Atrial fibrillation and frailty:
An observational cohort study using electronic healthcare records

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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:


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.

A summary of findings from Chapter 7 has been accepted as an abstract at the European Society of Cardiology Congress:


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

Contribution of other authors: MY and MH assisted with coding. MH, CPG and AC provided supervision. All authors advised on methodology, contributed to the preparation of the manuscript and approved the final version.
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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.
# Table of Contents

**Acknowledgements** ........................................................................................................ iii

**Abstract** .............................................................................................................................. v

**List of Tables** ....................................................................................................................... x

**List of figures** ....................................................................................................................... xiii

**Abbreviations** ..................................................................................................................... xvii

**Chapter 1 – Frailty and the heart** ......................................................................................... 1

1.1 Aims and objectives ........................................................................................................ 2

1.2 Frailty ............................................................................................................................. 4

1.3 Frailty and cardiovascular disease .............................................................................. 15

1.4 Atrial fibrillation ........................................................................................................ 18

1.5 Atrial fibrillation and frailty ....................................................................................... 31

1.6 Summary ....................................................................................................................... 32

1.7 Conclusion ..................................................................................................................... 33

**Chapter 2 - Literature review** ............................................................................................. 35

2.1 Abstract ......................................................................................................................... 35

2.2 Introduction ................................................................................................................ 36

2.3 Methods ....................................................................................................................... 36

2.4 Results ......................................................................................................................... 40

2.5 Discussion .................................................................................................................. 53

2.6 Conclusion ................................................................................................................ 56

**Chapter 3 - Potential electronic health record data sources** .............................................. 63

3.1 Introduction ................................................................................................................ 63

3.2 Electronic health records ........................................................................................... 64

3.3 Summary ..................................................................................................................... 72

3.4 Conclusion ................................................................................................................ 72

**Chapter 4 - Development of the research cohort data set** ............................................... 73
4.1 Chapter introduction ........................................................................................................... 73
4.2 Chapter summary .................................................................................................................. 73
4.3 Study design ........................................................................................................................ 74
4.4 Data .................................................................................................................................. 74
4.5 Housing and security ......................................................................................................... 75
4.6 Ethics ................................................................................................................................. 79
4.7 Data extract ......................................................................................................................... 80
4.8 Cleaning and coding ............................................................................................................ 82
4.9 Participants ........................................................................................................................ 89
4.10 Variables ............................................................................................................................ 90
4.11 Summary ........................................................................................................................ 110
4.12 Conclusion ......................................................................................................................... 110

Chapter 5 - Analytical methods .............................................................................................. 111
5.1 Chapter introduction .......................................................................................................... 111
5.2 Chapter summary ............................................................................................................... 111
5.3 Descriptive statistics at study entry .................................................................................... 112
5.4 Rates of outcome events ..................................................................................................... 113
5.5 Prescription of oral anticoagulation in patients with AF ...................................................... 113
5.6 Survival models .................................................................................................................. 114
5.7 Sensitivity analyses ............................................................................................................ 116
5.8 Summary ............................................................................................................................ 117
5.9 Conclusion ........................................................................................................................ 118

Chapter 6 – Baseline characteristics and clinical outcomes for the whole cohort ......... 119
6.1 Chapter introduction .......................................................................................................... 119
6.2 Chapter summary ............................................................................................................... 119
6.3 Participants and data .......................................................................................................... 119
6.4 Clinical outcomes .............................................................................................................. 128


<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5</td>
<td>Summary of key findings</td>
<td>137</td>
</tr>
<tr>
<td>6.6</td>
<td>Conclusion</td>
<td>138</td>
</tr>
<tr>
<td>7.1</td>
<td>Chapter introduction</td>
<td>139</td>
</tr>
<tr>
<td>7.2</td>
<td>Chapter summary</td>
<td>139</td>
</tr>
<tr>
<td>7.3</td>
<td>Participants</td>
<td>140</td>
</tr>
<tr>
<td>7.4</td>
<td>Frailty and clinical outcomes in patients with AF</td>
<td>150</td>
</tr>
<tr>
<td>7.5</td>
<td>Summary of key findings</td>
<td>171</td>
</tr>
<tr>
<td>7.6</td>
<td>Conclusion</td>
<td>171</td>
</tr>
<tr>
<td>8.1</td>
<td>Chapter introduction</td>
<td>173</td>
</tr>
<tr>
<td>8.2</td>
<td>Chapter summary</td>
<td>173</td>
</tr>
<tr>
<td>8.3</td>
<td>Participants</td>
<td>174</td>
</tr>
<tr>
<td>8.4</td>
<td>Frailty and clinical outcomes</td>
<td>185</td>
</tr>
<tr>
<td>8.5</td>
<td>Oral anticoagulation and clinical outcomes</td>
<td>188</td>
</tr>
<tr>
<td>8.6</td>
<td>Sensitivity analyses</td>
<td>199</td>
</tr>
<tr>
<td>8.7</td>
<td>Summary of key findings</td>
<td>220</td>
</tr>
<tr>
<td>8.8</td>
<td>Conclusion</td>
<td>221</td>
</tr>
<tr>
<td>9.1</td>
<td>Introduction</td>
<td>223</td>
</tr>
<tr>
<td>9.2</td>
<td>Summary of key and novel findings</td>
<td>224</td>
</tr>
<tr>
<td>9.3</td>
<td>Findings in the context of the literature</td>
<td>226</td>
</tr>
<tr>
<td>9.4</td>
<td>Strengths and limitations</td>
<td>240</td>
</tr>
<tr>
<td>9.5</td>
<td>Implications of the study</td>
<td>256</td>
</tr>
<tr>
<td>9.6</td>
<td>Recommendations for future research</td>
<td>258</td>
</tr>
<tr>
<td>9.7</td>
<td>Conclusion</td>
<td>261</td>
</tr>
</tbody>
</table>
List of Tables

Table 1: The five indicators included in the phenotype model ........................................... 6

Table 2: The 36 deficits included in the electronic frailty index ........................................ 13

Table 3: Frailty categories using the eFI score. Also showing prevalence of frailty, and HR for all-cause mortality and nursing home (NH) admission ........................................ 14

Table 4: Rates of stroke or systemic embolism in patients with AF reported in the literature ................................................................................................................................................ 24

Table 5: Assessment of stroke risk using CHA$_2$DS$_2$-VASc ........................................... 26

Table 6: Stroke or Other Thromboembolism Events per Patient Year Based on the CHA$_2$DS$_2$-VASc Scoring System, adapted from Lip et al. 157 ........................................ 27

Table 7: Risk scores for bleeding associated with warfarin use in patients with AF .... 28

Table 8: Search strategy for Ovid Medline. Rows combined with 'OR', columns combined with 'AND' .................................................................................................................. 38

Table 9: Summary of included studies .................................................................................... 42

Table 10: Risk of bias assessment .......................................................................................... 43

Table 11: Summary of participant characteristics in the included studies ....................... 46

Table 12: Reported prevalence and definitions of frailty in included studies ................. 48

Table 13: Studies reporting the association between frailty and OAC status ................. 49

