%)	<5 (0.0%)	<5 (0.0%)	0 (0.0%)	8 (0.0%)
Sinthrome		<5 (0.1%)	11 (0.1%)	10 (0.1%)	7 (0.1%)	30 (0.1%)
Acenocoumarol		<5 (0.1%)	14 (0.1%)	19 (0.2%)	13 (0.2%)	48 (0.2%)
Phenindione		0 (0.0%)	0 (0.0%)	0 (0.0%)	<5 (0.0%)	<5 (0.0%)

8.3.6 Oral anticoagulation agents at study entry

Of those patients that were prescribed OAC at study entry, 76% (n=23,502) were prescribed warfarin and 24% (n=7,329) a DOAC, Table 34. The rates of DOAC prescription varied by frailty category, ranging from 21.6% of prescriptions in the robust group to 29.5% of OAC prescriptions in the group with severe frailty. Overall, rivaroxaban accounted for 74% of all DOAC prescriptions.

Sinthrome, acenocoumarol and phenindione were prescribed uncommonly. Combined, these three medications accounted for less than 1% of all OAC prescriptions.

8.4 Frailty and clinical outcomes

The rates of clinical outcomes in all patients with AF have previously been reported (with any CHA_2DS_2-VASc score, Table 31). The rates for patients with AF and a CHA_2DS_2-VASc score of two or more are shown in Table 35. The stroke rates were similar in the two sub-groups (8.5, 95% CI 7.8 to 9.1 in all patients with AF, and 8.7, 8.1 to 9.5 in patients with a CHA_2DS_2-VASc score of two or more, p=0.568).

Rates (/1000pys) of GI bleed, IC bleed, fall and TIA were similar between the whole cohort of patients with AF and patients with a CHA_2DS_2-VASc score of two or more (GI bleed: 8.0, 95% CI 7.4 to 8.7 vs 8.3, 7.6 to 9.0, p=0.572; IC bleed 1.9, 1.6 to 2.2 vs 1.9, 1.6 to 2.3, p=0.806; Fall 37.1, 36.3 to 39.1 vs 39.4, 37.9 to 40.9, p=0.108; TIA 5.1, 4.6 to 5.6 vs 5.2, 4.7 to 5.8, p=0.764). The rates by frailty status are reported in Table 35, showing a positive association between eFI category and rates of clinical events, as shown in section 7.4.

The all-cause mortality rate was higher in the cohort restricted to patients with a CHA_2DS_2-VASc score of two or more than in all patients with AF (87.4, 95% CI 85.3 to 89.6, compared with 83.8, 81.7 to 85.9, p-value for difference in proportions = 0.014). The stroke rate was similar (8.5, 7.8 to 9.1 in all patients

with AF, and 8.7, 8.1 to 9.5 in patients with a CHA_2DS_2-VASc score of two or more, p=0.568).

Rates of GI bleed, IC bleed, fall and TIA were similar between the whole cohort of patients with AF and patients with a CHA_2DS_2-VASc score of two or more (GI bleed: 8.0, 95% CI 7.4 to 8.7 vs 8.3, 7.6 to 9.0, p=0.572; IC bleed 1.9, 1.6 to 2.2 vs 1.9, 1.6 to 2.3, p=0.806; Fall 37.1, 36.3 to 39.1 vs 39.4, 37.9 to 40.9, p=0.108; TIA 5.1, 4.6 to 5.6 vs 5.2, 4.7 to 5.8, p=0.764), Table 35.

Table 35: Rates of clinical outcomes (/1000pys) in patients with AF and CHA_2DS_2-VASc score of 2 or more by frailty status. n=58,204.

	All		Robust		Mild		Moderate		Severe	
n	58,204		4,863		19,198		20,099		14,044	
Person years follow-up	69,610.31		6079.80		23,676.68		24,053.19		15,800.64	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
Death	6,085	87.4 (85.3-89.6)	139	22.9 (19.4-27.0)	1,019	43.0 (40.5-45.8)	2,088	86.8 (83.2-90.6)	2,839	179.7 (173.2-186.4)
Stroke	605	8.7 (8.1-9.5)	36	5.9 (4.3-8.2)	177	7.5 (6.5-8.7)	223	9.3 (8.2-10.6)	169	10.8 (9.2-12.5)
Ischaemic	271	3.9 (3.5-4.4)	21	3.5 (2.3-5.3)	78	3.3 (2.6-4.1)	105	4.4 (3.6-5.3)	67	4.3 (3.3-5.4)
Unspecified	334	4.8 (4.3-5.4)	15	2.5 (1.5-4.1)	99	4.2 (3.4-5.1)	118	4.9 (4.1-5.9)	102	6.5 (5.3-7.9)
GI bleed	572	8.3 (7.6-9.0)	33	5.5 (3.9-7.7)	137	5.8 (4.9-6.9)	217	9.1 (8.0-10.4)	185	11.8 (10.2-13.7)
IC bleed	133	1.9 (1.6-2.3)	9	1.5 (0.8-2.9)	29	1.2 (0.9-1.8)	46	1.9 (1.4-2.6)	49	3.1 (2.4-4.1)
Fall	2,682	39.4 (37.9-40.9)	45	7.1 (5.3-9.6)	488	20.9 (19.1-22.8)	949	40.4 (37.9-43.0)	1,202	79.6 (75.2-84.2)
TIA	361	5.2 (4.7-5.8)	22	3.6 (2.4-5.5)	86	3.6 (3.0-4.5)	134	5.6 (4.7-6.6)	119	7.6 (6.3-9.1)

Abbreviations GI: gastrointestinal; IC: intracranial; TIA: transient ischaemic attack

8.5 Oral anticoagulation and clinical outcomes

Overall, the standardised stroke rate for patients with AF and any CHA_2DS_2-VASc score was 8.45 (95% CI 7.81 to 9.14) /1000pys. In patients that were not prescribed OAC at study entry, the rate was 9.66 (8.67 to 10.75) /1000pys, compared with 7.38 (6.57 to 8.29) /1000pys in the group that were prescribed OAC. The highest stroke rate was observed in patients that were not prescribed OAC at study entry and had a score of 7, in whom the rate was 23.56 (15.51 to 35.78) /1000pys.

No patients with a CHA_2DS_2-VASc score of nine had a stroke during the follow-up period, and there were no stroke events recorded in patients that were prescribed OAC and had a CHA_2DS_2-VASc score of one. There were 12 patients that experienced a stroke event with a CHA_2DS_2-VASc score of one who were not prescribed OAC (rate 5.30, 95% CI 3.01 to 9.33 /1000pys).

For a given CHA_2DS_2-VASc score, stroke rates were lower in patients taking an OAC at study entry, as shown in Figure 47 and Table 36. However, there were a relatively small number of events for each CHA_2DS_2-VASc score category, and the confidence intervals were wide and often overlapping between those prescribed OAC and those that were not prescribed OAC.

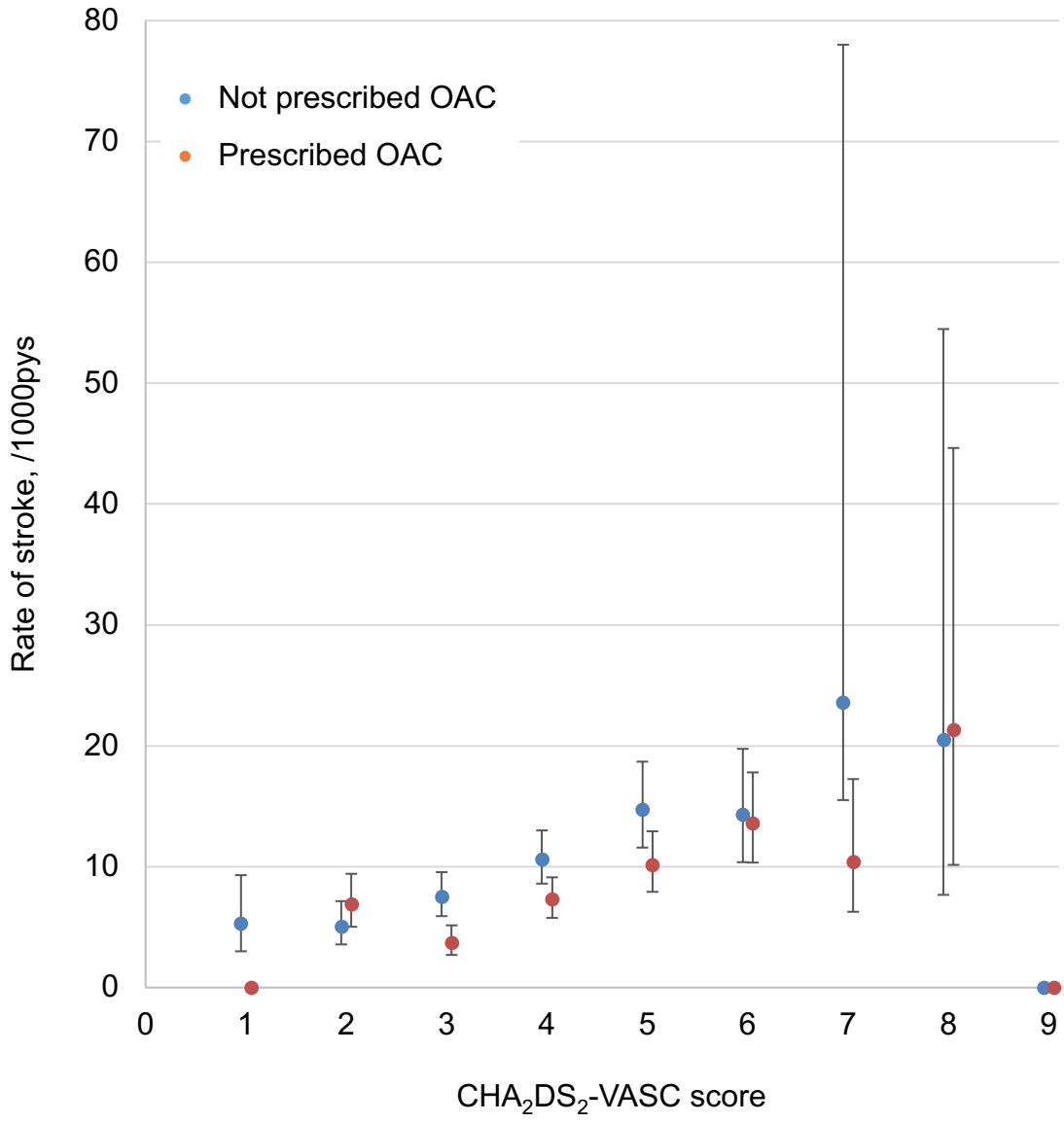


Figure 47: Rate of stroke per 1000 patient years by CHA_2DS_2-VASc score and OAC status, n=61,177

Table 36: Stroke rates by OAC status, stratified by CHA_2DS_2-VASc score

CHA_2DS_2-VASc		All patients with AF, n=61,177		Not prescribed OAC, n=29,098	Prescribed OAC, n=32,079	Difference between group prescribed OAC and group not prescribed OAC	
Score	n=	Stroke events	Rate, /1000pys (95%CI)	Rate, /1000pys (95%CI)	Rate, /1000pys (95%CI)	Difference in proportions (95%CI)	p-value
0	0	0	-	-	-	0	-
1	2,973	12	3.22 (1.83-5.68)	5.30 (3.01-9.33)	0	0.0003 (0.0002, 0.0005)	<0.001
2	9,758	71	5.92 (4.69-7.46)	5.05 (3.57-7.15)	6.88 (5.03-9.41)	-0.0001 (-0.0005, 0.0004)	0.732
3	15,117	102	5.55 (4.57-6.74)	7.51 (5.91-9.55)	3.70 (2.66-5.15)	0.0010 (0.0005, 0.0016)	<0.001
4	15,678	164	8.80 (7.55-10.25)	10.61 (8.64-13.03)	7.25 (5.76-9.12)	0.0008 (0.0001, 0.0015)	0.031
5	9,349	131	12.04 (10.15-14.29)	14.71 (11.58-18.69)	10.12 (7.92-12.93)	0.0003 (-0.0003, 0.0009)	0.353
6	5,614	89	13.87 (11.27-17.07)	14.31 (10.37-19.75)	13.57 (10.34-17.81)	-0.0003 (-0.0008, 0.0002)	0.296
7	2,143	37	15.57 (11.28-21.49)	23.56 (15.51-35.78)	10.40 (6.27-17.25)	0.0003 (-0.0001, 0.0006)	0.132
8	485	11	20.97 (11.61-37.87)	20.45 (7.67-54.48)	21.28 (10.15-44.64)	-0.0001 (-0.0002, 0.0001)	0.476
9	60	0	-	-	-	0 (0,0)	-
All	61,177	617	8.45 (7.81-9.14)	9.66 (8.67-10.75)	7.38 (6.57-8.29)	0.0023 (0.0009, 0.0036)	0.001

Abbreviation OAC: oral anticoagulation

Overall, in patients with AF and a CHA_2DS_2-VASc score of two or more, all-cause mortality rates were higher in patients that were not prescribed OAC compared to those that were prescribed OAC. There were 3,267 (12.0%) deaths in the group that were not prescribed OAC, with a mortality rate of 101.2 (95% CI 97.8 to 104.7) per 1000 patient years. In comparison, there were 2,818 deaths (9.12%) in the group that were prescribed OAC, with a rate of 75.50 (72.76 to 78.34) per 1000 patient years ($p<0.001$).

Rates of stroke were also lower in patients prescribed OAC than those that were not (10.0, 95% CI 8.9 to 11.1 per 1000 patient-years compared with 7.7, 6.8 to 8.6 /1000pys, $p<0.001$). There was no statistically significant difference in the rates of GI bleed (7.8, 6.9 to 8.8 compared with 8.7 (7.8 to 9.7, $p=0.170$), or IC bleed (1.6, 1.2 to 2.1 compared with 2.2, 1.8 to 2.7, $p=0.063$) between patients that were prescribed OAC and those that were not, Figure 48.

There was no statistically significant difference in the rates of falls and TIA by OAC prescription at study entry, Table 37. For completeness, the rates of clinical outcome events in all patients with AF, regardless of CHA_2DS_2-VASc score are also reported in Table 38.

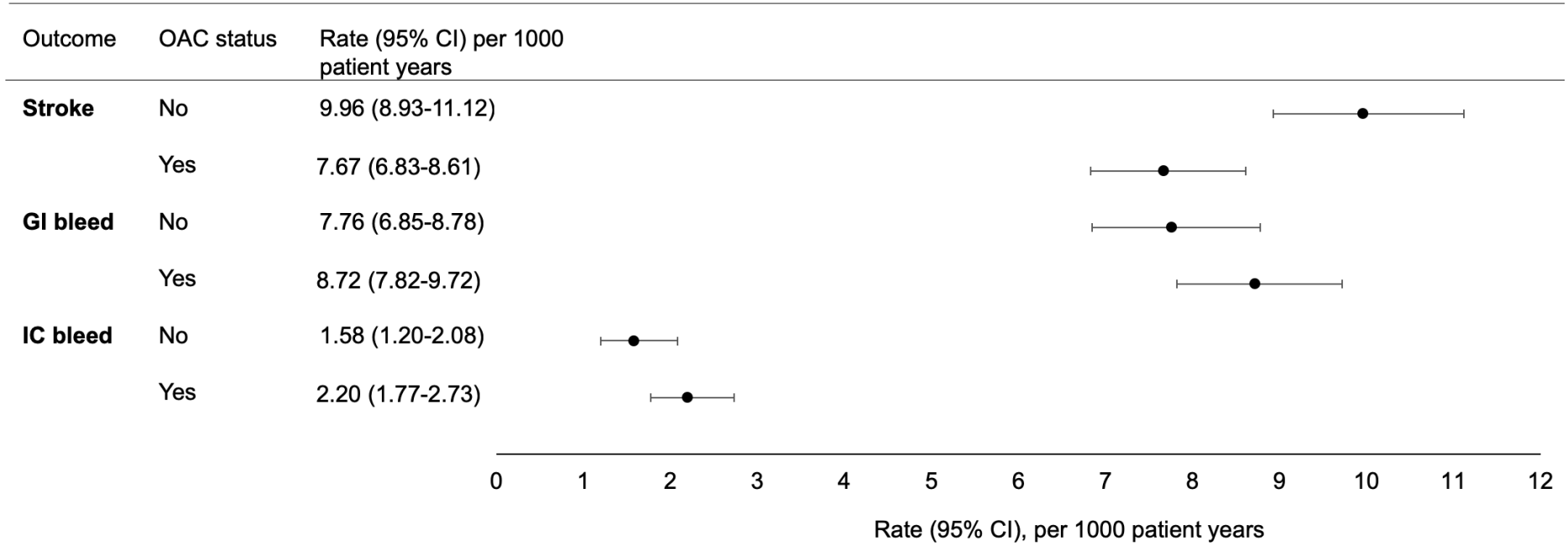


Figure 48: Rates of outcome events by oral anticoagulation status in patients with AF and a CHA_2DS_2-VASc score of 2 or more, n=58,204

Table 37: Rates of outcome events (per 1000 person-years) by OAC status in patients with AF and a CHA_2DS_2-VASc score of two or more

	All n=58,204		Not prescribed OAC at study start n=27,288		Prescribed OAC at study start n=30,916		Difference in proportions (95%CI)	p-value
	Events	Rate	Events	Rate	Events	Rate		
Death	6,085	87.4 (85.3-89.6)	3,267	101.2 (97.8-104.7)	2,818	75.5 (72.8-78.3)	0.026 (0.021, 0.030)	<0.001
Stroke	605	8.7 (8.1-9.5)	320	10.0 (8.9-11.1)	285	7.7 (6.8-8.6)	0.002 (0.0009, 0.0037)	<0.001
Ischaemic	271	3.9 (3.5-4.4)	160	5.0 (4.3-5.8)	111	3.0 (2.5-3.6)	0.002 (0.001, 0.003)	<0.001
Unspecified	334	4.81 (4.3-5.4)	160	5.0 (4.3-5.8)	174	4.7 (4.0-5.4)	0.0003 (-0.0007, 0.0013)	0.576
GI bleed	572	8.27 (7.6-9.0)	249	7.8 (6.9-8.8)	323	8.7 (7.8-9.7)	-0.0009 (-0.0023, 0.0004)	0.170
IC bleed	133	1.9 (1.6-2.3)	51	1.6 (1.2-2.1)	82	2.2 (1.8-2.7)	-0.0006 (-0.00126, 0.00003)	0.063
Falls	2,682	39.4 (37.9-40.9)	1,242	39.4 (37.2-41.6)	1,440	39.5 (37.5-41.5)	-.0001 (-0.003, 0.003)	0.939
TIA	361	5.2 (4.7-5.8)	181	5.6 (4.9-6.5)	180	4.8 (4.2-5.6)	0.0008 (-0.0003, 0.0019)	0.151

Abbreviations GI: gastrointestinal; IC: intracranial; TIA: transient ischaemic attack; OAC: oral anticoagulation

Table 38: Rates (per 1000 person-years) of outcome events by anticoagulation status in all patients with AF

	AF, not prescribed OAC n=29,098		AF, prescribed OAC n=32,079		Difference in proportions (95%CI)	p value
	Events	Rate	Events	Rate		
Death	3,302	95.6 (92.4–98.9)	2,841	73.3 (70.6-76.0)	0.022 (0.018-0.026)	<0.001
Stroke	332	9.7 (8.7-10.8)	285	7.4 (6.6-8.3)	0.002 (0.0009-0.0036)	0.001
Ischaemic	168	4.9 (4.2-5.7)	111	2.9 (2.4-3.5)	0.002 (0.001-0.003)	<0.001
Unspecified	164	4.8 (4.1-5.5)	174	4.5 (3.9-5.2)	0.0003 (-0.0007-0.0012)	0.605
Gastrointestinal bleed	253	7.4 (6.5-8.3)	330	8.6 (7.7-9.6)	-0.001 (-0.0025-0.0001)	0.071
Intracranial bleed	53	1.5 (1.2-2.0)	83	2.1 (1.7-2.7)	-0.0006 (-0.00122-0.00001)	0.057
Falls	1,258	37.2 (35.2-39.3)	1,449	38.2 (36.3-40.2)	-0.001 (-0.004-0.002)	0.492
Transient ischaemic attack	189	5.5 (4.8-6.3)	183	4.7 (4.1-5.5)	0.0008 (-0.0003-0.0018)	0.153

In patients with AF and a CHA_2DS_2-VASc score of two or more, prescription of OAC at study entry was associated with a reduced hazard of all-cause mortality (unadjusted HR 0.75, 95% 0.71 to 0.79; adjusted 0.81, 0.77 to 0.85) and stroke (unadjusted HR 0.77, 0.66 to 0.90, adjusted 0.78, 0.67 to 0.92), but no significant association was shown between OAC status and IC bleed, GI bleed, falls, or TIA, Table 39.

When stratified by frailty status, there was a statistically significant reduction in mortality associated with OAC therapy amongst the moderate and severe frailty groups. Overall, however, there was no evidence of an interaction effect by frailty category for any of the clinical outcomes.

Table 39: Association between frailty category and clinical outcomes by OAC status in patients with AF and CHA_2DS_2-VASC of ≥ 2, n=58,204

		Unadjusted hazard ratio (95% CI)			Adjusted hazard ratio (95% CI) †			
		No OAC n=27,288	OAC n=30,916	p value§	No OAC	OAC	p value§	p-value for interaction by frailty *
Death	All	1 (ref)	0.75 (0.71-0.79)	<0.001	1 (ref)	0.81 (0.77-0.85)	<0.001	
	Robust	1 (ref)	0.97 (0.69-1.36)	0.857	1 (ref)	0.91 (0.64-1.30)	0.608	
	Mild	1 (ref)	0.84 (0.75-0.95)	0.007	1 (ref)	0.88 (0.77-0.99)	0.041	
	Moderate	1 (ref)	0.71 (0.65-0.77)	<0.001	1 (ref)	0.75 (0.69-0.82)	<0.001	
	Severe	1 (ref)	0.67 (0.62-0.72)	<0.001	1 (ref)	0.76 (0.71-0.82)	<0.001	p=0.334
Stroke	All	1 (ref)	0.77 (0.66-0.90)	0.001	1 (ref)	0.78 (0.67-0.92)	0.004	
	Robust	1 (ref)	0.70 (0.35-1.39)	0.303	1 (ref)	0.64 (0.31-1.32)	0.230	
	Mild	1 (ref)	0.92 (0.69-1.24)	0.598	1 (ref)	0.94 (0.69-1.26)	0.661	
	Moderate	1 (ref)	0.59 (0.45-0.77)	<0.001	1 (ref)	0.61 (0.47-0.80)	<0.001	
	Severe	1 (ref)	0.86 (0.64-1.67)	0.337	1 (ref)	0.88 (0.64-1.21)	0.443	p=0.130
GI bleed	All	1 (ref)	1.13 (0.95-1.33)	0.162	1 (ref)	1.10 (0.93-1.30)	0.271	
	Robust	1 (ref)	0.91 (0.45-1.82)	0.783	1 (ref)	0.81 (0.38-1.70)	0.570	
	Mild	1 (ref)	1.39 (0.98-1.95)	0.063	1 (ref)	1.33 (0.93-1.89)	0.118	
	Moderate	1 (ref)	1.07 (0.81-1.39)	0.644	1 (ref)	1.05 (0.80-1.39)	0.727	
	Severe	1 (ref)	1.00 (0.75-1.34)	1.000	1 (ref)	0.98 (0.73-1.32)	0.897	p=0.478

IC bleed	All	1 (ref)	1.39 (0.98-1.97)	0.064	1 (ref)	1.40 (0.97-2.00)	0.069	
	Robust	1 (ref)	2.79 (0.70-11.15)	0.147	1 (ref)	1.98 (0.47-8.28)	0.352	
	Mild	1 (ref)	1.43 (0.67-3.02)	0.352	1 (ref)	1.47 (0.67-3.21)	0.335	
	Moderate	1 (ref)	1.62 (0.87-3.00)	0.126	1 (ref)	1.68 (0.89-3.20)	0.110	
	Severe	1 (ref)	1.02 (0.58-1.79)	0.946	1 (ref)	1.03 (0.58-1.85)	0.918	p=0.622
Fall	All	1 (ref)	1.00 (0.93-1.08)	0.943	1 (ref)	1.10 (1.02-1.19)	0.015	
	Robust	1 (ref)	1.46 (0.80-2.66)	0.213	1 (ref)	1.58 (0.83-3.00)	0.160	
	Mild	1 (ref)	1.04 (0.87-1.24)	0.697	1 (ref)	1.04 (0.86-1.24)	0.709	
	Moderate	1 (ref)	0.92 (0.81-1.04)	0.195	1 (ref)	1.03 (0.90-1.18)	0.658	
	Severe	1 (ref)	0.94 (0.84-1.05)	0.288	1 (ref)	1.06 (0.94-1.19)	0.340	p=0.485
TIA	All	1 (ref)	0.86 (0.70-1.06)	0.156	1 (ref)	0.88 (0.71-1.09)	0.236	
	Robust	1 (ref)	0.80 (0.33-1.90)	0.609	1 (ref)	0.76 (0.32-1.82)	0.539	
	Mild	1 (ref)	0.66 (0.43-1.01)	0.055	1 (ref)	0.70 (0.45-1.09)	0.111	
	Moderate	1 (ref)	0.97 (0.69-1.36)	0.845	1 (ref)	0.95 (0.67-1.35)	0.783	
	Severe	1 (ref)	0.87 (0.61-1.25)	0.453	1 (ref)	0.93 (0.64-1.35)	0.691	p=0.675
Stroke or TIA	All	1 (ref)	0.80 (0.71-0.91)	<0.001	1 (ref)	0.81 (0.71-0.93)	0.002	
	Robust	1 (ref)	0.73 (0.43-1.26)	0.256	1 (ref)	0.68 (0.39-1.19)	0.180	
	Mild	1 (ref)	0.83 (0.65-1.05)	0.120	1 (ref)	0.85 (0.66-1.09)	0.195	
	Moderate	1 (ref)	0.71 (0.58-0.87)	0.001	1 (ref)	0.72 (0.58-0.89)	0.002	
	Severe	1 (ref)	0.85 (0.67-1.07)	0.164	1 (ref)	0.89 (0.70-1.13)	0.330	p=0.541

† adjusted for age, sex, smoking status, index of multiple deprivation quintile, and general practice ID
§ p value for difference between groups prescribed OAC and not prescribed OAC.
* p value for interaction by frailty category, using adjusted model.
Abbreviations GI: gastrointestinal; IC: intracranial; TIA: transient ischaemic attack; OAC: oral anticoagulation

8.6 Sensitivity analyses

As described in section 5.7, a series of sensitivity analyses were carried out to test how robust the findings were to a stricter definition of AF using a more specific code-set, and account for the different duration of OAC therapy that patients were prescribed during the study.

8.6.1 Recording of AF in the dataset

Of the 37 CTV-3 codes used to identify AF in the cohort, four codes accounted for over 75% of the codes used: G5730 - Atrial fibrillation; 2432. - O/E - pulse irregularly irreg., 3272. - ECG: atrial fibrillation, and Xa2E8 - Paroxysmal atrial fibrillation. Table 40 shows how frequently each CTV-3 code was used to record AF in the 61,177 patients with AF. Within the EHR of the cohort, a CTV-3 code was used to identify AF on 244,782 occasions. The median number of times that a CTV-3 code was used to record the presence of AF in an individual was 3 per patient (minimum 1, maximum 381, IQR 1 to 6). Often, different CTV-3 codes for AF were used in the same individual (median of 2 different codes; minimum 1, maximum 10, IQR 1 to 2).

Table 40: Frequency of the use of each CTV-3 code in the electronic health record of patients with AF, n=61,177

CTV-3 code		Number of times CTV-3 code used in total	Number of patient EHR the CTV-3 code appears in	Percentage of patient EHR the code appears in
G5730	Atrial fibrillation	101,108	39,966	32.00%
2432	O/E - pulse irregularly irreg.	46,323	23,716	18.99%
3272	ECG: atrial fibrillation	27,754	20,836	16.68%
Xa2E8	Paroxysmal atrial fibrillation	24,671	10,962	8.78%
G573.	Atrial fibrillation and flutter	9,133	4,957	3.97%
XaLFz	Atrial fibrillation resolved	6,417	5,442	4.36%
G5731	Atrial flutter	6,346	3,528	2.82%
XaIIT	Atrial fibrillation monitoring	5,458	2,948	2.36%
XaMGD	Atrial fibrillation annual review	3,699	2,060	1.65%
XaLFi	Excepted from atrial fibrillation quality indicators: Patient unsuitable	2,405	1,912	1.53%
XaMDG	Atrial fibrillation monitoring first letter	2,121	1,076	0.86%
XaDv6	H/O: atrial fibrillation	1,893	1,469	1.18%
XaLFj	Excepted from atrial fibrillation quality indicators: Informed dissent	1,466	1,173	0.94%
3273	ECG: atrial flutter	1,429	1,202	0.96%
G573z	Atrial fibrillation and flutter NOS	933	464	0.37%
XaEga	Rapid atrial fibrillation	800	712	0.57%
XaOfa	Persistent atrial fibrillation	557	506	0.41%
XaMDH	Atrial fibrillation monitoring second letter	416	324	0.26%
XaOft	Permanent atrial fibrillation	397	368	0.29%
XaMDF	Atrial fibrillation monitoring administration	321	264	0.21%
Xa7nI	Controlled atrial fibrillation	291	263	0.21%
XaXrZ	Referral to atrial fibrillation clinic	277	263	0.21%
XaMDI	Atrial fibrillation monitoring third letter	135	108	0.09%
XaaUH	Paroxysmal atrial flutter	114	103	0.08%
XaMFn	Atrial fibrillation monitoring telephone invite	64	60	0.05%
X202R	Lone atrial fibrillation	57	56	0.04%
XaLFh	Exception reporting: atrial fibrillation quality indicators	42	39	0.03%
XaNRA	History of atrial flutter	58	47	0.04%

CTV-3 code		Number of times CTV-3 code used in total	Number of patient EHR the CTV-3 code appears in	Percentage of patient EHR the code appears in
7936A	Implantation of intravenous pacemaker for atrial fibrillation	13	13	0.01%
X202S	Non-rheumatic atrial fibrillation	22	15	0.01%
XE0Wk	(Atrial fibrillation) or (atrial flutter)	33	28	0.02%
XaMDK	Atrial fibrillation monitoring verbal invite	22	21	0.02%
XaZdc	Atrial fibrillation care pathway	<5	<5	0%
XaeUP	Chronic atrial fibrillation	<5	<5	0%
Total		**244,782**	**124,908**	
Abbreviations	CTV-3: Clinical Terms Version 3; EHR: electronic health records			

8.6.2 Evaluating the impact of a more specific AF code-set

A more specific code-list for AF was developed (outlined in section 5.7.1), excluding the following codes from the AF definition:

- XaaaD: Provision of written information about atrial fibrillation
- XaLFh: Exception reporting: atrial fibrillation quality indicators
- XaLFi: Excepted from atrial fibrillation quality indicators: Patient unsuitable
- XaLFj: Excepted from atrial fibrillation quality indicators: Informed dissent
- 2432: O/E - pulse irregularly irreg.

After removing these codes to form a reduced AF cohort, the number of patients remaining with a diagnosis of AF reduced by 14% to 52,605. The remaining 8,572 patients were excluded from the sensitivity analysis, Figure 49.

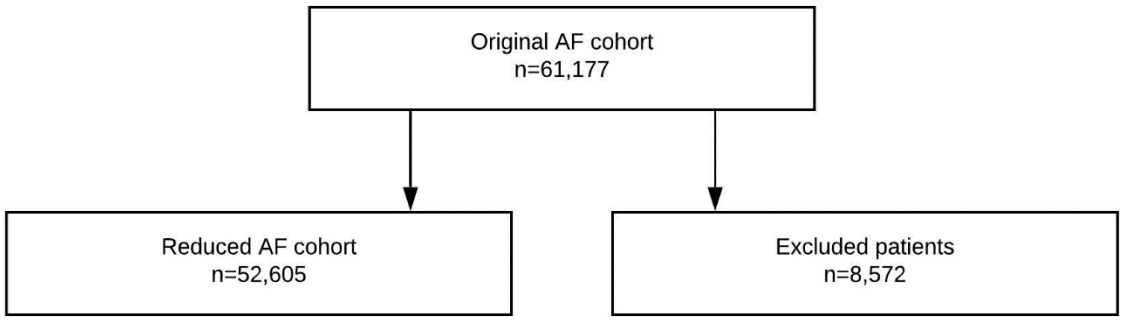


Figure 49: Illustration of the derivation of the reduced analytical cohort for a sensitivity analysis using a more specific AF code set

Baseline patient characteristics for the original AF cohort, compared to the reduced AF cohort showed that there were small but statistically significant differences between the groups. Patients in the reduced AF cohort were, on average, five months older than those in the excluded group ($p<0.001$). The reduced AF cohort had a lower proportion of women than the excluded group (45.4% compared with 47.8%, $p<0.001$), and tended to have higher levels of frailty than those the excluded group (median 9, IQR 7-12 eFI deficits compared with 8, IQR 6 to 11, $p<0.001$,Table 41).

The excluded group had a lower prescription rate of OAC than the original analytical cohort or the reduced cohort. In the original analytic cohort, 52.4% of patients were prescribed OAC. In the reduced analytical cohort, 60.3% were prescribed OAC, and in the excluded group, 4.4% were prescribed OAC (p-value for the difference between excluded and reduced analytical cohort p<0.001, Table 41).

Table 41: Baseline characteristics of patients with specific code-list for sensitivity analysis

	Original analytical cohort n=61,177	Reduced analytical cohort n=52,605	Excluded patients n=8,572	p-value
Age. Median (IQR)	79.7 (73.3-85.5)	79.8 (73.4-85.5)	79.33 (73.0-85.3)	<0.001
Female. n (%)	27,987 (45.8)	23,886 (45.4)	4,101 (47.8)	<0.001
Number of eFI deficits, median (IQR)	9 (6-12)	9 (7-12)	8 (6-11)	
Frailty category. n (%)				
Robust	6,443 (10.5)	5,153 (9.8)	1,290 (15.1)	<0.001
Mild	2,352 (33.3)	17,286 (32.9)	3,066 (35.8)	
Moderate	20,315 (33.2)	17,657 (33.6)	2,658 (31.0)	
Severe	14,067 (23.0)	12,509 (23.8)	1,558 (18.2)	
Prescribed OAC. n(%)	32,079 (52.4)	31,699 (60.3)	380 (4.4)	<0.001

Abbreviations IQR: interquartile range; OAC: oral anticoagulation

Comparing outcome event rates between the reduced analytical cohort and the excluded group in patients with CHA_2DS_2-VASc score of two or more, each of the following clinical outcomes occurred more frequently in the reduced analytical cohort: all-cause mortality 91.5, 95% CI 89.2 to 94.0 /1000pys in reduced cohort and 62.7, 58.0 to 67.8 /1000pys in the excluded group, p<0.001; unspecified stroke: 5.1, 4.5 to 5.7 compared with 3.2, 2.3- to 4.5 /1000pys, p=0.006; GI bleeding event: 8.6, 7.9 to 9.4 compared with 6.4, 5.0 to 8.2 /1000pys, p=0.012 and falls: 40.6, 39.0 to 42.2 compared with 32.6, 29.2 to 36.4 /1000pys, p<0.001.

There were no statistically significant differences between the groups in rates of stroke overall, ischaemic stroke, or IC bleeding events or TIA (p-values for difference >0.05), Table 42.

Table 42: Clinical outcome events by AF sensitivity analysis analytical cohort subgroups, in patients with CHA_2DS_2-VASc score of two or more. Rates, /1000pys (95% CI)

Outcome	Original analytical cohort n= 58,204	Reduced analytical cohort n=50,010	Excluded patients n= 8,194	p-value*
Death	87.4 (85.3-89.6)	91.5 (89.2-94.0)	62.7 (58.0-67.8)	<0.001
Stroke	8.7 (8.1-9.5)	8.9 (8.1-9.7)	8.0 (6.4-9.9)	0.197
Ischaemic	3.9 (3.5-4.4)	3.8 (3.3-4.3)	4.7 (3.6-6.3)	0.262
Unspecified	4.8 (4.3-5.4)	5.1 (4.5-5.7)	3.2 (2.3-4.5)	0.006
GI bleed	8.3 (7.6-9.0)	8.6 (7.9-9.4)	6.4 (5.0-8.2)	0.012
IC bleed	1.9 (1.6-2.3)	2.0 (1.6-2.4)	1.6 (1.0-2.6)	0.349
Falls	39.4 (37.9-40.9)	40.6 (39.0-42.2)	32.6 (29.2-36.4)	<0.001
TIA	5.2 (4.7-5.8)	5.2 (4.7-5.8)	5.0 (3.8-6.6)	0.568

*p-value for difference between the reduced analytical cohort and excluded patients
Abbreviations GI: gastrointestinal; IC: intracranial; TIA: transient ischaemic attack

There was a step-wise increase in event rates by frailty category in both the reduced analytical cohort and the excluded patient group in the clinical outcomes of all-cause mortality, stroke, and falls. This pattern was not apparent in either group for ischaemic stroke. The stepwise increase was seen in the reduced analytical cohort, but not the excluded group in the outcomes of unspecified stroke, GI bleed, IC bleed. In the clinical outcome of TIA, a stepwise positive association was seen in the excluded group, but not the reduced analytical cohort, Table 43.

Table 43: Rates of outcome events (/1000pys) in patients with AF and a CHA_2DS_2-VASC score of two or more, by frailty status. Results shown for the reduced analytical cohort (n=52,605) and the excluded group (n=8,194).

	All n	Rate	Robust Rate	Mild Rate	Moderate Rate	Severe Rate
Death						
Excluded group	626	62.7 (58.0-67.8)	12.7 (7.9-20.5)	34.1 (28.6-40.6)	69.3 (60.7-79.1)	146.7 (130.0-165.6)
Reduced cohort	5,459	91.5 (89.2-94.0)	25.7 (21.5-30.7)	44.7 (41.8-47.7)	89.4 (41.8-47.7)	183.9 (176.9-191.1)
Stroke						
Excluded group	79	8.0 (6.4-9.1)	5.3 (2.5-11.1)	6.3 (4.2-9.5)	10.1 (7.1-14.3)	9.5 (5.9-15.3)
Reduced cohort	526	8.9 (8.1-9.7)	6.1 (4.3-8.8)	7.7 (6.6-9.1)	9.2 (8.0-10.6)	10.9 (9.3-12.8)
Ischaemic stroke						
Excluded group	47	4.7 (3.6-6.3)	1.5 (0.4-6.0)	3.6 (2.1-6.1)	7.2 (4.8-10.9)	5.0 (2.6-9.7)
Reduced cohort	224	3.8 (3.3-4.3)	4.0 (2.6-6.3)	3.3 (2.6-4.1)	3.9 (3.2-4.9)	4.2 (3.2-5.4)
Unspecified stroke						
Excluded group	32	3.2 (2.3-4.5)	3.8 (1.6-9.0)	2.7 (1.5-5.1)	2.8 (1.5-5.4)	4.5 (2.2-8.9)
Reduced cohort	302	5.1 (4.5-5.7)	2.1 (1.4-3.9)	4.5 (3.6-5.5)	5.2 (4.3-6.3)	6.7 (5.5-8.2)
Gastrointestinal bleed						
Excluded group	64	6.4 (5.0-8.2)	6.0 (3.0-12.0)	6.0 (4.0-9.2)	4.4 (2.6-7.5)	11.3 (7.3-17.5)
Reduced cohort	508	8.6 (7.9-9.4)	5.3 (3.6-7.8)	5.8 (4.8-6.9)	9.8 (8.5-11.3)	11.9 (10.2-13.9)
Intracranial bleed						
Excluded group	16	1.6 (1.0-2.6)	0	1.4 (0.6-3.3)	1.3 (0.5-3.4)	3.9 (1.9-8.2)
Reduced cohort	117	2.0 (1.6-2.4)	1.9 (1.0-3.6)	1.2 (0.8-1.8)	2.0 (1.5-2.7)	3.0 (2.2-4.1)
Fall						
Excluded group	319	32.6 (29.2-36.4)	4.5 (2.0-10.0)	19.6 (15.6-24.8)	35.1 (29.1-42.4)	77.3 (65.2-91.7)
Reduced cohort	2,363	40.6 (39.0-42.2)	7.8 (5.7-10.8)	21.1 (19.2-23.2)	41.2 (38.5-44.1)	79.9 (75.3-84.8)
TIA						
Excluded group	50	5.0 (3.8-6.6)	1.5 (0.4-6.0)	4.7 (2.9-7.5)	4.7 (2.8-7.8)	9.0 (5.5-14.6)
Reduced cohort	311	5.2 (4.7-5.8)	4.2 (2.7-6.6)	3.5 (2.7-4.4)	5.7 (4.8-6.9)	7.4 (6.1-9.0)

Repeating the survival analysis showed that the effect size for OAC was greater in the reduced analytical cohort than in the original cohort for the outcomes of all-cause mortality (unadjusted HR for mortality compared with patients not prescribed OAC 0.75, 95%CI 0.71 to 0.79 in original cohort, compared with 0.63, 0.60 to 0.67) in the reduced cohort). There was also a greater reduction in stroke associated with prescription of OAC, although the confidence intervals overlap between the two groups (HR 0.77, 0.66 to 0.90 compared with 0.71, 0.60 to 0.84), Figure 50.

There was no difference in the association between OAC prescription and the hazard ratio for IC or GI bleeding between the original analytical cohort and the reduced analytical cohort. Adjusted estimates of the association between OAC prescription and clinical outcomes in the reduced analytical cohort are shown in Table 44.

Table 44: Association between OAC at study entry and clinical events in patients with CHA_2DS_2-VASC score ≥ 2, in the reduced analytical cohort. n=50,010

	Unadjusted hazard ratio (95% CI)			Adjusted hazard ratio (95% CI)		
	No OAC n=19,464	OAC n=30,546	p-value*	No OAC n=19,464	OAC n=30,546	p-value*
Death	1 (ref)	0.63 (0.60-0.67)	<0.001	1 (ref)	0.70 (0.66-0.74)	<0.001
Stroke	1 (ref)	0.7 (0.6-0.8)	<0.001	1 (ref)	0.7 (0.6-0.9)	<0.001
GI bleed	1 (ref)	1.0 (0.8-1.2)	0.924	1 (ref)	1.0 (0.9-1.2)	0.997
IC bleed	1 (ref)	1.4 (0.9-2.1)	0.102	1 (ref)	1.4 (1.0-2.2)	0.078

* p-value for difference in HR associated with prescription of OAC.
Abbreviations OAC: oral anticoagulation; GI: gastrointestinal; IC: intracranial

Outcome	Comparison	HR (95% CI)
Death	No OAC	1 (ref)
	OAC, original cohort	0.75 (0.71-0.79)
	OAC, reduced cohort	0.63 (0.60-0.67)
Stroke	No OAC	1 (ref)
	OAC, original cohort	0.77 (0.66-0.90)
	OAC, reduced cohort	0.71 (0.60-0.84)
Gastrointestinal bleed	No OAC	1 (ref)
	OAC, original cohort	1.13 (0.95-1.33)
	OAC, reduced cohort	1.01 (0.84-1.21)
Intracranial bleed	No OAC	1 (ref)
	OAC, original cohort	1.39 (0.98-1.97)
	OAC, reduced cohort	1.39 (0.94-2.05)

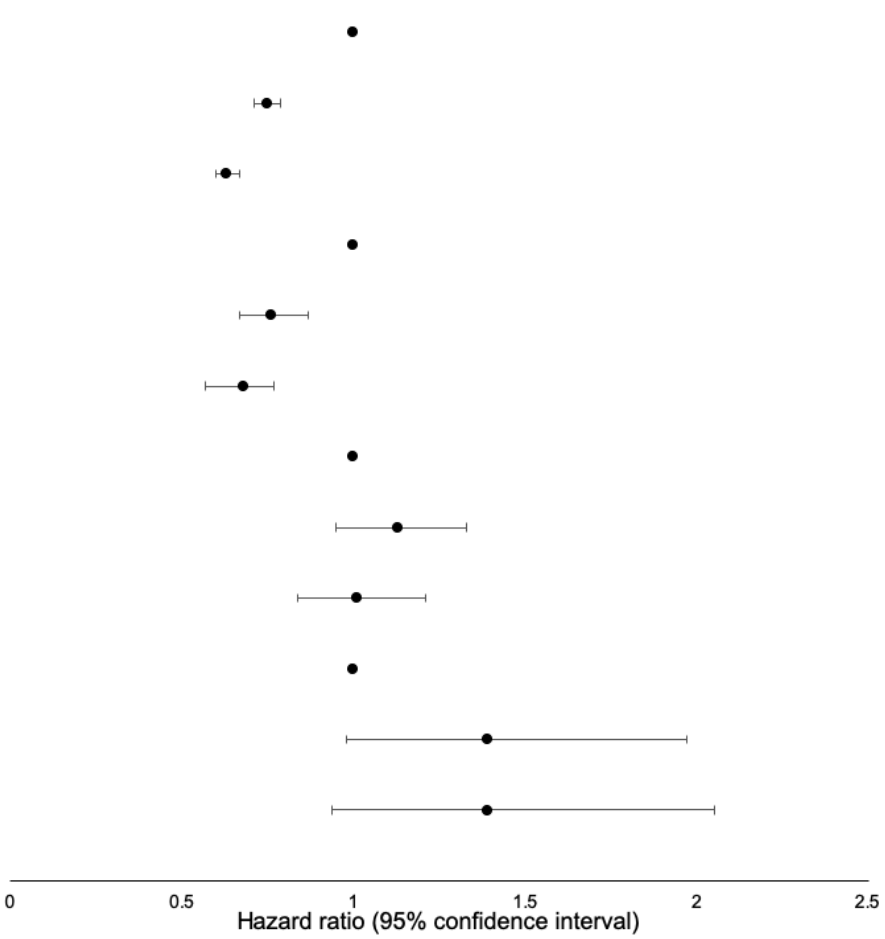


Figure 50: Sensitivity analysis showing the unadjusted association between OAC and clinical outcomes in patients with AF and CHA_2DS_2-VASc score of two or more

8.6.3 Evaluating the intention to treat assumption

This section will report the characteristics of patients that did not persist on OAC, and investigate the impact of removing patients that were not persistent on OAC therapy in a sensitivity analysis. Of the 58,204 patients with AF and a CHA_2DS_2-VASC score of two or more, 34,030 (58.5%) were prescribed OAC at study entry. Of these, 28,356 (83.3%) persisted with an OAC prescription for the duration of follow-up, and 5,674 (16.7%) discontinued OAC during the study, Figure 51.

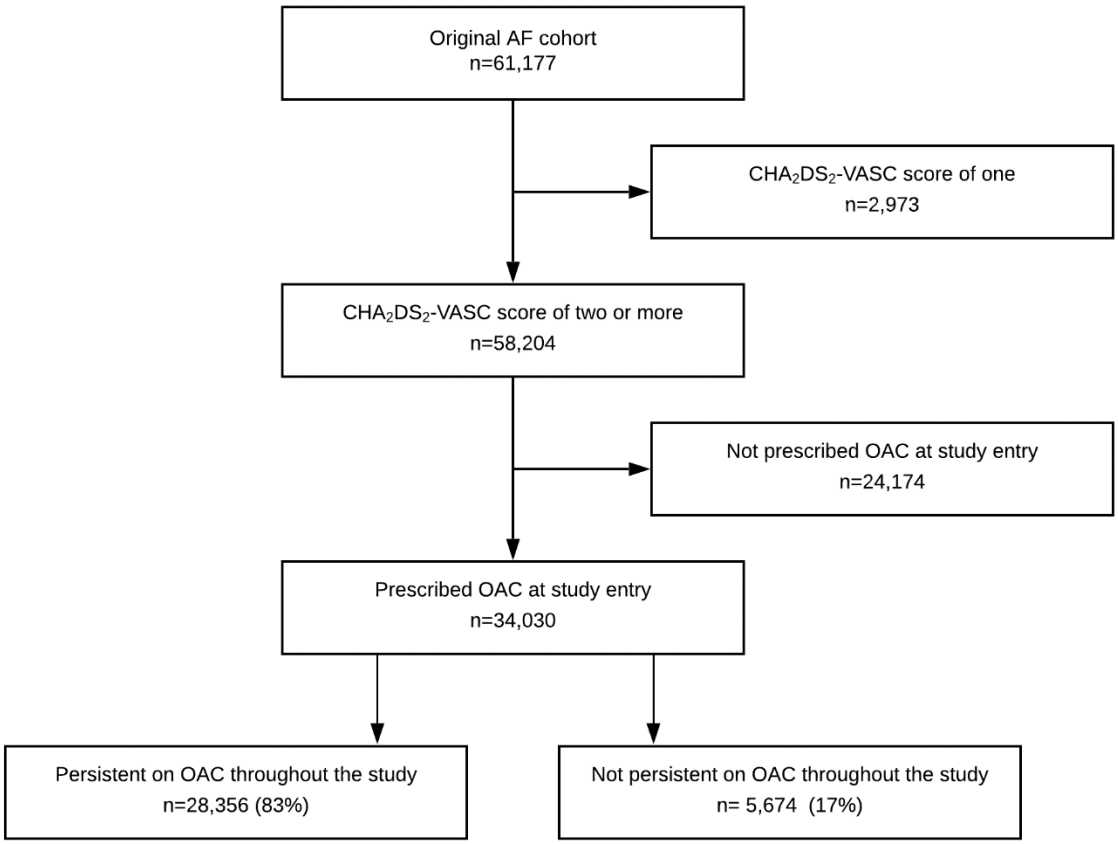


Figure 51: Illustration of the derivation of the subgroups for a sensitivity analysis of OAC persistence

In patients with AF and a CHA_2DS_2-VASC score of two or more, patients that discontinued OAC were older and tended to have higher baseline frailty category than those that were persistent on OAC (or were not prescribed OAC). The group that were not persistent on OAC had the greatest proportion of patients in the most deprived quintile (14.4% compared with 12.3% of the persistent group and 13.7% of the group that were not prescribed OAC), and

had the highest proportion living in a nursing home (13.8%, compared with 5.5% in the persistent group and 12.1% in the group that were not prescribed OAC). The group that discontinued OAC had the highest proportion of patients with a history of GI bleed, but not IC bleed.

Patients that persisted with OAC had the lowest proportion of patients taking anti-platelet medications at study entry, or be prescribed an anti-platelet during the study period (2.1% and 0.8%) compared with those that were not prescribed OAC (11.0% and 2.4%) or discontinued OAC (8.0% and 4.2%). Patients that were persistent on OAC also had the lowest proportion taking a PPI at entry, or prescribed a PPI during the study, Table 45.

Table 45: Characteristics of patients with AF and CHA_2DS_2-VASC score ≥ 2, by OAC persistence

	All n=58,204	Persistent on OAC n=28,356	Not persistent on OAC n=5,674	Not prescribed OAC n=24,174	p value
Demographics					
Age, Median (IQR)	80.3 (74.3-85.8)	79.9 (74.5-85.1)	81.3 (75.3-86.4)	80.4 (73.9-86.6)	<0.001[a]
Electronic frailty index category, n (%)					
Robust	4,863 (8.4)	1,914 (6.8)	382 (6.7)	2,567 (10.6)	
Mild	19,198 (33.0)	9,532 (33.6)	1,691 (29.8)	7,975 (33.0)	
Moderate	20,099 (34.5)	10,251 (36.2)	1,990 (35.1)	7,858 (32.5)	
Severe	14,044 (24.1)	6,659 (23.5)	1,611 (28.4)	5,774 (23.9)	<0.001
IMD rank, n (%)					
Most deprived quintile	7,118 (13.1)	3,299 (12.3)	774 (14.4)	3,115 (13.7)	<0.001
Living in a nursing home	5,246 (9.0)	1,547 (5.5)	782 (13.8)	2,917 (12.1)	<0.001
Duration of AF, years prior to study start, Median (IQR)	4.76 (2.2-9.4)	5.4 (2.5-10.2)	4.3 (1.6-8.9)	4.2 (2.0-8.4)	<0.001[a]
Risk scores					
CHA_2DS_2-Vasc, Mean (SD)	3.9 (1.4)	4.0 (1.4)	4.0 (1.4)	3.8 (1.4)	<0.001[a]
ATRIA, Median (IQR)	3 (2-6)	4 (2-6)	4 (2-6)	3 (2-6)	<0.001[a]
Past medical history, n (%)					
Cancer	9,862 (16.9)	4,535 (16.0)	1,048 (18.5)	4,279 (17.7)	<0.001
Varices	82 (0.14)	22 (0.08)	10 (0.18)	50 (0.21)	<0.001
Upper gastrointestinal bleed	890 (1.5)	348 (1.2)	118 (2.1)	424 (1.8)	<0.001
Lower gastrointestinal bleed	5,940 (10.2)	2,804 (9.9)	609 (10.7)	2,527 (10.5)	0.040
Intracranial haemorrhage	972 (1.7)	269 (0.95)	88 (1.55)	615 (2.54)	<0.001
Falls	11,637 (20.0)	5,209 (18.4)	1,28 (22.6)	5,147 (21.3)	<0.001
Medications in the previous year n (%)					
Steroid	1,684 (2.9)	829 (2.9)	166 (2.9)	689 (2.9)	0.872
NSAID	5,209 (9.0)	2,096 (7.4)	500 (8.8)	2,613 (10.8)	<0.001
Macrolide	402 (0.69)	176 (0.62)	49 (0.86)	177 (0.73)	0.078
Proton pump inhibitor	23,695 (40.7)	10,734 (37.9)	2,526 (44.5)	10,435 (43.2)	<0.001
Anti-epileptic					
Carbemazepine	224 (0.38)	100 (0.35)	25 (0.44)	99 (0.41)	0.208
Phenytoin	176 (0.30)	73 (0.26)	25 (0.44)	78 (0.32)	

	All n=58,204	Persistent on OAC n=28,356	Not persistent on OAC n=5,674	Not prescribed OAC n=24,174	p value
Medication at study entry, n (%)					
Antiplatelet prescription	3,688 (6.3)	581 (2.1)	453 (8.0)	2,654 (11.0)	<0.001
Medications prescribed during the study period, n (%)					
Antiplatelet*	1,040 (1.8)	233 (0.82)	237 (4.2)	570 (2.4)	<0.001
Steroid	1,820 (3.1)	862 (3.0)	227 (4.0)	731 (3.0)	<0.001
NSAID	4,979 (8.6)	1,977 (7.0)	494 (8.7)	2,508 (10.4)	<0.001
Macrolide	448 (0.77)	188 (0.66)	53 (0.93)	207 (0.86)	0.014
Proton pump inhibitor	25,058 (43.1)	11,195 (39.5)	2,916 (48.6)	10,947 (45.3)	<0.001

* This figure is the number of patients that started on an antiplatelet during the study period, who were not on an anti-platelet at study entry
Conditions in *italics* are also a deficit in the eFI
p-value for difference between the three subgroups. a: Kruskall-Wallis, all other statistical comparisons used Chi-square
Abbreviations IMD: index of multiple deprivation; IQR: interquartile range; NSAID: non-steroidal anti-inflammatory drug

It was shown in section 8.5 that prescription of OAC at study entry was associated with a reduced risk of stroke and all-cause mortality during the follow-up period. Persistent OAC was associated with a further reduction in the risk of death. OAC at study entry was associated with a HR of 0.75 (95% CI 0.71-0.79), compared with a HR associated with persistent OAC (compared with no OAC) of 0.63 (0.60 to 0.67). Restricting the cohort to the reduced AF analytic cohort used in section 8.6.2 resulted in a further strengthening of the association between OAC and mortality reduction, with a HR of 0.52 (0.49 to 0.55), Figure 52. Adjusted estimates showed the same pattern of association, Figure 53.

The increased strength of association shown for mortality was also shown in stroke, although as in the main analysis, the confidence intervals overlap between groups. Compared to the reference group of patients not prescribed OAC, OAC at study entry was associated with a HR of 0.77 (95%CI 66 to 90); persistent OAC with a HR of 0.75 (0.62 to 0.90); and persistent OAC with a reduced AF analytic cohort was associated with a HR for stroke of 0.69 (0.56 to 0.84).

As in the main analysis, the sensitivity analyses showed no statistically significant association between OAC and bleeding events, as the confidence intervals of the hazard ratio cross one.

Outcome	Comparison	HR (95% CI)
Death	No OAC	1 (ref)
	OAC: at entry	0.75 (0.71-0.79)
	OAC: persistent	0.63 (0.60-0.67)
	OAC: persistent, AF reduced cohort	0.52 (0.49-0.55)
Stroke	No OAC	1 (ref)
	OAC: at entry	0.77 (0.66-0.90)
	OAC: persistent	0.75 (0.62-0.90)
	OAC: persistent, AF reduced cohort	0.69 (0.56-0.84)
GI bleed	No OAC	1 (ref)
	OAC: at entry	1.13 (0.95-1.33)
	OAC: persistent	1.04 (0.86-1.24)
	OAC: persistent, AF reduced cohort	0.91 (0.75-1.11)
IC bleed	No OAC	1 (ref)
	OAC: at entry	1.39 (0.98-1.97)
	OAC: persistent	0.73 (0.48-1.13)
	OAC: persistent, AF reduced cohort	0.74 (0.46-1.20)

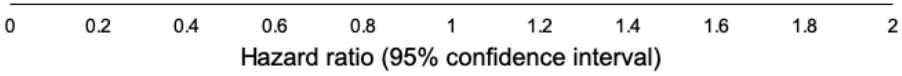


Figure 52: Forest plot showing the unadjusted results of the sensitivity analyses

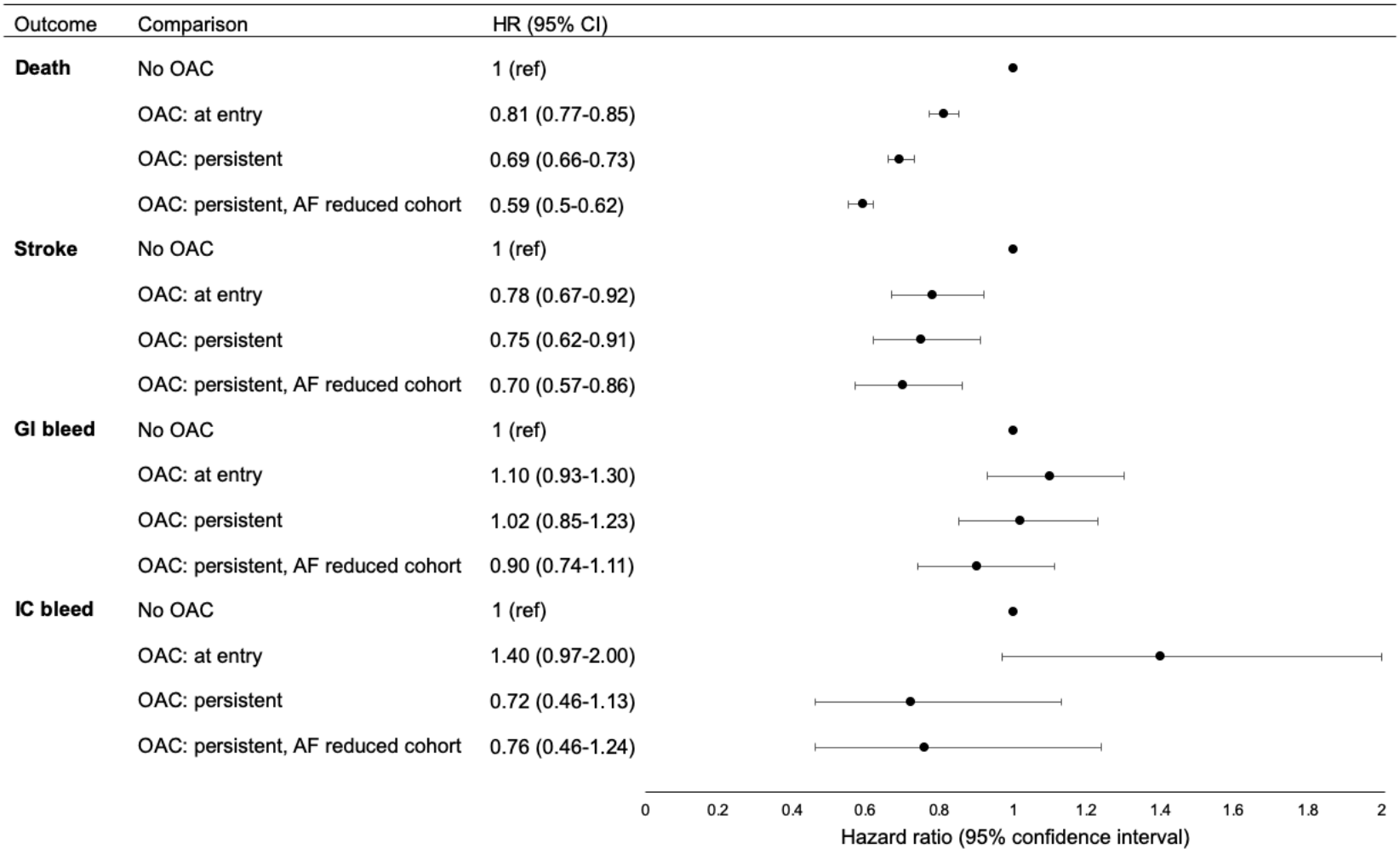


Figure 53: Forest plot showing the results of the sensitivity analyses, adjusted for age, sex, smoking status, IMD quintile, and GP practice ID

When stratified by eFI category, OAC prescription was associated with a reduction in all-cause mortality for mild, moderate and severe frailty categories, but there was no statistically significant reduction among patients in the robust category. Whilst the confidence intervals overlap between the groups, the point estimates suggest an inverse ‘dose response’ relationship in the reduction in mortality associated with OAC prescription and eFI category. A statistically significant reduction associated with OAC prescription in the robust category was only seen in the reduced AF analytical cohort with persistent OAC prescription. The HR for all-cause mortality associated with OAC prescription was 0.6 (95% CI 0.4 to 0.9) in this group, with no change in the estimate with adjustment, Figure 54.

For the outcome of stroke, there was little difference in the HR across the different analyses. In each, the moderate frailty category was the only one in which there was a statistically significant reduction in stroke associated with OAC prescription, HR 0.59 (95% CI 0.45 to 0.77) for OAC prescription at study entry compared with a HR of 0.55 (0.40 to 0.77) in the reduced AF analytical cohort and persistent OAC prescription, Figure 55.

There was no statistically significant difference in bleeding outcomes between the groups prescribed OAC or not prescribed OAC across each of the sensitivity analyses and eFI categories, Figure 56 and Figure 57.

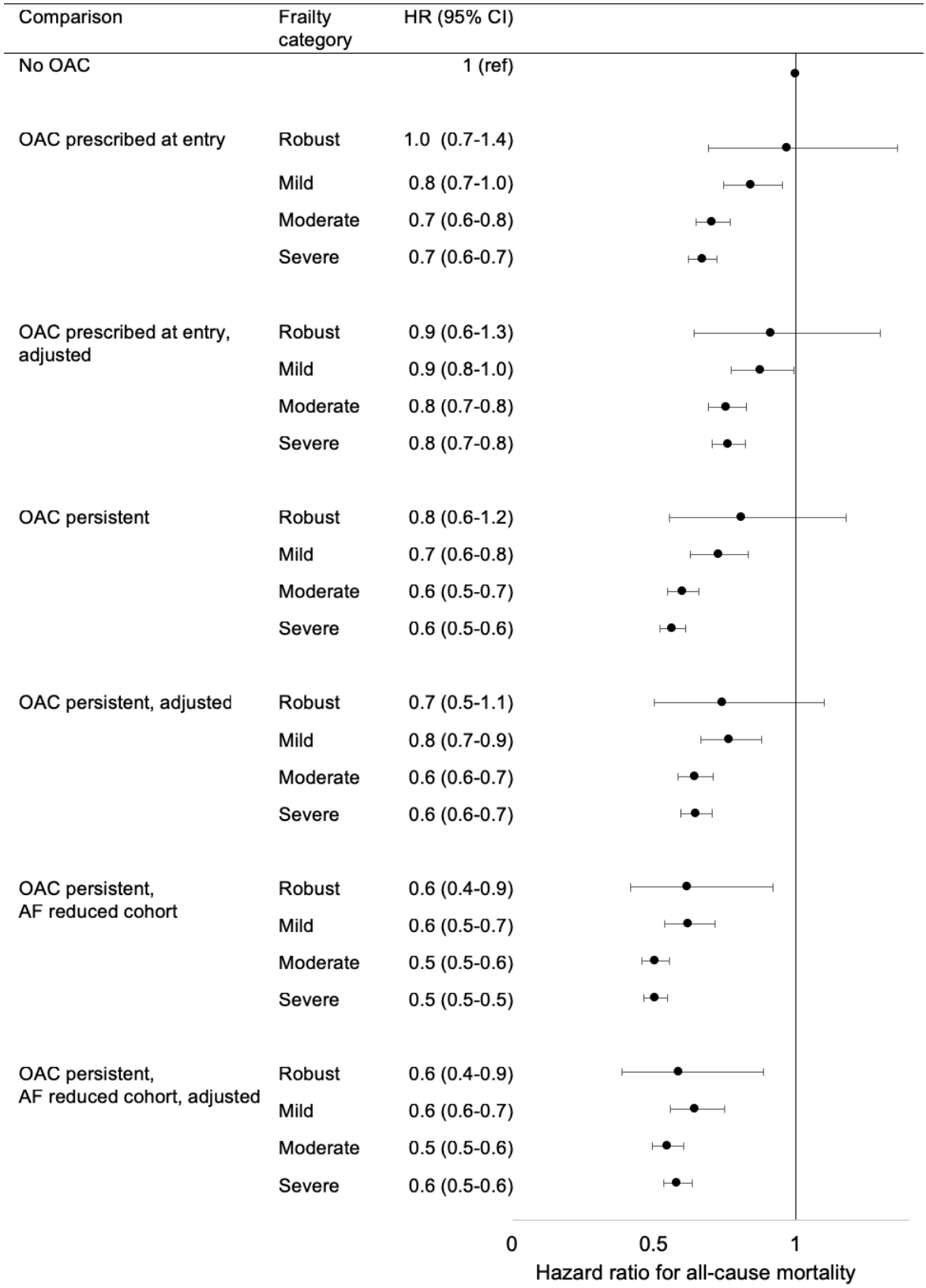


Figure 54: Forest plot showing results of the sensitivity analyses for all-cause mortality by electronic frailty index category

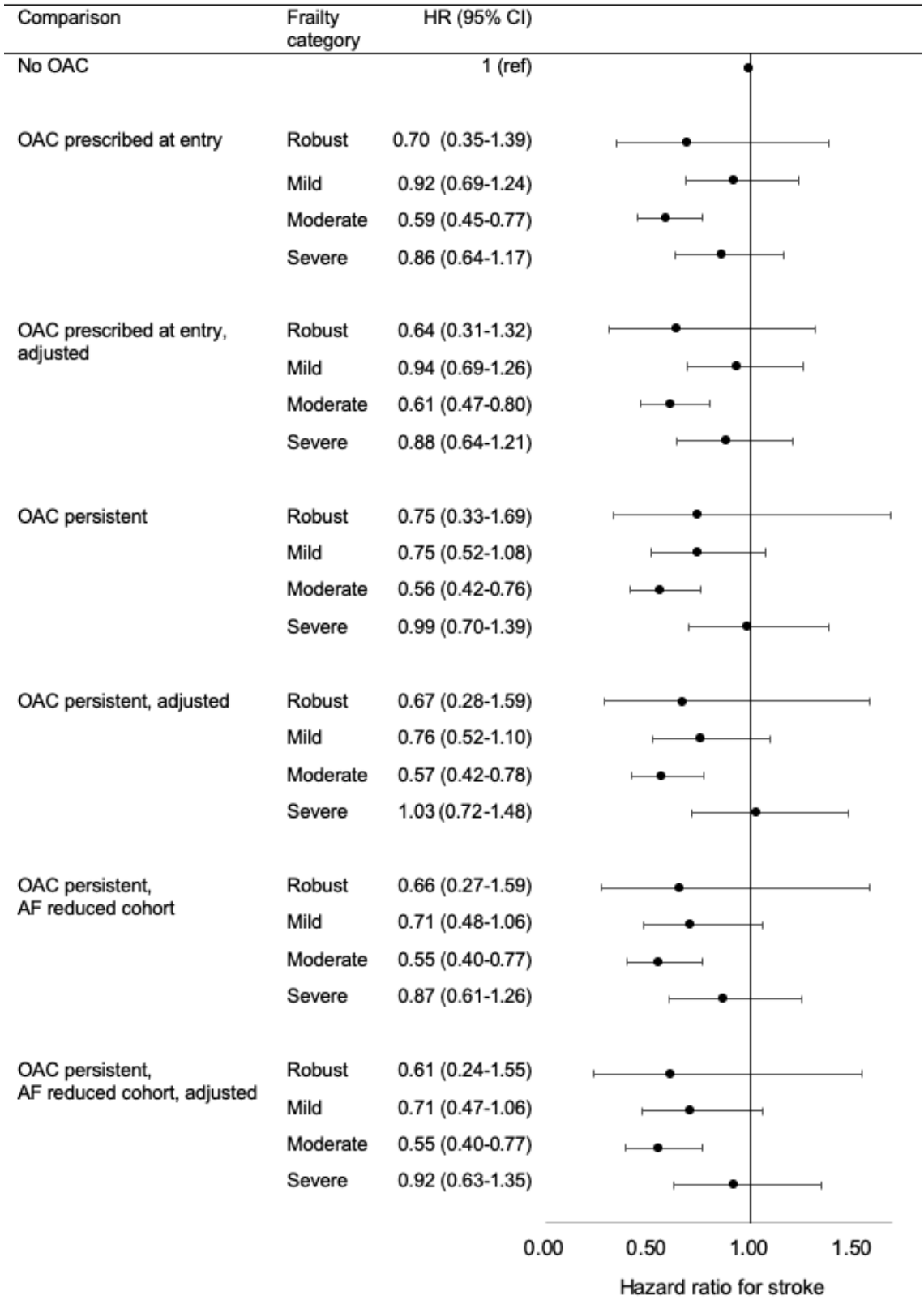


Figure 55: Forest plot showing results of the sensitivity analyses for stroke by electronic frailty index category

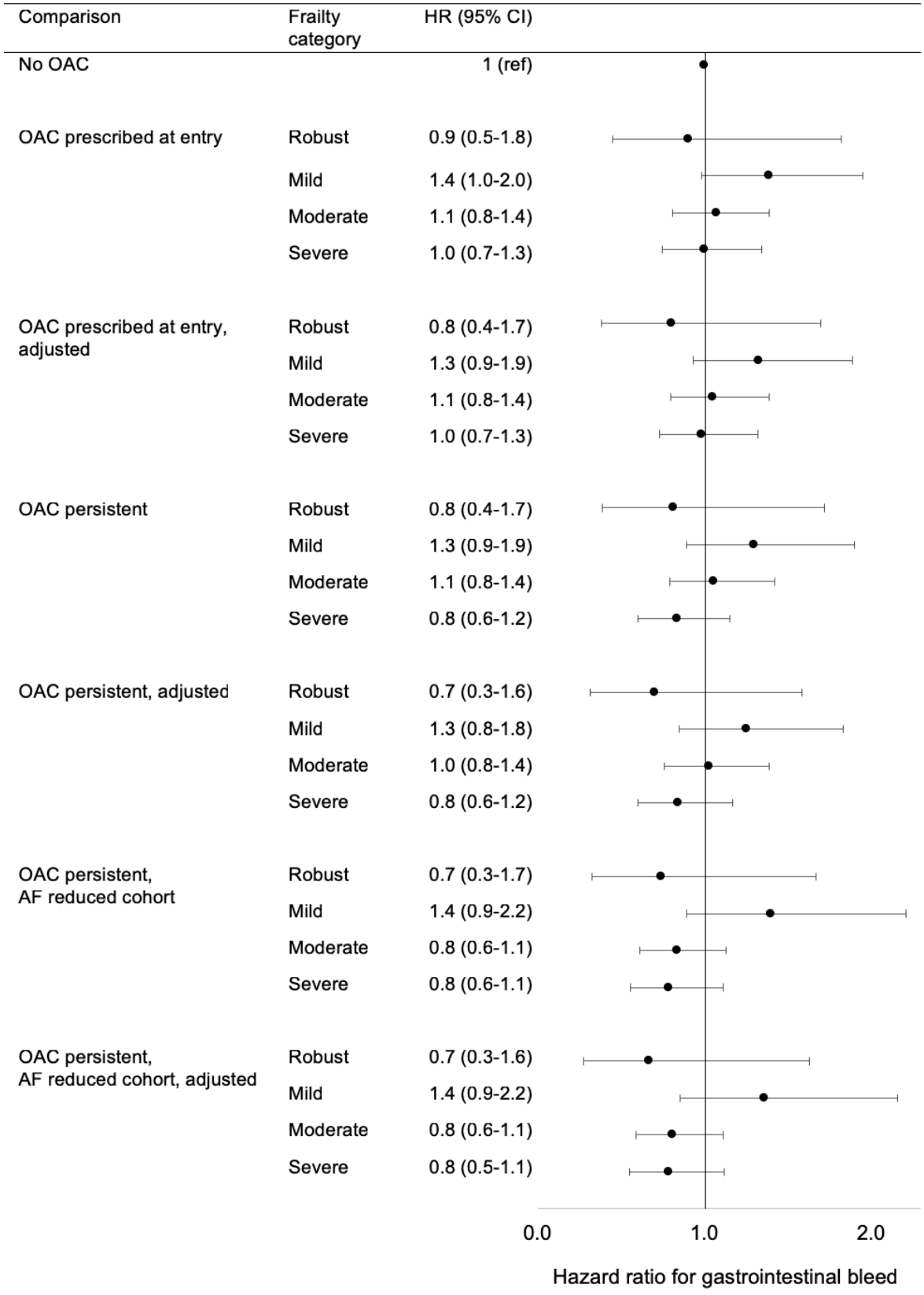


Figure 56: Forest plot showing results of the sensitivity analyses for gastrointestinal bleeding event by electronic frailty index category

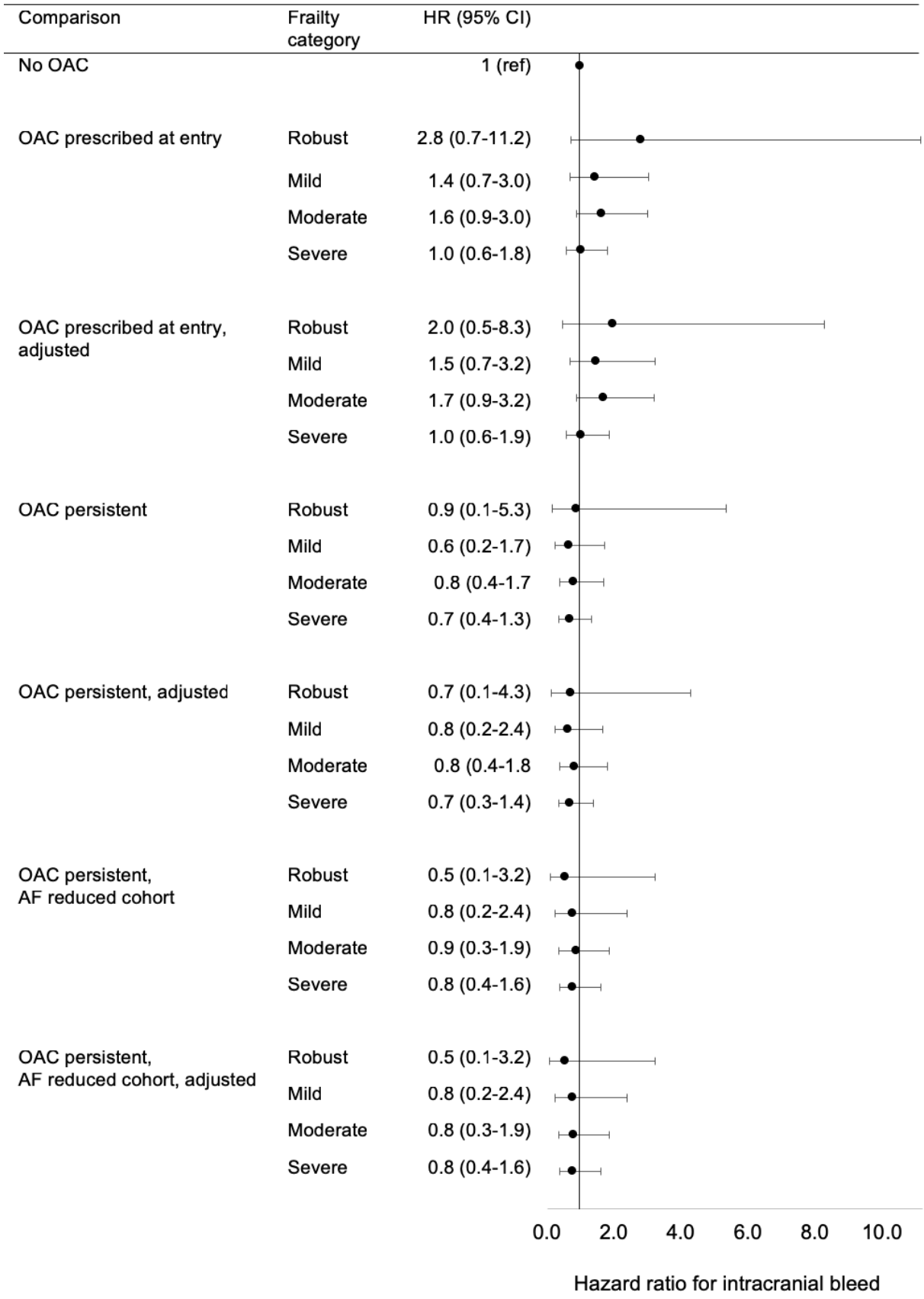


Figure 57: Forest plot showing results of the sensitivity analyses for intracranial bleeding event by electronic frailty index category

8.7 Summary of key findings

- Of patients that were eligible for OAC prescription according to NICE guidelines, OAC was prescribed in 30,916 (53.1%).
- Patients that were prescribed OAC tended to be younger, were more often male, with a longer duration of AF, and had a slightly higher average CHA_2DS_2-VASc score than patients that were not prescribed OAC. They were also less likely to have a past medical history of falls, anaemia, cancer and memory loss than patients that were prescribed OAC.
- Patients that were not prescribed OAC were more commonly prescribed an anti-platelet medication than patients that were prescribed OAC (2.1% compared with 11.2%, $p<0.001$).
- Patients with frailty were more likely to be prescribed OAC than the robust group.
- OAC prescription was associated with a lower rate of all-cause mortality and stroke, but there was no statistically significant difference in the outcomes of GI bleed or IC bleeding event.
- OAC prescription was associated with a lower mortality rate in patients in each eFI category. When stratified by frailty status, OAC was associated with a decreased point estimate for the outcome of stroke, but the confidence intervals were wide and crossed one in each category except moderate frailty.
- Sensitivity analyses showed that the direction of associations that were demonstrated in the main analyses were unchanged, and that restricting the cohort to a more specific definition of AF and accounting for persistence of OAC prescription increased the effect size of the association.