Table 14: Adjustments in studies reporting association between frailty and OAC status ...................................................................................................................................................... 57

Table 15: Summary of included studies .................................................................................... 58

Table 16: Summary of data tables that were supplied by ResearchOne ....................... 81

Table 17: Ethnic category codes ............................................................................................ 86

Table 18: Illustrative anonymised extract from the medications table .............................. 88

Table 19: CTV-3 codes used to define the AF cohort .......................................................... 92

Table 20: Search terms used to identify oral anticoagulants ............................................. 93
Table 21: DOAC dosing regimens that were considered as therapeutic for patients with AF, and alternative possible indications for each dose .................................. 95

Table 22: Examples of how persistence has been defined in the literature .................. 97

Table 23: ATRIA risk score and risk of bleeding ......................................................... 103

Table 24: Search terms used to identify medications of interest ................................. 109

Table 25: Prevalence of atrial fibrillation by age category ........................................ 123

Table 26: Electronic frailty index category by AF status ............................................. 124

Table 27: Baseline characteristics of the cohort by AF status ..................................... 126

Table 28: Rates of outcome events by AF status ....................................................... 130

Table 29: Baseline characteristics of patients with AF by frailty status ....................... 142

Table 30: Medication history of patients with AF, by frailty status ............................. 149

Table 31: Outcomes by frailty status, all patients with AF stratified by age category.
Rates per 1000 patient years ...................................................................................... 152

Table 32: Baseline characteristics of patients with AF, by OAC status ...................... 176

Table 33: Medication history by oral anticoagulation prescription at study entry
status. Patients with AF and CHA₂DS₂-VASc score of two or more, n=58,204 181

Table 34: Prescription rates of each OAC, of those prescribed OAC at study entry .. 184

Table 35: Rates of clinical outcomes (/1000pys) in patients with AF and CHA₂DS₂-VASc
score of 2 or more by frailty status. n=58,204 ......................................................... 187

Table 36: Stroke rates by OAC status, stratified by CHA₂DS₂-VASc score ............... 190

Table 37: Rates of outcome events (per 1000 person-years) by OAC status in patients
with AF and a CHA₂DS₂-VASc score of two or more ............................................. 193

Table 38: Rates (per 1000 person-years) of outcome events by anticoagulation status
in all patients with AF .............................................................................................. 194

Table 39: Association between frailty category and clinical outcomes by OAC status in
patients with AF and CHA₂DS₂-VASC of ≥2, n=58,204 .................................. 196
Table 40: Frequency of the use of each CTV-3 code in the electronic health record of patients with AF, n=61,177 ..............................................................200

Table 41: Baseline characteristics of patients with specific code-list for sensitivity analysis ........................................................................................................................................203

Table 42: Clinical outcome events by AF sensitivity analysis analytical cohort subgroups, in patients with CHA₂DS₂-VASC score of two or more. Rates, /1000pys (95% CI) ........................................................................................................................................204

Table 43: Rates of outcome events (/1000pys) in patients with AF and a CHA₂DS₂-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). ......................205

Table 44: Association between OAC at study entry and clinical events in patients with CHA₂DS₂-VASC score ≥2, in the reduced analytical cohort. n=50,010 ..................206

Table 45: Characteristics of patients with AF and CHA₂DS₂-VASC score ≥2, by OAC persistence ........................................................................................................................................210
List of figures

Figure 1: Diagram of the heart, showing the anatomical location of the left atrium and the left atrial appendage. Artist: Bryony Cousins ........................................ 19

Figure 2: Virchow’s triad of criteria for thrombus formation ........................................ 22

Figure 3: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of the included studies ........................................ 40

Figure 4: Forest plot to show the association between frailty and anticoagulation status at admission, at discharge, and in the community ........................................ 51

Figure 5: Examples of electronic health records available in the UK ........................................ 64

Figure 6: Chart to illustrate data flow ........................................................................ 75

Figure 7: Illustration of the effect of coding on a dummy dataset ........................................ 84

Figure 8: Example of the ‘parent’ and ‘child’ structure of CTV-3 codes ........................................ 85

Figure 9: Categories of subgroups for analysis ........................................................................ 89

Figure 10: Illustration of censoring in survival analysis ........................................ 100

Figure 11: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram to show the derivation of the analytic cohort ........................................ 120

Figure 12: Histogram of age at study entry by AF status ........................................ 121

Figure 13: Histogram of frailty categories for the complete cohort, n=536,955 ....... 122

Figure 14: Bar chart to show the prevalence of AF by electronic frailty index category ........................................................................ 123

Figure 15: Number of electronic frailty index deficits by AF status at the time of study entry ........................................................................ 124

Figure 16: Difference in recorded past medical history between those with and without AF ........................................................................ 127

Figure 17: Kaplan-Meier graph showing all-cause mortality by frailty category, with 95% confidence interval. n=536,955 ........................................................................ 128
Figure 18: Kaplan-Meier graph showing all-cause mortality by AF status, with 95% confidence interval. n=536,955 .................................................................129

Figure 19: Kaplan-Meier graph showing incidence of first stroke event by frailty category, with 95% confidence interval. n=536,955 ........................................131

Figure 20: Kaplan-Meier graph showing first stroke event by AF status, with 95% confidence interval. n=536,955 .................................................................132

Figure 21: Kaplan-Meier graph showing incidence of first gastrointestinal bleeding event by frailty category, with 95% confidence interval. n=536,955 ............133

Figure 22: Kaplan-Meier graph showing first gastrointestinal bleeding event by AF status, with 95% confidence interval. n=536,955 ................................................134

Figure 23: Kaplan-Meier graph showing incidence of first intracranial bleeding event by frailty category, with 95% confidence interval. n=536,955 .....................135

Figure 24: Kaplan-Meier graph showing first intracranial bleeding event by AF status, with 95% confidence interval. n=536,955 ................................................136

Figure 25: Box plot showing CHA\textsubscript{2}-DS\textsubscript{2}-Vasc score at study entry by electronic frailty index category .................................................................144

Figure 26: Box plot showing ATRIA score at study entry by electronic frailty index category ...........................................................................................................145

Figure 27: Chart showing percentage of patients with past medical history recorded of each condition of interest, by frailty category ........................................146

Figure 28: Bar chart showing proportion of patients prescribed key medications of interest, by frailty status ..................................................................................147

Figure 29: Kaplan-Meier graph showing all-cause mortality by frailty category in patients with AF, with 95% confidence interval. n=61,177 ......................150

Figure 30: Mortality rates /1000pys by age category in patients with AF, n=61,177151

Figure 31: Association between frailty status and all-cause mortality in patients with AF, n=61,177 ..............................................................................................155

Figure 32: First stroke event by frailty category. Patients with AF, n=61,177 .........156
Figure 33: Association between frailty status and ischaemic or unspecified stroke in patients with AF, n=61,177

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

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

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

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

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

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

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

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

Figure 43: Stroke and bleeding risk (CHA_{2}DS_{2}-VASc and ATRIA) scores by oral anticoagulation prescription status, in patients with CHA_{2}DS_{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
Figure 45: Proportion of patients with AF and a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of two or more that were prescribed OAC at study entry by electronic frailty index category, n=58,204 ………………………………………………………………………………………………………182