8.8 Conclusion

Among patients with AF and a CHA_2DS_2-VASc score of two or more, those with frailty were more commonly prescribed OAC. OAC was associated with a greater reduction in all-cause mortality with increasing eFI category. OAC was associated with a reduction in stroke events overall, but when stratified by eFI category remained statistically significant only in the moderate frailty group. These findings were robust to sensitivity analyses that accounted for persistence on OAC and in a more specifically defined cohort of patients with AF.

The findings of the thesis will be discussed in the context of the existing literature and critically evaluated in the next chapter, as will the strengths and limitations of the study.

Chapter 9 - Discussion

9.1 Introduction

Atrial fibrillation and frailty are increasing in prevalence, more frequently present in older people, and are associated with substantial morbidity and mortality.[10, 131, 136, 184, 187]. Whilst each are important severally, this thesis has demonstrated, for the first time in a large national study of electronic health records, that in combination they are associated with particularly poor clinical outcomes. However, the scale of the problem is not matched by the current evidence base.

My published systematic review and meta-analysis found that in people with AF, frailty is associated with an increased incidence of stroke, mortality, symptom severity, and length of hospital stay.[185] Yet, there were no community-based studies that examined whether frailty modifies the association between the use of oral anticoagulation and subsequent clinical outcomes in people with AF. This thesis has contributed to addressing this knowledge gap

In addition to the systematic review of the literature, I report analyses from a nationwide dataset of the electronic health records of over half a million older people registered in primary care. Guided by the gaps in knowledge identified in the literature review, the objectives of this study have been met by:

1. Establishing the population prevalence of atrial fibrillation, stratified by frailty category
2. Reporting prescription rates of OAC in patients with AF by eFI category
3. Estimating the association between frailty and OAC prescription.
4. Reporting rates of clinical outcomes (stroke, death and major bleeding) by eFI category and OAC status.
5. Quantifying the association between OAC and clinical outcomes (stroke, death and major bleeding), and how it is modified by frailty.

By addressing each of these objectives, this study makes novel and important contributions to the understanding of the epidemiology, management and clinical outcomes of older people with frailty and AF. The key findings of the thesis will now be summarised and discussed in the context of the existing literature. The strengths and limitations of the study will then be critically appraised, and the implications of the results assessed.

9.2 Summary of key and novel findings

The findings of the literature review, and in particular the gaps in the existing evidence base, guided the questions that this thesis set out to address in the quantitative analysis. Key and novel findings from each component of the thesis will now be summarised.

9.2.1 Systematic review and meta-analysis

Twenty research articles were included in the systematic review. The main findings were that in patients with AF, those that also had frailty were at a higher risk of stroke, all-cause mortality, and a greater symptom burden. In those that were hospitalised with AF, those with frailty in addition tended to have a longer hospital admission. A diagnosis of AF was associated with a higher risk of frailty, falls, and physical performance decline compared to patients without AF.

Data on the association between OAC prescription and frailty in patients with AF was conflicting in the literature. A meta-analysis was performed to synthesise the existing evidence. A single community-based study found that frailty was associated with increased OAC prescription. However, the findings were more complex amongst patients that were admitted to hospital. At hospital admission, frailty was associated with decreased OAC prescription. This represents prescribing decisions made in the community, and this finding may reflect a cohort of patients that are sicker (hence requiring hospitalisation) being less likely to be prescribed OAC. There was no statistically significant association between OAC prescription and frailty at hospital discharge.

9.2.2 Quantitative analysis

Overall, the prevalence of AF in the primary care analytical cohort of 536,995 patients aged 65 years or older was 11.4%. The prevalence of AF was higher with increasing frailty category, affecting 2.9% of robust patients, 11.2% of those with mild frailty, 22.2% with moderate, and 31.5% with severe frailty.

Patients with AF and frailty tended to be older, with a longer history of AF and higher levels of deprivation. Patients with AF and frailty were also more commonly women and were more likely to live in a nursing home than patients in the robust group.

The burden of frailty was higher in patients with AF than those without. AF was associated with higher all-cause mortality, bleeding events, falls and transient ischaemic attack compared to patients without AF (all $p<0.001$). In patients with AF, frailty was associated with a higher risk of all-cause mortality, stroke, gastrointestinal and intracranial bleeding. Patients with frailty had a higher estimated risk of stroke associated with AF than those in the robust category, but also had higher bleeding risk scores. They were also more commonly prescribed medications including anti-platelets, macrolide antibiotics, non-steroidal anti-inflammatory drugs, corticosteroids and statins than the robust group.

Among 58,204 patients aged 65 years or older with AF and a CHA_2DS_2-VASc score of two or more, OAC was prescribed in 30,916 (53.1%). Of these, 23.7% (n=7,329) were prescribed a DOAC. Patients that were prescribed OAC tended to be younger, were more often male, with a longer duration of AF, and had a slightly higher predicted stroke risk than patients that were not prescribed OAC. They were also less likely to have a past medical history of falls, anaemia, cancer and memory loss than patients that were prescribed OAC. Frailty was positively associated with OAC prescription, compared with the robust category. Compared with older people in the robust group, OAC prescription was more likely for people with mild frailty (OR 1.6, 95% CI 1.5 to 1.7), moderate frailty (OR 1.8, 1.6 to 1.9) and severe frailty (OR 1.6, 1.5 to 1.7)

Importantly, the prescription of OAC was associated with a greater reduction in all-cause mortality with increasing frailty, and with a reduction in stroke events overall. When stratified by frailty category, the reduction in stroke events associated with OAC prescription was only statistically significant in older people with moderate frailty. There was no statistically significant difference in the recorded bleeding events between patients that were and were not prescribed OAC. These findings were robust to sensitivity analyses that accounted for persistence on OAC and in an analysis using a stricter definition of AF.

9.3 Findings in the context of the literature

The main findings of the quantitative analysis will now be critically discussed it the context of the existing evidence base.

9.3.1 Prevalence of AF

In this study, the prevalence of AF at baseline was 11.4%, which is somewhat higher than that reported in the literature. In a study of opportunistic versus systematic screening for AF in UK primary care, Hobbs *et al* reported a baseline prevalence of AF identified from GP records of 7.2% of patients aged 65 years or older in 2001 who receiving routine care.[335] The median age of the two cohorts was similar, at 73.8 (IQR 69.0 to 80.5) in this thesis compared with 74.1 (IQR not reported) in the study by Hobbs *et al*. However, a recent study of temporal trends in AF prevalence showed that age and sex standardised AF prevalence has increased over time, from 2.14% (95% CI 2.11% to 2.17%) in 2000 to 3.29% (95% CI 3.27% to 3.32%) in 2016,[131] suggesting that the prevalence in patients aged 65 years or over in 2015 is likely to be higher than that reported in the Hobbs *et al* study, which was based on data from 2001.

In an analysis of insurance claims data of 8.3 million patients in Germany, prevalence estimates for AF increased with age. AF was diagnosed in 1.8% of those aged 65 to 69 years; 7.6% aged 70 to 74 years; 11.0% aged 75 to 79 years; 13.7% aged 80 to 84 years; 15.1% aged 85 to 89 years; and 12.7% of patients aged over 89 years.[336] AF was identified from claims data if they had

received at least two outpatient diagnoses of AF in two different quarters of the year and/or had received at least one main AF diagnosis during inpatient treatment between 1 January 2007 and 12 December 2008. These inclusion criteria are more restrictive than in the thesis, as a single recorded episode of AF was sufficient to be included in the AF cohort which may explain the finding the higher prevalence estimates in this thesis: 4.5% aged 65 to 69 years; 8.2% aged 70 to 74 years; 13.0% aged 75 to 79 years; 18.3% aged 80 to 84 years; 22.6% aged 85 to 90 years. The decision to take a more inclusive approach was made on the basis of evidence that the risk of stroke remains elevated even in patients with 'resolved AF',[286] suggesting that AF is never really 'cured'. This judgement is supported by findings that even following clinically successful radiofrequency pulmonary vein isolation (AF ablation) followed by a three month blanking period, 48% of patients continued to have episodes of AF lasting six minutes or more recorded by implantable loop recorder monitoring.[337]

9.3.2 Prevalence of frailty

A study comprising 493,737 participants in the UK Biobank (a population-based cohort, recruited between 2006 and 2010[338]) which used the phenotype criteria for frailty found that 15.9% of the population aged 65 to 73 years of age were classified pre-frail, and 18.5% as frail.[339] However, it is known that there is a wide variation in the estimates of the population prevalence of frailty depending on the clinical setting and frailty measure.[27] Secondly, there is evidence of a healthy participant bias in UK Biobank, meaning that patients with frailty are likely to be under-represented with in the dataset.[338]

Unlike UK Biobank, ResearchOne, has inclusive enrolment criteria, and is less likely to have the same susceptibility to healthy participant bias.[257] The most direct comparison for this study is therefore with the ResearchOne cohort used in the original eFI validation study, in which 50% of patients were categorised as fit, 35% with mild frailty, 12% with moderate frailty and 3% with severe frailty.[11] On average, patients tended to have a higher frailty category in this thesis: 41% were categorised as fit, 34% as mildly frail, 17% as moderately frail, and 8% as severely frail. The discrepancy may be related to improvements in recording of

deficits due to an increased awareness of frailty (and in particular functional impairment), but also due to population ageing and a general increase in frailty over the time period between 2008 and 2015.

A greater proportion of AF patients were moderately and severely frail compared with patients without AF. Possible explanations for this include the higher average age of patients with AF compared to those without, and the possibility that patients with AF have clustering of cardiovascular risk factors relating to the AF diagnosis, and therefore to some extent reflects the model that was used to identify frailty.[126] As identified in the literature review, the prevalence of frailty in patients with AF varies widely and is dependent on the setting and population included.[27] For example, 6% of participants in a registry of outpatients with AF aged 18 years or over were classified as frail,[202] whereas 100% of patients with AF living in a nursing home were classified as frail.[213] I believe this to be the first study to report prevalence of frailty in patients with AF using a large, national primary care cohort.

9.3.3 Atrial fibrillation and mortality

As has been shown in the general population,[11] in this study mortality was significantly associated with frailty category. In addition, AF was an independent risk factor for mortality. In an unadjusted analysis, AF was associated with a 2.7 fold increase in the risk of death, compared to those without AF (HR 2.7, 95% CI 2.6 to 2.8). After adjustment (for eFI category, age, sex, smoking status, IMD quintile and GP practice identifier), the HR reduced to 1.6 (1.55 to 1.64). There are two key conclusions from this. The first, is that there are significant differences between the groups with AF and those without in terms of baseline characteristics that are associated with mortality. The second, is that even after accounting for these differences, AF was associated with a significant mortality disadvantage. This is consistent with a nationwide case-control study of 272,186 patients admitted to hospital in Sweden, in which the long-term adjusted all-cause mortality risk was higher among patients with AF compared with patients without AF.[136] The Swedish study reported that in patients with a primary diagnosis of AF (rather than patients with AF secondary to another

identified cause), the adjusted HR for mortality in patients aged 65 to 74 years was 1.44 (1.29 to 1.61) in women and 1.18 (1.09 to 1.28) in men.[136] In those aged 75 to 85 years, there appears to be a reduction in the mortality disadvantage associated with AF (HR 1.20, 1.14 to 1.26 in women; 1.01, 0.96 to 1.06 in men), perhaps due to the development of other age-related competing risks for mortality, such as myocardial infarction or cancer, in the older age category. Importantly, the study did not go on to assess how frailty modifies the association with mortality, or consider additional outcomes

9.3.4 Atrial fibrillation, stroke, and transient ischaemic attack

The rates of TIA were only slightly higher in patients with AF than those without: 5.1 events (95% CI 4.6 to 5.6) per 1000 person-years in patients with AF, and 3.3 (3.2 to 3.5) per 1000 person-years in patients without AF, p<0.001. Rates vary within the literature, but in a recent epidemiological study rates were reported as 0.7 per 1000 person-years in patients aged 65 to 74 years, 1.41 per 1000 person-years in those aged 75 to 84 years, and 2.29 per 1000 person-years in patients aged 85 years or over.[340] As the method of participant recruitment involved individual clinicians submitting patient's details to the study team, this may have resulted in a non-representative population. Also, the diagnosis of TIA was subject to the patient having normal brain imaging (in order to exclude a stroke), which would not be known at the time a TIA was clinically diagnosed in general practice in ReserachOne. Further evidence that TIA rates in this thesis may be an overestimate is shown in a study showing that only 54% of patients referred to the TIA clinic have their diagnosis confirmed by the specialist team,[301] suggesting that the reported TIA rates in the thesis should be interpreted with caution, and that stroke rates may be a more robust end-point.

AF is a major risk factor for stroke, which is demonstrated in these data. In this study, AF was associated with a doubling of stroke risk (HR 2.1, 95% CI 1.9 to 2.2). However, there were differences in the baseline characteristics of patients with AF compared to those without, and after adjustment for sex, smoking status, deprivation, age and GP practice, the relative increase in risk was 50%

(HR 1.5, 1.4 to 1.6). Further adjustment for electronic frailty index category reduced the estimate further to 30% (HR 1.3, 1.2 to 1.4). This final adjustment suggests that frailty explains some of the difference in stroke risk between patients with AF and without, independently of the other factors. The reasons for this association cannot be established from these data. Serum levels of factor VIII and fibrinogen are higher in patients with phenotype-defined frailty compared with non-frail patients.[341] The elevated markers of blood clotting seen in patients with frailty may be implicated in the excess stroke risk observed in patients with frailty. The links between cardiovascular disease, multimorbidity and frailty are currently under investigation, and it has been hypothesized that inflammation may be part of a common root cause.[342]

9.3.5 Atrial fibrillation and falls

Falls are most likely under-reported in this study dataset (and, indeed, in similar community based national EHR datasets), since patients may not consult their GP following a fall. However, the finding of an increased falls rate in patients with AF compared to those without (38 per 1000 person-years compared with 19 per 1000 person-years) is of interest, as falls have historically been a commonly reported reason for non-prescription of OAC.[343, 344] In this dataset, 20% of patients with AF and a CHA_2DS_2-Vasc score of two or more had a recorded past medical history of falls. In patients that were prescribed OAC, 2.9% had a history of falls compared with 21.2% of those that were not prescribed OAC, $p<0.001$. This finding indicates that history of falls may have an important influence on anticoagulation prescribing decisions in AF.

It may be appropriate to consider falls as part of the decision making process when considering OAC prescription, as there is evidence from a cohort study of patients that were admitted to hospital with recurrent falls had similar rates of bleeding injury if they were prescribed OAC as those that were not (12.8% vs 12.7%, $p=0.97$), but patients prescribed OAC had significantly higher rates of mortality if they did have a bleeding injury 21.5% vs 6.9%, $p<0.01$).[299]

An influential and highly cited study[d] that provided support for prescribing OAC to patients with recurrent falls was published in 1999.[233] Man-Son-Hing *et al* sought to determine whether the risk of falling should influence the choice of antiplatelet or anticoagulation in older people with AF, and concluded that older people taking warfarin 'must fall about 295 times in 1 year for warfarin to not be the optimal therapy'.[233] The authors used a Markov model, where clinical events are represented by the transition between a series of discrete health states, and movement between states can be modelled based upon probabilities. However, there were a number of limitations to the clinical assumptions that may affect the validity of their conclusions. The modelled treatment strategies were not collectively exhaustive, encompassing just three variations of a wide range of clinical possibilities. For example, they include the strategy of 'no treatment then switch to aspirin in the event of a TIA or reversible ischaemic neurologic deficit', but not the use of warfarin in such a scenario. The disease-specific and treatment-related hazards were assumed to be constant over time, but this judgement was reached based upon studies of patients followed up for two years or less.

An average case fatality rate for strokes was used across both treatments, and 'for simplicity' major stroke disability was given an average of the utilities of a moderate and major disability. The utilities used were based upon a survey of 69 patients with AF, but there is a high degree of inter-patient variability in views. Where 0 is death and 1 is full health, Gage *et al* found that 10% of respondents rated a major stroke with a utility of 0.5, while 83% rated it as equal to or worse than death.[345] Perhaps these complex, subjective, and nuanced evaluations are not well reflected in the utility value for major disability used by Man-Son-Hing of 0.11. Interestingly a TIA, where symptoms and signs resolve within 24 hours, was assigned the same utility value as a minor stroke, despite the fact that in a stroke these deficits persist.[346] An assumption was made that the probability of sub-dural haematoma (SDH) fatality was identical amongst those taking aspirin and those that were not, and that patients that survived a SDH or intracerebral haemorrhage were left with moderate disability. In fact, of

[d] 379 citations on Google Scholar, 281 on Scopus, 30/01/2018

the 50% of people that survive an intracerebral haemorrhage, most are left with significant disability.[347]

Many of these assumptions have the potential to overestimate the benefit and underestimate the harm associated with OAC, and therefore the conclusion that 'the risk of falling is not an important factor in the decision about whether to offer antithrombotic therapy to elderly patients with AF' is not, in my view, substantiated by the evidence that the authors provide. NICE recommend that OAC prescription decisions should be tailored to the individual, and take into account their risks and preferences.[348] An updated analysis using estimates based upon contemporary data that includes DOAC, and with a more nuanced evaluation of the utilities associated with stroke and associated disability is needed.

9.3.6 Stroke rates in patents with atrial fibrillation

In this study, stroke rates were lower than those reported in the literature. In all patients with AF regardless of CHA_2DS_2-VASc score, the stroke rate was 0.85 (95% CI 0.78 to 0.91) per 100 person-years. Stroke rates were lower in patients that were prescribed OAC than those that were not (0.97, 0.87 to 1.08 compared with 0.74, 6.57 to 8.29 per 100 person-years, $p<0.001$).

The latest publication from the Global Anticoagulant Registry in the Field (GARFIELD-AF) reports stroke rates of 1.2 per 100 person-years.[349] Although this study included 28,628 patients with AF, medication details were available in 28,211, of whom 63.3% (n=17,872) were prescribed OAC, 24.5% (n=6,905) were prescribed antiplatelet alone, and 12.2% (n=3,444) were prescribed neither. The stroke rate was not reported by OAC prescription status, but the authors do report that OAC was associated with decreased all-cause mortality and stroke/systemic embolism (30% and 28% reduction in risk respectively) associated with OAC prescription. There was active ascertainment of clinical events, as patients were reviewed every four months. In contrast, there is evidence of under-reporting of a range of conditions in primary care records, including acute myocardial infarction and bleeding.[242, 294] This may also be true

of stroke, particularly when relying on coded data in the absence of free-text comments.[350] These limitations may in part explain the discrepancy between the thesis rates and those reported in GARFIELD-AF.

An earlier cohort study from 2003 reported rates of stroke or systemic embolism of 1.2 per 100 person-years in patients prescribed warfarin, compared to 2.0 per 100 patient-years in patients without OAC.[207] Rates in the clinical trials range from 1.2 to 2.4 per 100 person-years in patients prescribed warfarin and 1.2 to 2.1 per 100 person-years in patients prescribed DOAC.[149-152] In addition to possible under-reporting in routine data that may account lower rates reported in the thesis, there were also differences in the definitions for clinical outcomes in the trials. Indeed, there are differences between the clinical trials, which means that they are not directly comparable. To improve comparability, the rates of stroke (not stroke and systemic embolism) will be briefly summarised. In ROCKET-AF study, the rates of ischaemic or unknown stroke was 1.4 per 100 person-years in the Rivaroxaban arm, and 1.5 per 100 person-years in the warfarin arm.[149] In RE-LY, the rates were 1.34 per 100 person-years in the Dabigatran 100mg group, 0.92 per 100 person-years in the Dabigatran 150mg group and 1.20 per 100 person-years in the warfarin group.[150] Ischaemic stroke rates in the ENGAGE AF-TIMI 48 were 1.25 per 100 person-years in both the warfarin and Edoxaban arms.[151] In the ARISTOTLE study, rates of ischaemic or uncertain type of stroke were 0.97 per 100 person-years in the Apixaban group and 1.05 per 100 person-years in the warfarin group.[152] These rates are much closer to those reported in this study, suggesting that whilst it is likely that some events were not captured, the discrepancy is not large, considering that recording is based upon ‘real world’ clinical practice as opposed to a clinical trial setting.

9.3.7 Prescription rates of oral anticoagulation

In this study, among 58,204 patients with AF and a CHA_2DS_2-VASc score of two or more, OAC was prescribed in 53.1% (n=30,916). This proportion is similar to that reported elsewhere. In a UK primary care population of 13.1 million patients, Cowan *et al* found that 132,099 patients had AF and a $CHADS_2$

score of two or more.[145] Of these, OAC was prescribed in 72,211 (54.7%). Although $CHADS_2$ and CHA_2DS_2-VASc are not equivalent, a score of two in either is deemed 'high risk', and eligible for OAC prescription,[157] and therefore comparison of prescription rates between the two is reasonable. The authors analysed data that was uploaded from general practices using the Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) tool up until 2012.

The results from a study using Q-Research were similar. In patients with AF and a $CHADS_2$ score of two or more, 53.0% were prescribed OAC in 2010.[351] This had increased from 49.7% in 2007. In Danish registry data from 2007 to 2014, prescription of OAC was found to vary by geographical region in patients with AF and a CHA_2DS_2-VASc score of two or more, from 49.5% to 62.4%.[352]

The concordance between OAC prescription rates and other sources of data suggests that the prescription data recorded within ResearchOne is likely to be representative of the general population. These rates are still lower than one might expect, given that a CHA_2DS_2-VASc score of two or more is associated with an annual stroke risk of at least 2.2%.[157] Cowan *et al* identified that of those with a $CHADS_2$ score of two or more, 14,987 (11.3%) were recorded as having refused or had a contraindication to OAC.[145] However, this left 44,901 patients (34.0%) that were not prescribed OAC therapy and without a recorded contraindication or refusal. It was noted that among patients that were not prescribed OAC, 79.9% were prescribed an antiplatelet drug. The authors comment that whilst this was not recommended by NICE at that time, it still met the requirements of the recommendations of the NHS Quality and Outcomes Framework, which may in part have influenced prescribing behaviour.[145]

Previous qualitative work has shown a tendency for clinicians and patients to overestimate the risk (but also benefit) of OAC on stroke risk prevention in AF,[353, 354] suggesting that there may be a role for improved communication of the efficacy and safety of OAC therapy. Understanding the reasons for non-prescription of OAC is likely to benefit from a mixed methods approach

including qualitative work within primary care to explore perceptions of risk and benefit in greater detail, alongside a granular quantitative analysis using detailed patient records.

9.3.8 Oral anticoagulation prescription and frailty status

The analyses presented within this thesis showed that patients with AF and frailty were more likely to be prescribed OAC than the robust group. To the best of my knowledge, this is the first study that uses a large cohort of primary care patients evaluate the association between frailty status and OAC prescription. It is also the only such study to date that used the eFI to identify frailty, so direct comparisons between other studies are not possible. However, this finding has previously been reported by Frewen *et al,* who showed that in mobile community-dwelling participants in The Irish Longitudinal Study on Ageing (TILDA) with AF (n=118), frailty as measured by the Fried criteria was associated with an increased probability of OAC prescription (OR 2.33, 95% CI 1.03-5.23, adjusted for age, sex, and educational level).[30, 212] TILDA is a prospective cohort study, and was designed to be representative of the Irish population. Sampling was in geographic clusters, and every member of the Irish population aged 50 years and older had an equal probability of being invited to participate.[355] The results contrast with a recent study by Madhavan *et al,* which showed that patients with frailty were less likely to be prescribed OAC (67.5% of participants with frailty were prescribed OAC compared with 76.9% of participants without frailty, $p<0.001$).[325] Their analysis was based upon participants in the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF), with a median age of 75.0 (IQR 67.0 to 82.0). Frailty was identified using the American Geriatric Society's Geriatric Evaluation and Management Tool at enrolment (which is based upon the Fried criteria[30]).

The methods used to identify frailty were similar in both studies, which aids comparisons between them. However, each had limitations. Whilst their recruitment process appears to be representative of the overall population, Frewen *et al* included just 118 participants with AF. They do not report the number of patients with frailty and AF, but the 95% confidence interval for their

OR is wide (and the lower limit is 1.03), reflecting the imprecision of the point estimate. Madhavan *et al* report that a small proportion (6%, n=575) of the participants with AF also had frailty, whereas in this thesis 89% (n=54,734) of the participants with AF had mild, moderate or severe frailty. The difference in apparent frailty burden between the studies is likely to be related to differences in frailty ascertainment and in the population sampled. There is only a moderate correlation between the eFI and the phenotype model in identifying frailty (Spearman's rho = 0.51, 95% CI 0.42 to 0.59 [356]) which limits comparability (frailty assessment will be discussed in detail in section 9.4.4.2). Secondly, there may be a "healthy participant effect", where those that are enrolled in cohort studies may differ from the general population, as there may be a requirement to be physically fit enough to participate, and people that choose to take part may exhibit other health-conscious behaviours that may influence care provision and clinical outcomes.[357]

It is not possible to establish why patients with frailty were more commonly prescribed OAC than those without frailty from these data. One possible contributing factor could be that patients with frailty tend to consult clinicians more frequently,[358] which may potentially provide opportunities for OAC prescription. However, patients with AF that are not prescribed OAC are easily identified in EHR using automated tools such as GRASP-AF,[145, 267] which would be expected to decrease reliance on opportunistic clinical encounters to target and initiate guideline indicated prescription of OAC in patients with a known history of AF.

Patients that are admitted to hospital are a different population. As discussed in chapter 2, eight studies of hospital inpatients showed a range of estimates of the association between frailty and OAC prescription. Five studies reported that frailty was associated with decreased prescription of OAC,[181, 190, 197] and three studies showed no statistically significant association.[1, 193, 199, 200, 210] Meta-analysis showed that at hospital admission frailty was associated with decreased OAC prescription, but there was no statistically significant association at the time of discharge.[185]

9.3.9 Efficacy of oral anticoagulation in patients with AF

The analyses in this thesis showed that there was a 25% reduction in mortality (HR 0.75, 95%CI 0.71 to 0.79) and 23% reduction in stroke (HR 0.77, 0.66 to 0.90) associated with OAC prescription. As OAC now has a substantial evidence-base of benefit for patients with AF in stroke prevention, there are no contemporary studies that compare OAC with placebo. In 1999, a meta-analysis was performed of six randomised trials (2,900 patients) published between 1989 and 1993.[359] This showed that adjusted dose warfarin was associated with a 62% (95% CI 48% to 72%) relative risk reduction of stroke, and a 26% (95% CI 4% to 43%) relative risk reduction in mortality compared with placebo.[359] However, these figures should not be directly compared with those reported in this thesis. Stroke incidence has reduced substantially over the intervening years. One study using GP records showed a 30% reduction in stroke incidence in the UK between 1999 and 2008.[360] Similar trends have been observed in Sweden,[361] despite population ageing. However, even when compared with trial outcomes of a similar era, it has been shown that the efficacy of warfarin appears to be lower in 'real-world' settings.[362] This could be related to sub-optimal compliance and difficulties in healthcare access.[362] It is also possible that the active ascertainment of clinical outcomes that takes place in clinical trials allows events to be identified that are not captured in observational research.

9.3.10 Efficacy and safety of oral anticoagulation in patients with AF and frailty

In this thesis, frailty category did not have a statistically significant interaction in the association between OAC and the reported clinical outcomes, suggesting that the differences in safety and efficacy endpoints that are reported above are not significantly different across the frailty categories. Without accounting for OAC prescription, the risk of stroke was 40% higher in the mild frailty group than the robust group (HR 1.4, 1.0 to 1.9), 70% higher in the moderate group (HR 1.7, 1.3 to 2.4), and double in the severe frailty category (HR 2.0, 1.4 to 2.8). However, the confidence intervals were wide, and only the moderate and

severe groups were statistically significantly different from the robust group. There was no statistically significant difference between the groups following adjustment for age, sex, smoking, deprivation and GP practice.

Whilst there was a reduction in stroke risk associated with OAC, when stratified by frailty category the reduction only remained statistically significant in the group with moderate frailty. It may be that the number of events were sufficient to detect a difference between the groups prescribed OAC and those not prescribed OAC overall, but not when stratified, and that the attainment of pre-specified statistical significance in the moderate frailty category is a product of chance. Alternatively, I have presented evidence in this thesis that patients in the moderate and severe categories of frailty are at higher risk of stroke, and therefore are most likely to derive benefit from treatment. It is conceivable that the benefit may be demonstrated only in the moderate frailty group because patients in the severe group are at proportionately higher risk of mortality (or had a stroke that resulted in death) as a competing event. Future work with a longer period of follow-up and access to hospital-linked data and death certificates would be useful to investigate this further, along with an *a priori* power calculation.

The systematic literature review identified evidence that frailty in patients with AF was associated with a greater incidence of cardio-embolic stroke and all-cause mortality compared to those without frailty.[181] However, there were limited data on whether the association between OAC and clinical outcomes in patients with AF was different in patients in the presence of concurrent frailty. One study in the review addressed this question in a retrospective cohort study of community dwelling adults aged 65 years or over, although patients were selected for the study on the basis of a previous hospitalisation for AF. Pilotto *et al* reported lower mortality in patients with AF who were prescribed OAC compared to those that were not across the three categories of multidimensional prognostic index (overall at two years follow-up, for OAC prescription compared with no OAC prescription, HR 0.6, 95% CI 0.6 to 0.7).[191]

More recent evidence suggests that patients with AF and frailty may have a similar reduction in clinical outcome events as patients without frailty. Madhavan *et al* reported that although patients with frailty were less likely to be prescribed OAC, that 'the benefits of OAC were similar in patients with and without frailty'.[325] They reported that there was no interaction between OAC use and frailty and the association with mortality, major bleeding and a composite end point of stroke, non-central nervous system systemic embolism, TIA, myocardial infarction or cardiovascular death. However, the authors did not report the hazard ratios for the reduction in events associated with OAC by frailty status. They present (unadjusted) Kaplan-Meier curves showing that there is separation of the lines for patients without frailty associated with OAC. However, in patients with frailty the lines do not appear to separate for the outcome of all-cause mortality, and there is no discernable difference by OAC treatment in either group for the outcome of cardiovascular death, myocardial infarction, stroke/systemic embolism or TIA. The authors were contacted for extra information, but this was not provided. In the absence of numerically reported outcome data, it is difficult to reconcile the apparent discrepancies between the author's conclusions and the survival plots.

Whilst there was a lack of clinical trial data identified in the literature review, a *post-hoc* sub-group analysis of the ARISTOTLE trial was recently published by Alexander *et al*.[363] They categorised patients aged 55 years or older by the number of comorbidities they had at baseline: no multi-morbidity (0–2 comorbid conditions), moderate multi-morbidity (3–5 comorbid conditions), and high multi-morbidity (≥6 comorbid conditions). They found that the adjusted rates of stroke or systemic embolism, death, and major bleeding increased with multi-morbidity category (compared with no multi-morbidity, moderate multi-morbidity was associated with HR for stroke or systemic embolism of 1.4, 95% CI 1.2 to 1.6; and high multi-morbidity HR 1.9, 1.6 to 2.3). The authors report that there was no interaction in relation to efficacy or safety of apixaban, as the difference in outcome rates between the warfarin and apixaban groups was not statistically significant overall. However, these findings should be interpreted with a degree of caution.

Firstly, selection bias is likely, whereby patients that are entered into an RCT may be fitter than a general population.

Secondly, whilst the paper refers to frailty, what is actually measured is the number of co-morbidities a patient had at baseline, out of seventeen. The reason for the selection of the included co-morbidities or the cut-off points is not described by the authors. Such decisions are particularly susceptible to bias given the *post-hoc* nature of the analysis.

Thirdly, the inclusion criteria age was 55 years or older, a threshold that is not commonly used for an entry point to consider frailty, and this choice is not explained. The overall age distribution of the cohort is not reported in the study, but as expected, the median age increased with multimorbidity group: 69 years (IQR 63 to 75) in the 'no multi-morbidity' group; 71 years (65 to 77) for 'moderate' and 74 years (68 to 79) in the 'high' multimorbidity group.

Fourthly, the characteristics of patients allocated to each treatment arm (Apixaban and warfarin) are not reported for comparison.

Finally, the absence of a statistically significant difference between the warfarin and Apixaban arms does not mean that there is not a difference between the groups. In the absence of a reported power calculation, it is possible that the study was underpowered to detect a difference as a consequence of the relatively small number of events.

On the basis of this analysis, a linked editorial concludes that 'in the absence of contradictory evidence, the key message stands: OAC prescription should not be deterred by presence of multi-morbidities or frailty', although the authors do call for the pooling of similar trial evidence.[364]

9.4 Strengths and limitations

This, to the best of my knowledge, is the first study to use a large, national dataset from primary care to investigate AF, frailty and clinical outcomes. As has been discussed, the population of patients with frailty and AF is growing, and yet evidence to guide optimal management of this vulnerable group is lacking. This study and its outputs are genuinely novel, and the questions that this thesis has addressed are of clinical importance.

The study was inclusive, with a cohort of over 500,000 older people. This large dataset increases the probability that the findings are generalisable to patients aged 65 years and over across the UK, and increases the precision of estimates, particularly when quantifying rare events such as intracranial bleeding. Whilst traditional prospective cohort studies potentially introduce healthy participator bias, routine data is likely to be representative of the overall clinical population, and better represents the data available to a treating clinician. The dataset is contemporaneous, with follow-up until April 2017, and reflects modern-day clinical practice in a real-world setting. This increases the likelihood that the findings are generalisable to current patients.

Generally, randomised controlled trials provide the strongest evidence of an association between an intervention and outcome, and are considered the 'gold standard'.[365] A key strength of a randomised design is a lower susceptibility to bias, by ensuring that participants in the different groups are comparable at the study baseline, and that the only systematic difference between them is the clinical intervention that is under investigation.[365] However, a RCT does not give insights into clinical practice in a 'real world' setting, and under-representative recruitment of older patients with more advanced frailty has limited the generalisability of existing studies to this population.[78] There is therefore an important role for the cohort study, but the limitations of observational research must be acknowledged. Sources of bias associated with cohort studies may include missing data, ascertainment bias, contamination, selection bias and bias by indication.[366] The limitations of this study specifically will now be discussed in the context of the literature.

9.4.1 The dataset

9.4.1.1 Coverage

SystmOne has wide population coverage extending to 34% of general practices in England and Wales, and is second only to EMIS (56% of practices).[276] It may therefore be considered nationwide and population-representative. However, whilst a third of primary care patients in England and Wales are registered with SystmOne, geographical coverage is heterogeneous. For example, it is not

used by any practices in some Clinical Commissioning Groups in the North West of England, the West Midlands, London and the South East of England.[276] This geographical clustering has the potential to introduce systematic bias through local variations in population demographics, referral pathways, links with secondary care and clinical commission group level prescribing guidelines. The computing and coding systems themselves may be related to heterogeneity in clinical recording between different software providers, and therefore any associated research databases, as demonstrated in a study showing that there is variation in the recording of quality of care indicators by which clinical computer system was in use at the general practice.[367] These factors may influence the external validity of the findings of EHR from a single research database. A way of mitigating the risk of inductive fallacy is to undertake external validation in a second dataset, potentially in a different healthcare system. The duration of follow-up that was available in the dataset will be discussed in section 9.4.6.

9.4.1.2 Opt-out

Patients that 'opt out' of inclusion in research databases using EHR may be systematically different from those that assent to use of their records, which may introduce bias. Unfortunately, despite requests to ResearchOne, data are not available on the number or characteristics of patients that have opted out inclusion in ResearchOne. However, national figures from NHS Digital show that opt out rates in general are low – currently 2.8% of patients registered with a practice within a Clinical Commissioning Group in England have registered to opt out of sharing their identifiable data outside of NHS Digital for purposes beyond direct care.[368] Whilst there is substantial variation in opt out rates between Clinical Commissioning Groups, in 95.2% of groups the proportion of patients opting out is 5% or less.[368] Thus it is unlikely that this had a substantive impact on the reliability of the findings of this study. Moreover, I have included GP practice as a confounder in the time to event models, which accounts for variations between practices that may be a result of different opt-out rates between areas.

9.4.1.3 Missing data

Missing data may be considered according to four categories:

1. Missing completely at random: the probability that a data point is missing is not related to any other variable;
2. Missing at random: the probability that a data point is missing does not depend on the value of the data-point after accounting for other known variables;
3. Not missing at random: the probability that a data point is missing depends on the value of that data point or of another unmeasured variable.[328]
4. Missing by design: planned missing data designs may involve randomly assigning participants to have missing items or measurement occasions in order to reduce participant burden and the cost of data collection.[369]

Various approaches can be used to account for missing data if they are missing at random or completely at random, such as using a complete case analysis or by multiple imputation, which has the advantage of maintaining statistical power and mitigating potential biases introduced by excluding missing data.[328] Missing data in EHR present particular challenges, however, as positive recording datasets are frequently used. For some variables, the absence of a recording equates to the absence of the event. For example, if a patient does not have a recorded prescription for OAC in a practice that uses electronic prescribing then it is highly unlikely that the patient is taking OAC. This is not an unreasonable assumption, as OAC are prescription-only medications,[154] and repeat prescriptions are provided through primary care. However, it has been shown that recording of clinical outcome events in cardiovascular disease is incomplete in primary care records.[370] For example, the absence of a CTV-3 coded diagnosis of AF from a patient's EHR does not mean that AF is absent from the patient. It is possible a diagnosis has been made in secondary care and has not entered the primary care record, that the diagnosis was recorded incorrectly in the primary care record, or was entered as free-text which is not available in the research database. It is also possible that the condition of interest may be phenotypically manifest, but not yet been diagnosed.

For this study, the only variables where it was possible to truly identify missing data were sex, age, and IMD rank. There was missing data for IMD rank, which was a co-variate in the adjusted models, in 6% of records. A complete case analysis was used for the adjusted models, which will have reduced statistical power to detect a difference between groups. However, there was no change in the direction of the associations between adjusted and unadjusted models. Future work may consider making use of multiple imputation to maintain the sample size, and could include the number of healthcare encounters as a predictor variable to account for the fact that each encounter gives an opportunity for documentation.[370] This will be discussed further in the following section. The use of multiple linked sources of outcome data would reduce the probability of under-recording of key events that may otherwise be 'missing'.[294]

9.4.1.4 Informed presence bias

The fact that patients that feature in EHR is not random, but rather indicates that the subject is ill, leads to the possibility of informed presence bias,[371] whereby more frequent interactions with healthcare professionals may give more opportunities for illnesses to be identified. In a trial, occurrence of a clinical event is often actively sought for each participant at set time intervals, so that the recorded incidence is not contingent on the participant's engagement with the healthcare sector. However, in this study a positive recording dataset was used, meaning that if a patient did not seek healthcare, then no diagnosis would be recorded. Frailty is associated with increased healthcare utilisation, which may introduce a differential effect between groups. For example, people aged 65 years or older who were enrolled in the Irish longitudinal study on ageing visited their GP an average of 5 times in the year prior to enrolment (95% CI 4.8 to 5.2). However, this varied by frailty index category, whereby the robust group made an average of 3.0 (2.8 to 3.2) visits; pre-frail made 4.9 (4.7 to 5.2) visits; and frail made 7.5 (6.9 to 8.1) visits.[358] The implications of this will be discussed in section 9.4.4.2.

9.4.2 Definition of AF

Atrial fibrillation and flutter has been analysed as a single entity throughout this work. However, there are clinically important distinctions based upon the pattern and duration of arrhythmia, and whether the patient has any concomitant valvular disease. These limitations will now be discussed in more detail.

9.4.2.1 Sub-types of atrial fibrillation

In this thesis, patients with atrial fibrillation/flutter were considered eligible for OAC prescription regardless of AF subtype (paroxysmal, persistent, long-standing persistent or permanent [126]). This is in line with NICE and ESC guidelines, which do not differentiate between the subtypes in their OAC recommendations.[126, 140] However, there is some evidence that AF burden may influence stroke risk. In a post hoc analysis of the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial, 46% (n=2,072) of the participants had non-permanent AF, and 54% (n=2,484) had permanent AF.[372] Permanent AF was associated with a 59% higher risk of cardiovascular death or stroke/systemic embolism than non-permanent AF, (HR 1.59, 95% CI 1.04-2.44). The authors do not, however, report how patients were categorised into the permanent and non-permanent groups. There was the potential for misclassification bias, as there is evidence that the classification of AF by a clinician into paroxysmal or persistent has poor correlation with objectively measured persistence as measured by implantable cardiac devices (Cohen's kappa 0.12, 0.05 to 0.18).[138] The decision of the authors to use pooled data from both arms of the trial may have been reasonable, as the AMADEUS study concluded that idraparinux was non-inferior to warfarin in terms of efficacy (although it did cause significantly more bleeding).[373] Nevertheless, the *post hoc* nature of the study increases the susceptibility to bias, and no sensitivity analysis is reported stratified by drug treatment.[372]

A pre-specified analysis of The ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) showed that the group with

paroxysmal AF had fewer recorded thromboembolic events than the persistent and permanent AF groups (1.49, 1.83 and 1.95 per 100 person-years respectively), an effect that was observed even after adjustment for baseline variables.[374]

An observational study, from the Stockholm Cohort of AF, found that in 855 patients with paroxysmal AF and 1,126 with permanent AF, there was no significant difference in ischaemic stroke over 3.6 years follow-up between individuals who had paroxysmal AF and individuals who had permanent AF (adjusted HR 1.07, 95% CI 0.71 to 1.61)[e] without a prior stroke.[375] A similar study of individuals from the Loire Valley of France showed that pattern of AF was were not independently associated with stroke and thromboembolism (in multivariate analysis, paroxysmal AF was associated with HR 1.13, 0.76 to 1.70, and permanent with HR 1.44, 0.96–2.16).[376] Both studies have the same potential for misclassification bias with regard to AF type that was previously discussed.[138]

Overall, the evidence that AF subtype may influence stroke is conflicting, and inclusion as a co-variate in this study would have been associated with a high risk of misclassification. This is due to inaccuracies in clinical categorisation,[138] and the dynamic and progressive nature of AF which may evolve in pattern from paroxysmal to persistent to permanent.[139] The resolution of the data within ResearchOne is likely to be insufficient to differentiate between AF subtypes. For example, the code for ‘persistent AF’ was recorded in 0.41% of EHRs, whereas the code for ‘atrial fibrillation’ featured in 32.0%. The ESC conclude that the evidence that AF burden may influence stroke risk is weak, and “should not be a major factor” in management decisions,[126] which supports the pragmatic approach taken in this thesis.

The management of thromboembolic risk in AF differs between valvular and non-valvular AF, as discussed in section 1.4.6. Valvular AF usually refers to AF

[e] Adjusted for age, sex, heart failure, hypertension, diabetes mellitus, mitral stenosis, previous myocardial infarction, and warfarin treatment on the latest documented contact or on the occasion of the event.

in the presence of a mechanical heart valve replacement or moderate/severe mitral stenosis. These are conditions that are associated with an increased thromboembolic risk, and therefore patients tend to have more intensive OAC therapy.[126, 153] DOACs are not currently licenced in this clinical situation.[154] As a consequence, patients with non-valvular AF are likely to be at increased risk of thromboembolic stroke, but also of bleeding complications as a consequence of more intensive therapy (this will be discussed further in section 9.4.5). However, it was not possible to differentiate between these different categories in the dataset, as the CTV-3 codes in use were not sufficiently specific. This is unlikely to have had a large impact on the results of this study, as the prevalence of valvular AF is relatively low. The PREFER in AF registry (Prevention of thromboembolic events – European Registry in Atrial Fibrillation) recorded valvular AF at baseline in just 1.9% of AF cases recruited in the UK.[377]

9.4.3 Duration of AF

Patients with higher eFI categories tended to have a longer duration of AF history in this study, which may theoretically have contributed to increased event rates in that group. It is known that persistence of AF leads to structural remodelling of the atria, characterized by chamber enlargement and tissue fibrosis.[128] These changes increase the burden of atrial substrate, thereby sustaining the arrhythmia,[127] and left atrial enlargement, in particular, has been associated with an increased risk of thrombus formation.[125] Thus, the duration of AF prior to study entry could have been included as a potential confounder.

The decision was taken *a priori* to not standardise for AF duration, on the basis that the quality of recording of first event was unknown, and this may have introduced bias that was differential across different ages as clinical records gradually became computerised. Should the onset of AF be accurate one could have included duration of AF as an adjustment within each model, but also undertaken analyses that examined time from diagnosis to first clinical outcome event.

Secondly, stroke risk is a dynamic phenomenon. There is evidence that even brief periods of atrial tachyarrhythmia identified by implantable cardiac devices are associated with an increased risk of stroke. A pooled analysis of 10,016 patients with such devices showed that one hour of AF was associated with a HR for ischaemic stroke of 2.1 (95% CI 1.2 to 3.6), but the risk of stroke was increased after just five minutes of arrhythmia (HR 1.8, 1.02 to 3.02).[378] However, a definitive temporal relationship between episodes of AF and stroke is yet to be established. The Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT) showed that of the 51 patients who experienced a stroke or systemic embolism during follow-up, only 4 (8%) had subclinical AF detected by their device in the 30 days prior to their stroke.[379] The Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial aims to identify whether OAC is beneficial in this setting.[380]

Thirdly, there is a risk of over-adjustment by including prior duration of AF, which is a component of the eFI, as a confounder in the Cox regression model. Future work could include sensitivity analyses to evaluate the impact of duration of AF on the associations measured.

9.4.4 Ascertainment of exposures and outcomes

9.4.4.1 Coding

Coding of the source clinical data within general practice is likely to be imperfect. In the Newcastle 85+ Study, health assessment identified participants with clinical evidence of disease that was not in the medical notes, including hypertension, ischaemic heart disease and AF.[370] It is possible that these were diagnoses that were previously unidentified, or alternatively that these diagnoses were known but not correctly recorded in the primary care records.[273, 367] This could have led to systematic underestimation of the conditions of interest. Secondly, differentiating between a current condition and a past medical history of a condition is problematic in a positive recording dataset. This is unlikely to have been a significant limitation in this study, as

resolved AF was considered in the AF category, and outcome events were analysed by the first recorded episode.

The code-lists used within the study to identify every condition of interest were carefully identified using existing code lists and hand searching the NHS clinical code list browser, with decisions made for inclusion or exclusion based upon clinical expertise. Still, these judgements are subjective and subject to the potential for error. In future work, code lists should be defined using a more formal approach. Watson *et al* recommend using a three-stages.[381] Firstly, clearly define the clinical feature of interest. Next, use software to comprehensively search all available codes that are potentially of interest. Finally, they suggest using a modified Delphi process to reach consensus including a measure of uncertainty, which can be used for sensitivity analysis. This approach is rigorous, but time-consuming, and unfortunately was not feasible within the time constraints of this project. Instead, I have adopted an approach recommended by Bhattarai *et al*: my reporting of case definitions has been transparent, and I have conducted a sensitivity analysis with an alternative, more stringent, code-list.[273]

The sensitivity analysis restricting the cohort to a more specific definition of AF showed no change in the direction of associations that were demonstrated in the main analyses but did increase the effect size of the association. The probable effect of excluding the five CTV-3 codes outlined was to limit the cohort to those most likely to benefit from OAC. By removing patients with an irregularly irregular pulse may have taken patients out of the cohort that had ventricular ectopy rather than AF and were therefore did not have an indication for OAC. It may also have removed patients that were too unwell to attend the GP for a confirmatory ECG, who may also be less likely to benefit from OAC, but in this case due to competing risks for death. Removing patients that had been provided with written information about AF could have led to a purer AF cohort, as being given written information does not necessarily mean that individual has a diagnosis of AF – it could be that they had an affected relative and were interested in learning more. These patients would therefore not have

an indication for OAC themselves. The exclusion of patients that had exception reports for QOF as their only identifying feature of AF were excluded, as it was felt that this alone was insufficient to diagnose AF. This will have had the effect of removing some patients that did not have AF, but also of removing patients that had valid clinical reasons for not being prescribed OAC. In each case, restricting the cohort was likely to strengthen the observed association, which is what was observed.

This finding lends support to the conclusions of the main analyses, but in my view, should not supplant the main analysis. Firstly, p*ost-hoc* changes of the analytical plan have the potential to introduce bias. Secondly, one of the key objectives was to evaluate whether frailty modifies the association between OAC and clinical outcomes in patients with AF in an unrestricted population of people aged 65 or over. For this question, it is important to be as inclusive as possible. As frailty itself has been identified as a reason by physicians for non-prescription of OAC,[382] excluding patients where a clinical decision of ineligibility has been made is likely to exclude some of the core group of particular interest. Rather, future work could include a subgroup analysis of patients that were deemed ineligible, and their characteristics and clinical outcomes described in detail.

9.4.4.2 Frailty

Whilst there is general acceptance that frailty describes a ‘state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes’,[10] there is currently no consensus on how to operationalise the concept into clinical practice. This study used the eFI to identify patients with frailty. The reasons for this choice were that the eFI has been validated both in ResearchOne and externally, has robust predictive validity for outcomes of mortality, hospitalisation and nursing home admission, and has been nationally implemented.[11, 219] As previously discussed, the eFI is based upon the cumulative deficit model of frailty as a theoretical framework.[10, 36] The phenotype model offers an alternative approach to considering frailty,[30] and could be a useful addition to any future prospective work. The inclusion of a

frailty index with a greater weighting for functional impairment, which contributes only one deficit to the eFI, may also yield interesting insights.[356]

Recent work has shown that whilst the eFI is a strong predictor of mortality at a population level, but at an individual level single time point frailty scores have a low predictive value for mortality in older adults.[383] However, the eFI is not solely a tool for mortality prediction, but an instrument for identifying patients that are particularly vulnerable to a range of adverse outcomes. Mortality is a useful outcome to measure the predictive validity of a frailty index because it is available, dichotomous, non-arbitrary and relevant.[37]

In this study, frailty was treated as a categorical variable throughout using the cut-points defined within the eFI.[11] However, there is potentially large clinical heterogeneity within each category, particularly in the severe frailty category which encompasses patients that may be medically stable and also patients that are terminally ill.[11, 60] Using the eFI as a continuous variable would have accounted for this to some extent. Many studies in the literature take an alternative approach and consider frailty as binary, or use the categories of robust, pre-frail and frail. In this study, the decision to use the eFI categories as validated in the original work means that the results may be readily interpreted, and will hopefully be more easily translated into clinical practice.

As discussed previously, there is an association between the number of times that a patient encounters a healthcare professional and their underlying health state.[358] At each encounter, there is a new opportunity for a diagnosis to be added to the EHR, which could potentially be a deficit of a frailty index. It is therefore feasible that the association reported by Roe *et al* (discussed in section 9.4.1.4) between frailty category and healthcare provider utilisation in the 12 months prior to frailty assessment is as a consequence of deficits accumulated during those appointments.[358] Similarly, in this thesis there may have been systematic differences in the recording of clinical events between patients with different categories of frailty due to differences in the number of times they encounter healthcare professionals. This is particularly relevant to

the case ascertainment of AF which is frequently a sub-clinical phenomenon,[138] and may therefore lead to a relatively greater rate of AF diagnosis in patients with frailty. Any potential biases in recording related to health seeking behaviour is likely to be lower in the clinical outcomes of this study, as they are sufficiently serious that healthcare professionals are likely to have been involved (stroke, intracranial or gastrointestinal bleeding, death), and therefore recorded in the EHR. In future work, one could consider the impact of the number of healthcare encounters as a sensitivity analysis.[371] This was not undertaken as a part of this thesis, as the size of the dataset and the complexity of the structure with which events are recorded meant that this was not feasible within the timeframe.

9.4.5 Oral anticoagulation

The recording of medication prescriptions in ResearchOne was highly detailed, allowing analysis of the impact of OAC persistence on clinical outcomes. A further strength of this study was the inclusion of DOAC, which make up an increasing proportion of OAC prescriptions.[188] In this study, 23.7% (n=7,329 of patients that were prescribed OAC at study entry were prescribed a DOAC. This is important in an era of rapid change in DOAC usage – In CPRD and QResearch, warfarin use declined between 2011 and 2016 from accounting for 98% of OAC prescriptions to 23%. The rate that different DOAC agents were prescribed was highly dynamic during that interval – for example, Dabigatran was licenced in 2008, reached a peak of 10% of all OAC prescriptions in 2013, but this dropped to 3% in 2016 as Rivaroxaban and Apixaban became more common choices.[188]

There were limitations to the approach taken to analyse OAC data. Prescription information was available, but we did not have data on treatment concordance. This limitation is shared with most clinical trials and other observational studies.[149-152, 188] It is known that warfarin management generally is suboptimal - a meta-analysis showed that patients taking warfarin spent just 63.6% of time (95% CI 61.6 to 65.6) with an INR in the therapeutic range.[384] However, we did not have access to INR data as part of this study to account for this. Nor did we have access to blood results or weight measurements that would have allowed

an analysis to assess the appropriateness of DOAC dose adjustments, therefore an assumption was made that the dosing was correct for the individual. This assumption is not ideal, as there is evidence from registry data that almost a third of patients may not be on the correct dose of DOAC.[385] In the absence of INR results or the data needed to check dose adjustments, a decision was taken to treat OAC as binary – prescribed OAC, or not prescribed OAC. This is a limitation, as there is evidence that different agents are associated with different efficacy and safety profiles.[188] As prescription of parenteral anticoagulation is not recommended in chronic AF, only oral agents were included.[126, 140, 289, 386]

In order to reflect real world practice, patients with prior use of OAC before AF onset were not deselected, and so there are patients in the AF cohort with other concomitant indications for OAC such as pulmonary embolism or deep vein thrombosis. Nonetheless, the OAC prescription or target therapeutic range would be the same as that for AF.[154, 386] In patients with a mechanical heart valve, a greater intensity of OAC with warfarin is indicated. In patient with AF alone, the target INR is usually 2.5. An INR target of 2.5 is also recommended in patients with a modern mechanical valve replacement in the aortic position, meaning that the risk of bleeding is theoretically the same as for AF alone. However, in patients with one of the older mechanical valves (Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves) in the mitral position, the recommended target INR is 4, which is associated with a greater risk of bleeding complications.[386] As discussed in section 9.4.2.1, it was not possible to identify patients with valvular AF within the cohort, but patients with mechanical heart valves are likely to account for around 1.9% of patients with AF in the UK,[377] of whom a small number are likely to have a first generation mechanical heart valve, and no evidence has been identified that shows a differential prevalence of valvular AF by frailty category. In view of these factors, it seems unlikely that the findings of this study would be significantly affected by the limitations in the available OAC data that has been outlined.

9.4.6 Outcomes

The major outcomes studied in this thesis are clearly and transparently defined, and are relevant to patients with AF as well as clinical practice.[292] The results of the analyses have been discussed in the context of the literature in section 9.3.

Limitations in the ascertainment of the clinical outcomes were discussed in section 9.4.4. Additional limitations include a relatively short follow-up period (mean of 15 months), but the large sample size meant that 671,135 person-years of data were available for analysis of which 74,238 person-years of follow-up were in patients with AF. During the study, 24,254 participants died (4.5%). Cardiovascular-specific death rates would be useful additions to future work, as it is possible that in this analysis patients were censored from follow-up due to death, when the cause of death was a stroke. This is particularly important in an older population with frailty, who have competing risks for mortality. A further limitation as a consequence of the relatively short duration of follow-up is that inaccuracy in the date of death has a proportionally larger effect. In this study, mortality was established from clinical records, rather than data linked to the Office for National Statistics (ONS). This has the potential for inaccuracy: a study of 118,571 deaths using a CPRD dataset linked to ONS death records found that in 7.8% of cases the recorded dates differed between the two sources by more than two weeks.[387] In this study, there was the addition limitation of the ‘rounding’ of the date of death to comply with Health Research Authority guidance for confidentiality.[293]

The decision to evaluate time to first event, rather than including multiple events in the analysis is a commonly used,[349] but cautious approach. An alternative would be to consider codes that were recorded within a pre-specified timeframe as belonging to the same clinical event. However, in the absence of a linked dataset this approach is highly subjective and may introduce bias. Future work using a linked dataset would mitigate this, as a new episode of any of the main outcome events is likely to be marked by an admission to hospital. A linked dataset is also likely to enable more complete ascertainment of clinical outcome events. Recent work in patients with AF using CPRD data linked to hospital

episodes statistics has shown that coding of inpatient bleeding events in their primary care record was incomplete.[294] Overall, just 39% of intra-cranial bleeds and 14% of gastrointestinal bleeds were coded in their primary care record in the subsequent 12 weeks. In these CPRD data, the probability of having a bleed recorded in the primary care record were higher in patients that were prescribed an OAC compared with those that were not prescribed an OAC (OR 2.3, 95%CI 1.6 to 3.2).[294] This discrepancy between groups has the potential to introduce bias, although an apparent excess of bleeding events in the group prescribed OAC was not identified in this thesis. Future work could also investigate how well systemic embolism is represented in primary care data, as inclusion of this outcome would make the results more easily comparable with the clinical trials, as mentioned in section 9.3.6.[149-152]

9.4.7 Confounding by indication

Where a variable is an independent risk factor for the outcome, is associated with the exposure, and is not an intermediate variable between the exposure and the outcome, then the variable is considered a confounder.[388] In this study, adjustments were made to account for differences in potential confounders between groups, such as age, sex and deprivation. Confounding by indication is where the clinical indication for selecting a treatment also affects the outcome.[388] An example of this is severity of illness, where more severe cases have a worse clinical outcome, and illness severity also affects a clinician's choice of treatment. In this study, patients with the most advanced multimorbidity may be at highest risk of stroke, and the presence of advanced multimorbidity may also affect whether or not a clinician prescribes OAC, which gives rise the potential for confounding by indication. This presents a challenge when investigating the impact of frailty, as differences in baseline risk of adverse clinical events are fundamental to the concept.[10] This study demonstrated that patients with frailty were more likely to be prescribed OAC than those without frailty, but that there was no statistically significant interaction by frailty category in the association between OAC prescription and the reduction in stroke and all-cause mortality, whereas the reverse may be expected if there was substantial confounding by indication. Further work could

use propensity score analysis to account for systematic differences (except for frailty category) between patients that were prescribed OAC and those that were not, with weighting of the survival models by propensity score.[389, 390] This advanced statistical analysis is beyond the scope of this project, and therefore the risk of confounding by indication must be acknowledged as a limitation.

9.5 Implications of the study

To the best of my knowledge, this thesis reports the first systematic review of the existing evidence in AF and frailty, and is the first study to report the utilisation and clinical outcomes of OAC in patients with frailty in an unselected primary care cohort.

The thesis reports the burden of AF and frailty, and the clinical characteristics of patients with these conditions. This may be of use to policy makers and care providers in planning the provision of health and care services for this large and growing population. In particular, this study has shown that AF affects over one in ten people aged 65 years or over in a community setting. A diagnosis of AF is associated with a greater burden of frailty, and a higher incidence of adverse clinical outcomes than in people without AF, including all-cause mortality, stroke, and bleeding events. In people aged 65 years or over with AF, frailty was associated with a greater risk of mortality, stroke, intracranial bleeding and gastrointestinal bleeding. In this cohort, frailty was associated with an increased rate of OAC prescription.

In those aged 65 years or older with AF and a CHA_2DS_2-Vasc score of two or more, OAC prescription was associated with a lower rate of all-cause mortality and stroke. However, there was no statistically significant difference in the outcomes of gastrointestinal or intracranial bleeding between those prescribed OAC and those that were not.

Of note, 89% of those aged 65 years or over with AF have concomitant frailty, suggesting a high degree of clinical complexity amongst this group. In the face

of multiple competing health priorities, single-organ guidelines may be challenging for clinicians to implement. They may also feel that the recommendations may not be applicable to patients with frailty due to limitations in the studies on which they are based. However, in this study, OAC was associated with improved mortality and stroke rates, with no statistically significant interaction by frailty category. Overall, just over half of patients that were considered eligible for OAC were prescribed OAC, suggesting that existing clinical guidelines on stroke prophylaxis are not being followed.

My findings of a reduction in stroke and all-cause mortality associated with OAC, without an apparent increase in bleeding complications is of clinical importance, and is in line with the recently published *post-hoc* analysis of the ARISTOTLE study,[363] although both studies may be underpowered to detect a difference between the groups in these rare events. However, the data from this thesis and the above analysis lend support to the suggestion that in the absence of contradictory evidence, the presence of frailty should not necessarily deter prescription of OAC.[364] Ultimately, the most robust estimates of the risks and benefits of OAC in older people with frailty would come from a randomised trial with the inclusion of pre-specified, formal frailty measurement. However, as OAC is an established therapy with a robust evidence base for stroke prevention in AF, the inclusion of a placebo arm would not be considered ethical. A pragmatic approach may be to construct a frailty index using existing DOAC trial data, and to investigate whether outcomes differed by frailty status.

Plans are in place for dissemination of the work. Two manuscripts are in preparation reporting the results of the quantitative analysis, and an abstract is being presented at the European Society of Cardiology Congress in Paris in August 2019. The systematic review and meta-analysis has been published in Age and Ageing,[185] and the findings were presented at the British Geriatric Society Conference in April 2019.

9.6 Recommendations for future research

In my opinion, key recommendations for further research that have emerged during this MD thesis include:

1. An investigation into the factors associated with prescription, discontinuation and switching between OACs in older people.
2. A study of the health trajectories of older people with frailty with and without AF, stratified by OAC prescription.
3. Research into the impact of recurrent falls on the risk-benefit balance associated with OAC in patients with AF.
4. Exploration of whether the mortality benefit associated with OAC is explained solely by a reduction in stroke and systemic embolism, or whether factors such as a reduction in other thromboembolic events such as pulmonary embolism are also significant.
5. Using a linked-dataset with a longer duration of follow-up to externally validate the findings of this study.
6. To include frailty assessment in future trials of OAC
7. To construct a frailty index from existing trial data, and investigate whether outcomes differ by frailty category.

There is scope for developing the work outlined in this thesis further using the existing dataset. In particular, the highly granular prescription data within ResearchOne could be used to characterise and explore the patterns of patient-level OAC usage in clinical practice in more detail, and identify factors associated with prescription, discontinuation, and switching between agents. Qualitative work aimed at identifying the key reasons for non-prescription of OAC by clinicians in an era of DOAC agents would be useful alongside this work, to understand reasons for the discrepancy between guideline-indicated OAC use and the real-life experience that has been described in this thesis.

Trajectories of frailty in patients with AF compared to those without AF could be investigated, using this dataset to quantify the rate of deficit accumulation. These analyses could be stratified by OAC prescription. The large amount of historic data could also be used to identify predictors of both frailty and AF, and

therefore identify patients at particularly high risk of developing these conditions. If this was in parallel with ongoing international projects aimed at modifying individual level risk factors for AF and slowing progression of frailty, then this could be of clinical value in an era of personalised medicine.[391]

The extent to which recurrent falls should influence OAC prescribing is currently unclear.[233, 299] Yet, recurrent falls is a commonly encountered clinical problem in patients with AF.[203, 392] Research to quantify the burden of harm associated with OAC in patients with AF according to robustly ascertained annualised falls rates would be valuable to clinicians and patients in order to guide risk and benefit estimation in patients with AF and recurrent falls.

We have secured funding for further study that will build upon the work set out in this thesis using a dataset linked to hospital admissions and a longer period of follow-up. Outcome data in a linked dataset are likely to be more reliable and representative than in a single primary care source,[294, 387] and will be important validation work for the results of this thesis. Access to death certificate data would allow a more detailed analysis of cause-specific mortality. This could be used to investigate the extent to which OAC may be contributing to a reduction in causes of death other than stroke or systemic embolus, such as pulmonary embolism. A linked dataset would enable more accurate ascertainment and severity assessment of bleeding events, which is a key consideration. Ultimately, observational studies of this type have significant limitations due to the presence of bias and residual confounding. The best way to address these would be to include frailty assessment in future trials of OAC.

9.7 Conclusion

This is the first study to investigate AF and frailty in a large primary care population of older people in the UK. In a cohort of over half a million patients, this thesis identified that AF and frailty commonly co-exist and are associated with particularly poor clinical outcomes. Despite a relatively high calculated risk of stroke amongst patients with AF, OAC was prescribed in just over half of those that were eligible, and in whom a DOAC was prescribed in 24%. Patients with AF and frailty were more commonly prescribed OAC than those without frailty. Prescription of oral anticoagulation was associated with a greater reduction in all-cause mortality with increasing frailty category, and with a reduction in stroke events overall. There was no statistically significant difference in the recorded bleeding events between patients that were and were not prescribed OAC.

There is strong evidence from the systematic review and quantitative analysis that frailty is an important adverse prognostic factor in older people with AF. However, in this study as in others, appropriate prescription of OAC substantially reduced the risk of death and stroke, without a statistically significant increase in the risk of harm. Future work using a dataset linked to hospital admissions data is likely to give more robust ascertainment of bleeding events but will not be free of the potential biases inherent to observational research. A randomised clinical trial is ultimately required to evaluate the risks and benefits of OAC for stroke prophylaxis in older people with AF and frailty, however, this study found no evidence that OAC should be withheld on the basis that they also have frailty.

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Appendix A CHA_2DS_2-Vasc codes

The correspondence below is from Dr John Parry, the Clinical Director of SystmOne. This definition of CHA_2DS_2-Vasc was used in the quantitative analysis.

What follows are the definitions of CHADSVASc terms as approved by Professor G Lip, Professor of Cardiovascular Medicine at Birmingham University and lead author of the leading paper on CHADSVASc.

C: Patients who have had a recent decompensated heart failure irrespective of ejection fraction OR symptomatic / asymptomatic moderate or severe left ventricle impairment or dysfunction (by any cardiac imaging).
H: History of hypertension or uncontrolled blood pressure. Identified via coded event, antihypertensive medication or most recent blood pressure for untreated hypertension of >= 160/90.
A: Age >= 75
D:Diabetes – Type I or II. The duration is irrelevant. There is currently no data on diabetes resolved, neonatal and gestational diabetes.
S: All strokes – both ischemic or haemorrhagic; TIAs included. Note: Stroke caused by injury / trauma from RTA not included. Systemic embolism – arterial yes but not venous for the purposes of this score (venous was included in the original research but should not be considered a risk factor).
V: Established myocardial infarction, peripheral artery disease, imaging showing complex aortic plaque or h/o angioplasty. This also includes carotid surgery, gangrene, leg angioplasty and leg amputation. Note that there is no distinction between STEMI / non-STEMI. Ischemic heart disease alone is not sufficient as the limited data appears to show that mild coronary-arterial trauma is not sufficiently a risk factor. Codes for angina should be ignored as these are often incorrectly recorded.

Mechanical heart valves / bio-prosthesis should be taken as exceptional and so should be considered separately. These patients usually have consultant review but it is important that GPs choose medication correctly (e.g. warfarin only for mechanical heart valve).

A: Patient age is >= 65 or <75

Sc: Sex Category. There is no data on gender reassignment.

In SystmOne, we use the following codes as approximations for these definitions.

These approximations have also been approved by Professor G Lip.

- C - G58.. (and its children) Heart failure

- H - XE0Ub (and its children) Hypertension

- A - Age Patient is over 75

- D - C10.. (and its children) Diabetes mellitus

- S - The below codes and their children:

XE0VK Transient ischaemic attack

X00D1 Cerebrovascular accident

XE0VS Arterial embolus and thrombosis

XaDyM Head and neck arterial embolus

X203k Coronary embolus

X202x Pulmonary thromboembolism

L432. Obstetric blood-clot pulmonary embolism

Xa6YU Coeliac artery embolus

Xa07T Mesenteric embolus

Xa6Yb Suprarenal artery embolus

K1380 Renal artery embolus

X203m Aortic bifurcation embolus

XaDtF Upper limb arterial embolus

XaDtI Lower limb arterial embolus

Xa3fY Peripheral arterial embolism

- V - The below codes and their children:

X200E Myocardial infarction

Xa0lV Peripheral vascular disease

G71.. Aortic aneurysm

XE0VR Intermittent claudication

- A – Age Patient is 65 years or older and below 75

Sc – Patient's gender is set as female. If any other gender is set, this will not add to the CHADSVASc score.

Appendix B Research ethic committee letter

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 1
TEDCO Business Centre
Room 002
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 428 3564
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04 October 2012

Dr Christopher J Bates
TPP
Mill House
Troy Road
Horsforth
Leeds
LS18 5TN

Dear Dr Bates

Title of the Research Database: **ResearchOne**
REC reference: **11/NE/0184**

Thank you for your letter (sent by Samantha Crossfield), responding to the Committee's request for further information on the above research database and submitting revised documentation

The further information has been considered on behalf of the Committee by the Chair

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion of the above research database on the basis described in the application form and supporting documentation as revised.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Databases set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research database.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter	Dr Christopher Bates	18 June 2011
Other: List of Stored Data Items		
Other: Data Protection Registration	Dr John Parry (TPP)	

Other: System Level Security Policy	May 2011	
Other: Response from NIGB	Natasha Dunkley (NIGB Approvals Manager)	03 October 2012
Other: GP Poster	Version 1.0	03 October 2012
Participant Information Sheet: Information for Healthcare Providers	Version 1.0	03 October 2012
Participant Information Sheet: Information Leaflet for Patients	Version 1.0	03 October 2012
Protocol for Management of the Database	Version 1.0	01 June 2011
REC application	IRAS Version 3.1 76446/224560/9/964	20 June 2011
Response to Request for Further Information	Samantha Crossfield (TPP)	
Summary of Research Programme(s)		

Research governance

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

Research permission is also not required by collaborators at data collection centres (DCCs) who provide data under the terms of a supply agreement between the organisation and the database. DCCs are not research sites for the purposes of the RGF.

Database managers are advised to provide R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All DCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using data supplied by a database must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the database has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research databases. There is no need to inform Local Research Ethics Committees.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

Here you will find links to the following:

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Annual Reports. Please refer to the attached conditions of approval.
c) Amendments. Please refer to the attached conditions of approval.