Figure 46: Association between eFI category and OAC prescription at study entry in patients with AF and CHA\textsubscript{2}DS\textsubscript{2}-VASc score of two or more. n=58,204 …………183

Figure 47: Rate of stroke per 1000 patient years by CHA\textsubscript{2}DS\textsubscript{2}-VASc score and OAC status, n=61,177 ………………………………………………………………………………………………………189

Figure 48: Rates of outcome events by oral anticoagulation status in patients with AF and a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 2 or more, n=58,204 …………………………………………………………………………………………………………………192

Figure 49: Illustration of the derivation of the reduced analytical cohort for a sensitivity analysis using a more specific AF code set ……………………………………………………………………………………………202

Figure 50: Sensitivity analysis showing the unadjusted association between OAC and clinical outcomes in patients with AF and CHA\textsubscript{2}DS\textsubscript{2}-VASc score of two or more …………………………………………………………………………………………………………………………………………………………………………………207

Figure 51: Illustration of the derivation of the subgroups for a sensitivity analysis of OAC persistence………………………………………………………………………………………………………………………………………………………………………………208

Figure 52: Forest plot showing the unadjusted results of the sensitivity analyses …………………………………………………………………………………………………………………………………………………………………………………213

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>/1000pys</td>
<td>per 1000 person-years</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>BD</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BGS</td>
<td>British Geriatric Society</td>
</tr>
<tr>
<td>BNF</td>
<td>British National formulary</td>
</tr>
<tr>
<td>CALIBER</td>
<td>Clinical research using Ilked bespoke studies and electronic health Records</td>
</tr>
<tr>
<td>CCS</td>
<td>Charlson comorbidity score</td>
</tr>
<tr>
<td>CFS</td>
<td>Clinical frail scale</td>
</tr>
<tr>
<td>CGA</td>
<td>Comprehensive geriatric assessment</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CPRD</td>
<td>Clinical practice research datalink</td>
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<tr>
<td>CSV</td>
<td>Comma-separated values</td>
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<tr>
<td>CTV-3</td>
<td>Clinical terms version 3</td>
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<tr>
<td>DOAC</td>
<td>Direct oral anticoagulant</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>eFI</td>
<td>Electronic frailty index</td>
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<tr>
<td>EFS</td>
<td>Edmonton frail scale</td>
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<tr>
<td>EHR</td>
<td>Electronic health records</td>
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<tr>
<td>EMIS</td>
<td>Egton medical information systems</td>
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<tr>
<td>ESC</td>
<td>European society of cardiology</td>
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<tr>
<td>GARFIELD-AF</td>
<td>Global anticoagulant registry in the field - atrial fibrillation</td>
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<tr>
<td>GFI</td>
<td>Groningen frailty indicator</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GRASP-AF</td>
<td>Guidance on risk assessment in stroke prevention for atrial fibrillation</td>
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<tr>
<td>GUG&amp;G</td>
<td>Get-up and go test</td>
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<tr>
<td>H/O</td>
<td>History of</td>
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<tr>
<td>HES</td>
<td>Hospital episode statistics</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>IC</td>
<td>Intracranial</td>
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ICD-10 / 11  International statistical classification of diseases and related health problems 10th/11th 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
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VRE</td>
<td>Virtual research environment</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
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<tr>
<td>WHO</td>
<td>World health organisation</td>
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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. 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. 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. 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.

Multimorbidity is the coexistence of two or more long-term conditions in an individual. 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. However, there is limited evidence that ‘more healthcare’ will necessarily improve outcomes. 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, 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. Frailty provides an insight into biological age and is more useful than chronological age in predicting adverse events including death.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10,13} These changes have been described in skeletal muscle, the brain, and in the endocrine, immune, cardiovascular, respiratory and renal systems.\textsuperscript{10}

Frailty may explain the differential vulnerability to adverse outcomes of people of the same chronological age.\textsuperscript{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.\textsuperscript{11,17} However, frailty is considered to have greater reversibility than disability,\textsuperscript{18-20} and there is now an increased focus on frailty prevention in mid-life,\textsuperscript{3} and on identifying patients at risk of frailty through National Health Services (NHS) general practices with the aim of improved holistic patient care.\textsuperscript{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.\textsuperscript{23} The British Geriatric Society (BGS) recommends routine assessment for frailty during all encounters with health and social care professionals.\textsuperscript{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.\textsuperscript{25} This is in-keeping with an international consensus that patients aged over 70 years should be screened for frailty.\textsuperscript{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. 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%, \( p<0.001 \)). 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. 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. The authors suggest that at least 4,000 patients with frailty are admitted per month to hospitals in England.

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. In Europe, 25% of the population are aged 60 years or over, but this is projected to increase to 35% by 2050. 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. 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. 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. 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. 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. |

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), 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.

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. 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. 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. 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.

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”. 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. 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.

The original frailty index consisted of 92 items from the cross-sectional and longitudinal components of the Canadian Study of Health and Ageing. 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.
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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{40} and allows a graded approach to evaluating frailty in a number of different clinical settings.\textsuperscript{32}

\subsection{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{57}

1.2.6.3 Grip strength
Low grip strength is predictive of functional decline and mortality in community-dwelling adults.\textsuperscript{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).\textsuperscript{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.\textsuperscript{29}

1.2.7.1 QMortality
QMortality is a risk prediction algorithm to estimate short term risk of death and assess frailty.\textsuperscript{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).\textsuperscript{26}

\subsection*{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 (\textit{n}=22,139) of patients aged 75 years or older who had been discharged from hospital.\textsuperscript{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 \textit{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).\textsuperscript{29}

\subsection*{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.\textsuperscript{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.\textsuperscript{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

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

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 widespread 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.

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

Adapted from Clegg and de Biase.\textsuperscript{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.\textsuperscript{63} There is evidence that manifest or subclinical frailty is an important consideration across a range of cardiovascular conditions,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{67}

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

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. Frailty is common in patients with acute coronary syndrome, and is a risk factor for mortality. Trials are ongoing to establish the optimal care strategy in patients with frailty and acute coronary syndrome, who were under-represented in the evidence that underpins clinical guideline recommendations, and who may not be best served by single-organ orientated care strategies.

1.3.3 Heart failure

In the UK, the mean age at first diagnosis of heart failure is 77.0 years (SD 12.9). 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. As in acute coronary syndrome, patients with heart failure and frailty are underrepresented in clinical trials.

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, who also have higher complication and mortality rates following implantation. 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.
Age should not necessarily be a barrier to defibrillator implant, as rates of appropriate shocks are similar across age categories. Instead, defibrillator specific risk scores alongside frailty assessment are advised, particularly when deciding between resynchronisation pacing, which is associated with symptomatic improvement and left ventricular remodelling in older people, and a defibrillator alone, which does not improve symptoms. 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.

1.3.4 Valvular heart disease

In Europe, valvular heart disease is predominantly degenerative and age-related. By way of example, aortic stenosis affects 9.8% of people over 80 years of age, many of whom are also frail. 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. 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. Although the procedure is associated with an increased risk of post-procedural mortality and delirium in patients with frailty, 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.

1.3.5 Stroke

There were 84,184 patients admitted to hospitals in England, Wales and Northern Ireland with stroke between 2015 and 2016. 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, 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, raising the concept of frailty as an important consideration. Frailty is independently associated with increased mortality and care home admission following stroke, and frailty status may be a greater determinant of clinical outcome than the currently available optimal
medical therapy for hyper-acute stroke. 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.

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. 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. 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). Subsequent thromboembolism may then cause cerebral infarction leading to a stroke, or infarction elsewhere. Atrial flutter is a more 'organised' rhythm that commonly coexists with or precedes AF, and also carries an elevated stroke risk.
Over time, oxidative stress promotes remodelling of the electromechanical activity of the atria. 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.
1.4.2 Epidemiology of atrial fibrillation

Atrial fibrillation affects 2-3% of the population of Europe.\textsuperscript{130} In the UK, age and sex standardised prevalence of AF was 3.3\% (95\% CI 3.27\% to 3.32\%) in 2016.\textsuperscript{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.\textsuperscript{132} The incidence and prevalence of AF is higher with increasing age.\textsuperscript{131, 132} The prevalence of the risk factors for developing AF are also increasing over time.\textsuperscript{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’.\textsuperscript{130}

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

Atrial fibrillation is associated with a range of adverse outcomes, including stroke, heart failure, unplanned hospital admission and death.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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’, 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 defibrillators. In England, NICE recommend investigating for AF as part of the assessment of a symptomatic patient. There is currently no consensus on population-based screening for AF, although this is a rapidly developing area. Watches are now being marketed that include technology that may identify episodes of AF, 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. 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.
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.\textsuperscript{125, 142} If the symptoms and signs related to cerebral ischaemia resolve within 24 hours, this is known as a transient ischaemic attack (TIA).\textsuperscript{143} However, if they persist for longer than 24 hours then the criteria for a diagnosis of stroke are met.\textsuperscript{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\%\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{112}

\textbf{1.4.6 Oral anticoagulation for stroke prophylaxis in atrial fibrillation}

Until 2012, warfarin was the only commonly used OAC in the UK.\textsuperscript{154} Warfarin has a narrow therapeutic window, and requires blood test monitoring to guide dose-adjustment.\textsuperscript{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.\textsuperscript{148} Each has been shown to be non-inferior to warfarin in stroke reduction, Table 4.
<table>
<thead>
<tr>
<th>Study, year (ref)</th>
<th>Warfarin, compared with:</th>
<th>Patients enrolled</th>
<th>Stroke or systemic embolism, rate per 100 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warfarin</td>
</tr>
<tr>
<td>ROCKET AF. 2011</td>
<td>Rivaroxaban 20mg OD</td>
<td>14,143</td>
<td>2.4</td>
</tr>
<tr>
<td>RE-LY. 2009</td>
<td>Dabigatran 150mg BD*</td>
<td>18,113</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 110mg BD</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48. 2013</td>
<td>Edoxaban 60mg OD</td>
<td>21,105</td>
<td>1.5</td>
</tr>
<tr>
<td>ARISTOTLE. 2011</td>
<td>Apixaban 5mg BD</td>
<td>18,201</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**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. Valvular AF is associated with a particularly high stroke risk, requiring more intensive anticoagulation using warfarin. 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, and left atrial dilatation is associated with further blood stasis and propensity to thrombosis. None of the DOAC agents are currently licenced for use in valvular AF. Where a patient has a prosthetic heart valve, there is clear guidance for OAC directed for the specific valvular indication. Where a patient has AF and OAC is not indicated for the prosthetic valve, for example in the case of a bioprosthetic 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\textsuperscript{140} and the ESC\textsuperscript{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\textsubscript{2}DS\textsubscript{2}-VASc score.\textsuperscript{157} There were four thromboembolic risk scoring systems identified in a recent meta-analysis.\textsuperscript{158} These were the Framingham,\textsuperscript{159} ABC,\textsuperscript{160} CHADS\textsubscript{2},\textsuperscript{161} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{160} The score was developed using data from the ARISTOTLE trial,\textsuperscript{152} and validated using data from the STABILITY trial.\textsuperscript{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\textsubscript{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).\textsuperscript{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.\textsuperscript{158} One particular weakness of the CHADS\textsubscript{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\textsubscript{2} score of zero was 1.9 (1.2 to 3.0) per 100 person-years.\textsuperscript{161} The CHA\textsubscript{2}DS\textsubscript{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\textsubscript{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\textsubscript{2}DS\textsubscript{2}-VASc**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;65 years old</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>65-74 years old</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>≥ 75 years old</td>
<td>+2</td>
</tr>
<tr>
<td>Sex</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>+1</td>
</tr>
<tr>
<td>Congestive heart failure history</td>
<td>Yes / no</td>
<td>+1</td>
</tr>
<tr>
<td>Hypertension history</td>
<td>Yes / no</td>
<td>+1</td>
</tr>
<tr>
<td>Stroke / TIA / thromboembolism history</td>
<td>Yes / no</td>
<td>+2</td>
</tr>
<tr>
<td>Vascular disease history</td>
<td>Yes / no</td>
<td>+1</td>
</tr>
<tr>
<td>Diabetes mellitus history</td>
<td>Yes / no</td>
<td>+1</td>
</tr>
</tbody>
</table>

**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.\textsuperscript{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.\textsuperscript{144} In this model, a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 9 was associated with a stroke risk of 15.2 per 100 person-years, Table 6.\textsuperscript{157}
In a meta-analysis of 17 studies, the c-statistic for prediction of stroke using CHA$_2$DS$_2$-VASc was 0.67 (95% CI 0.64 to 0.70). On the basis of their meta-analysis, the authors suggest that there is little difference between the four scores. At present, CHA$_2$DS$_2$-VASc is recommended in national and international guidelines, and is widely used. NICE guidelines state that OAC should be considered in men with a CHA$_2$DS$_2$-VASc score of one, and should be offered to men or women with a CHA$_2$DS$_2$-VASc of two or more.