11/NE/0184	Please quote this number on all correspondence

Yours sincerely

(pp)

Mr Chris Turnock
Chair

E-mail: nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net

Enclosures: *Approval conditions*

Copy to: *Ms Samantha Crossfield, TPP*

Appendix C CTV-3 code lists

The code lists below are those that featured in the ResearchOne extract, and were used to define the variables of interest.

Activity limitation	Y3502	Allowance / DLA applied for
	13O5.	Attendance allowance
	13VC.	Disability
	9EB5.	DS 1500 Disability living allowance completed
	Y1558	Blue Badge disabled driver
	Y3501	Already receiving attendance allowance / DLA
	13V8.	Has disabled driver badge
	Y0700	Physical - motor disability
Alcohol excess	XE0b4	Alcoholic cirrhosis of liver
	E23z.	Alcohol dependence syndrome NOS
	E010.	Delirium tremens
	J613.	Alcoholic liver damage unspecified
	E01y0	Alcohol withdrawal syndrome
	E230.	Acute alcoholic intoxication in alcoholism
	8BA8.	Alcohol detoxification
	J611.	Acute alcoholic hepatitis
	XaKAC	Alcohol consumption counselling
	8H35.	Admitted to alcohol detoxification centre
	XaPPv	Brief intervention for excessive alcohol consumptn completed
	XE1YQ	Chronic alcoholism
	Xa1yZ	Alcohol abuse
	Xa2lt	Persistent alcohol abuse
	X3071	Alcoholic liver disease
	XaBDY	[V] Alcohol use
	ZV6D6	[V]Alcohol abuse counselling and surveillance
	Ua1Mm	Alcohol withdrawal regime
	Xa25J	Alcoholic dementia
	X306r	Alcoholic hepatitis
	E01..	Alcoholic psychoses
	Xa17e	Alcoholic hallucinosis
	XE1YX	Nondependent alcohol abuse
	XaPty	Brief intervention for excessive alcohol consumptn declined
	XaX4S	Extended interven for excessive alcohol consumption declined
	XE0dF	Alcoholic liver damage NOS
	E2312	Episodic chronic alcoholism
	J610.	Alcoholic fatty liver
	Ua1Ml	Alcohol reduction programme
	E231z	Chronic alcoholism NOS
	X20Bo	Alcohol-related macrocytosis
	XaPwp	Declined referral to specialist alcohol treatment service
	SM0z.	Alcohol causing toxic effect NOS
	XaLWu	[X]Alcohol withdrawal-induced seizure
	E011.	Korsakov psychosis
	X006u	Alcohol-induced epilepsy
	E250z	Nondependent alcohol abuse NOS
	XaPPy	Extended intervention for excessive alcohol consumptn complt
	E2500	Nondependent alcohol abuse, unspecified

	E01yz	Other alcoholic psychosis NOS
	E2313	Chronic alcoholism in remission
	E2311	Continuous chronic alcoholism
	E014.	Pathological alcohol intoxication
	XaIN4	Under care of community alcohol team
	X0053	Wernicke encephalopathy
	Eu104	[X]Men & behav dis due alcohl: withdrawl state with delirium
	Xa7On	Alcoholism counselling
	XaJni	Alcohol disorder monitoring
	Eu103	[X]Mental and behav dis due to use alcohol: withdrawal state
	E2302	Episodic acute alcoholic intoxication in alcoholism
	E01z.	Alcoholic psychosis NOS
	XE1ZF	[X]Mental & behav dis due to use alcohol: psychotic disorder
	XaamS	In-house alcohol detoxification
	XaA1V	Ethanol abuse
	E2310	Unspecified chronic alcoholism
	E2300	Acute alcoholic intoxication, unspecified, in alcoholism
	F11x0	Alcoholic encephalopathy
	E2502	Nondependent alcohol abuse, episodic
	E011z	Alcohol amnestic syndrome NOS
	E015.	Alcoholic paranoia
	XE1Xu	Other alcoholic dementia
	XE1ZG	[X]Men & behav dis due alcoh: resid & late-onset psychot dis
	Eu106	[X]Mental and behav dis due to use alcohol: amnesic syndrome
	E2501	Nondependent alcohol abuse, continuous
	XE1ZE	[X]Mental and behav dis due to use alcohol: dependence syndr
	Eu101	[X]Mental and behav dis due to use of alcohol: harmful use
	E0112	Wernicke-Korsakov syndrome
	E01y.	Other alcoholic psychosis
	X00Rk	Alcoholic dementia NOS
	SM0..	Alcohol causing toxic effect
	XaLrN	Alcohol abuse monitoring
	E0111	Korsakov's alcoholic psychosis with peripheral neuritis
	XaBE3	Chronic alcoholic hepatitis
	ZV113	[V]Personal history of alcoholism
	Xa1bS	Othello syndrome
	E0120	Chronic alcoholic brain syndrome
	Eu10z	[X]Ment & behav dis due use alcohol: unsp ment & behav dis
	Eu10y	[X]Men & behav dis due to use alcohol: oth men & behav dis
	XSBcu	Alcohol rehabilitation
	X3072	Alcoholic fibrosis and sclerosis of liver
	E2503	Nondependent alcohol abuse in remission
	XaLsx	Delivery of rehabilitation for alcohol addiction
	XaKAo	Alcohol counselling by other agencies
	X3073	Alcoholic hepatic failure
	E2303	Acute alcoholic intoxication in remission, in alcoholism
	E230z	Acute alcoholic intoxication in alcoholism NOS
	XacTX	Emergency dept attendanc related to personl alcohl consumptn
	XaPmB	Advised to contact primary care alcohol worker
	du5..	Acamprosate calcium
Anaemia	C2620	Folic acid deficiency
	XE13c	Iron deficiency anaemia
	D00..	Iron deficiency anaemias (& [hypochromic - microcytic])
	XM05A	Anaemia
	42T2.	Serum vitamin B12 low
	66E5.	B12 injections - at surgery
	i312.	Hydroxocobalamin 1mg/1mL injection

XE2ro	Pernicious anaemia
XE13b	Deficiency anaemias
XE140	Anaemia unspecified
X20Bw	Microcytic anaemia
42R41	Ferritin level low
C2621	Cobalamin deficiency
D00zz	Iron deficiency anaemia NOS
D011z	Other vitamin B12 deficiency anaemia NOS
Xa7n0	Normocytic anaemia
Xa9Aw	Vitamin B12-deficient megaloblastic anaemia
Dyu06	[X]Vitamin B12 deficiency anaemia, unspecified
D001.	Iron deficiency anaemia due to dietary causes
X20Bu	Anaemia of chronic disorder
D00y1	Microcytic hypochromic anaemia
1451	H/O: anaemia - iron deficient
XE13g	Other vitamin B12 deficiency anaemias
XE13h	Vitamin B12 deficiency anaemia due to dietary causes
D000.	Anaemia due chron blood loss: [iron defic] or [normocytic]
XE13x	Acute posthaemorrhagic anaemia
X20CA	Megaloblastic anaemia due to dietary causes
XE14W	B12 deficiency anaemia (& other)
X20Bv	Anaemia of renal disease
X20C6	Macrocytic anaemia
XaCLx	Anaemia secondary to renal failure
D010.	Pernicious anaemia (& [Biermers][congen def intrins factor])
D21z.	Anaemia: [unsp][secondary NOS][normocyt/macrocyt unsp cause]
XE13d	Iron deficiency anaemia due to chronic blood loss
Dyu00	[X]Other iron deficiency anaemias
D214.	Chronic anaemia
D00z2	Idiopathic hypochromic anaemia
D00y.	(Kelly-Paterson's)/(Plumm-Vinson's)/(oth sp iron def anaem)
X20Br	Secondary anaemia NOS
X20C8	Megaloblastic anaemia
D012z	Folate deficiency anaemia NOS
D2z..	Other anaemias NOS
D0...	Deficiency anaemiasm (& [asiderotic] or [sideropenic])
Dyu02	[X]Other vitamin B12 deficiency anaemias
D00z.	Unspecified iron deficiency anaemia
D1114	Drug-induced haemolytic anaemia
1452	H/O: Anaemia vit.B12 deficient
D1...	Haemolytic anaemia
Xaa65	Recurrent anaemia
i1...	Oral iron for iron-deficiency anaemias
D11..	Acquired haemolytic anaemia
1453	H/O: haemolytic anaemia
X20Bp	Normocytic anaemia due to unspecified cause
i2...	Parenteral iron for iron-deficiency anaemias
D012.	Folate-deficient megaloblastic anaemia
145..	H/O: blood disorder (& [anaemia])
XE13o	Autoimmune haemolytic anaemia
D01..	Anaemia: [megaloblastic] or [other deficiency]
X20C9	Megaloblastic anaemia NOS
XaCLy	Anaemia secondary to chronic renal failure
XaYv2	Refractory anaemia with multilineage dysplasia
D014.	Protein-deficiency anaemia
Dyu22	[X]Anaemia in other chronic diseases classified elsewhere
D00yz	Other specified iron deficiency anaemia NOS

D20..	Aplastic anaemia
XE14S	(Anaem: [iron def][microcyt]) or (Kelly-Pat) or (Plumm-Vins)
X20C7	Macrocytic anaemia of unspecified cause
Dyu03	[X]Other folate deficiency anaemias
D011.	Vitamin B12 deficiency anaemia (& pleural)
D210.	Sideroblastic anaemia
Dyu01	[X]Other dietary vitamin B12 deficiency anaemia
1454	H/O: anaemia NOS
D0130	Combined B12 and folate deficiency anaemia
D0110	Vit B12 def anaem: [diet][Imersl-Grasbeck][Imerslund][Vegan]
D104.	(Thalassaemia (& Mediterr anaemia)) or (leptocytosis, hered)
X20CK	Refractory anaemia
D21..	Other and unspecified anaemia
D2010	Aplastic anaemia due to chronic disease
Dyu1.	[X]Haemolytic anaemias
XE13i	Folate deficiency anaemia due to dietary causes
XE13e	Other specified iron deficiency anaemia
D212.	Anaemia in neoplastic disease
D110.	(Autoimmun haemolyt anaemia) or (Coombs positive haemolysis)
D106.	Sickle cell anaemia
X20Ce	Warm autoimmune haemolytic anaemia
B9371	Refractory anaemia with sideroblasts
BBmA.	[M] Refractory anaemia with sideroblasts
D0z..	Deficiency anaemias NOS
D21yz	Other specified anaemia NOS
D110z	Autoimmune haemolytic anaemia NOS
D1111	Microangiopathic haemolytic anaemia
XE14U	Anaemia: [deficiency excluding iron] or [megaloblastic]
D01z0	[X]Megaloblastic anaemia NOS
D0111	Vit B12 defic anaemia due to malabsorption with proteinuria
D2y..	Other specified anaemias
XE13f	Other deficiency anaemias
XE14i	Other anaemias
D210z	Sideroblastic anaemia NOS
Xa9FH	Normocytic anaemia following acute bleed
Xa3ev	Nutritional anaemias NOS
XaM6S	Hypoplastic haemolytic and renal anaemia drugs Band 1
D0122	Folate deficiency anaemia, drug-induced
ByuHC	[X]Refractory anaemia, unspecified
Xa36n	Cold autoimmune haemolytic anaemia
D01z.	Anaemia NOS: [other deficiency] or [megaloblastic]
D1060	Sickle cell anaemia of unspecified type
Dyu24	[X]Other specified anaemias
D20z.	Aplastic anaemia NOS
D1z..	Haemolytic anaemias NOS
D1y..	Other specified haemolytic anaemias
Xa0Sf	Refractory anaemia with excess blasts
Dyu0.	[X]Nutritional anaemias
D104z	(Mediterranean anaemia) or (thalassaemia NOS)
D2017	Transient hypoplastic anaemia
D013.	Other specified megaloblastic anaemia NEC
B9372	Refractory anaemia with excess of blasts
D21yy	Other specified other anaemia
D2...	Aplastic and other anaemias
D00z1	Chlorotic anaemia
D0y..	Other specified deficiency anaemias
D00z0	Achlorhydric anaemia

	D1100	Primary cold-type haemolytic anaemia
	D013z	Other specified megaloblastic anaemia NEC NOS
	XE13q	Constitutional aplastic anaemia
	XE13w	Acquired aplastic anaemia NOS
	D1101	Primary warm-type haemolytic anaemia
	D0123	Folate deficiency anaemia due to malabsorption
	X20CG	Combined deficiency anaemia
	XE13t	Acquired aplastic anaemia
	XE13j	Other deficiency anaemias NOS
	D0121	Anaemia: [folate def or megaloblast, diet cause]/[goat milk]
	D01y.	Other specified nutritional deficiency anaemia
	D1110	Mechanical haemolytic anaemia
	D0124	Folate deficiency anaemia due to liver disorders
	D2011	Anaemia: [aplast due drug][hypoplast due drug or chem subst]
	D204.	Idiopathic aplastic anaemia
	D2014	Aplastic anaemia due to toxic cause
	D11z.	Acquired haemolytic anaemia NOS
	D1102	Secondary cold-type haemolytic anaemia
	Dyu15	[X]Other autoimmune haemolytic anaemias
	D2101	Acquired sideroblastic anaemia
	XaBC5	[M] Refractory anaemia with excess of blasts
	XaBDS	Anaemia in ovarian carcinoma
	Dyu23	[X]Other sideroblastic anaemias
Atrial fibrillation	3272	ECG: atrial fibrillation
	G5730	Atrial fibrillation
	2432	O/E - pulse irregularly irreg.
	XaOfa	Persistent atrial fibrillation
	XaIIT	Atrial fibrillation monitoring
	XaMGD	Atrial fibrillation annual review
	XaLFj	Excepted from atrial fibrillation qual indic: Inform dissent
	XaOft	Permanent atrial fibrillation
	XaDv6	H/O: atrial fibrillation
	Xa2E8	Paroxysmal atrial fibrillation
	G5731	Atrial flutter
	Xa7nI	Controlled atrial fibrillation
	X202R	Lone atrial fibrillation
	XaLFz	Atrial fibrillation resolved
	XaEga	Rapid atrial fibrillation
	G573.	Atrial fibrillation and flutter
	XaLFi	Except from atr fib quality indicators: Patient unsuitable
	3273	ECG: atrial flutter
	XaaUH	Paroxysmal atrial flutter
	XE0Wk	(Atrial fibrillation) or (atrial flutter)
	G573z	Atrial fibrillation and flutter NOS
	XaMDG	Atrial fibrillation monitoring first letter
	XaXrZ	Referral to atrial fibrillation clinic
	XaeUP	Chronic atrial fibrillation
	XaNRA	History of atrial flutter
	XaLFh	Exception reporting: atrial fibrillation quality indicators
	XaMFn	Atrial fibrillation monitoring telephone invite
	XaeUQ	Typical atrial flutter
	XaMDF	Atrial fibrillation monitoring administration
	XaMDH	Atrial fibrillation monitoring second letter
	XaMDI	Atrial fibrillation monitoring third letter
	X202S	Non-rheumatic atrial fibrillation
	7936A	Implant intravenous pacemaker for atrial fibrillation
	XaZdc	Atrial fibrillation care pathway

	XaMDK	Atrial fibrillation monitoring verbal invite
	XaeUR	Atypical atrial flutter
Bleeding disorder	XE24o	Thrombocytopenia
	D306.	Disseminated intravascular coagulation
	X20FX	Essential thrombocythaemia
	D30..	Coagulation disorder
	XM1V8	Autoimmune thrombocytopenia
	XE146	Idiopathic thrombocytopenic purpura
	D315.	Thrombocytopenia NOS
	D3y0.	Essential thrombocytosis
	Xa8Hh	Thrombocytopenic disorder
	XaAz4	Heterozygous factor V Leiden mutation
	X20FJ	Immune thrombocytopenic purpura
	D3130	Idiopathic purpura (& thrombocytopenic)
	D304.	von Willebrand's disease
	X20FY	Reactive thrombocytosis
	XE145	Primary thrombocytopenia
	XaBBu	Idiopathic thrombocythaemia
	D31..	Purpura and other haemorrhagic conditions
	XaAyb	Factor V Leiden mutation
	X20EZ	Dysfibrinogenaemia
	D314.	Secondary thrombocytopenia
	X20Ej	Thrombophilia
	D3141	Thrombocytopenia due to drugs
	XM0qK	Haemophilia - disorder
	D300.	Congenital factor VIII deficiency
	Xa0hN	Anticoagulant excess without bleeding
	D3z..	Clotting or bleeding disorder NOS
	D311.	Platelet defects: [qualitative][Bernard-Soulier thrombopath]
	Xa9Ay	Thrombocytopenic purpura
	D309.	Protein S deficiency
	D3035	Factor XII deficiency
	D3036	Factor XIII deficiency
	X20F8	Essential thrombocytopenia NOS
	X20EV	Fibrinogen abnormality
	X20Ek	Antithrombin deficiency
	D3133	[X]Essential thrombocytopenia NOS
	D30z.	Coagulation defect NOS
	G756.	Thrombotic thrombocytopenic purpura
	D1111	Microangiopathic haemolytic anaemia
	D3050	Haemorrhagic disorder due to antithrombinaemia
	D1113	Haemolytic uraemic syndrome
	XaAz3	Homozygous factor V Leiden mutation
	XE14o	(Other coagulation defects) or (Dissemin intravascular coag)
	Q450.	Haemorrhagic disease of the newborn
	D31z.	Haemorrhagic condition NOS
	D3033	Factor VII deficiency
	XE1g9	Haemorrhagic disease (& [perinatal])
	Xa0hM	Anticoagulant-induced bleeding
	XE149	Secondary thrombocytopenia NOS
	D308.	Haemophilia carrier
	D302.	Factor XI deficiency
	Dyu32	[X]Other primary thrombocytopenia
	Xa36j	Heparin-induced thrombocytopenia
	D303y	Congenital deficiency of other clotting factor OS
	X20F5	Acquired platelet disorder

	D3032	Factor V deficiency
	D301.	Congenital factor IX deficiency
	D3031	Deficiency of factor II &/or prothrombin
	XE148	Primary thrombocytopenia NOS
	XE143	Qualitative platelet defects
	G756z	Thrombotic microangiopathy NOS
	Dyu30	[X]Other specified coagulation defects
	X20EE	Haemophilia A carrier
	D3034	Factor X deficiency
	X20EX	Hypofibrinogenaemia
	X20EL	Congenital von Willebrand's disease
	D3y..	Other specified disorders of clotting or bleeding
	D3070	Deficiency of coagulation factor due to liver disease
	D3051	Haemorrhagic disorder due to hyperheparinaemia
	D313y	Other specified primary thrombocytopenia
	X20F2	Cyclooxygenase deficiency
	X20FG	Hereditary thrombocytopenia NEC
	Xa0lB	Afibrinogenaemia
	D311z	Qualitative platelet deficiency NOS
	XE147	Congenital thrombocytopenic purpura
	XaB8v	Idiopathic factor VIII deficiency
	X20Et	Bernard-Soulier syndrome
	D303.	Congenital deficiency of other clotting factors
	X20EH	Factor IX deficiency
	X20FK	Autoimmune thrombocytopenic purpura
	D305z	Haemorrhagic disorder due to circulating anticoagulants NOS
	D305.	Haemorrhagic disorder due to circulating anticoagulants
	D31y.	Other specified haemorrhagic conditions
	D314y	Other specified secondary thrombocytopenia
	D31yz	Other specified haemorrhagic condition NOS
	XaYgo	Hereditary thrombophilia
	D3072	Acquired factor II deficiency
	XE2rp	Post-transfusion thrombocytopenic purpura
	X20EN	Congenital von Willebrand's disease type II
	X20EP	Acquired von Willebrand's disease
	XE141	Factor II deficiency
	X20EM	Congenital von Willebrand's disease type I
	X20EF	Haemophilia A with inhibitor
Cancer	B34..	Malignant neoplasm of female breast
	C332z	Paraproteinaemia NOS
	X78gO	Adenocarcinoma of colon
	B46..	Malignant tumour of prostate
	XaIyc	Cancer care review
	B1101	Malignant neoplasm of cardio-oesophageal junction of stomach
	X78Xw	Squamous cell carcinoma of vulva
	Xa9Jk	Metastasis to lower limb lymph node
	B3...	[Mal neop][carc] bone (& [sarc]), connect tiss, skin, breast
	B4y..	Malignant neoplasm of genitourinary organ OS
	Xa9Jm	Metastasis to intrapelvic lymph node
	Byu6.	[X]Malignant neoplasm of breast
	B641.	Chronic lymphoid leukaemia
	XaZdn	Diffuse large B-cell lymphoma
	B133.	Malignant tumour of sigmoid colon
	B496.	Malignant tumour of ureteric orifice
	X78Y6	Carcinoma of prostate
	Xa0KG	Malignant tumour of lung
	XE1vc	Malignant neoplasm of bronchus or lung NOS

XE1vb	Malignant neoplasm of upper lobe, bronchus or lung
B134.	Malignant neoplasm of caecum (& carcinoma)
B13..	Malignant tumour of colon
X78ef	Malignant tumour
B650.	Acute myeloid leukaemia
B65..	Myeloid leukaemia
X78iu	Malignant tumour of kidney
Xa0G9	Squamous cell carcinoma of tongue
B17..	Malignant tumour of pancreas
Xa0TG	Diffuse malignant lymphoma - large cell
B307.	Malignant neoplasm of long bones of leg
Xa0DF	Adenocarcinoma of oesophagus
X78j2	Transitional cell carcinoma of bladder
B49z.	Malignant neoplasm of urinary bladder NOS
XE1vW	Malignant tumour of rectum
X78it	Malignant tumour of urinary tract
B49..	Malignant tumour of urinary bladder
XaFrL	Local recurrence of malignant tumour of urinary bladder
XaYii	Extranod marg zone B-cell lymphom mucosa-assoc lymphoid tiss
Xa36r	Carcinoma of cervix
Xa34H	Carcinoma of sigmoid colon
X78gM	Carcinoma of caecum
X78QP	Squamous cell carcinoma of lung
B577.	Metastasis to liver
B2221	Malignant neoplasm of upper lobe of lung
B34z.	Malignant neoplasm of female breast NOS
X78gA	Carcinoma of stomach
XaYim	Follicular lymphoma grade 3b
B060.	Malignant tumour of tonsil
B4A1z	Malignant neoplasm of renal pelvis NOS
ByuDC	[X]Diffuse non-Hodgkin's lymphoma, unspecified
Xa0l6	Paraproteinaemia
Xa0Ge	Carcinoma of larynx
X78eE	Malignant tumour of head and neck
X78gN	Malignant tumour of large intestine
Xa0SY	Myelodysplastic syndrome
B61..	Hodgkin's disease
B65y1	Acute promyelocytic leukaemia
Xa97q	Malignant tumour of liver
X78gK	Malignant tumour of intestine
XE11b	Monoclonal paraproteinaemia
X78XO	Endometrial carcinoma
X78OK	Adenocarcinoma of rectum
B627.	Non-Hodgkin's lymphoma - disorder
XaDc7	Carcinoma of descending colon
XE20N	Multiple myeloma etc.
B630.	Myeloma
X78io	Teratoma of testis
Xa0SP	Myeloproliferative disorder
B934.	Polycythaemia rubra vera
XaBmX	Adenocarcinoma of uterus
XE1xL	Carcinoma of colon
X78Yx	Clear cell carcinoma of kidney
B585.	Metastasis to bone
Xa0Dp	Malignant glioma of brain
XaFr7	Local recurrence of malignant tumour of lung
X78QS	Non-small cell lung cancer

B340z	Malignant neoplasm of nipple or areola of female breast NOS
Xa0bT	Intraduct carcinoma of breast
B5811	Metastasis to bladder
Xa0GC	Squamous cell carcinoma of floor of mouth
B58y5	Metastasis to prostate
Xa3eL	Carcinoma of breast - upper, inner quadrant
XaFrl	Local recurrence of malignant tumour of colon
Xa84V	Adenocarcinoma of sigmoid colon
B16..	Malignant tumour of biliary tract
Xa0bU	Lobular carcinoma of breast
B141.	Malignant neoplasm of rectum (& carcinoma)
Xa0QP	B-cell chronic lymphocytic leukaemia
XE1xT	Ca sigmoid colon
B13z.	Malignant neoplasm of colon (& NOS)
Xa3AC	Metastasis to colon of unknown primary
B35..	Malignant neoplasm of male breast
X78YK	Carcinoma of glans penis
XE2t9	[X]Non-Hodgkin's lymphoma, unspecified type
X78cP	Follicular thyroid carcinoma
B580.	Metastasis to kidney
XE1vQ	Malignant neoplasm of oesophagus NOS
B10..	Malignant tumour of oesophagus
X78QG	Adenocarcinoma of lung
XaFrw	Metastasis from malignant tumour of lung
B570.	Metastasis to lung
B53..	Malignant tumour of thyroid gland
X78JO	Carcinoma of submandibular gland
Xa980	Metastasis to lymph node
X78kl	Metastasis to omentum
XaDc9	Carcinoma of splenic flexure
B58y0	Metastasis to breast
XacSF	Prostate cancer care review
B302.	Malignant neoplasm of vertebral column
ByuDE	[X]Unspecified B-cell non-Hodgkin's lymphoma
Xa0ko	Mixed seminoma teratoma of testis
X78ip	Seminoma of testis
B4A00	Hypernephroma
B6275	Malignant lymphoma - mixed small and large cell
X78g3	Carcinoma of oesophagus
XE1vl	Malignant tumour of adrenal gland
Xa36T	Metastasis to vertebral column
Xa0Rn	Chronic lymphocytic prolymphocytic leukaemia syndrome
X78cQ	Papillary thyroid carcinoma
X78j1	Carcinoma of bladder
B4A1.	Malignant tumour of renal pelvis
Xa982	Metastatic malignant disease
XaFr8	Local recurrence of malignant tumour of breast
B47..	Malignant tumour of testis
XE1vj	Malignant neoplasm of vulva unspecified
B170.	Malignant tumour of head of pancreas
X78Wk	Endometrioid carcinoma ovary
X78WR	Paget's disease of nipple
B440.	Malignant tumour of ovary
B41..	Malignant neoplasm of cervix uteri (& carcinoma)
X78Xg	Adenocarcinoma of cervix
B587.	Metastasis to adrenal gland
XaFrJ	Local recurrence of malignant tumour of rectum

Xa9Jc	Metastasis to head and neck lymph node
B5761	Metastasis to peritoneum
X78jy	Malignant tumour of endocrine gland
Xa0T2	Diffuse low grade B-cell lymphoma
B344.	Malignant neoplasm of upper-outer quadrant of female breast
XaBA5	Osteosarcoma of bone
X78iC	Malignant tumour of female genital organ
X78e9	Malignant tumour of unknown origin
XE1vU	Malignant tumour of caecum
B564z	Secondary and unspec malig neop of inguinal and leg LN NOS
Xa0QI	Lymphoproliferative disorder
Xa0GA	Squamous cell carcinoma of gum
B1503	Hepatocellular carcinoma
B621z	Mycosis fungoides NOS
Xa8Jb	T-cell lymphoma
B621.	Mycosis fungoides
B01..	Malignant tumour of tongue
B1...	Malig neoplasm digest organs and peritoneum (& [carcinoma])
XaYij	Follicular lymphoma grade 1
X78if	Malignant tumour of penis
Xa36a	IgA myeloma
XE1vi	Malignant tumour of cervix
B135.	Malignant tumour of appendix
B4A..	Malignant renal neoplasm (& [other unspecif urinary organs])
B22..	Malignant neoplasm of trachea, bronchus and lung
Xa99k	Malignant lymphoma
X78Q8	Squamous cell carcinoma of bronchus
X78Q2	Squamous cell carcinoma of trachea
XM0ps	Malignant melanoma of eye
XaDc8	Carcinoma of hepatic flexure
B47z.	Malign neoplasm of testis: [NOS] or [seminoma] or [teratoma]
XM0pb	Tonsil carcinoma
B624.	Hairy cell leukaemia
XaFrD	Local recurrence of malignant tumour of oesophagus
B21..	Malignant tumour of larynx
X78QI	Carcinoid tumour of lung
Xa0T3	High grade B-cell lymphoma
Xa3eQ	Carcinoma of breast NOS
X78Xf	Squamous cell carcinoma of cervix
B691.	Chronic myelomonocytic leukaemia
B4A0.	Malignant tumour of kidney parenchyma
XE2vP	Malignant neoplasm of genitourinary organ
B04y.	Malignant neoplasm of other sites of floor of mouth
X78gL	Malignant tumour of small intestine
B136.	Malignant tumour of ascending colon
XaDc5	Carcinoma of ascending colon
X78bw	Malignant melanoma of choroid
X78ke	Metastasis to spleen
X77nQ	Neuroendocrine carcinoma
XaEJf	Squamous cell carcinoma of bronchus in left upper lobe
Xa0Dj	Malignant melanoma of rectum
B616.	Hodgkin's disease, lymphocytic depletion
Xa3Bc	Metastasis to lymph node of unknown primary
B130.	Malignant tumour of hepatic flexure
Xa0QQ	B-cell chronic lymphocytic leukaemia variant
B2241	Malignant neoplasm of lower lobe of lung
Xa0WG	Primary malignant tumour of peritoneum

B4302	Malignant neoplasm of endometrium of corpus uteri
Xa34F	Carcinoma of anal canal
Xa0DG	Squamous cell carcinoma of oesophagus
X78el	Squamous cell carcinoma of lip
B5831	Metastasis to spinal cord
XaEfj	Cystadenocarcinoma of ovary
Xa0Sz	Cutaneous/peripheral T-cell lymphoma
B140.	Malignant tumour of rectosigmoid junction
XE1vY	Malignant tumour of gallbladder
Xa0GN	Squamous cell carcinoma of palate
X78Hz	Carcinoma of lingual tonsil
XaFrH	Local recurrence of malignant tumour of pancreas
X78gd	Carcinoma of pancreas
XaFrp	Metastasis from malignant tumour of pancreas
XaEJg	Squamous cell carcinoma of bronchus in right lower lobe
B121.	Malignant tumour of jejunum
B454.	Malign neoplasm of vulva: [unspecified] or [primary cancer]
Xa3A5	Metastasis to lung of unknown primary
Xa3AE	Metastasis to liver of unknown primary
B5830	Metastasis to brain
XE1wp	Tongue carcinoma
X78e2	Leukaemia
XaFrM	Local recurrence of malignant tumour of prostate
X78QN	Small cell carcinoma of lung
B640.	Acute lymphoid leukaemia
XaBAn	Carcinomatosis
XaB1p	Metastatic adenocarcinoma of unknown origin
XaFro	Metastasis from malignant tumour of colon
B010.	Malignant tumour of base of tongue
Xa0LD	Malignant tumour of middle ear
B4A2.	Malignant tumour of ureter
XaDc6	Carcinoma of transverse colon
XaFrx	Metastasis from malignant tumour of thyroid
Xa3eK	Ca breast - nipple/central
XaYv2	Refractory anaemia with multilineage dysplasia
XaDbr	Cholangiocarcinoma of biliary tract
B670.	(Acute erythraemia+erythroleukaemia) or(Di Guglielmo's dis)
Xa983	Disseminated malignancy
XaPQD	Mantle cell lymphoma
B627C	Follicular lymphoma: [non-Hodgkin's] or [NOS]
XE2vS	Malignant brain tumour
XaEJi	Squamous cell carcinoma of bronchus in right upper lobe
X78Wo	Undifferentiated carcinoma of ovary
B43..	Malignant tumour of body of uterus
Xa0T1	Low grade B-cell lymphoma
B342.	Malignant neoplasm of upper-inner quadrant of female breast
Xa9Ji	Metastasis to upper limb lymph node
B174.	Malignant tumour of Islets of Langerhans
B4301	Malignant neoplasm of fundus of corpus uteri
B18y3	Malignant neoplasm of omentum
B651z	Chronic myeloid leukaemia NOS
B651.	Chronic myeloid leukaemia
B430z	Malignant neoplasm of corpus uteri NOS
B341.	Malignant neoplasm of central part of female breast
X78fO	Malignant tumour of pharynx
XaFru	Metastasis from malignant tumour of breast
ByuHD	[X]Myelodysplastic syndrome, unspecified

B3121	Malig neop of connective and soft tissue thigh and upper leg
X78Qc	Malignant mesothelioma of pleura
Xa3AJ	Metastasis to bone of unknown primary
X78es	Malignant tumour of oral cavity
X78cR	Mixed follicular and papillary thyroid carcinoma
XE1vV	Malignant neoplasm of colon NOS
B340.	Malignant neoplasm of nipple and areola of female breast
Xa9Jo	Metastasis to multiple lymph nodes
Xa0SN	Non-secretory myeloma
XaBB3	Plasma cell leukaemia
XaBAp	Bronchioloalveolar adenocarcinoma of lung
XE1vZ	Malignant tumour of respiratory and intrathoracic organ
X78lF	Carcinoma of other and unspecified sites
B64..	Lymphoid leukaemia
B586.	Metastasis to ovary
B162.	Malignant tumour of ampulla of Vater
XE1vp	Nodular lymphoma
X78Xx	Malignant melanoma of vulva
Byu51	[X]Mesothelioma, unspecified
X78g1	Malignant tumour of digestive organ
B620z	Nodular lymphoma NOS
XE2vQ	Malig neop of kidney and other unspecified urinary organs
X78QJ	Carcinoma of lung parenchyma
XaELK	Seminoma of descended testis
X78fC	Malignant tumour of salivary gland
Xa0bK	Malignant seminoma of mediastinum
B501.	Malignant tumour of orbit
XaYjl	Primary cutaneous CD30 antigen positive large T-cell lymphom
Xa36b	IgG myeloma
Xaa1N	Clinical stage A chronic lymphocytic leukaemia
Xa0Dr	Glioblastoma multiforme of brain
XaZdD	Follicular lymphoma grade 3
Xa0T4	Follicular low grade B-cell lymphoma
X78j4	Squamous cell carcinoma of bladder
Xa7n9	Transitional cell carcinoma of ureter
B08..	Malignant tumour of hypopharynx
X00eS	Retinoblastoma
Xa0bS	Malignant lymphoma of breast
C331.	Monoclonal paraproteinaemia (& gammopathy)
Xa0DX	Gastric lymphoma
B41y1	Malignant neoplasm of squamocolumnar junction of cervix
Xa0TS	Large cell anaplastic lymphoma
X78LV	Malignant tumour of vocal cord
XM0pZ	Palate carcinoma
B0551	Malignant tumour of palate
Xa0Ei	Carcinoma of fallopian tube
B441.	Malignant tumour of fallopian tube
X78Vj	Liposarcoma
B40..	Malignant neoplasm of uterus, part unspecified
XM1Pr	Cerebral metastasis
Xa3BZ	Metastasis to brain of unknown primary
B050.	Malignant tumour of buccal mucosa
B112.	Malignant tumour of pyloric antrum
B14..	Malignant neoplasm of rectum, rectosigmoid junction and anus
B120.	Malignant tumour of duodenum
XaFrR	Local recurrence of malignant tumour of soft tissue
Xa0Rp	Splenic lymphoma with villous lymphocytes

B51z.	Malignant neoplasm of brain NOS
X78QK	Large cell carcinoma of lung
X78XN	Sarcoma of uterus
B0100	Malignant neoplasm of base of tongue dorsal surface
XE2rk	Malignant neoplasm of lip, oral cavity and pharynx
XaFsw	Hereditary nonpolyposis colon cancer
Xa97z	Malignant tumour of unknown origin or ill-defined site
XaFrN	Local recurrence of malignant tumour of cervix
X78PC	Extrahepatic bile duct carcinoma
Xa9AA	Plasmacytoma - disorder
XaB1g	Carcinoma of head of pancreas
X78PX	Carcinoma of ampulla of Vater
B63..	Multiple myeloma and immunoproliferative disease
B200.	Malignant tumour of nasal cavity
B1z0.	Malignant neoplasm of intestinal tract, part unspecified
B6...	Malig neoplasm lympha & haemopoiet tiss (& [histiocyt tiss])
B213z	Malignant neoplasm of laryngeal cartilage NOS
Xa0TE	Diffuse high grade B-cell lymphoma
B572.	Metastasis to pleura
XaBBN	Malignant lymphoma - lymphoplasmacytic
B020.	Malignant tumour of parotid gland
XaIt4	Benign paraproteinaemia
B224.	Malignant neoplasm of lower lobe, bronchus or lung
XE1zj	(Carcinoma bladder) or (bladder Ca)
B11z.	Malignant neoplasm of stomach NOS
XaB8h	Squamous cell carcinoma of mouth
B10z.	(Malignant neoplasm of oesophagus NOS or oesophageal cancer
B4Az.	Malignant neoplasm of kidney or urinary organs NOS
Xaa1O	Clinical stage B chronic lymphocytic leukaemia
B02z.	Malignant neoplasm of major salivary gland NOS
B07..	Malignant tumour of nasopharynx
Xa1oQ	Carcinoma of vocal cord
XE1yD	Ca larynx - NOS
XE1y7	Ca larynx - glottis
X78kk	Carcinomatosis of peritoneal cavity
Xa0DQ	Late gastric cancer
Xa0bQ	Sarcoma of breast
B44..	Malignant neoplasm of ovary and other uterine adnexa
B8yy0	Carcinoma in situ of thyroid
X78id	Malignant tumour of male genital organ
Xa3eR	Carcinoma genital organs
XE1vk	Malignant neoplasm of testis NOS
B211.	Malignant tumour of supraglottis
B21z.	Malignant neoplasm of larynx NOS
B05z.	Malignant neoplasm of mouth NOS
B132.	Malignant tumour of descending colon
XM0Ac	Carcinoma of base of tongue
B06..	Malignant tumour of oropharynx
B04..	Malignant tumour of floor of mouth
Xa0T9	Monocytoid B-cell lymphoma
B613.	Lymphocyte-rich classical Hodgkin lymphoma
XE1vd	Malignant tumour of bone and articular cartilage
B61z.	Hodgkin's disease NOS
B150z	Primary malignant neoplasm of liver NOS
B511.	Malignant neoplasm of frontal lobe
B137.	Malignant tumour of splenic flexure
X78gY	Carcinoma gallbladder

B303.	Malignant neoplasm of ribs, sternum and clavicle
C332.	Other paraproteinaemias
B22y.	Malignant neoplasm of other sites of bronchus or lung
B22z.	Malig neopl lung: [of bronchus or lung NOS] or [lung cancer]
Xa3eG	Carcinoma liver/biliary system NOS
B5z..	Malignant neoplasm of other and unspecified site NOS
XaBAu	Pseudomyxoma peritonei
X78Q7	Malignant tumour of bronchus
B602z	Burkitt's lymphoma NOS
B2220	Malignant neoplasm of upper lobe bronchus
Xa0TX	Follicular malignant lymphoma - large cell
Xa0WH	Malignant peritoneal local recurrence
X78Wi	Serous papillary cystadenocarcinoma ovary
B4A3.	Malignant tumour of urethra
Xa0T8	Mucosa-associated lymphoma
B210.	Malignant tumour of glottis
B0720	Malignant tumour of pharyngeal recess
B550z	Malignant neoplasm of head, neck and face NOS
B58y3	Metastasis to vagina
B41z.	Malignant neoplasm of cervix uteri NOS
X78Pq	Malignant tumour of peritoneum
XaBAk	Malignant mastocytosis
ByuDA	[X]Oth spcf mal neoplsm/lymphoid,haematopoietic+rltd tissue
XaCJ1	Primary malignant neoplasm of unknown site
Xa97y	Malignant tumour of vulva
B202.	Malignant tumour of maxillary sinus
B937W	(Myelodysplastic syndrome, unspecified) or (myelodysplasia)
X78Wl	Clear cell tumour of ovary
B56z.	Secondary and unspec malig neop lymph nodes NOS
XE2vj	Malignant hydatidiform mole
B4501	Malignant neoplasm of vaginal vault
X78YR	Carcinoma of foreskin
B142.	Malignant neoplasm of anal canal (& anal carcinoma)
XaBLv	Malignant neoplasm of epiglottis NOS
B26..	Malignant neoplasm, overlap lesion of resp & intrathor orgs
XE1zf	Ca penis
XE1yF	(Bronchus carc) or (lung carc) or (Ca trachea/bronchus/lung)
Xa0SB	Large granular lymphocytic leukaemia
B02..	Malignant tumour of major salivary gland
B105.	Malignant tumour of lower third of oesophagus
B615.	Hodgkin's disease, mixed cellularity
B11y.	Malignant neoplasm of other specified site of stomach
B620.	(Nodular lymphoma: Brill-Symmers) or (reticulosarc foll/nod)
B131.	Malignant tumour of transverse colon
ByuD8	[X]Other specified leukaemias
B34y.	Malignant neoplasm of other site of female breast
XE2xB	Secondary and unspecified malignant neoplasm of lymph nodes
XE1y9	Ca larynx - supraglottis
B3401	Malignant neoplasm of areola of female breast
B50..	Malignant tumour of eye
X2032	Pulmonary tumour embolism
B213.	Malignant tumour of laryngeal cartilage
B053.	Malignant tumour of soft palate
XE1yB	Ca larynx - subglottis
B052.	Malignant tumour of hard palate
X78j7	Malignant tumour of nervous system
ByuD3	[X]Other specified types of non-Hodgkin's lymphoma

ByuD1	[X]Other types of follicular non-Hodgkin's lymphoma
B602.	Burkitt's lymphoma - disorder
B014.	Malignant neoplasm of anterior 2/3 of tongue unspecified
XE1wv	(Ca oro/naso/hypopharynx) or (carc: [pharynx] or [tonsil])
XaBLx	Plasmacytoma NOS
XE1yT	(Ca bone/artic cart) or (bone carc) or (sarc bone/art cart)
Xa0SL	Light chain myeloma
XaELl	Lambda light chain myeloma
XE1zd	Ca vulva: [clitoral Ca] or [labial Ca]
XE1xH	Ca greater curvature - stomach
B653.	Myeloid sarcoma
B110.	Malignant tumour of cardia
B35zz	Malignant neoplasm of male breast NOS
B040.	Malignant tumour of anterior floor of mouth
Xa3eM	Carcinoma of breast - lower, inner quadrant
XaELL	Teratoma of descended testis
B150.	Primary malignant neoplasm of liver
B143.	Malignant neoplasm of anus unspecified
B550.	Malignant neoplasm of head, neck and face
B486.	Malignant tumour of scrotum
B55..	Malignant neoplasm of other and ill-defined sites
XE1xN	Ca hepatic flexure - colon
B58..	Secondary [malig neopl] or [carcinoma] of other specif sites
XE1vX	Malignant tumour of anal canal
B0zz.	Malignant neoplasm of lip, oral cavity and pharynx NOS
XE1zl	Ca kidney/other urinary organs
XE20J	(Lymphatic tissue carcinoma) or (lymphoma)
B2003	Malignant tumour of nasal vestibule
Byu20	[X]Malignant neoplasm of bronchus or lung, unspecified
Xa3Bd	Disseminated malignancy of unknown primary
B45z.	Malignant neoplasm of female genital organ NOS
B6531	Granulocytic sarcoma
XE2vO	Malig neop of bone, connective tissue, skin and breast
B45..	Malig neop of other and unspecified female genital organs
B31..	Malignant neoplasm of connective and other soft tissue
B62x.	Malignant lymphoma otherwise specified
XE20X	Malignant neoplasm NOS (& sarcoma NOS)
XE1xR	Ca descending colon
B553z	Malignant neoplasm of pelvis NOS
B517.	Malignant neoplasm of brainstem
B681.	Chronic leukaemia NOS
X78Wj	Mucinous cystadenocarcinoma of ovary
XE1wj	Malignant neoplasms (& carcinoma)
B152.	Malignant neoplasm of liver unspecified
X78fH	Malignant tumour of ear, nose and throat
Xa0SI	Plasma cell disorder
X78cS	Anaplastic thyroid carcinoma
X78M7	Malignant tumour of neck
Xa0TD	Follicular malignant lymphoma - small cleaved cell
XM0Ad	Metastasis to large intestine
X78NL	Carcinoma of duodenum
B3022	Malignant neoplasm of lumbar vertebra
XE2vT	Secondary malignant neoplasm of other specified sites
B006.	Malignant neoplasm of overlapping lesion of lip
B540.	Malignant neoplasm of adrenal gland (& phaeochromocytoma)
B5602	Secondary and unspec malig neop superficial cervical LN
B495.	Malignant tumour of bladder neck

X78Mg	Carcinoma of lower third of oesophagus
B481.	Malignant tumour of glans penis
B117.	Malignant neoplasm, overlapping lesion of stomach
B450.	Malignant tumour of vagina
B345.	Malignant neoplasm of lower-outer quadrant of female breast
B113.	Malignant tumour of fundus of stomach
B43z.	Malignant neoplasm of body of uterus NOS
XaFrE	Local recurrence of malignant tumour of stomach
XE1z9	Ca breast-upper,inner quadrant
B6277	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
B30z.	Malignant neoplasm of bone and articular cartilage NOS
B01z.	Malignant neoplasm of tongue NOS
B18..	Malignant tumour of peritoneum and retroperitoneum
XE1wn	Carcinoma of lip
Xa0SD	B-cell acute lymphoblastic leukaemia
X78YP	Malignant tumour of skin of penis
X78kT	Metastasis to respiratory and intrathoracic organ
B58y2	Secondary malignant neoplasm of cervix uteri
Xa3AH	Metastasis to peritoneum of unknown primary
XE2vR	Malignant neoplasm of other and unspecified sites
XE1zX	Ca ovary/other uterine adnexa
B301.	Malignant neoplasm of mandible
X78ei	Carcinoma of bone, connective tissue, skin and breast
B58yz	Secondary malignant neoplasm of other specified site NOS
Xa0Ri	Malignant white blood cell disorder
Xa3eF	Carcinoma liver/biliary system
B626.	Malignant mast cell tumours
XE1xX	Ca ascending colon
B31z.	Malignant neoplasm of connective and soft tissue, site NOS
XE1xP	Ca transverse colon
X78WP	Inflammatory carcinoma of breast
B4701	Malignant tumour of retained testis
X78ks	Metastasis to urinary tract
B081.	Malignant tumour of pyriform fossa
X78ci	Parathyroid carcinoma
XaFzu	Malignant neoplasm of bone
XE1xV	(Ca caecum) or (caecum carcinoma)
XE1zv	Malign tumour eye: [Ca eye][malign melanoma][retinoblastoma]
XE1wt	(Ca gum, + rest of mouth) or (carc: [cheek][mouth][palate])
XE1zb	Malig tumour testis: [carcinoma] or [seminoma] or [teratoma]
XaFrc	Metastases by primary malignancy
B516.	Malignant neoplasm of cerebellum
B4...	Malignant neoplasm of genitourinary organ (& [carcinoma])
B221.	Malignant neoplasm of main bronchus
B5...	Malignant neopl other unspecified sites: (& [[carcinoma])
B240.	Malignant tumour of thymus
B4100	Malignant neoplasm of endocervical canal
B6300	Malignant plasma cell neoplasm, extramedullary plasmacytoma
B5632	Secondary and unspec malig neop infraclavicular lymph nodes
B41y.	Malignant neoplasm of other site of cervix
B1500	Primary carcinoma of liver
XE1vn	Disseminated malignancy NOS
Byu57	[X]Malignant neoplasm of peritoneum, unspecified
B494.	Malignant neoplasm of posterior wall of urinary bladder
B305D	Malignant neoplasm of phalanges of hand
B601z	Lymphosarcoma NOS
B20y.	Malig neop other site nasal cavity, middle ear and sinuses

B200z	Malignant neoplasm of nasal cavities NOS
B514.	Malignant neoplasm of occipital lobe
X78QO	Oat cell carcinoma of lung
X78OP	Malignant tumour of anus
B03..	Malignant tumour of gum
B507.	Malignant tumour of lacrimal gland
Xa3eP	Carcinoma of breast - axillary tail
X78Xq	Carcinoma of vagina
Xa0So	Acute myelofibrosis
X78VS	Malignant mesothelioma of peritoneum
B5630	Secondary and unspec malig neop axillary lymph nodes
B5633	Secondary and unspec malig neop pectoral lymph nodes
X78NB	Carcinoma of lesser curve of stomach
B5619	Secondary and unspec malig neop pulmonary lymph nodes
XM1Ps	Cerebral tumour - malignant
X78Wm	Borderline epithelial tumour
XE1vO	Malignant tumour of lip
X78bN	Malignant melanoma of conjunctiva
B492.	Malignant neoplasm of lateral wall of urinary bladder
B12..	Malignant neoplasm of small intestine and duodenum
B160.	Malignant neoplasm of gallbladder (& carcinoma)
X78VQ	Malignant tumour of mesothelial tissue
Xa9Jg	Metastasis to intra-abdominal lymph node
B5500	Malignant neoplasm of head NOS
B115.	Malignant neoplasm of lesser curve of stomach unspecified
B172.	Malignant tumour of tail of pancreas
B173.	Malignant tumour of pancreatic duct
B690.	Acute myelomonocytic leukaemia
X78hk	Malignant infiltration of skin
B43y.	Malignant neoplasm of other site of uterine body
XaFr6	Local recurrence of malignant tumour of thyroid gland
B343.	Malignant neoplasm of lower-inner quadrant of female breast
B583z	Secondary malignant neoplasm of brain or spinal cord NOS
B5760	Metastasis to retroperitoneum
X78WT	Malignant phyllodes tumour of breast
X78X8	Malignant germ cell tumour of ovary
X77nT	Carcinoid bronchial adenoma
B560z	Secondary unspec malig neop lymph nodes head/face/neck NOS
ByuC0	[X]Malignant neoplasm of other specified sites
X78hq	Malignant tumour of mesothelial and soft tissue
Xa0Rk	T-cell chronic lymphocytic leukaemia
Xa9AM	Acute leukaemia
B64y1	Prolymphocytic leukaemia
Xa3eO	Carcinoma breast - lower, outer quadrant
B110z	Malignant neoplasm of cardia of stomach NOS
XM1Oc	Carcinoma ventral surface of tongue
Xa0QD	Anaplastic astrocytoma of brain
B3y..	Malig neop of bone, connective tissue, skin and breast OS
ByuC7	[X]Secondary malignant neoplasm of other specified sites
XaB1i	Carcinoma of tail of pancreas
XE1xJ	Ca stomach NOS
B63z.	Immunoproliferative neoplasm or myeloma NOS
B69..	Myelomonocytic leukaemia
Byu5.	[X]Malignant neoplasm of mesothelial and soft tissue
XE20B	Secondary Ca NOS
ByuC2	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
Xa3BN	Metastasis to kidney of unknown primary

XE1y5	Ca pancreas NOS
B58y6	Metastasis to testis
Xa0Sq	Tumour lysis syndrome
B5400	Malignant tumour of adrenal cortex
B6278	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
XE1zt	Ca uterus NOS: [carcinoma] or [cancer]
X78QT	Pancoast tumour
XE1wr	Ca major saliv gland) or (carc: [parotid][subling][submand])
B300B	Malignant neoplasm of turbinate
B13y.	Malignant neoplasm of other specified sites of colon
XaB1h	Carcinoma of body of pancreas
B17z.	Malignant neoplasm of pancreas NOS
B68z.	Leukaemia NOS
C333.	Macroglobulinaemia
X78l5	Metastasis to thyroid
Xaa1P	Clinical stage C chronic lymphocytic leukaemia
Xa3BH	Metastasis to breast of unknown primary
Xa0St	Hodgkin's disease, lymphocytic predominance - nodular
B013.	Malignant neoplasm of ventral surface of tongue
B627B	Other types of follicular non-Hodgkin's lymphoma
B601.	Lymphosarcoma
B6z..	Malignant neoplasm lymphatic or haematopoietic tissue NOS
ByuDD	[X]Oth and unspecif peripheral & cutaneous T-cell lymphomas
B512.	Malignant neoplasm of temporal lobe
B67..	Other specified leukaemia
X78l8	Local tumour spread
XaB1e	Retroperitoneal sarcoma
X78QF	Malignant tumour of lung parenchyma
Xa9FC	Malignant lymphoma, follicular centre cell
XaEJe	Squamous cell carcinoma of bronchus in left lower lobe
B543.	Malignant tumour of pineal gland
B5512	Malignant neoplasm of intrathoracic site NOS
XE1x5	Ca oesophagus NOS
B552.	Malignant tumour of abdomen
B063.	Malignant tumour of vallecula
B6151	Hodgkin's mixed cellularity of lymph nodes head, face, neck
Byu81	[X]Malignant neoplasm/overlapping lesion/male genital organs
X309D	Cystadenocarcinoma of pancreas
B4A10	Malignant tumour of renal calyx
B506.	Malignant tumour of choroid
B49y.	Malignant neoplasm of other site of urinary bladder
B222z	Malignant neoplasm of upper lobe, bronchus or lung NOS
B057.	Overlapping lesion of other and unspecified parts of mouth
B614z	Hodgkin's disease, nodular sclerosis NOS
B3115	Malignant neoplasm of connective and soft tissue of thumb
XE203	Secondary nodes NOS
B490.	Malignant tumour of trigone of urinary bladder
B3001	Malignant neoplasm of frontal bone
B055z	Malignant neoplasm of palate NOS
XE1va	Malignant tumour of middle ear and mastoid
Xa0bR	Malignant lymphoma of thyroid gland
Xa0eC	Erythraemia
B5000	Malignant tumour of ciliary body
X78gc	Malignant tumour of exocrine pancreas
X78l3	Metastasis to choroid
X78bc	Malignant melanoma of iris
B571.	Metastasis to mediastinum

B614.	Hodgkin's disease, nodular sclerosis
B6214	Mycosis fungoides of lymph nodes of axilla and upper limb
Xa99l	Malignant lymphoma - small lymphocytic
B58y1	Metastasis to uterus
XaZdF	Follicular lymphoma grade 2
X78l7	Secondary carcinoma of other specified sites
B012.	Malignant neoplasm of tongue, tip and lateral border
XaA0C	Adenocarcinoma of ileum
B31z0	Kaposi's sarcoma of soft tissue
B3060	Malignant neoplasm of ilium
XaBAo	Linitis plastica
XaFrK	Local recurrence of malignant tumour of kidney
XaOrB	Siewert type III adenocarcinoma
X78Wz	Malignant granulosa cell tumour of ovary
B12z.	Malignant neoplasm of small intestine NOS
B171.	Malignant tumour of body of pancreas
XE20R	Leukaemia: [lymphoid][monocytic][myeloid][specif cell type]
B161.	Malignant tumour of extrahepatic bile duct
B103.	Malignant tumour of upper third of oesophagus
XaOrV	Siewert type I adenocarcinoma
Xa3rj	Secondary carcinoma NOS
B180.	Malignant retroperitoneal tumour
B6135	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg
B411.	Malignant neoplasm of exocervix
B410.	Malignant neoplasm of endocervix
B5001	Malignant tumour of iris
XE1zn	Ca kidney/urinary organs NOS
X78eg	Carcinoma of genitourinary organ
Byu9.	[X]Malignant neoplasm of urinary tract
Byu1.	[X]Malignant neoplasm of digestive organs
XaabR	Bowel scope (flexible sigmoidoscopy) screen: cancer detected
X78ej	Carcinoma of lip, oral cavity and pharynx
X78l1	Metastasis to eye
B545z	Malignant neoplasm of aortic body or paraganglia NOS
X78cT	Medullary thyroid carcinoma
X78ek	Malignant tumour of oral cavity, lips, salivary glands
B56..	(Lymph node metast) or (sec unsp malig neop lymph nodes)
B48z.	Malignant neoplasm of penis and other male genital organ NOS
B55y0	Malignant neoplasm of back NOS
B505.	Malignant tumour of retina
B451.	Malignant neoplasm of labia majora
X78Q1	Adenoid cystic carcinoma of trachea
X00ZB	Malignant melanoma of eyelid
B3400	Malignant neoplasm of nipple of female breast
X78b0	Adenoid cystic carcinoma of lacrimal gland
B522.	Malignant tumour of spinal cord
X78Wh	Malignant epithelial tumour of ovary
Xa9Je	Metastasis to intrathoracic lymph node
Xa0U5	Malignant lymphoma of testis
B6200	Nodular lymphoma of unspecified site
Xa3BL	Metastasis to ovary of unknown primary
XE1zR	Ca cervix uteri - exocervix
Xa0ik	Malignant infiltration of soft tissue
B480.	Malignant tumour of foreskin
B31y.	Malig neop connective and soft tissue other specified site
B3104	Malignant neoplasm of tarsus of eyelid
B4303	Malignant neoplasm of myometrium of corpus uteri

XaYj4	Acute myeloid leukaemia with myelodysplasia-related changes
B491.	Malignant tumour of vault of bladder
B5502	Malignant neoplasm of nose NOS
B563.	Secondary and unspec malig neop axilla and upper limb LN
Xa3AG	Metastasis to spleen of unknown primary
B114.	Malignant tumour of body of stomach
B57..	Secondary malign neoplasm of resp &/or digest syst (& carc)
Byu8.	[X]Malignant neoplasm of male genital organs
B591.	Other malignant neoplasm NOS
B106.	Malignant neoplasm, overlapping lesion of oesophagus
XE1wl	(Ca lip, oral, pharynx) or (oral carcinomas)
XE1y3	Ca tail of pancreas
X78fN	Malignant tumour of nasal sinuses
B5505	Malignant neoplasm of supraclavicular fossa NOS
B14z.	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
B300.	Malignant neoplasm of bones of skull and face
Xa3Bb	Metastasis to adrenal gland of unknown primary
B503.	Malignant tumour of conjunctiva
B222.	Malig neopl of upper lobe/bronchus/lung: (& [Pancoast synd])
B1110	Malignant neoplasm of prepylorus of stomach
B67y.	Other and unspecified leukaemia
B483.	Malignant neoplasm of penis, part unspecified
B304z	Malig neop of scapula and long bones of upper arm NOS
B493.	Malignant neoplasm of anterior wall of urinary bladder
XM0pv	Secondary malignant neoplasm of unknown site
B054.	Malignant tumour of uvula
XE1vm	Secondary malig neop of respiratory and digestive systems
B5420	Malignant tumour of pituitary gland
B5504	Malignant neoplasm of neck NOS
XaFr4	Local recurrence of malignant tumour of tongue
B4510	Malignant neoplasm of greater vestibular (Bartholin's) gland
B060z	Malignant neoplasm tonsil NOS
B0z0.	Malignant neoplasm of pharynx unspecified
B223.	Malignant neoplasm of middle lobe, bronchus or lung
B031.	Malignant tumour of lower gingiva
Xa97u	Malignant tumour of soft tissue of shoulder
Byu2.	[X]Malignant neoplasm of respiratory and intrathoracic orga
Xa3BX	Metastasis to bladder of unknown primary
XE205	(Sec Ca sp site) or (metast sp site) or (sec Ca known site)
B430.	Malignant neoplasm of corpus uteri, excluding isthmus
B18y5	Malignant neoplasm of pelvic peritoneum
B2...	Malign neopl resp tract and intrathor organs (& [carcinoma])
XaQbT	Poikiloderma vasculare atrophicans
B68..	Leukaemia of unspecified cell type
B3040	Malignant neoplasm of scapula
B5810	Metastasis to ureter
B061.	Malignant tumour of tonsillar fossa
ByuD.	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
X78IG	Carcinoma of anterior part of floor of mouth
B2211	Malignant neoplasm of hilus of lung
Xa97s	Malignant tumour of soft tissue
B2001	Malignant neoplasm of nasal conchae
B48..	Malignant neoplasm of penis and other male genital organs
B122.	Malignant tumour of ileum
B111.	Malignant tumour of pylorus
XaELM	Teratoma of undescended testis
B1111	Malignant neoplasm of pyloric canal of stomach

B525.	Malignant neoplasm of cauda equina
B2133	Malignant neoplasm of thyroid cartilage
B3113	Malignant neoplasm of connective and soft tissue of hand
XE1x3	Ca lower third oesophagus
B34yz	Malignant neoplasm of other site of female breast NOS
B30..	Malig neopl bone and artic cartilag (& [chondroma][osteoma])
B59..	Malignant neoplasm of unspecified site
B450z	Malignant neoplasm of vagina NOS
B576z	Secondary malig neop of retroperitoneum or peritoneum NOS
B082.	Malignant tumour aryepiglottic fold - hypopharyngeal aspect
Byu90	[X]Malignant neoplasm of urinary organ, unspecified
B61z3	Hodgkin's disease NOS of intra-abdominal lymph nodes
X78kd	Metastasis to pancreas
B06z.	Malignant neoplasm of oropharynx NOS
B541.	Malignant tumour of parathyroid gland
XaYin	Cutaneous follicle centre lymphoma
X78bM	Squamous cell carcinoma of conjunctiva
B300A	Malignant neoplasm of maxilla
B412.	Malignant neoplasm, overlapping lesion of cervix uteri
ByuA2	[X]Malignant neoplasm of meninges, unspecified
B61z1	Hodgkin's disease NOS of lymph nodes of head, face and neck
B553.	Malignant tumour of pelvis
X78N1	Carcinoma of pyloric antrum
X78Zc	Malignant tumour of urethral stump
B5450	Malignant neoplasm of glomus jugulare
X78IR	Carcinoma of hard palate
B6205	Nodular lymphoma of lymph nodes of inguinal region and leg
B5608	Secondary and unspec malig neop anterior cervical LN
X78Ib	Carcinoma of uvula
XaYgm	Primary mediastinal (thymic) large B-cell lymphoma
B453.	Malignant neoplasm of clitoris
B51y0	Malignant neoplasm of corpus callosum
B471.	Malignant neoplasm of descended testis
B564.	Secondary and unspec malig neop inguinal and lower limb LN
B452.	Malignant neoplasm of labia minora
B64yz	Other lymphoid leukaemia NOS
B574z	Secondary malig neop of small intestine or duodenum NOS
B07z.	Malignant neoplasm of nasopharynx NOS
Byu7.	[X]Malignant neoplasm of female genital organs
XE1y1	Ca body of pancreas
XE1zh	(Epidid carc) or (Ca epidid/spermat cord) or (sperm cord Ca)
B5750	Secondary malignant neoplasm of colon
XaYip	Sarcoma of dendritic cells
B138.	Malignant neoplasm, overlapping lesion of colon
X78Wn	Mixed epithelial tumour of ovary
B21y.	Malignant neoplasm of larynx, other specified site
B2210	Malignant neoplasm of carina of bronchus
B521z	Malignant neoplasm of cerebral meninges NOS
B5105	Malignant neoplasm of thalamus
B220z	Malignant neoplasm of trachea NOS
B220.	Malignant tumour of trachea
XaOqX	Siewert type II adenocarcinoma
B4300	Malignant neoplasm of cornu of corpus uteri
X78l2	Metastasis to orbit
X309C	Malignant cystic tumour of exocrine pancreas
XaJM3	Osteosarcoma - disorder
B6276	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma

B431.	Malignant neoplasm of isthmus of uterine body
B056.	Malignant tumour of retromolar area
Xa0Di	Malignant melanoma of anus
Xa3AF	Metastasis to pancreas of unknown primary
B3070	Malignant neoplasm of femur
XE1wg	[X]Mesothelioma of other sites
Xa0Sk	Acute myeloblastic leukaemia
XE2vN	Malignant neoplasm of common bile duct
B583.	Secondary malignant neoplasm of brain and spinal cord
B600.	Reticulosarcoma
B1611	Malignant neoplasm of hepatic duct
Xa0S9	T-cell prolymphocytic leukaemia
ByuB.	[X]Malignant neoplasm of thyroid and other endocrine glands
B100.	Malignant tumour of cervical part of oesophagus
Xa3A7	Metastasis to heart of unknown primary
X78kb	Metastasis to gastrointestinal tract
B08z.	Malignant neoplasm of hypopharynx NOS
X78Yz	Papillary cystadenocarcinoma of kidney
B3031	Malignant neoplasm of sternum
X78kV	Metastasis to bronchus
B3101	Malignant tumour of soft tissue of face
B111z	Malignant neoplasm of pylorus of stomach NOS
B59z.	Malignant neoplasm of unspecified site NOS
B3071	Malignant neoplasm of fibula
X78e6	Malignant tumour of spleen
Xa0Tr	Peripheral T-cell lymphoma - pleomorphic small cell
B3030	Malignant neoplasm of rib
B104.	Malignant tumour of middle third of oesophagus
B203.	Malignant tumour of ethmoid sinus
B6140	Hodgkin's disease, nodular sclerosis of unspecified site
B6133	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node
Xa9AO	Chronic leukaemia
X78g2	Malignant tumour of oesophagus, stomach and duodenum
B482.	Malignant tumour of body of penis
B320.	Malignant melanoma of lip
X78ky	Metastasis to pituitary
B561.	Secondary and unspec malig neop intrathoracic lymph nodes
B3123	Malig neop of connective and soft tissue of lower leg
B6210	Mycosis fungoides of unspecified site
B55yz	Malignant neoplasm of specified site NOS
B6021	Burkitt's lymphoma of lymph nodes of head, face and neck
B14y.	Malig neop other site rectum, rectosigmoid junction and anus
XaB47	Atypical hairy cell leukaemia
B540z	Malignant neoplasm of adrenal gland NOS
B212.	Malignant tumour of subglottis
B2231	Malignant neoplasm of middle lobe of lung
B653z	Myeloid sarcoma NOS
B5531	Malignant neoplasm of presacral region
B161z	Malignant neoplasm of extrahepatic bile ducts NOS
B151.	Malignant neoplasm of intrahepatic bile ducts
XE1zp	(Carcinoma brain) or (brain Ca) or (cerebral tumour - malig)
XaELJ	Seminoma of undescended testis
B1100	Malignant neoplasm of cardiac orifice of stomach
X78IW	Carcinoma of soft palate
B3124	Malignant neoplasm of connective and soft tissue of foot
B064.	Malignant neoplasm of anterior epiglottis
B021.	Malignant tumour of submandibular gland

XE1vS	Malignant tumour of lesser curve of stomach
B6274	Malignant lymphoma - small cleaved cell
Xa97p	Malignant tumour of anterior two-thirds of tongue
B2000	Malignant neoplasm of cartilage of nose
X78WQ	Cancer en cuirasse
B16y.	Malignant neoplasm other gallbladder/extrahepatic bile duct
B5103	Malignant neoplasm of globus pallidus
B1zy.	Malignant neoplasm other spec digestive tract and peritoneum
ByuD0	[X]Other Hodgkin's disease
B16z.	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
B680.	Acute leukaemia NOS
B3100	Malignant tumour of soft tissue of head
B18y.	Malignant neoplasm of specified parts of peritoneum
XaFrz	Metastasis from malignant tumour of tongue
B6130	Hodgkin's, lymphocytic-histiocytic predominance unspec site
B15..	Malignant neoplasm of liver and intrahepatic bile ducts
Xa0TY	Low grade T-cell lymphoma
X78NG	Carcinoma of greater curve of stomach
Xa0Ro	Richter's syndrome
B2240	Malignant neoplasm of lower lobe bronchus
B1511	Malignant neoplasm of interlobular biliary canals
B346.	Malignant neoplasm of axillary tail of female breast
B23z.	Malignant neoplasm of pleura NOS
B661.	Chronic monocytic leukaemia
B5654	Secondary and unspec malig neop obturator lymph nodes
XaC2J	Malignant neoplasm of lip, unspecified
B67z.	Other specified leukaemia NOS
B6020	Burkitt's lymphoma of unspecified site
B592.	Malignant neoplasms of independent (primary) multiple sites
B080.	Malignant tumour of postcricoid region
B581.	Secondary malignant neoplasm of other urinary organs
B51y.	Malignant neoplasm of other parts of brain
Xa9A0	Nephroblastoma
Byu12	[X]Malignant neoplasm of intestinal tract, part unspecified
B5503	Malignant neoplasm of jaw NOS
Byu70	[X]Malignant neoplasm of uterine adnexa, unspecified
X77nj	Klatskin's tumour
X78kg	Metastasis to soft tissue
B18z.	Malignant neoplasm of retroperitoneum and peritoneum NOS
B5613	Secondary and unspec malig neop ant mediastinal lymph nodes
B016.	Malignant tumour of lingual tonsil
Byu82	[X]Malignant neoplasm of male genital organ, unspecified
B05..	Malignant neoplasm of other and unspecified parts of mouth
B066.	Malignant neoplasm of lateral wall of oropharynx
B013z	Malignant neoplasm of ventral tongue surface NOS
B6y..	Malignant neoplasm lymphatic or haematopoietic tissue OS
B10y.	Malignant neoplasm of other specified part of oesophagus
B410z	Malignant neoplasm of endocervix NOS
B64y.	Other lymphoid leukaemia
B01y.	Malignant neoplasm of other sites of tongue
B15z.	Malignant neoplasm of liver and intrahepatic bile ducts NOS
B3122	Malig neop connective and soft tissue of popliteal space
X78OX	Malignant tumour of anorectal junction
Xa99n	Diffuse malignant lymphoma - centroblastic
X78XB	Embryonal carcinoma of ovary
X30L8	Lymphoma of kidney
X78ca	Adrenal carcinoma

X78ap	Malignant tumour of acoustic vestibular nerve
B48y0	Malignant tumour of seminal vesicle
XE1xD	Ca Body - stomach
B517z	Malignant neoplasm of brainstem NOS
XE2vi	Acute erythraemia and erythroleukaemia
B544.	Malignant neoplasm of carotid body
XaYis	Atypical chronic myeloid leukaemia, BCR/ABL negative
X78kX	Secondary lymphangitic carcinoma
B660.	Acute monocytic leukaemia
B64y2	Adult T-cell leukaemia
B55y1	Malignant neoplasm of trunk NOS
B5501	Malignant neoplasm of cheek NOS
B5100	Malignant neoplasm of basal ganglia
B5510	Malignant neoplasm of axilla NOS
XM1FE	Combined hepatocellular carcinoma and cholangiocarcinoma
B6011	Lymphosarcoma of lymph nodes of head, face and neck
Xa3AK	Metastasis to vertebral column of unknown primary
B223z	Malignant neoplasm of middle lobe, bronchus or lung NOS
B560.	Secondary and unspec malig neop lymph nodes head/face/neck
B022.	Malignant tumour of sublingual gland
B055.	Malignant neoplasm of palate unspecified
B510.	Malignant neoplasm cerebrum (excluding lobes and ventricles)
B004.	Malignant neoplasm of lip unspecified, inner aspect
B35z.	Malignant neoplasm of other site of male breast
XE1vr	Chronic erythraemia
B5640	Secondary and unspec malig neop superficial inguinal LN
XaYeq	Secondary malignant neoplasm of liver intrahepatic bile duct
Xa0bb	Endometrioid carcinoma of prostate
B06yz	Malignant neoplasm of other specified site of oropharynx NOS
B06y.	Malignant neoplasm of oropharynx, other specified sites
B451z	Malignant neoplasm of labia majora NOS
XaEY9	Malignant neoplasm of mesentery
B562z	Secondary and unspec malig neop intra-abdominal LN NOS
B3150	Malignant neoplasm of connective and soft tissue of buttock
B573.	Secondary malignant neoplasm of other respiratory organs
B512z	Malignant neoplasm of temporal lobe NOS
B25..	Malig neo, overlapping lesion of heart, mediastinum & pleura
X78kf	Metastasis to bone marrow
B03z.	Malignant neoplasm of gum NOS
B6208	Nodular lymphoma of lymph nodes of multiple sites
B224z	Malignant neoplasm of lower lobe, bronchus or lung NOS
Xa0T7	Malignant lymphomatous polyposis
Byu71	[X]Malignant neoplasm/other specified female genital organs
B062z	Malignant neoplasm of tonsillar fossa NOS
X78Wy	Malignant sex cord tumour of ovary
B23..	Malignant tumour of pleura
B347.	Malignant neoplasm, overlapping lesion of breast
ByuC.	[X]Malignant neoplasm of ill-defined, secondary and unspeci
B306z	Malignant neoplasm of pelvis, sacrum or coccyx NOS
B5751	Secondary malignant neoplasm of rectum
XaYi5	Diffuse follicle centre lymphoma
B0z..	Malig neop other/ill-defined sites lip, oral cavity, pharynx
B05y.	Malignant neoplasm of other specified mouth parts
B41yz	Malignant neoplasm of other site of cervix NOS
B622.	Sezary's disease
B302z	Malignant neoplasm of vertebral column NOS
B205.	Malignant tumour of sphenoid sinus

XE1x9	Ca pylorus - stomach
B64z.	Lymphoid leukaemia NOS
XE1vT	Malignant tumour of greater curve of stomach
Xa0TZ	High grade T-cell lymphoma
B66..	Monocytic leukaemia
B6131	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
B5812	Metastasis to urethra
B5511	Malignant neoplasm of chest wall NOS
ByuD4	[X]Other malignant immunoproliferative diseases
Xa3eT	Carcinoma of genital organs NOS
B504.	Malignant tumour of cornea
B4A11	Malignant tumour of pelviureteric junction
B562.	Secondary and unspec malig neop intra-abdominal lymph nodes
B576.	Secondary malig neop of retroperitoneum and peritoneum
Byu73	[X]Malignant neoplasm of female genital organ, unspecified
X78MW	Carcinoma of upper third of oesophagus
B487.	Malignant neoplasm, overlapping lesion of penis
ByuD2	[X]Other types of diffuse non-Hodgkin's lymphoma
Xa3BG	Metastasis to soft tissue of unknown primary
B3102	Malignant tumour of soft tissue of neck
X78bk	Malignant melanoma of ciliary body
B6207	Nodular lymphoma of spleen
B61z7	Hodgkin's disease NOS of spleen
XaYj0	Chronic myelogenous leukaemia, BCR/ABL positive
X78g0	Carcinoma of respiratory tract and intrathoracic organs
B3z..	Malig neop of bone, connective tissue, skin and breast NOS
B45y0	Malignant neoplasm of overlapping lesion of vulva
B304.	Malignant neoplasm of scapula and long bones of upper arm
B612.	Hodgkin's sarcoma
B11yz	Malignant neoplasm of other specified site of stomach NOS
B3103	Malignant neoplasm of cartilage of ear
B521.	Malignant neoplasm of cerebral meninges
B312.	Malig neop of connective and soft tissue of hip and leg
B316.	Malig neop of connective and soft tissue trunk unspecified
B04z.	Malignant neoplasm of floor of mouth NOS
B5y..	Malignant neoplasm of other and unspecified site OS
B030.	Malignant tumour of upper gingiva
X78Lx	Malignant tumour of laryngeal ventricle
Xa0Tj	Lymphoepithelioid lymphoma
XE1xZ	Ca splenic flexure - colon
B6165	Hodgkin's lymphocytic depletion lymph nodes inguinal and leg
B201.	Malig neop auditory tube, middle ear and mastoid air cells
B50y.	Malignant neoplasm of other specified site of eye
B5623	Secondary and unspec malig neop common iliac lymph nodes
B062.	Malignant tumour of tonsillar pillar
Xa0Dd	Lymphoma of intestine
B55y.	Malignant neoplasm of other specified sites
B1zz.	Malignant neoplasm of digestive tract and peritoneum NOS
B3112	Malignant neoplasm of connective and soft tissue of fore-arm
B6273	Diffuse malignant lymphoma - small non-cleaved cell
B116.	Malignant neoplasm of greater curve of stomach unspecified
B4z..	Malignant neoplasm of genitourinary organ NOS
X78kn	Metastasis to female genital organ
X78Oz	Sarcoma of liver
B1z1z	Malignant neoplasm of spleen NOS
B124.	Malignant neoplasm, overlapping lesion of small intestine
B5003	Malignant neoplasm of sclera