### 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. Four commonly used scores for estimating bleeding risk in patients taking warfarin and the evidence supporting their use are summarised in Table 7.
**Table 7: Risk scores for bleeding associated with warfarin use in patients with AF**

<table>
<thead>
<tr>
<th>Bleeding risk score</th>
<th>Components of score</th>
<th>Cohort</th>
<th>Risk thresholds</th>
<th>Definition of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAS-BLED</strong>(^\text{171})**</td>
<td>1 point each for: Hypertension, abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition, labile INR, age &gt;65 years, concomitant use of antiplatelet or NSAID, alcohol consumption.</td>
<td>Euro Heart Survey n= 3,978</td>
<td>Low: 0–1</td>
<td>any bleed requiring hospitalization or causing a decrease in haemoglobin level of 2 g/L or requiring blood transfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 ESC member countries</td>
<td>Intermediate: 2–3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High: ≥ 4</td>
<td></td>
</tr>
<tr>
<td><strong>HEMORR(_2)HAGES</strong>(^\text{172})**</td>
<td>1 point each for: Hepatic or renal disease, alcohol abuse, malignancy, age &gt;75 years, reduced platelet count or function, uncontrolled hypertension, anaemia, genetic factors (CYP 2C9 single-nucleotide polymorphisms), excessive fall risk, stroke.</td>
<td>National Registry of Atrial Fibrillation (NRAF), USA n= 3791</td>
<td>Low: 0 - 1</td>
<td>Hospital admission, any site of bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate: 2-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High: ≥4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 points for: previous haemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding risk score</td>
<td>Components of score</td>
<td>Cohort</td>
<td>Risk thresholds</td>
<td>Definition of major bleeding</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------</td>
<td>--------</td>
<td>-----------------</td>
<td>-----------------------------</td>
</tr>
</tbody>
</table>
| **ORBIT**<sup>173</sup>  
(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.<sup>218</sup> |
| **ATRIA**<sup>174</sup> | 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 CHADS₂ score two or more. The score includes age, prior bleeding, haemoglobin, baseline high-sensitivity troponin T, and growth differentiation factor-15. 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.

NICE guidelines currently recommend the HAS-BLED score, which was first published in 2010. Two recent meta-analyses have concluded that HAS-BLED has the best evidence for predicting bleeding risk. 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. 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. 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.
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.\textsuperscript{126,167} This is supported by evidence that generally there is no mortality advantage to a rhythm control strategy,\textsuperscript{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.\textsuperscript{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.\textsuperscript{178,180} However, all of the eight studies included were at high risk of bias, partly due to incomplete blinding.\textsuperscript{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 \textit{CHA}\textsubscript{2DS}\textsubscript{2}-VASc score of two or more, and would therefore be considered eligible for treatment.\textsuperscript{145} Older people, who tend to have the highest baseline risk of stroke, are often not prescribed OAC.\textsuperscript{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.\textsuperscript{11,184} However, clinical guidelines tend to focus upon single-organ conditions, and take little account of frailty.\textsuperscript{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.\textsuperscript{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.\textsuperscript{186} As the prevalence of AF and of frailty are increasing,\textsuperscript{131,187} and each condition is associated with a substantial burden of
morbidity and mortality,\textsuperscript{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 \textit{CHA}\textsubscript{2}D\textsubscript{S}\textsubscript{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 0.13-0.72]).
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.
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<thead>
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<th>frail elderly/</th>
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<td>(frail* or sarcop?eni* or prefrailty).tw.</td>
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<td>(multimorbid* or multi-morbid*).tw.</td>
</tr>
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<td>(electric* adj2 ablation*).tw.</td>
<td>(multidisease? or multi-disease? or (multiple adj (ill* or disease? or condition? or syndrom* or disorder??)).tw.</td>
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<td>anti-arrhythmhi*.tw.</td>
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<td>exp Anticoagulants/</td>
<td>&quot;comprehensive geriatric assessment&quot;.tw.</td>
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<td>(multimorbid* or multi-morbid*).tw.</td>
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<td>antithrombotic*.tw.</td>
<td>(multidisease? or multi-disease? or (multiple adj (ill* or disease? or condition? or syndrom* or disorder??))).tw.</td>
</tr>
</tbody>
</table>

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

![Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of the included studies](image)

Figure 3: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of the included studies228
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, and fourteen in a narrative synthesis. All were observational studies.

2.4.2 Study characteristics

Twelve cross-sectional and eight cohort studies were included, with a total of 30,883 participants, Table 9. 15 studies were based in hospital, and five were community-based, one of which involved nursing home residents. Thirteen studies were conducted in Europe, three in Australia, three in North America, and one in Taiwan.

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 and follow-up duration. However, these did not relate to the specific meta-analysis question of OAC and frailty associations.
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<th>Study</th>
<th>Setting</th>
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<td>GU&amp;G</td>
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<td>225</td>
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<tr>
<td>Polidoro, 2013 198</td>
<td>Hospital</td>
<td>none</td>
<td>79.3</td>
<td>Italy</td>
<td>Frailty index&lt;sup&gt;17&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td><strong>Retrospective cross-sectional studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annoni, 2016 189</td>
<td>Hospital</td>
<td>≥65</td>
<td>84.6</td>
<td>Italy</td>
<td>Robinson criteria&lt;sup&gt;192&lt;/sup&gt;</td>
<td>1619</td>
</tr>
<tr>
<td>Induruwa, 2017 197</td>
<td>Hospital</td>
<td>≥75</td>
<td>85.3</td>
<td>England</td>
<td>CFS</td>
<td>419</td>
</tr>
<tr>
<td>Lefebvre, 2016 190</td>
<td>Hospital</td>
<td>≥80</td>
<td>85.9</td>
<td>Canada</td>
<td>CFS</td>
<td>682</td>
</tr>
<tr>
<td><strong>Prospective cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bo, 2017 199</td>
<td>Hospital</td>
<td>≥65</td>
<td>81.6</td>
<td>Italy</td>
<td>GFI</td>
<td>452</td>
</tr>
<tr>
<td>Doucet, 2008 1</td>
<td>Hospital</td>
<td>&gt;65</td>
<td>84.7</td>
<td>France</td>
<td>GU&amp;G</td>
<td>209</td>
</tr>
<tr>
<td>Gullón, 2017 194</td>
<td>Hospital</td>
<td>&gt;75</td>
<td>85</td>
<td>Spain</td>
<td>FRAIL scale</td>
<td>804</td>
</tr>
<tr>
<td>Magnani, 2016 201</td>
<td>Community</td>
<td>70-79</td>
<td>N/A</td>
<td>USA</td>
<td>Health ABC battery</td>
<td>2753</td>
</tr>
<tr>
<td>Nguyen, 2016 210</td>
<td>Hospital</td>
<td>≥65</td>
<td>84.7</td>
<td>Australia</td>
<td>Reported EFS</td>
<td>302</td>
</tr>
<tr>
<td>Nguyen, 2016 211</td>
<td>Hospital</td>
<td>≥65</td>
<td>84.7</td>
<td>Australia</td>
<td>Reported EFS</td>
<td>302</td>
</tr>
<tr>
<td>Perera, 2009 181</td>
<td>Hospital</td>
<td>≥70</td>
<td>82.7</td>
<td>Australia</td>
<td>Modified EFS</td>
<td>207</td>
</tr>
<tr>
<td><strong>Retrospective cohort study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilotto, 2016 191</td>
<td>Community, previous hospitalisation</td>
<td>≥65</td>
<td>84.4</td>
<td>Italy</td>
<td>MPI</td>
<td>1287</td>
</tr>
</tbody>
</table>

**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.
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.

### Table 10: Risk of bias assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection of exposed cohort</th>
<th>Represntative of non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Controls and adjustment</th>
<th>Ascertainment of outcome</th>
<th>Statistical test</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonmil, 2016</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Bo, 2015 vs. 2016</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Donohue, 2014</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Frewen, 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Hess, 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Hung, 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Induruwa, 2017</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Lefevre, 2016</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Mlynarska, 2017</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>O’Caoimh, 2017</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Pollono, 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Saelens, 2017</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
44