	X78kc	Metastasis to small intestine
	X78QR	Lymphomatoid granulomatosis of lung
	B221z	Malignant neoplasm of main bronchus NOS
	B674.	Acute panmyelosis
	XM00E	Malignant tumour of lower labial mucosa
	B555.	Malignant neoplasm of lower limb NOS
	B6010	Lymphosarcoma of unspecified site
	B431z	Malignant neoplasm of isthmus of uterine body NOS
	XaYjf	Subcutaneous panniculitic T-cell lymphoma
	Xa0SH	T-cell acute lymphoblastic leukaemia
	B017.	Malignant overlapping lesion of tongue
	B5622	Secondary and unspec malig neop inferior mesenteric LN
	B520z	Malignant neoplasm of cranial nerves NOS
	XaFrG	Local recurrence of malignant tumour of liver
	B3153	Malig neopl of connective and soft tissue - sacrum or coccyx
	B20z.	Malignant neoplasm of accessory sinus NOS
	B6241	Leukaemic reticuloend of lymph nodes of head, face and neck
	B6510	Chronic eosinophilic leukaemia
	B6123	Hodgkin's sarcoma of intra-abdominal lymph nodes
	B5605	Secondary and unspec malig neop submandibular lymph nodes
	B3000	Malignant neoplasm of ethmoid bone
	B0010	Malignant neoplasm of lower lip, external
	B350.	Malignant neoplasm of nipple and areola of male breast
	B12y.	Malignant neoplasm of other specified site small intestine
	B2131	Malignant neoplasm of cricoid cartilage
	Xa0SX	Atypical chronic myeloid leukaemia
	X78aB	Pituitary carcinoma
	B163.	Malignant neoplasm, overlapping lesion of biliary tract
	XE1yV	Ca skull/face/jaw bone
	X78WS	Familial cancer of breast
	B510z	Malignant neoplasm of cerebrum NOS
	X78Pf	Malignant tumour of endocrine pancreas
	Byu72	[X]Malignant neoplasm/overlapping lesion/feml genital organs
	X78b3	Mucoepidermoid tumour of lacrimal gland
Cerebrovascular disease	XE0VK	Transient ischaemic attack
	XaEGq	Stroke NOS
	X00D1	Cerebrovascular accident
	XaAsI	Referral to stroke service
	662M.	Stroke monitoring
	XaJYc	Referral to stroke clinic
	XaJkS	Stroke / transient ischaemic attack referral
	14AB.	H/O: TIA
	XaAsJ	Admission to stroke unit
	G65z.	Transient cerebral ischaemia NOS
	XaJ4b	Excepted from stroke quality indicators: Patient unsuitable
	XaJ4c	Excepted from stroke quality indicators: Informed dissent
	XaJwA	Stroke/transient ischaemic attack monitoring status
	X00DA	Lacunar infarction
	G6...	Cerebrovascular disease
	X00DI	Haemorrhagic cerebral infarction
	XaKSH	Haemorrhagic stroke monitoring
	XE2te	H/O: CVA/stroke
	XSAbR	Stroke rehabilitation
	G66..	CVA - cerebrovascular accident (& unspecified [& stroke])
	XaLKH	Seen in stroke clinic
	XaIzF	Stroke annual review

XE2aB	Stroke and cerebrovascular accident unspecified
XE0X2	(Cereb infarc)(cerebrovas acc)(undef stroke/CVA)(stroke NOS)
XM1R3	H/O: stroke
XA0BD	Traumatic subdural haematoma
G634.	Carotid artery stenosis
XaAsR	Seen by stroke service
G667.	Left sided cerebral hemisphere cerebrovascular accident
X00D7	Partial anterior cerebral circulation infarction
F4236	Amaurosis fugax
X00DR	Stroke of uncertain pathology
G640.	Cerebral thrombosis
14A7.	H/O: CVA &/or stroke
XaJDX	Did not attend stroke clinic
G6711	Chronic cerebral ischaemia
X00D6	Total anterior cerebral circulation infarction
S620.	Haemorrh: [closed traum subarach] or [mid mening follow inj]
XM1R2	H/O: CVA
X003j	Vascular parkinsonism
X00DT	Posterior circulation stroke of uncertain pathology
G61..	Intracerebral haemorrhage (& [cerebrovasc accident due to])
G664.	Cerebellar stroke syndrome
XE0VF	Cerebral parenchymal haemorrhage
S628.	Traumatic subdural haemorrhage
XaBL3	H/O: Stroke in last year
XaJi5	Ref to multidisciplinary stroke function improvement service
G65y.	Other transient cerebral ischaemia
X00DS	Anterior circulation stroke of uncertain pathology
G64..	Cereb art occl (& [cerebvasc acc][stroke]) or (cereb infarc)
XA0BH	Traumatic subarachnoid haemorrhage
XaKba	Stroke/transient ischaemic attack monitoring verbal invitati
XE0VL	Cerebral atherosclerosis
Gyu6C	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
XE2w4	Non-traumatic subdural haematoma
XaLtA	Delivery of rehabilitation for stroke
XaR8M	Did not attend stroke review
XaKcm	Stroke/transient ischaemic attack monitoring invitation
XaMGv	Stroke/transient ischaemic attack monitoring telephone invte
XaJuX	Stroke/transient ischaemic attack monitoring second letter
XaJuY	Stroke/transient ischaemic attack monitoring third letter
G663.	Brainstem stroke syndrome
Xa0Ml	Central post-stroke pain
G65z1	Intermittent cerebral ischaemia
XE0X0	(Trans isch attacks) or (vert-basil insuf) or (drop attacks)
XaR68	Stroke 6 month review
XA0BE	Traumatic intracranial subdural haematoma
G621.	Subdural haemorrhage - nontraumatic
XE1m2	Traumatic intracranial haemorrhage
XA0BI	Traumatic intracranial subarachnoid haemorrhage
S622.	Closed traumatic subdural haemorrhage
XA0BG	Traumatic intracerebral haemorrhage
Xa1hE	Extension of cerebrovascular accident
X00E5	Spinal cord stroke
Xa1uU	Non-traumatic intracranial subdural haematoma
XE1m3	Closed traumatic subarachnoid haemorrhage
G670.	Atherosclerosis: [precerebral] or [cerebral]
G682.	Sequelae of other non-traumatic intracranial haemorrhage
XaFsk	Traumatic subdural haematoma without open intracranial wound

Chronic kidney disease	XaLHl	Chronic kidney disease stage 3
	XaO3w	Chronic kidney disease stage 3A without proteinuria
	XaO3t	Chronic kidney disease stage 3 with proteinuria
	XaNbo	Chronic kidney disease stage 3B
	XaO3u	Chronic kidney disease stage 3 without proteinuria
	4677	Urine protein test = ++++
	XaO3y	Chronic kidney disease stage 3B without proteinuria
	XaO3z	Chronic kidney disease stage 4 with proteinuria
	XaLFm	Except chronic kidney disease qual indic: Patient unsuitable
	XaMGE	Chronic kidney disease annual review
	XaLHJ	Chronic kidney disease stage 4
	XaO40	Chronic kidney disease stage 4 without proteinuria
	XaO3v	Chronic kidney disease stage 3A with proteinuria
	XaNbn	Chronic kidney disease stage 3A
	XaIyz	Diabetes mellitus with persistent microalbuminuria
	XaIzR	Type II diabetes mellitus with persistent microalbuminuria
	XaIz0	Diabetes mellitus with persistent proteinuria
	X30In	Chronic renal impairment
	R110.	[D]Proteinuria
	XaO3x	Chronic kidney disease stage 3B with proteinuria
	XaLHK	Chronic kidney disease stage 5
	XaO41	Chronic kidney disease stage 5 with proteinuria
	XaIzQ	Type II diabetes mellitus with persistent proteinuria
	C1090	Type II diabetes mellitus with renal complications
	C104.	Diabetes mellitus: [with renal manifestatn] or [nephropathy]
	K05..	Renal failure: [chronic] or [end stage]
	XaO42	Chronic kidney disease stage 5 without proteinuria
	XaLFn	Exc chronic kidney disease quality indicators: Inform dissen
	C104z	Diabetes mellitus with nephropathy NOS
	XaXTz	H/O: chronic kidney disease
	PD13.	Multicystic kidney
	C1093	Type II diabetes mellitus with multiple complications
	XaF05	Type II diabetes mellitus with nephropathy
	C1080	Type I diabetes mellitus with renal complications
	XE10G	Diabetes mellitus with renal manifestation
	XaF04	Type I diabetes mellitus with nephropathy
	XaIzM	Type 1 diabetes mellitus with persistent proteinuria
	XaIzN	Type 1 diabetes mellitus with persistent microalbuminuria
	C104y	Other specified diabetes mellitus with renal complications
Chronic obstructive pulmonary disease	H3...	Chronic obstructive lung disease
	XaYZO	COPD self-management plan review
	Xa35l	Acute infective exacerbation chronic obstruct airway disease
	XaElY	Severe chronic obstructive pulmonary disease
	H3122	Acute exacerbation of chronic obstructive airways disease
	XaElW	Moderate chronic obstructive pulmonary disease
	XaElV	Mild chronic obstructive pulmonary disease
	XaZd1	Acute non-infective exacerbation of COPD
	X101i	Chron obstruct pulmonary dis wth acute exacerbation, unspec
	XaXCb	Chronic obstructive pulmonary disease 6 monthly review
	XaXCa	Chronic obstructive pulmonary disease 3 monthly review
	H3z..	Chronic obstructive airways disease NOS
	XaZoz	Seen in chronic obstructive pulmonary disease clinic
	Hyu31	[X]Other specified chronic obstructive pulmonary disease

	XaY0w	Referral to COPD community nursing team
	H312z	Obstructive chronic bronchitis NOS
	XaJFu	Admit COPD emergency
	XaIND	End stage chronic obstructive airways disease
	XaN4a	Very severe chronic obstructive pulmonary disease
	H3y0.	Chronic obstruct pulmonary dis with acute lower resp infectn
	XaZp7	Chronic obstructive pulmonary disease rescue pack declined
	XaZ6U	On chronic obstructive pulmonary disease supprtv cre pathway
	H3y..	Other specified chronic obstructive airways disease
Cirrhosis	XE0b4	Alcoholic cirrhosis of liver
	X307L	Cirrhosis of liver
	J6160	Primary biliary cirrhosis
	X307M	Cirrhosis of liver NOS
	X307O	Cryptogenic cirrhosis
	J6617	Primary sclerosing cholangitis
	XE0b5	Cirrhosis - non-alcoholic
	X307W	Fibrosis of liver
	J616.	Biliary cirrhosis
	J615.	(Cirrhosis - non alcoholic) or (portal cirrhosis)
	J6155	Macronodular cirrhosis
	J61..	Cirrhosis and chronic liver disease
	J615z	(Liver cirrhos: [named vars] or [NOS]) or (hepat fibrosis)
	J612.	Cirrhosis: [florid] or [alcoholic]
	X307Q	Micronodular cirrhosis
	XE0bA	Non-alcoholic cirrhosis NOS
	Xa9C7	Cardiac cirrhosis
	XaC1d	Oesophageal varices in alcoholic cirrhosis of the liver
	J616z	Biliary cirrhosis NOS
	X307Z	Hepatic sclerosis
	XE0dJ	Biliary cirrhosis (& [primary])
	XaBM6	Oesophageal varices in cirrhosis of the liver
	X307b	Hepatic fibrosis with hepatic sclerosis
	X307X	Congenital hepatic fibrosis
	J615H	Infectious cirrhosis NOS
	X3072	Alcoholic fibrosis and sclerosis of liver
	J615y	Portal cirrhosis unspecified
	J6356	Toxic liver disease with fibrosis and cirrhosis of liver
	X3073	Alcoholic hepatic failure
	X307R	Portal cirrhosis
	J6161	Secondary biliary cirrhosis
	J6152	Mixed portal cirrhosis
	J6153	Diffuse nodular cirrhosis
	J6150	Unilobular portal cirrhosis
Deep vein thrombosis	Xa9Bs	Deep vein thrombosis of lower limb
	14A81	H/O: Deep Vein Thrombosis
	X205n	Ileofemoral deep vein thrombosis
	XaBMc	[V] Personal history deep vein thrombosis
	L413.	Antenatal deep vein thrombosis
	Xacvd	Unprovoked deep vein thrombosis
	SP122	Postoperative deep vein thrombosis
	XE0xL	Postnatal deep vein thrombosis
	XE0XS	(Deep ven thromb leg)(nonpuer milk-leg)(deep thrombophl leg)
	L414.	DVT: [postnatal] or [obstetric phlegmasia alba dolens]
	XaaBG	On deep vein thrombosis care pathway
	XaQIV	Deep venous thrombosis of peroneal vein
	XaZ43	Recurrent deep vein thrombosis

	L4140	Postnatal deep vein thrombosis unspecified
	L414z	Postnatal deep vein thrombosis NOS
	Xacve	Provoked deep vein thrombosis
	L4130	Antenatal deep vein thrombosis unspecified
	XaIlo	Deep vein thrombosis of leg related to air travel
	L4131	Antenatal deep vein thrombosis - delivered
	XaJxo	Deep vein thrombosis of leg related to intravenous drug use
	X205m	Lower venous segment thrombosis
	X76Lh	Phlegmasia caerula dolens
	L413z	Antenatal deep vein thrombosis NOS
	L4142	Postnatal deep vein thrombosis with postnatal complication
	Xa1aj	Phlegmasia alba dolens - obstetric
	L4132	Antenatal deep vein thrombosis with antenatal complication
Diabetes	XaMFF	Referral for diabetic retinopathy screening
	66A4.	Diabetic on oral treatment
	Y3579	Diabetic review
	66A..	Diabetic monitoring
	X40J5	Type II diabetes mellitus
	66AS.	Diabetic annual review
	C10..	Diabetes mellitus
	XaIlj	Diabetic retinopathy screening
	XaJO9	Under care of diabetic foot screener
	XaJYg	Diabetes clinical management plan
	9OL1.	Attends diabetes monitoring
	XaIyt	Diabetic peripheral neuropathy screening
	XaBLn	Self-monitoring of blood glucose
	XaJ4Q	Exception reporting: diabetes quality indicators
	XaJ5j	Patient on maximal tolerated therapy for diabetes
	66AD.	Fundoscopy - diabetic check
	F420.	Diabetic retinopathy
	XaKwQ	Diabetic 6 month review
	C101.	Diabetic ketoacidosis
	XaPQH	Diabetic foot screen
	F4200	Background diabetic retinopathy
	XaIuE	Diabetic foot examination
	XaJLa	Diabetic retinopathy 12 month review
	66A5.	Diabetic on insulin
	C100.	Diabetes mellitus with no mention of complication
	XaE46	Referral to diabetes nurse
	XaELQ	Type II diabetes mellitus without complication
	XaE5c	Diabetic macular oedema
	XaJ4i	Excepted from diabetes quality indicators: Informed dissent
	C1001	Diab mell: [adult ons, no ment comp][mat onset][non-ins dep]
	C1097	Type II diabetes mellitus - poor control
	XaJK3	Diabetic medicine
	XaIP5	Non proliferative diabetic retinopathy
	XaJOi	O/E - right eye preproliferative diabetic retinopathy
	XaXZR	H/O: diabetes mellitus type 2
	XaJOk	O/E - right eye proliferative diabetic retinopathy
	XaE5V	Severe non proliferative diabetic retinopathy
	XaJOj	O/E - left eye preproliferative diabetic retinopathy
	XaE5U	Moderate non proliferative diabetic retinopathy
	XaIyz	Diabetes mellitus with persistent microalbuminuria
	XaJLb	Diabetic retinopathy 6 month review
	XaXZv	H/O: diabetes mellitus type 1
	X40J6	Insulin treated Type 2 diabetes mellitus
	XE1T3	Diabetic - poor control

66AH0	Conversion to insulin
66AZ.	Diabetic monitoring NOS
XaE5T	Mild non proliferative diabetic retinopathy
XaJ4h	Excepted from diabetes qual indicators: Patient unsuitable
F4640	Diabetic cataract
XaIzR	Type II diabetes mellitus with persistent microalbuminuria
XE12M	Diabetes with other complications
42W3.	Hb. A1C > 10% - bad control
66AR.	Diabetes management plan given
XaKT5	Diabetic patient unsuitable for digital retinal photography
XaCES	HbA1 - diabetic control
XaIz0	Diabetes mellitus with persistent proteinuria
Y1286	Diabetic Clinic
C106.	Diab mell + neuro manif: (& [amyotroph][neurop][polyneurop])
XaIIe	Diabetes care by hospital only
XaFn8	Type II diabetes mellitus with arthropathy
XaIzQ	Type II diabetes mellitus with persistent proteinuria
XaIeK	O/E - Left diabetic foot - ulcerated
X40J4	Type I diabetes mellitus
C1090	Type II diabetes mellitus with renal complications
C104.	Diabetes mellitus: [with renal manifestatn] or [nephropathy]
C1096	Type II diabetes mellitus with retinopathy
F3721	Chronic painful diabetic neuropathy
X00Ah	Diabetic distal sensorimotor polyneuropathy
XE12A	Diabetes mellitus: [adult onset] or [noninsulin dependent]
F1711	Diabetic autonomic neuropathy
C1087	Type I diabetes mellitus with retinopathy
C1010	Type 1 diabetes mellitus with ketoacidosis
F420z	Diabetic retinopathy NOS
C1094	Type II diabetes mellitus with ulcer
F3720	Acute painful diabetic neuropathy
XaFmA	Type II diabetes mellitus with diabetic cataract
C104z	Diabetes mellitus with nephropathy NOS
XaXbW	Symptomatic diabetic peripheral neuropathy
XE128	Diabetes mellitus (& [ketoacidosis])
XE10F	Diabetes mellitus, adult onset, no mention of complication
F3722	Asymptomatic diabetic neuropathy
XaKyX	Type II diabetes mellitus with gastroparesis
XE12G	Diabetes + eye manifestation (& [cataract] or [retinopathy])
C10B0	Steroid-induced diabetes mellitus without complication
M2710	Ischaemic ulcer diabetic foot
XaELP	Type I diabetes mellitus without complication
XE15k	Diabetic polyneuropathy
C1091	Type II diabetes mellitus with ophthalmic complications
XE10H	Diabetes mellitus with neurological manifestation
XaFn9	Type II diabetes mellitus with neuropathic arthropathy
XE12I	Diabetes + neuropathy (& [amyotrophy])
C1093	Type II diabetes mellitus with multiple complications
X40JJ	Diabetes mellitus autosomal dominant type 2
XaJQp	Type II diabetes mellitus with exudative maculopathy
F372.	Diabetic neuropathy &/or diabetic polyneuropathy
C1092	Type II diabetes mellitus with neurological complications
XaF05	Type II diabetes mellitus with nephropathy
C10y.	Diabetes mellitus with other specified manifestation
C1089	Type I diabetes mellitus maturity onset
C1061	Diabetes mellitus, adult onset, + neurological manifestation
XaEnq	Type II diabetes mellitus with polyneuropathy

	X00Al	Diabetic mononeuropathy
	C1088	Type I diabetes mellitus - poor control
	C1080	Type I diabetes mellitus with renal complications
	C100z	Diabetes mellitus NOS with no mention of complication
	C10zz	Diabetes mellitus NOS with unspecified complication
	XE10G	Diabetes mellitus with renal manifestation
	C106z	Diabetes mellitus NOS with neurological manifestation
	C102.	Diabetes mellitus with hyperosmolar coma
	C1011	Type 2 diabetes mellitus with ketoacidosis
	C105.	Diabetes mellitus with ophthalmic manifestation
	C1081	Type I diabetes mellitus with ophthalmic complications
	XaKyW	Type 1 diabetes mellitus with gastroparesis
	XaJSr	Type 1 diabetes mellitus with exudative maculopathy
	XaF04	Type I diabetes mellitus with nephropathy
	XE10I	Diabetes mellitus with peripheral circulatory disorder
	X00Aj	Diabetic chronic painful polyneuropathy
	XaIzM	Type 1 diabetes mellitus with persistent proteinuria
	XaIzN	Type 1 diabetes mellitus with persistent microalbuminuria
	C101z	Diabetes mellitus NOS with ketoacidosis
	X00Ai	Diabetic acute painful polyneuropathy
	C1095	Type II diabetes mellitus with gangrene
	C1083	Type I diabetes mellitus with multiple complications
	XaFWl	Type II diabetes mellitus with hypoglycaemic coma
	XaJUl	Diabetes mellitus induced by non-steroid drugs
	C102z	Diabetes mellitus NOS with hyperosmolar coma
	XaOPu	Latent autoimmune diabetes mellitus in adult
	Xa0lK	Diabetic (femoral mononeuropathy) & (Diabetic amyotrophy)
	C104y	Other specified diabetes mellitus with renal complications
	C107z	Diabetes mellitus NOS with peripheral circulatory disorder
	XaFm8	Type I diabetes mellitus with diabetic cataract
	XaEnp	Type II diabetes mellitus with mononeuropathy
	C105z	Diabetes mellitus NOS with ophthalmic manifestation
	C1082	Type I diabetes mellitus with neurological complications
	C107.	Diabetes mellitus with: [gangrene] or [periph circul disord]
	C101y	Other specified diabetes mellitus with ketoacidosis
	C108y	Other specified diabetes mellitus with multiple comps
	XaFWG	Type I diabetes mellitus with hypoglycaemic coma
	C103.	Diabetes mellitus with ketoacidotic coma
	XM1Qx	Diabetes mellitus with gangrene
	XaEnn	Type I diabetes mellitus with mononeuropathy
	XaFn7	Type II diabetes mellitus with peripheral angiopathy
	f8...	Diabetic neuropathy treatment [no drugs here]
	X40JI	Diabetes mellitus autosomal dominant
	C10z.	Diabetes mellitus with unspecified complication
	C105y	Other specified diabetes mellitus with ophthalmic complicatn
	C1086	Type I diabetes mellitus with gangrene
	C106y	Other specified diabetes mellitus with neurological comps
	C1085	Type I diabetes mellitus with ulcer
Falls	16D..	Falls
	TC...	Accidental fall
	Xa1GP	Recurrent falls
	Xa6uH	Elderly fall
	TCz..	Accidental falls NOS
	TC5..	Fall on same level from slipping, tripping or stumbling
	XaLqJ	Referral to falls service
	XaMGj	Referral to elderly falls prevention clinic
	Xa6uG	Observation of falls

	Y3356	Unable to get off floor
	YA756	Has pendant alarm services
	XaN4s	Provision of telecare community alarm service
Gastrointestinal bleed, lower	J5730	Rectal haemorrhage
	X30Bj	Bleeding per rectum
	XaJuv	Painless rectal bleeding
	J573.	(Haemorrhage of rectum & anus) or (PR - bleeding per rectum)
	XE0d3	Anal &/or rectal haemorrhage
	XaJuu	Painful rectal bleeding
	G8480	Bleeding haemorrhoids NOS
	X76fy	Bleeding pile
	J5731	Anal haemorrhage
	X30Bk	Fresh blood passed per rectum
	G8450	External bleeding haemorrhoids
	X76fR	Bleeding from anus
	X30Bi	Lower gastrointestinal haemorrhage
	G8420	Internal bleeding haemorrhoids
	XE0b0	Haemorrhage of rectum and anus
	J573z	Haemorrhage of rectum and anus NOS
	X30Ct	Stomal bleeding
Gastrointestinal bleed, unspecified	J68..	Gastrointestinal haemorrhage
	XaB3J	Recurrent gastrointestinal bleeding
	XaB3K	Massive gastrointestinal bleed
	J68z.	Gastrointestinal bleeding (& [unspecified])
	XE0bJ	Gastrointestinal haemorrhage unspecified
	J68z1	Intestinal haemorrhage NOS
	J68zz	Gastrointestinal tract haemorrhage NOS
	Xa00e	Sepsis-associated gastrointestinal haemorrhage
Gastrointestinal bleed, upper	J680.	Haematemesis
	XE0rB	Vomiting blood - fresh
	X30Bh	Bleeding duodenal ulcer
	X30Be	Upper gastrointestinal haemorrhage
	XaBfG	Haematemesis - cause unknown
	G850.	Bleeding oesophageal varices
	J1201	Acute duodenal ulcer with haemorrhage
	J68z0	Gastric haemorrhage NOS
	J1211	Chronic duodenal ulcer with haemorrhage
	X30Bg	Bleeding gastric ulcer
	J1101	Acute gastric ulcer with haemorrhage
	J1111	Chronic gastric ulcer with haemorrhage
	XaB5h	Haemorrhagic oesophagitis
	J11y1	Unspecified gastric ulcer with haemorrhage
	Xa7TU	Oesophageal bleeding
	J1103	Acute gastric ulcer with haemorrhage and perforation
	Xa363	Vomiting stale blood
	J1113	Chronic gastric ulcer with haemorrhage and perforation
	XaBel	Bleeding stress ulcer of stomach
	J11y3	Unspecified gastric ulcer with haemorrhage and perforation
	760J4	Balloon tamponade of oesophagus
Haematuria	K1972	Microscopic haematuria
	XE0e5	Haematuria
	XE0rU	Blood in urine - haematuria

	K1973	Frank haematuria
	K1971	Painful haematuria
	K1970	Painless haematuria
	XaB5q	Haematuria NOS
	X76YJ	Bleeding from urethra
	Xa1uK	Persistent microscopic haematuria
	Xa1uJ	Recurrent frank haematuria
	Xa1uL	Recurrent microscopic haematuria
	X30Pw	Traumatic haematuria
	Xa1uM	Persistent haematuria
	K197.	Haematuria (& [traumatic] or [essential])
	1A45.	Blood in urine (& symptom)
	Xa1uN	Recurrent haematuria
	Xa1uI	Persistent frank haematuria
	XE0un	Blood in urine - haematuria (& [symptom])
	X30Q0	Chemical haematuria
	K0A2.	Recurrent and persistent haematuria
	K1974	Clot haematuria
	X30Px	Loin pain - haematuria syndrome
	X30Ih	Benign familial haematuria
	X30Pz	Upper urinary tract haematuria
	K0A23	Recur+persist haemuria df mesangial prolif glomerulnephritis
	K0A20	Recurrent+persistnt haematuria minor glomerular abnormality
Haemoptysis	R063.	[D]Haemoptysis
	XE0qp	Blood in sputum - haemoptysis
	172..	Blood in sputum - haemoptysis [& symptom]
	R0630	[D]Cough with haemorrhage
	Xa7vG	Bloodstained sputum
	R063z	[D]Haemoptysis NOS
	Xa7vH	Blood streaked sputum
	Xa7vI	Frank blood in sputum
	XaZy3	Massive haemoptysis
	R0631	[D]Pulmonary haemorrhage NOS
	XM0zJ	Pulmonary haemorrhage [D]
Heart failure	XaJ98	Echocardiogram shows left ventricular systolic dysfunction
	XaIIq	Left ventricular systolic dysfunction
	XE2QG	Left ventricular failure
	XaJ9H	New York Heart Association classification - class II
	G58..	Heart failure
	XaLN7	Heart failure review completed
	G580.	Heart failure: [right] or [congestive]
	XaKNa	Seen by community heart failure nurse
	XaKNN	Seen in heart failure clinic
	G5801	Chronic congestive heart failure
	XM1Qn	Impaired left ventricular function
	XaMJA	Excepted heart failure quality indicators: Patient unsuitabl
	XaKNX	Referral to heart failure nurse
	XE0V8	Biventricular failure
	1736	Paroxysmal nocturnal dyspnoea
	G581.	(L ventric:[fail][imp func]) or (card asth) or (ac pulm oed)
	XaIQN	Heart failure annual review
	XaWyi	Heart failure with normal ejection fraction
	G5800	Acute congestive heart failure
	XE0V9	Heart failure NOS
	G582.	Acute heart failure
	XaMJB	Excepted heart failure quality indicators: Informed dissent
	X202I	Right ventricular failure

	XaJ9l	New York Heart Association classification - class III
	XaLon	Heart failure 6 month review
	14A6.	H/O: heart failure
	XaO5n	Congestive heart failure due to valvular disease
	XaIIU	Congestive heart failure monitoring
	G58z.	Heart: [weak] or [failure NOS]
	XE0Wo	(Conges card fail)(dropsy)(card insuf)(R hrt fail)(LV fail)
	XaXgq	Referral to heart failure exercise programme declined
	XE0WE	Heart disease: [arteriosclerotic] or [chronic ischaemic NOS]
	XaLCj	Referred by heart failure nurse specialist
	XaIL7	New York Heart Assoc classification heart failure symptoms
	X102Y	Acute cardiac pulmonary oedema
	XaLNA	Heart failure care plan discussed with patient
	XaKNW	Admit heart failure emergency
	XaIpn	Heart failure confirmed
	XaMGu	Heart failure monitoring third letter
	XaQdP	Heart failure self management plan
	XaNUf	Heart failure education
	XaEgY	Refractory heart failure
	XaLGJ	Did not attend practice nurse heart failure clinic
	G5y4z	Post cardiac operation heart failure NOS
	XaBwi	H/O: Heart failure in last year
	XaMHD	Did not attend heart failure clinic
	XaLMw	Heart failure information given to patient
	XaLMx	Referral to heart failure exercise programme
	X202k	Heart failure as a complication of care
	bm...	Vasodilators in heart failure [no drugs here]
Hypertension	XE0Ub	Hypertension
	XE0Uc	Essential hypertension
	XaJ4e	Excepted from hypertension qual indicators: Patient unsuit
	G2...	Hypertensive disease
	XaJ4P	Exception reporting: hypertension quality indicators
	XaJ4f	Excepted from hypertension qual indicators: Informed dissent
	XE0Ud	Essential hypertension NOS
	XaQaV	Lifestyle advice regarding hypertension
	14A2.	H/O: hypertension
	G2z..	Hypertensive disease NOS
	9N1y2	Seen in hypertension clinic
	F4211	Hypertensive retinopathy
	6628	Poor hypertension control
	G20..	High blood pressure (& [essential hypertension])
	G201.	Benign essential hypertension
	Gyu21	[X]Hypertension secondary to other renal disorders
	G20z.	Hypertension NOS (& [essential])
	G24..	Secondary hypertension
	G202.	Systolic hypertension
	662F.	Hypertension treatm. started
	6627	Good hypertension control
	XSDSb	Diastolic hypertension
	Xa8HD	On treatment for hypertension
	Xa0Cs	Labile hypertension
	XaJYi	Hypertension clinical management plan
	Xa3fQ	Malignant hypertension
	XaIy8	Moderate hypertension control
	G24z1	Hypertension secondary to drug
	XE0W8	(Hypertensive disease) or (hypertension)
	G200.	Malignant essential hypertension

	Xa0kX	Renovascular hypertension
	G24z.	Secondary hypertension NOS
	G24z0	Secondary renovascular hypertension NOS
	G240.	Malignant secondary hypertension
	G22z.	(Renal hypertension) or (hypertensive renal disease NOS)
	G241z	Secondary benign hypertension NOS
	G240z	Secondary malignant hypertension NOS
	G244.	Hypertension secondary to endocrine disorders
	G241.	Secondary benign hypertension
	Gyu20	[X]Other secondary hypertension
Hyperthyroidism	4422	Thyroid hormone tests high
	XE104	Thyrotoxicosis
	1431	H/O: hyperthyroidism
	C022.	Toxic multinodular goitre
	XaZtG	Subclinical hyperthyroidism
	X40H0	Thyrotoxicosis on thyroxine therapy
	X40Gt	Borderline thyrotoxicosis
	X40Gj	Toxic goitre
	C02..	([Thyrotoxicosis] or [hyperthyroidism]) or (toxic goitre)
	X40Go	Toxic nodular goitre
	X40Gk	Thyrotoxicosis due to Graves' disease
	C1343	TSH deficiency
	C02zz	Thyrotoxicosis NOS
	C02z.	Thyrotoxicosis without mention of goitre or other cause
	XE122	Thyrotoxicosis: [+/- goitr][tox goitr][Graves dis][thyr nod]
	XaKcQ	Hyperthyroidism resolved
	C022z	Toxic multinodular goitre NOS
	C02z0	Thyrotoxicosis without mention of goitre or cause no crisis
	X40Gs	T3 toxicosis
	X40H2	Amiodarone-induced thyrotoxicosis
	X40Gl	Thyrotoxicosis due to Hashimoto's thyroiditis
	Cyu13	[X]Other thyrotoxicosis
	XE106	Thyrotoxicosis of other specified origin
	XaJDU	Did not attend hyperthyroidism clinic
	Xa3eb	Thyrotoxicosis with or without goitre
	C024.	Thyrotoxicosis from ectopic thyroid nodule
	C0220	Toxic multinodular goitre with no crisis
	XE105	Toxic diffuse goitre
	C023.	Toxic nodular goitre unspecified
	C021.	Toxic uninodular goitre
	C023z	Toxic nodular goitre NOS
	C02yz	Thyrotoxicosis of other specified origin NOS
	X40Gq	Toxic thyroid nodule
	X40H1	Iodine-induced thyrotoxicosis
	C0200	Toxic diffuse goitre with no crisis
	X40Gz	Iatrogenic thyrotoxicosis
	X40Gn	Thyrotoxicosis due to acute thyroiditis
	C021z	Toxic uninodular goitre NOS
	C02y0	Thyrotoxicosis of other specified origin with no crisis
	X40Gw	Thyrotoxicosis in pregnancy
	C02z1	Thyrotoxicosis without mention of goitre, cause with crisis
	C0201	Toxic diffuse goitre with crisis
	X40H5	Thyrotoxicosis due to TSHoma
	C0230	Toxic nodular goitre unspecified with no crisis
	C020z	Toxic diffuse goitre NOS
	X40Gu	Autonomous thyroid function
	C0221	Toxic multinodular goitre with crisis

	C02y.	Thyrotoxicosis: [other specified origin] or [factitia]
	X40H3	Thyroid crisis
	C0210	Toxic uninodular goitre with no crisis
	X40H4	Thyrotoxicosis due to inappropriate TSH secretion
Intracranial haemorrhage	G613.	Cerebellar haemorrhage
	G61z.	Intracerebral haemorrhage NOS
	XM0rV	Cerebral haemorrhage
	XE0VF	Cerebral parenchymal haemorrhage
	Gyu6F	[X]Intracerebral haemorrhage in hemisphere, unspecified
	XaBM4	Left sided intracerebral haemorrhage, unspecified
	X00DQ	Brainstem haemorrhage
	G614.	Pontine haemorrhage
	X00DO	Thalamic haemorrhage
	XE0Wy	Cerebral haemorrhage NOS
	G612.	Basal ganglia haemorrhage
	X00DP	Lacunar haemorrhage
	G611.	Internal capsule haemorrhage
	G617.	Intracerebral haemorrhage, intraventricular
	XaBM5	Right sided intracerebral haemorrhage, unspecified
	G610.	Cortical haemorrhage
	X00DM	Lobar cerebral haemorrhage
	G616.	External capsule haemorrhage
	X00DN	Subcortical cerebral haemorrhage
	G618.	Intracerebral haemorrhage, multiple localised
	G615.	Bulbar haemorrhage
Ischaemic heart disease	XaIwY	Acute non-ST segment elevation myocardial infarction
	XE2uV	Ischaemic heart disease
	G33..	Angina
	7928	Percutaneous balloon angioplasty of coronary artery
	X200E	Myocardial infarction
	XE0Uh	Acute myocardial infarction
	X2009	Unstable angina
	G33z.	Angina pectoris NOS
	G3z..	Ischaemic heart disease NOS
	792..	Coronary artery operations (& bypass)
	14A5.	H/O: angina pectoris
	662K0	Angina control - good
	X00tE	Coronary artery bypass grafting
	X2008	Stable angina
	XaIOW	Coronary heart disease review
	G34y1	Chronic myocardial ischaemia
	X00tU	Insertion of coronary artery stent
	XaI9h	Coronary heart disease annual review
	G308.	Inferior myocardial infarction NOS
	X2006	Triple vessel disease of the heart
	Xa7nH	Exercise-induced angina
	XE2aA	Old myocardial infarction
	G30z.	Acute myocardial infarction NOS
	G340.	Coronary (atheroscl or artery dis) or triple vess dis heart
	G3...	Ischaemic heart disease (& [arteriosclerotic])
	Y3657	H/O: Ischaemic heart disease
	G30..	(Myocard inf (& [ac][silent][card rupt])) or (coron thromb)
	322..	ECG: myocardial ischaemia
	XaNxN	Admit ischaemic heart disease emergency
	14A..	H/O: cardiovasc disease (& [heart disord][myocard problem])