Cohort studies

Doucet
20081

Bo
2017199

1

1

1

1

0

1

1

1

1

1

1

1

1

1

1

1

1

1

2

2

2

2

2

1

2

1

0

1

1

1

1

1

1

1

0

0

0

1

1

0

0

1

1

0

0

0

1

0

0

Adequate
follow-up

8

7

7

7

8

8

6

7

Total

Outcome

Gullón,
2017194
1

1

1

1

2

Comparability

Magnani
2016 201
1

1

1

1

Selection

Nguyen
2016 210
1

1

1

Ascertainment Was follow-up
long enough
of outcome

Nguyen
2016 211

1

0

Controls and
adjusted

Perera
2009 181

1

Representative Selection of Ascertainment Outcome not
of exposed
present at
non-exposed of exposure
cohort
cohort
start

Pilotto
2016 191


2.4.4 Participant characteristics

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

Eight studies also included patients without AF.\textsuperscript{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\textsuperscript{166, 189, 198, 201, 203, 206}), range 56 to 96 (2 studies\textsuperscript{198, 206}). 50.3\% were female (7 studies\textsuperscript{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\textsuperscript{56}, clinical frailty scale\textsuperscript{36}, and Edmonton frail scale\textsuperscript{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.\textsuperscript{189, 200, 203, 206, 212, 213} It varied by setting from 3\% in community-dwellers,\textsuperscript{206, 212} to 38\% in nursing home residents.\textsuperscript{213} In three studies of older patients admitted acutely to hospital, AF was identified in 14\%,\textsuperscript{200} 17\%,\textsuperscript{203} and 24\%\textsuperscript{189}, Table 11.
Table 11: Summary of participant characteristics in the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion age</th>
<th>AF prevalence</th>
<th>Participants with AF</th>
<th>Whole cohort (those with and without AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>Mean age [median]</td>
</tr>
<tr>
<td>Annoni</td>
<td>≥65</td>
<td>24.3%</td>
<td>403</td>
<td>84.6</td>
</tr>
<tr>
<td>Bo, 2015</td>
<td>≥65</td>
<td>-</td>
<td>631</td>
<td>81.7</td>
</tr>
<tr>
<td>Bo, 2017</td>
<td>≥65</td>
<td>-</td>
<td>513</td>
<td>81.6</td>
</tr>
<tr>
<td>Denoël</td>
<td>≥75</td>
<td>14%</td>
<td>142</td>
<td>NR</td>
</tr>
<tr>
<td>Donoghue</td>
<td>≥50</td>
<td>3.1%</td>
<td>112</td>
<td>70.7</td>
</tr>
<tr>
<td>Doucet</td>
<td>≥65</td>
<td>-</td>
<td>228</td>
<td>84.7</td>
</tr>
<tr>
<td>Frewen</td>
<td>≥50</td>
<td>3%</td>
<td>118</td>
<td>63.8</td>
</tr>
<tr>
<td>Gullón</td>
<td>&gt;75</td>
<td>-</td>
<td>804</td>
<td>85</td>
</tr>
<tr>
<td>Hess</td>
<td>≥18</td>
<td>-</td>
<td>10,096</td>
<td>[75]</td>
</tr>
<tr>
<td>Hung</td>
<td>≥75</td>
<td>16.5%</td>
<td>66</td>
<td>82.6</td>
</tr>
<tr>
<td>Induruwa</td>
<td>≥75</td>
<td>-</td>
<td>419</td>
<td>85.3</td>
</tr>
<tr>
<td>Lefebvre</td>
<td>≥80</td>
<td>-</td>
<td>682</td>
<td>85.9</td>
</tr>
<tr>
<td>Magnani</td>
<td>70-79</td>
<td>-</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mlynarska</td>
<td>None</td>
<td>-</td>
<td>132</td>
<td>72.7</td>
</tr>
<tr>
<td>Nguyen</td>
<td>≥65</td>
<td>-</td>
<td>302</td>
<td>84.7</td>
</tr>
<tr>
<td>Nguyen</td>
<td>≥65</td>
<td>-</td>
<td>302</td>
<td>84.7</td>
</tr>
<tr>
<td>O'Caomh</td>
<td>None</td>
<td>38%</td>
<td>86</td>
<td>[84]</td>
</tr>
<tr>
<td>Perera</td>
<td>≥70</td>
<td>-</td>
<td>220</td>
<td>82.7</td>
</tr>
<tr>
<td>Pilotto</td>
<td>≥65</td>
<td>-</td>
<td>1827</td>
<td>84.4</td>
</tr>
<tr>
<td>Polidoro</td>
<td>None</td>
<td>-</td>
<td>70</td>
<td>79.3</td>
</tr>
</tbody>
</table>

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.\textsuperscript{181, 189-191, 193, 194, 197-200, 202, 203, 209-211, 213} This varied between populations, affecting 6\% in a registry of outpatients aged \( \geq 18\),\textsuperscript{202} and 100\% in a nursing home population.\textsuperscript{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).\textsuperscript{198}

Hung \textit{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).\textsuperscript{203} However, the tendency to fall may have increased AF case-detection through use of ambulatory electrocardiography. Magnani \textit{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.\textsuperscript{201}
<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age [median], patients with AF</th>
<th>Frailty definition</th>
<th>Frailty prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Measure</td>
<td>Cut-point</td>
</tr>
<tr>
<td>Annoni</td>
<td>84.6</td>
<td>Robinson criteria</td>
<td>≥4</td>
</tr>
<tr>
<td>Bo</td>
<td>81.7</td>
<td>GFI</td>
<td>≥4</td>
</tr>
<tr>
<td>Bo</td>
<td>81.6</td>
<td>GFI</td>
<td>≥4</td>
</tr>
<tr>
<td>Denoël</td>
<td>NR</td>
<td>ISAR</td>
<td>≥2</td>
</tr>
<tr>
<td>Donoghue</td>
<td>70.7</td>
<td>GU&amp;G Gait speed</td>
<td>Comparison was made between groups with AF and without AF, no threshold was used</td>
</tr>
<tr>
<td>Doucet</td>
<td>84.7</td>
<td>GU&amp;G</td>
<td>Comparison was made between those prescribed OAC and those that weren't.</td>
</tr>
<tr>
<td>Frewen</td>
<td>63.8</td>
<td>Fried criteria</td>
<td>≥1</td>
</tr>
<tr>
<td>Gullón</td>
<td>85</td>
<td>FRAIL scale</td>
<td>≥3</td>
</tr>
<tr>
<td>Hess</td>
<td>[75]</td>
<td>Fried criteria</td>
<td>≥3</td>
</tr>
<tr>
<td>Hung</td>
<td>82.6</td>
<td>GU&amp;G</td>
<td>&gt;10 seconds</td>
</tr>
<tr>
<td>Induruwa</td>
<td>85.3</td>
<td>CFS</td>
<td>5-8</td>
</tr>
<tr>
<td>Lefebvre</td>
<td>85.9</td>
<td>CFS</td>
<td>≥7</td>
</tr>
<tr>
<td>Magnani</td>
<td>N/A</td>
<td>Health ABC PPB</td>
<td>Scores were compared over time for the same individuals, and the effect of developing AF estimated</td>
</tr>
<tr>
<td>Mlynarska</td>
<td>72.7</td>
<td>TFI</td>
<td>≥5</td>
</tr>
<tr>
<td>Nguyen</td>
<td>84.7</td>
<td>Reported EFS</td>
<td>≥8</td>
</tr>
<tr>
<td>Nguyen</td>
<td>84.7</td>
<td>Reported EFS</td>
<td>≥8</td>
</tr>
<tr>
<td>O’Caoimh</td>
<td>[84]</td>
<td>CFS</td>
<td>≥5</td>
</tr>
<tr>
<td>Perera</td>
<td>82.7</td>
<td>Modified EFS</td>
<td>≥8</td>
</tr>
<tr>
<td>Pilotto</td>
<td>84.4</td>
<td>MPI</td>
<td>≥2</td>
</tr>
<tr>
<td>Polidoro</td>
<td>79.3</td>
<td>Frailty index</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Association: frailty and OAC</th>
<th>Time of assessment</th>
<th>n=</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frewen, 2013</td>
<td>More use</td>
<td>Community sample</td>
<td>118</td>
<td>2.33 (1.03-5.23)</td>
<td>NR</td>
</tr>
<tr>
<td>Doucet, 2008</td>
<td>No difference</td>
<td>Hospital discharge</td>
<td>209</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nguyen, 2016</td>
<td>No difference</td>
<td>Hospital discharge</td>
<td>197</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bo, 2015</td>
<td>No difference</td>
<td>Hospital discharge</td>
<td>302</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Denoël, 2014</td>
<td>No difference</td>
<td>Hospital admission</td>
<td>412</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Perera, 2009</td>
<td>Less use</td>
<td>Hospital discharge</td>
<td>220</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Induruwa, 2017</td>
<td>Less use</td>
<td>Hospital admission</td>
<td>419</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lefebvre, 2016</td>
<td>Less use</td>
<td>Hospital admission</td>
<td>682</td>
<td>0.45 (0.31-0.65)</td>
<td>NR</td>
</tr>
<tr>
<td>Nguyen, 2016</td>
<td>Less use</td>
<td>Hospital discharge</td>
<td>142</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Denoël, 2014</td>
<td>More use</td>
<td>Community sample</td>
<td>118</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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.\textsuperscript{181, 190, 193, 197, 210} Two studies reported OR at admission,\textsuperscript{190, 197} and two at discharge.\textsuperscript{193, 210} One study reported both.\textsuperscript{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].\textsuperscript{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].\textsuperscript{200} The later was a small study using a brief screening tool with limited predictive validity (Identifying Seniors at Risk).\textsuperscript{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]).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{193}
Figure 4: Forest plot to show the association between frailty and anticoagulation status at admission, at discharge, and in the community.

All studies included in the meta-analysis were judged at low risk of bias.
2.4.9 Direct oral anticoagulation prescription

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

2.4.10 Age, co-morbidity, and oral anticoagulation

Six studies reported the association between increasing age and OAC prescription,\textsuperscript{166, 190, 193, 197, 210} five of which adjusted for other factors, Table 14.\textsuperscript{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]),\textsuperscript{190, 193, 197, 210} but not in the fifth (adjusted OR 1.02 [0.97 to 1.07]).\textsuperscript{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).\textsuperscript{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.\textsuperscript{193} The second showed no statistically significant difference in score between those prescribed OAC and those that were not.\textsuperscript{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.\textsuperscript{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]).\textsuperscript{181} Nguyen \textit{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.\textsuperscript{210}

Doucet \textit{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.\textsuperscript{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]).\textsuperscript{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\textsubscript{2}DS\textsubscript{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.\textsuperscript{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).\textsuperscript{199} A further study found that functional status, but not frailty (FRAIL scale), was independently associated with inpatient mortality.\textsuperscript{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, medium-term mortality, symptom severity, and length of hospital stay. One study showed frailty was not associated with stroke or major bleeding. Having AF was associated with a greater chance of being frail, having falls, and physical performance decline 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.

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.