	3222	ECG:shows myocardial ischaemia
	322Z.	ECG: myocardial ischaemia NOS
	X200C	Myocardial ischaemia
	XM0rN	Coronary atherosclerosis
	Xa0wX	Central crushing chest pain
	Ua1eH	Ischaemic chest pain
	662K3	Angina control - worsening
	662K1	Angina control - poor
	X200B	Coronary spasm
	X200c	Cardiac syndrome X
	XE0WA	Myocardial infarction (& [acute]) or coronary thrombosis
	14A4.	H/O: myocardial infarct at greater than 60
	XaFx7	Diab mellit insulin-glucose infus acute myocardial infarct
	X75rV	Crushing chest pain
	G3y..	Other specified ischaemic heart disease
	G30yz	Other acute myocardial infarction NOS
	G30y.	Other acute myocardial infarction
	XE0WC	Acute/subacute ischaemic heart disease NOS
	Gyu30	[X]Other forms of angina pectoris
	X200d	Post-infarction ventricular septal defect
	XaFsH	Transient myocardial ischaemia
	G34z.	Other chronic ischaemic heart disease NOS
	G361.	Atrial septal defect/curr comp folow acut myocardal infarct
	Y6999	H/O: myocardial infarct >60
	XE0WG	Chronic ischaemic heart disease NOS
	XaNMH	Cardiovascular disease annual review declined
	G31y2	Subendocardial ischaemia
	G36..	Certain current complication follow acute myocardial infarct
	G34yz	Other specified chronic ischaemic heart disease NOS
	bl...	Vasodilators used in angina pectoris
	G31yz	Other acute and subacute ischaemic heart disease NOS
Memory impairment	F110.	Alzheimer's disease
	XaMGF	Dementia annual review
	X002w	Dementia
	XaJua	Referral to memory clinic
	XE1Xs	Vascular dementia
	2841	Confused
	1461	H/O: dementia
	X75xH	Poor short-term memory
	XaMJC	Dementia monitoring
	X75xU	Memory impairment
	1B1A.	Memory disturbance (& amnesia (& symptom))
	Eu00.	[X]Dementia in Alzheimer's disease
	XaNbm	Seen in memory clinic
	Eu002	[X]Dementia in Alzheimer's dis, atypical or mixed type
	Ua196	Minor memory lapses
	E004z	Arteriosclerotic dementia NOS
	XaLFo	Excepted from dementia quality indicators: Patient unsuitabl
	Ua197	Memory lapses
	XE1Z6	[X]Unspecified dementia
	E2A10	Mild memory disturbance
	Xa3f0	Confusional state
	XaLFp	Excepted from dementia quality indicators: Informed dissent
	E0020	Senile dementia with paranoia
	X00RS	Mild cognitive disorder
	XaMGG	Dementia monitoring second letter

XaMGI	Dementia monitoring third letter
Xa0lH	Multi-infarct dementia
X75xG	Amnesia for recent events
E2A11	Organic memory impairment
X0030	Dementia in Alzheimer's disease with late onset
XaPpE	Lacks capacity to give consent (Mental Capacity Act 2005)
Xa25J	Alcoholic dementia
X00RT	Age-associated memory impairment
X003A	Lewy body disease
X003V	Mixed cortical and subcortical vascular dementia
XaKyY	[X]Lewy body dementia
X00R2	Senile dementia
X0034	Frontotemporal dementia
X002x	Dementia in Alzheimer's disease with early onset
Eu041	[X]Delirium superimposed on dementia
F21y2	Binswanger's disease
Xa0sE	Dementia of frontal lobe type
XE1bq	Memory disturbance: [mild]
XaMGK	Dementia monitoring telephone invite
X75xD	Amnesia for remote events
XaJPy	Anti-dementia drug therapy
XaMFy	Dementia monitoring administration
X003R	Vascular dementia of acute onset
Eu00z	[X]Dementia in Alzheimer's disease, unspecified
R00z0	[D]Amnesia (retrograde)
X003W	Semantic dementia
Eu023	[X]Dementia in Parkinson's disease
Eu01z	[X]Vascular dementia, unspecified
3A40.	Memory: present year not known
XaE74	Senile dementia of the Lewy body type
3AA1.	Memory: address recall unsucc.
Eu01y	[X]Other vascular dementia
Xa1GB	Cerebral degeneration presenting primarily with dementia
X75xC	Poor long-term memory
E001.	Presenile dementia
E000.	Uncomplicated senile dementia
Eu02z	[X] Dementia: [unspecified] or [named variants (& NOS)]
XaLFf	Exception reporting: dementia quality indicators
E012.	Alcoholic dementia: [other] or [NOS]
E0021	Senile dementia with depression
E0041	Arteriosclerotic dementia with delirium
E0010	Uncomplicated presenile dementia
XaJBQ	Global deterioration scale: assessment of prim deg dementia
3A70.	Memory: important event not kn
Ua190	Distortion of memory
X003T	Subcortical vascular dementia
XE1Xu	Other alcoholic dementia
3A91.	Memory: count down unsuccess.
3A60.	Memory: present month not knwn
Xa3ez	Other senile/presenile dementia
E041.	Dementia in conditions EC
X00Rk	Alcoholic dementia NOS
3A30.	Memory: present place not knwn
E004.	Arteriosclerotic dementia (including [multi infarct dement])
E0040	Uncomplicated arteriosclerotic dementia
3A20.	Memory: present time not known
X002m	Amyotrophic lateral sclerosis with dementia

	Eu022	[X]Dementia in Huntington's disease
	E003.	Senile dementia with delirium
	E001z	Presenile dementia NOS
	Eu011	[X]Dementia: [multi-infarct] or [predominantly cortical]
	Xa2Ve	Impairment of registration
	Eu02y	[X]Dementia in other specified diseases classif elsewhere
	3A10.	Memory: own age not known
	3A80.	Memory: import.person not knwn
	3A50.	Memory: own DOB not known
	XE1aG	Dementia (& [presenile] or [senile])
	Eu02.	[X]Dementia in other diseases classified elsewhere
	E002.	Senile dementia with depressive or paranoid features
	E0013	Presenile dementia with depression
	X003P	Acquired immune deficiency syndrome dementia complex
	X003X	Patchy dementia
	Eu020	[X]Dementia in Pick's disease
	Ub1T6	Language disorder of dementia
	XaKUo	Disturbance of memory for order of events
	E0011	Presenile dementia with delirium
	E0042	Arteriosclerotic dementia with paranoia
	E002z	Senile dementia with depressive or paranoid features NOS
	E0012	Presenile dementia with paranoia
	E0043	Arteriosclerotic dementia with depression
Myocardial infarction	XaIwY	Acute non-ST segment elevation myocardial infarction
	G301z	Anterior myocardial infarction NOS
	X200E	Myocardial infarction
	XE0Uh	Acute myocardial infarction
	X2009	Unstable angina
	G308.	Inferior myocardial infarction NOS
	14A3.	H/O: myocardial infarct at less than 60
	G301.	Other specified anterior myocardial infarction
	G300.	Acute anterolateral myocardial infarction
	G30z.	Acute myocardial infarction NOS
	G30..	(Myocard inf (& [ac][silent][card rupt])) or (coron thromb)
	G305.	Lateral myocardial infarction NOS
	323..	ECG: myocardial infarction
	G307.	Acute subendocardial infarction
	G310.	Post-myocardial infarction syndrome
	G302.	Acute inferolateral myocardial infarction
	323Z.	ECG: myocardial infarct NOS
	G303.	Acute inferoposterior infarction
	XE0WA	Myocardial infarction (& [acute]) or coronary thrombosis
	14A4.	H/O: myocardial infarct at greater than 60
	G35..	Subsequent myocardial infarction
	G304.	Posterior myocardial infarction NOS
	G30yz	Other acute myocardial infarction NOS
	G30y.	Other acute myocardial infarction
	XE0WC	Acute/subacute ischaemic heart disease NOS
	X200d	Post-infarction ventricular septal defect
	G361.	Atrial septal defect/curr comp folow acut myocardal infarct
	G350.	Subsequent myocardial infarction of anterior wall
	G366.	Thrombosis atrium,auric append&vent/curr comp foll acute MI
	Gyu34	[X]Acute transmural myocardial infarction of unspecif site
	G351.	Subsequent myocardial infarction of inferior wall
	G36..	Certain current complication follow acute myocardial infarct
	G364.	Ruptur chordae tendinae/curr comp fol acute myocard infarct

	G31yz	Other acute and subacute ischaemic heart disease NOS
Obesity	XaJJH	Body mass index 40+ - severely obese
	XM00v	Obese build
	XabHx	Obese class I (body mass index 30.0 - 34.9)
	222A.	O/E - obese
	X76dX	Obese abdomen
	XabHy	Obese class II (body mass index 35.0 - 39.9)
	XabHz	Obese class III (BMI equal to or greater than 40.0)
Peptic ulcer	J12..	Duodenal ulcer
	J11..	Gastric ulcer (& [prepyloric] or [pyloric])
	XE0aQ	Gastric ulcer NOS
	J13..	Ulcer: [peptic (PU) site unspecified] or [stress NOS]
	J120z	Acute duodenal ulcer NOS
	XM0sI	Perforated peptic ulcer
	XM1RO	H/O: gastric ulcer
	J12z.	Duodenal ulcer NOS
	XE0aP	Gastric ulcer
	14C1.	H/O: peptic ulcer (& [duodenal] or [gastric])
	J120.	Acute duodenal ulcer
	X302b	Duodenal ulcer disease
	J11z.	Gastric: [erosions] or [multiple ulcers] or [ulcer NOS]
	XE0qB	H/O: peptic ulcer
	J1202	Acute duodenal ulcer with perforation
	X30Bh	Bleeding duodenal ulcer
	XaELE	Multiple gastric ulcers
	1956	Peptic ulcer symptoms
	X302Q	Perforation of duodenal ulcer
	XM0BZ	Peptic ulcer disease
	J13z.	Peptic ulcer NOS
	J1020	Gastro-oesophageal reflux disease with ulceration
	J121.	Chronic duodenal ulcer
	XaMO7	Non steroidal anti inflammatory drug induced duodenal ulcer
	XaMO5	Non steroidal anti inflammatory drug induced gastric ulcer
	J1301	Acute peptic ulcer with haemorrhage
	XaB9d	Repair of perforated pyloric ulcer
	J131.	Chronic peptic ulcer
	Xa6ot	Prepyloric gastric ulcer
	J111.	Chronic gastric ulcer
	76270	Closure of perforated duodenal ulcer
	XM1RN	H/O: duodenal ulcer
	J124.	Recurrent duodenal ulcer
	Xa84h	Pyloric ulcer
	XE0aS	Gastrojejunal ulcer
	J110.	Acute gastric ulcer
	J12y1	Unspecified duodenal ulcer with haemorrhage
	J12y.	Unspecified duodenal ulcer
	X302c	Peptic ulcer of duodenum
	J1201	Acute duodenal ulcer with haemorrhage
	J130.	Acute peptic ulcer
	X302F	Chronic peptic ulcer of duodenum
	J13y.	Unspecified peptic ulcer
	X302X	Peptic ulcer of stomach
	X20VN	Oversewing perforated gastric ulcer
	X301o	Perforation of gastric ulcer
	J12y2	Unspecified duodenal ulcer with perforation
	J110z	Acute gastric ulcer NOS
	J1211	Chronic duodenal ulcer with haemorrhage

J17y8	Healed gastric ulcer leaving a scar
XE0aR	Peptic ulcer - (PU) site unspecified
J1200	Acute duodenal ulcer without mention of complication
J1100	Acute gastric ulcer without mention of complication
X30Bg	Bleeding gastric ulcer
J1212	Chronic duodenal ulcer with perforation
J12y0	Unspecified duodenal ulcer without mention of complication
J13yz	Unspecified peptic ulcer NOS
J1210	Chronic duodenal ulcer without mention of complication
761Jy	Other specified operation on gastric ulcer
J11y.	Unspecified gastric ulcer
761J0	Closure of perforated gastric ulcer
J121y	Chronic duodenal ulcer unspecified
J14..	Ulcer: [gastrojej]/[anast]/[gastrocol]/[jej]/[margin]/[stom]
J1311	Chronic peptic ulcer with haemorrhage
J110y	Acute gastric ulcer unspecified
J12yz	Unspecified duodenal ulcer NOS
J120y	Acute duodenal ulcer unspecified
761J.	Gastric ulcer operation
X20Vu	Oversewing perforated duodenal ulcer
XE0c1	Perforated DU (& [acute])
X301J	Chronic peptic ulcer of stomach
ZV127	[V]Pers hist digest syst disease (& [pept ulcer (& [duod])])
J121z	Chronic duodenal ulcer NOS
XaBmb	Bleeding peptic ulcer
XaB8q	Oversewing of bleeding duodenal ulcer
J1102	Acute gastric ulcer with perforation
7627z	Operation on duodenal ulcer NOS
J1101	Acute gastric ulcer with haemorrhage
X301E	Acute peptic ulcer of stomach
J11yz	Unspecified gastric ulcer NOS
7627	Duodenal ulcer operation
XaLWq	Anti-platelet induced gastric ulcer
J1111	Chronic gastric ulcer with haemorrhage
J111z	Chronic gastric ulcer NOS
XaLdV	Oversew of blood vessel of duodenal ulcer
J13y2	Unspecified peptic ulcer with perforation
J130z	Acute peptic ulcer NOS
J1203	Acute duodenal ulcer with haemorrhage and perforation
76271	Suture of duodenal ulcer not elsewhere classified
J131y	Chronic peptic ulcer unspecified
761Jz	Operation on gastric ulcer NOS
XE0bz	Perforated GU (& [acute])
J12yy	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
XaB2R	Suture of duodenal ulcer
XE0c3	Ulcer: [peptic NOS]/[gastrojejunal]/[stomal]/[anastomotic]
XaMO6	Non steroidal anti inflammatory drug induced gastric ulc NOS
XaFBq	Endoscopic injection haemostasis of duodenal ulcer
J1302	Acute peptic ulcer with perforation
XaB9e	Omental patch repair of perforated pyloric ulcer
XaCLu	[V] Personal history of gastric ulcer
J11y0	Unspecified gastric ulcer without mention of complication
J1114	Chronic gastric ulcer with obstruction
J1310	Chronic peptic ulcer without mention of complication
J14z.	Gastrojejunal ulcer NOS
J131z	Chronic peptic ulcer NOS
J130y	Acute peptic ulcer unspecified

	XaBlw	Gastric ulcer sample
	J1300	Acute peptic ulcer without mention of complication
	7627y	Other specified operation on duodenal ulcer
	XaB15	Laparoscopic closure of perforated gastric ulcer
	J13y1	Unspecified peptic ulcer with haemorrhage
	J11y1	Unspecified gastric ulcer with haemorrhage
	J1112	Chronic gastric ulcer with perforation
	J1110	Chronic gastric ulcer without mention of complication
	XaFBs	Endoscopic injection haemostasis of gastric ulcer
	XaMO8	Non steroidal anti inflammatory drug induced duoden ulc NOS
	XaLWs	Anti-platelet induced duodenal ulcer
	X301F	Acute drug-induced ulcer of stomach
	J1401	Acute gastrojejunal ulcer with haemorrhage
	J1312	Chronic peptic ulcer with perforation
	Xa3ti	Perforated peptic ulcer closure
	J1103	Acute gastric ulcer with haemorrhage and perforation
	Xa3u7	Stomach ulcer excision
	XaBel	Bleeding stress ulcer of stomach
	X301G	Stress ulcer of stomach
	J14y.	Unspecified gastrojejunal ulcer
	J57y8	Primary ulcer of intestine
	J12y4	Unspecified duodenal ulcer with obstruction
	X302A	Acute peptic ulcer of duodenum
	J12y3	Unspecified duodenal ulcer with haemorrhage and perforation
	XE0Cr	Closure of gastric ulcer NEC
	J111y	Chronic gastric ulcer unspecified
	J11y2	Unspecified gastric ulcer with perforation
	J1214	Chronic duodenal ulcer with obstruction
	J1213	Chronic duodenal ulcer with haemorrhage and perforation
Peripheral vascular disease	XaBL8	O/E - Absent right foot pulses
	24F9.	O/E - L.dorsalis pedis absent
	24E9.	O/E - R.dorsalis pedis absent
	X203T	Lower limb ischaemia
	XaJD3	O/E - Right dorsalis pedis abnormal
	G73z.	Peripheral vascular disease NOS
	X203Q	Peripheral ischaemia
	X203R	Upper limb ischaemia
	G73..	(Peri vasc dis (& [isch][oth])) or (isch leg) or (peri isch)
	XaVyB	History of peripheral vascular disease
	X203S	Critical upper limb ischaemia
	X203U	Critical lower limb ischaemia
	XaE3G	Critical ischaemia of foot
	M2710	Ischaemic ulcer diabetic foot
	X203M	Arterial ischaemia
	Xa0IV	Consistencies
	XE10l	Diabetes mellitus with peripheral circulatory disorder
	C107.	Diabetes mellitus with: [gangrene] or [periph circul disord]
	XM1Qx	Diabetes mellitus with gangrene
	G670.	Atherosclerosis: [precerebral] or [cerebral]
	XaFn7	Type II diabetes mellitus with peripheral angiopathy
	C1086	Type I diabetes mellitus with gangrene
Pulmonary embolism	XE0Um	Pulmonary embolus
	G4010	Postoperative pulmonary embolus
	X202x	Pulmonary thromboembolism

	XaOYV	Recurrent pulmonary embolism
	X202y	Acute massive pulmonary embolism
	L43..	Obstetric pulmonary embolism
	X202z	Subacute massive pulmonary embolism
	L43z1	Obstetric pulmonary embolism NOS - delivered
	L43z0	Obstetric pulmonary embolism NOS, unspecified
	L432.	Obstetric blood-clot pulmonary embolism
	L43z.	Obstetric pulmonary embolism NOS
Smoking	Ub0oq	Non-smoker
	XE0oh	Never smoked tobacco
	1371	Non-smoker (& [never smoked tobacco])
	Y6628	Ex smoker
	XaQUC	Non-smoker annual review
	XE0op	Ex-cigarette smoker amount unknown
	Ub1tI	Cigarette consumption
	137R.	Smoker
	Ub1na	Ex-smoker
	XE0oq	Cigarette smoker
	Xa1bv	Ex-cigarette smoker
	137K.	Stopped smoking
	1379	Ex-moderate smoker (10-19/day)
	1374	Moderate cigarette smoker (10-19 cigs/day)
	137G.	Trying to give up smoking
	Ub0p3	Age at starting smoking
	137C.	Keeps trying to stop smoking
	XaIQj	Negotiated date for cessation of smoking
	137..	[Tobacco consumption] or [smoker - amount smoked]
	137M.	Rolls own cigarettes
	XaIQk	Smoking status at 4 weeks
	XaBSp	Smoking restarted
	1375	Heavy cigarette smoker (20-39 cigs/day)
	137A.	Ex-heavy smoker (20-39/day)
	137H.	Pipe smoker
	137F.	Ex-smoker - amount unknown
	1378	Ex-light smoker (1-9/day)
	XaLQh	Wants to stop smoking
	XaIth	Smoking cessation programme start date
	XaIQl	Smoking status between 4 and 52 weeks
	137B.	Ex-very heavy smoker (40+/day)
	137O.	Ex-cigar smoker
	XaIkY	Not interested in stopping smoking
	137J.	Cigar smoker
	Ub1tJ	Cigar consumption
	1377	Ex-trivial smoker (<1/day)
	137T.	Date ceased smoking
	137L.	Current non-smoker
	XaIkW	Thinking about stopping smoking
	Ub0p1	Time since stopped smoking
	Ub1tK	Pipe tobacco consumption
	1373	Light cigarette smoker (1-9 cigs/day)
	1372	(Trivial smoker - < 1 cig/day) or (occasional smoker)
	Ub0oo	Tobacco smoking behaviour
	137Z.	Tobacco consumption NOS
	YA602	Contented smoker
	XE0og	Tobacco smoking consumption
	XaK28	Carbon monoxide reading at 4 weeks
	Ub1tR	Occasional cigarette smoker

	XE0ol	Ex-moderate cigarette smoker (10-19/day)
	XaWNE	Failed attempt to stop smoking
	XE0on	Ex-very heavy cigarette smoker (40+/day)
	XE0om	Ex-heavy cigarette smoker (20-39/day)
	Ub1tT	Moderate cigarette smoker
	XaQ8V	Ex roll-up cigarette smoker
	1376	Very heavy cigarette smoker (40+ cigs/day)
	XaIkX	Ready to stop smoking
	XaQzw	Recently stopped smoking
	Ub1tU	Heavy cigarette smoker
	Ub0p2	Total time smoked
	XaIr7	Smoking free weeks
	Ub1tV	Very heavy cigarette smoker
	XE0ok	Ex-light cigarette smoker (1-9/day)
	XE0oi	Trivial cigarette smoker (less than one cigarette/day)
	137N.	Ex-pipe smoker
	Ub1tS	Light cigarette smoker
	XaIQi	Smoking cessation milestones
	137P.	Smoker (& cigarette)
	XaW0h	Practice based smoking cessation programme start date
	XaItg	Reason for restarting smoking
	XaIQm	Smoking status at 52 weeks
	XE0oj	Ex-trivial cigarette smoker (<1/day)
	XaXUL	Lost to smoking cessation follow-up
	Y7110	Heavy smoker - 20-39 cigs/day
	XaJX2	Minutes from waking to first tobacco consumption
	XE1b4	Tobacco dependence (& [dependent smoker])
	Y0983	Smoking status at 4 weeks - Smoker
	137Q.	Smoking: [started] or [restarted]
	XE0or	Smoking started
	XaZIE	Waterpipe tobacco consumption
	XE0oo	Tobacco smoking consumption unknown
	137D.	Admitted tobacco cons untrue ?
	Y9843	Very heavy smoker - 40+cigs/d
	Ub1tW	Chain smoker
	XaXPX	Smoking status at 12 weeks
	XaIuQ	Cigarette pack-years
Stroke - haemorrhage	G613.	Cerebellar haemorrhage
	G61z.	Intracerebral haemorrhage NOS
	G61..	Intracerebral haemorrhage (& [cerebrovasc accident due to])
	XE0VF	Cerebral parenchymal haemorrhage
	XaBM4	Left sided intracerebral haemorrhage, unspecified
	X00DQ	Brainstem haemorrhage
	G614.	Pontine haemorrhage
	X00DO	Thalamic haemorrhage
	G612.	Basal ganglia haemorrhage
	X00DP	Lacunar haemorrhage
	G611.	Internal capsule haemorrhage
	XaBM5	Right sided intracerebral haemorrhage, unspecified
	G610.	Cortical haemorrhage
	X00DM	Lobar cerebral haemorrhage
	G616.	External capsule haemorrhage
	X00DN	Subcortical cerebral haemorrhage
	G618.	Intracerebral haemorrhage, multiple localised
	G615.	Bulbar haemorrhage
Stroke - infarct	Xa00I	Occipital cerebral infarction

	X00DA	Lacunar infarction
	Xa0kZ	Cerebral infarction
	X00DI	Haemorrhagic cerebral infarction
	X00D8	Posterior cerebral circulation infarction
	X00D7	Partial anterior cerebral circulation infarction
	Xa00K	Brainstem infarction
	G640.	Cerebral thrombosis
	X00D3	CVA - cerebral artery occlusion
	X00D6	Total anterior cerebral circulation infarction
	Xa00J	Cerebellar infarction
	XaBED	Right sided cerebral infarction
	XaBEC	Left sided cerebral infarction
	XaJgQ	Infarction of basal ganglia
	XaB4Z	Multiple lacunar infarcts
	XE0VJ	Cerebral infarction NOS
	X00DC	Pure sensory lacunar infarction
	XaQbK	Pure motor lacunar syndrome
	X00D5	Anterior cerebral circulation infarction
	G6410	Cerebral infarction due to embolism of cerebral arteries
	G64z.	Infarct (& [cerebell] or [cerebral NOS] or [brainstem NOS])
	Gyu64	[X]Other cerebral infarction
	G6400	Cerebral infarction due to thrombosis of cerebral arteries
	X00D9	Brainstem infarction NOS
	Xa00M	Wallenberg syndrome
	Gyu63	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
	G6760	Cereb infarct due cerebral venous thrombosis, non-pyogenic
	X00DK	Posterior cerebral circulation haemorrhagic infarction
	Gyu6G	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
	G63y1	Cerebral infarction due to embolism of precerebral arteries
	X00DJ	Anterior cerebral circulation haemorrhagic infarction
	G63y0	Cerebral infarct due to thrombosis of precerebral arteries
	X00DB	Pure motor lacunar infarction
	X00DD	Pure sensorimotor lacunar infarction
	Xa00P	Weber syndrome
	X00D4	Infarction - precerebral
Stroke - unspecified	XaEGq	Stroke NOS
	X00D1	Cerebrovascular accident
	G66..	CVA - cerebrovascular accident (& unspecified [& stroke])
	XE2aB	Stroke and cerebrovascular accident unspecified
	XE0X2	(Cereb infarc)(cerebrovas acc)(undef stroke/CVA)(stroke NOS)
	G667.	Left sided cerebral hemisphere cerebrovascular accident
	X00DR	Stroke of uncertain pathology
	G668.	Right sided cerebral hemisphere cerebrovascular accident
	X00DT	Posterior circulation stroke of uncertain pathology
	G664.	Cerebellar stroke syndrome
	X00DE	Lacunar ataxic hemiparesis
	X00DS	Anterior circulation stroke of uncertain pathology
	G663.	Brainstem stroke syndrome
	Xa00L	Benedict syndrome
	X00DF	Dysarthria-clumsy hand syndrome
	Xa1hE	Extension of cerebrovascular accident
	XaQbM	Pure sensory lacunar syndrome
Sub-dural haematoma	Xa0AB	Subdural haematoma
	XA0BD	Traumatic subdural haematoma
	XaA99	Chronic intracranial subdural haematoma

	XaEIh	Subdural haemorrhage
	S628.	Traumatic subdural haemorrhage
	XE2w4	Non-traumatic subdural haematoma
	XA0BE	Traumatic intracranial subdural haematoma
	XaKK3	Subdural haemorrhage NOS
	S622.	Closed traumatic subdural haemorrhage
	S6226	Subdural h'ge inj no open intracran wnd+LOC unspec duration
	Xa1uU	Non-traumatic intracranial subdural haematoma
	XaFsk	Traumatic subdural haematoma without open intracranial wound
	XaFsl	Traumatic subdural haematoma with open intracranial wound
	S6221	Subdural h'ge inj no open intracranial wound+no loss consc
Subarachnoid haemorrhage	Xa1uW	Subarachnoid haemorrhage
	G60z.	Subarachnoid haemorrhage NOS
	XA0BH	Traumatic subarachnoid haemorrhage
	Gyu61	[X]Other subarachnoid haemorrhage
	S6201	Subarachnoid h'ge inj no open intracran wnd+no loss consc
	XE2bF	Spontaneous subarachnoid haemorrhage
	Xa01k	Subarachnoid haemorrhage from post communic artery aneurysm
	Xa01l	Subarachnoid haemorrhage from basilar artery aneurysm
	Xa01b	Subarachnoid haemorrhage from multiple aneurysms
	Gyu6E	[X]Subarachnoid haemorrh from intracranial artery, unspecif
	Xa01j	Subarachnoid haemorrhage from ant communicat artery aneurysm
	Xa01h	Subarachnoid haemorrhage frm middle cerebral artery aneurysm
	XA0BI	Traumatic intracranial subarachnoid haemorrhage
	S6200	Subarachnoid h'ge inj no open intracran wound + unspec consc
	Xa0N7	Angiogram-negative subarachnoid haemorrhage
	Xa01i	Subarachnoid haemorrhage from post cerebral artery aneurysm
	X00Dg	Subarachnoid haemorrhage due to ruptured aneurysm
	Xa01m	Subarachnoid haemorrhage from post inf cerebell artery aneur
	Xa01c	Subarachnoid haemorrhage from ant cerebral artery aneurysm
	XE1m3	Closed traumatic subarachnoid haemorrhage
	S621.	Open traumatic subarachnoid haemorrhage
	G601.	Subarachnoid haemorrhage from carotid siphon and bifurcation
	G606.	Subarachnoid haemorrhage from vertebral artery
	Xa01o	Subarachnoid haemorrhage from carotid artery aneurysm
	Gyu60	[X]Subarachnoid haemorrhage from other intracranial arteries
Transient ischaemic attack	XE0VK	Transient ischaemic attack
	G65z.	Transient cerebral ischaemia NOS
	G65..	(Drop attack) or (trans cereb isch) or (verteb-basil insuff)
	X00DU	Carotid territory transient ischaemic attack
	X00DW	Vertebrobasilar insufficiency
	XaEGK	Transient ischaemic attacks
	F4236	Amaurosis fugax
	G661.	Anterior cerebral artery syndrome
	Fyu55	[X]Other transnt cerebral ischaemic attacks+related syndroms
	G660.	Middle cerebral artery syndrome
	G65y.	Other transient cerebral ischaemia
	X00DV	Vertebrobasilar territory transient ischaemic attack
	G662.	Posterior cerebral artery syndrome
	G6510	Vertebrobasilar artery syndrome
	G651.	Vertebral artery syndrome
	XE0X0	(Trans isch attacks) or (vert-basil insuf) or (drop attacks)
	G650.	Basilar artery syndrome

	G654.	Multiple and bilateral precerebral artery syndromes
	G653.	Carotid artery syndrome hemispheric
Valvular disease	X2011	Aortic stenosis
	X2017	Aortic regurgitation
	XE0Ux	Mitral regurgitation
	P6y0.	Subaortic stenosis
	G5414	Aortic valve stenosis with insufficiency
	X2013	Calcific aortic stenosis - bicuspid valve
	P641.	Bicuspid aortic valve
	X201L	Pulmonary regurgitation
	G541.	Aortic valve disease
	X777c	Aortic valve calcification
	XE0UZ	Mitral stenosis
	G5411	Aortic stenosis, non-rheumatic
	XM00K	Tricuspid regurgitation
	XSDVN	Aortic valve sclerosis
	X200s	Mitral restenosis
	G110.	Mitral stenosis (& [rheumatic])
	XE0UY	Mitral valve disease
	G11..	Mitral valve diseases (& [rheumatic])
	G5413	Aortic stenosis alone, cause unspecified
	X7786	Mitral valve annular calcification
	X77wI	Dilatation of mitral annulus
	X200u	Mitral valve prolapse
	X778h	Aortic root dilatation
	X777q	Mitral cusp prolapse
	X777i	Senile sclerosis of aortic cusp
	G5410	Aortic incompetence, non-rheumatic
	X200r	Rheumatic mitral stenosis
	G5412	Aortic incompetence alone, cause unspecified
	X201G	Functional tricuspid regurgitation
	G540.	Mitral valve: [regurgitation] or [prolapse]
	G5433	Pulmonary stenosis, cause unspecified
	G541z	Aortic valve disorders NOS
	G5401	Mitral incompetence, cause unspecified
	G5420	Tricuspid incompetence, non-rheumatic
	X77wL	Mitral leaflet abnormality
	X77wQ	True cleft of mitral leaflet
	X777u	Mitral valve appearance
	X778A	Mitral valve posterior leaflet prolapse
	G11z.	Mitral valve disease NOS
	X201I	Pulmonary valve stenosis
	XE0Vq	Rheumatic mitral valve disease (& [chronic])
	Xa0D0	Mitral valve anterior leaflet prolapse
	X201C	Tricuspid valve disease
	Xa7tG	Aortic valve vegetations
	Xa7tH	Mitral valve vegetations
	XaI9k	Non-rheumatic aortic sclerosis
	X777a	Aortic cusp regurgitation
	G540z	Mitral valve disorders NOS
	G111.	Rheumatic mitral regurgitation
	G1404	Tricuspid insufficiency, cause unspecified
	G5400	Non-rheumatic mitral regurgitation
	P63..	Congenital aortic valve stenosis
	Xa3fK	Chronic rheumatic mitral valve
	X2015	Senile aortic stenosis
	X777b	Aortic valve appearance

Xa0Ct	Isolated aortic stenosis
G112.	Mitral stenosis with insufficiency
G121.	Rheumatic aortic regurgitation
X77zp	Aortic valve dysplasia
G120.	Rheumatic aortic stenosis
G5431	Pulmonary stenosis, non-rheumatic
G5yy1	Papillary muscle degeneration
P61..	Congenital tricuspid atresia and stenosis
G543.	Pulmonary valve disease
G5432	Pulmonary incompetence, cause unspecified
G12..	Rheumatic aortic valve disease
G140.	Tricuspid valve disease NEC
P602z	Congenital pulmonary stenosis NOS
G543z	Pulmonary valve disorders NOS
G113.	Non-rheumatic mitral valve stenosis
G5430	Pulmonary incompetence, non-rheumatic
Xa3fM	Rheumatic mitral disease NOS
XE0Vu	Rheumatic aortic valve disease (& [chronic])
X777Y	Prosthetic aortic valve regurgitation
G5yy0	Papillary muscle atrophy
G1401	Rheumatic tricuspid regurgitation
G542.	Tricuspid valve disorders, non-rheumatic
XE0WW	Pulmonary regurgitation (& [non-rheumatic])
XE0Vs	Rheumatic mitral insufficiency (& [stenosis with])
Gyu10	[X]Other mitral valve diseases
X7782	Rheumatic mitral valve changes
P602.	Congenital pulmonary valve stenosis
X77wD	Mitral valve dysplasia
P62..	Ebstein's anomaly of tricuspid valve
X77wE	Mitral leaflet dysplasia
X201B	Congenital aortic valve abnormality
XE0WU	Tricuspid incompetence (& [non-rheumatic])
Gyu56	[X]Other aortic valve disorders
X201F	Congenital tricuspid regurgitation
X77zv	Aortic valve cusp abnormality
P65..	Congenital mitral stenosis
X2010	Congenital mitral valve abnormality
XE1KO	Supravalvar aortic stenosis
X777o	Prosthetic mitral valve regurgitation
X201D	Tricuspid stenosis
G12z.	Rheumatic aortic valve disease NOS
Gyu5A	[X]Aortic valve disorders in diseases classified elsewhere
P600.	Pulmonary valve anomaly, unspecified
X77zx	Accessory tissue on aortic valve cusp
X200x	Post-infarction mitral papillary muscle rupture
P60..	Congenital pulmonary valve abnormality
P652.	Parachute malformation of mitral valve
G141.	Rheumatic pulmonary valve disease
XE2bE	Mitral chordae rupture
X201M	Congenital pulmonary regurgitation
G542z	Tricuspid valve disorders NOS
X7787	Torn mitral leaflet
P64z.	Congenital aortic valve insufficiency NOS
G141z	Rheumatic pulmonary valve disease NOS
X77vm	Tricuspid valve dysplasia
X777W	Aortic stenosis with doming
X7783	Rheumatic mitral valve leaflet changes

	X77vw	Tricuspid valve prolapse
	G122.	Rheumatic aortic stenosis with insufficiency
	G5434	Pulmonary valve stenosis with insufficiency
	P66..	Congenital mitral regurgitation
	X777d	Aortic valve fibrosis
	G1403	Tricuspid stenosis, cause unspecified
	G5421	Tricuspid stenosis, non-rheumatic
	X200w	Mitral regurgitation due to dysfunct subvalvular apparatus
	Gyu59	[X]Mitral valve disorders in diseases classified elsewhere
	Gyu11	[X]Other rheumatic aortic valve diseases
	P651.	Fused commissure of the mitral valve
	P6yyC	Fusion of mitral valve cusps
	G140z	Rheumatic tricuspid valve disease NOS
	X2019	Aortic regurgitation due to cystic medial necrosis of aorta
	Gyu5B	[X]Tricuspid valve disorders/diseases CE
	Gyu58	[X]Other pulmonary valve disorders
	G1402	Rheumatic tricuspid stenosis and insufficiency
	G364.	Ruptur chordae tendinae/curr comp fol acute myocard infarct
	Gyu57	[X]Other non-rheumatic tricuspid valve disorders
	G1410	Rheumatic pulmonary valve stenosis
	X77vt	Tricuspid leaflet abnormality
	P64..	Congenital aortic valve insufficiency
	X7801	Aortic valve cusp prolapse
	Gyu5f	[X]Non-rheumatic tricuspid valve disorder, unspecified
	Xa7rx	Tricuspid valve vegetations
	Gyu55	[X]Other non-rheumatic mitral valve disorders
	P60zz	Other pulmonary valve anomaly NOS
Varices	X2063	Oesophageal varices
	X20UK	Operation on oesophageal varices
	G857.	Gastric varices
	G850.	Bleeding oesophageal varices
	760C5	Fibreoptic oesophagoscopy and banding of oesophageal varices
	XaE6u	Oesophageal varices NOS
	760F4	Rigid oesophagoscopy and banding of oesophageal varices
	76094	Open injection sclerotherapy to oesophageal varices
	G8520	Oesophageal varices with bleeding in diseases EC
	760C3	Fibreoptic oesophagoscopy & injection sclerotherapy varices
	7609z	Open operation on oesophageal varices NOS
	XaC1d	Oesophageal varices in alcoholic cirrhosis of the liver
	G851.	Oesophageal varices without bleeding
	G852.	Oesophageal varices in diseases EC
	Gyu94	[X]Oesophageal varices in diseases classified elsewhere
	XaBM6	Oesophageal varices in cirrhosis of the liver
	76093	Local ligation of oesophageal varices
	Xa9G4	Duodenal varices
	X20Ui	Sclerotherapy of oesophageal varices
	7609	Open operations on oesophageal varices
	G8521	Oesophageal varices without bleeding in diseases EC
	G852z	Oesophageal varices in diseases EC NOS
	X206R	Ruptured varix