In a community study with a relatively young population and low AF prevalence, frailty was associated with an increased OAC prescription rate. In contrast, in a nursing home population with a relatively high prevalence, just 25% of the eligible population were prescribed OAC. 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, and the trial evidence on which they are based frequently excludes people with frailty, including of DOACs. Furthermore, CHA₂DS₂-VASc has not been validated for use in the oldest old or people with frailty. 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.\textsuperscript{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.\textsuperscript{232, 233} A risk-treatment paradox exists, whereby those at the highest risk of stroke are not more likely to receive anticoagulation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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>
<thead>
<tr>
<th>Study</th>
<th>Association: frailty and OAC use</th>
<th>Time of OAC</th>
<th>n=</th>
<th>Estimate (95% CI)</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefebvre, 2016</td>
<td>Less use</td>
<td>Inpatient</td>
<td>682</td>
<td>OR 0.29 (0.16-0.54)</td>
<td>Falls history, CHADS₂ score, bleeding risk, age, length of hospital stay, use of antiplatelet agents or medication that increases bleeding risk</td>
</tr>
<tr>
<td>Induruwa, 2017</td>
<td>Less use</td>
<td>Admission</td>
<td>419</td>
<td>OR 0.77 (0.70-0.85)</td>
<td>Age, sex, and the components of CHA₂DS₂-VASc and HAS-BLED</td>
</tr>
<tr>
<td>Perera, 2009</td>
<td>Less use</td>
<td>Admission</td>
<td>220</td>
<td>OR 0.34 (0.17-0.68)</td>
<td>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 &gt; 75 years, diabetes mellitus, hypertension congestive heart failure, prior stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discharge</td>
<td>220</td>
<td>OR 0.12 (0.06-0.23)</td>
<td></td>
</tr>
<tr>
<td>Denoël, 2014</td>
<td>No difference</td>
<td>Admission</td>
<td>142</td>
<td>OR 1.12 (0.50-2.96)</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Bo, 2015</td>
<td>No difference</td>
<td>Discharge</td>
<td>430</td>
<td>OR 0.80 (0.41-1.57)</td>
<td>Age, AF subtype, CHA₂DS₂-VASc, HAS-BLED, CCI, ADL dependence, cognitive impairment, depression, malnutrition, discharge to a facility</td>
</tr>
<tr>
<td>Bo, 2017</td>
<td>No difference</td>
<td>Discharge</td>
<td>452</td>
<td>N/A</td>
<td>Propensity score analysis using a 1:1 nearest-neighbour-matching algorithm</td>
</tr>
<tr>
<td>Nguyen, 2016</td>
<td>No difference</td>
<td>Discharge</td>
<td>302</td>
<td>OR 0.66 (0.40-1.10)</td>
<td>Age, history of bleeding/ predisposition to bleeding and abnormal renal function, congestive heart failure</td>
</tr>
<tr>
<td>Doucet, 2008</td>
<td>No difference</td>
<td>Discharge</td>
<td>209</td>
<td>N/A</td>
<td>Simple comparison between groups, no adjustment</td>
</tr>
<tr>
<td>Frewen, 2013</td>
<td>More use</td>
<td>Community (TILDA)</td>
<td>118</td>
<td>OR 2.33 (1.03-5.23)</td>
<td>Age, sex and education</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Study population</th>
<th>Age criteria</th>
<th>Centres</th>
<th>Country</th>
<th>Frailty measure</th>
<th>n</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annoni 2016 189</td>
<td>Retrospective cross-sectional</td>
<td>Consecutive admissions to acute geriatric unit</td>
<td>≥65</td>
<td>1</td>
<td>Italy</td>
<td>Robinson criteria 192</td>
<td>1619</td>
<td>AF prevalence 24.9%. 86% of those with AF were frail or pre-frail. Those with AF had more comorbidities and medications.</td>
</tr>
<tr>
<td>Bo 2015 193</td>
<td>Prospective cross-sectional</td>
<td>Admissions with AF to internal medicine</td>
<td>≥65</td>
<td>3</td>
<td>Italy</td>
<td>GFI</td>
<td>513</td>
<td>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.</td>
</tr>
<tr>
<td>Bo 2017 199</td>
<td>Prospective cohort</td>
<td>Discharges with AF</td>
<td>≥65</td>
<td>3</td>
<td>Italy</td>
<td>GFI</td>
<td>452</td>
<td>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.</td>
</tr>
<tr>
<td>Denoël 2014 200</td>
<td>Prospective cross-sectional</td>
<td>Consecutive admissions to ED with AF.</td>
<td>≥75</td>
<td>1</td>
<td>Belgium</td>
<td>ISAR</td>
<td>995</td>
<td>AF prevalence 14%. OAC was guideline-recommended for 71%, and prescribed in 61%. OAC use not associated with CHADS2 score or geriatric characteristics.</td>
</tr>
<tr>
<td>Donoghue 2014 206</td>
<td>Prospective cross-sectional</td>
<td>Mobile, community-dwelling participants in the TILDA study</td>
<td>≥50</td>
<td>N/A</td>
<td>Republic of Ireland</td>
<td>GU&amp;G Gait speed</td>
<td>4525</td>
<td>AF prevalence 3.1% overall, 4.7% aged &gt;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.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Setting</td>
<td>Age Cut-off</td>
<td>Country</td>
<td>Measure</td>
<td>N</td>
<td>Results</td>
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<tr>
<td>Doucet</td>
<td>2008</td>
<td>Prospective cohort</td>
<td>Consecutive admissions with AF</td>
<td>&gt;65</td>
<td>France</td>
<td>GU&amp;G</td>
<td>209</td>
<td>49% discharged on OAC, the rest on aspirin. Physicians overestimated bleeding and underestimated thrombosis risks. There was no difference in GU&amp;G scores between the groups, or in stroke, haemorrhage or death at 3 months.</td>
</tr>
<tr>
<td>Frewen</td>
<td>2013</td>
<td>Prospective cross-sectional</td>
<td>Mobile, community-dwelling participants in the TILDA study</td>
<td>≥50</td>
<td>Republic of Ireland</td>
<td>Fried criteria</td>
<td>4890</td>
<td>AF prevalence 3%. 41% on OAC if CHA₂DS₂-VASc ≥2 OR for non-treatment with OAC associated with frailty 0.43 (95%CI 0.19-0.96).</td>
</tr>
<tr>
<td>Gullón</td>
<td>2017</td>
<td>Prospective cohort</td>
<td>Inpatients with NVAF</td>
<td>&gt;75</td>
<td>Spain</td>
<td>5 item FRAIL scale</td>
<td>804</td>
<td>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%.</td>
</tr>
<tr>
<td>Hess</td>
<td>2013</td>
<td>Prospective cohort</td>
<td>Outpatients in registry</td>
<td>≥18</td>
<td>USA</td>
<td>Health ABC physical performance battery</td>
<td>10,096</td>
<td>Frailty was significantly associated with not receiving evidence based therapy for co-morbidities, OR 0.75 (0.59-0.95).</td>
</tr>
<tr>
<td>Hung</td>
<td>2013</td>
<td>Prospective cross-sectional</td>
<td>Admissions to geriatric unit</td>
<td>≥75</td>
<td>Taiwan</td>
<td>GU&amp;G</td>
<td>401</td>
<td>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).</td>
</tr>
<tr>
<td>Induruwa</td>
<td>2017</td>
<td>Retrospective cross-sectional</td>
<td>General medical admissions with AF.</td>
<td>none</td>
<td>England</td>
<td>CFS</td>
<td>419</td>
<td>51% were not on OAC. Frailty was an independent predictor for non-use of OAC, OR 0.77 (0.70-0.85).</td>
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<tr>
<td>Study</td>
<td>Study type</td>
<td>Study population</td>
<td>Age criteria</td>
<td>Centres</td>
<td>Country</td>
<td>Frailty measure</td>
<td>n</td>
<td>Summary</td>
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</tr>
<tr>
<td>Lefebvre 2016</td>
<td>Retrospective cross-sectional</td>
<td>Admissions with AF</td>
<td>≥80</td>
<td>3</td>
<td>Canada</td>
<td>CFS</td>
<td>682</td>
<td>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&lt;sub&gt;2&lt;/sub&gt; score was positively (and HAS-BLED negatively) correlated with OAC.</td>
</tr>
<tr>
<td>Magnani 2016</td>
<td>Prospective cohort</td>
<td>Community based cohort receiving Medicare Two cities.</td>
<td>70-79</td>
<td>N/A</td>
<td>USA</td>
<td>Health ABC physical performance battery</td>
<td>2753</td>
<td>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.</td>
</tr>
<tr>
<td>Mlynarska 2017</td>
<td>Prospective cross-sectional</td>
<td>Inpatients with AF</td>
<td>none</td>
<td>1</td>
<td>Poland</td>
<td>TFI</td>
<td>132</td>
<td>60% were frail. Frailty was associated with a lower acceptance of AF diagnosis and a greater reported intensity of symptoms. 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.</td>
</tr>
<tr>
<td>Nguyen 2016</td>
<td>Prospective cohort</td>
<td>Inpatients with AF</td>
<td>≥65</td>
<td>1</td>
<td>Australia</td>
<td>Reported EFS</td>
<td>302</td>
<td>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.</td>
</tr>
<tr>
<td>Nguyen 2016</td>
<td>Prospective cohort</td>
<td>Inpatients with AF</td>
<td>≥65</td>
<td>1</td>
<td>Australia</td>
<td>Reported EFS</td>
<td>302</td>
<td>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.</td>
</tr>
<tr>
<td>O’Caoimh 2017</td>
<td>Prospective cross-sectional</td>
<td>Frail NH residents.</td>
<td>none</td>
<td>4</td>
<td>Republic of Ireland</td>
<td>CFS</td>
<td>225</td>
<td>AF prevalence 38%. All had CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc ≥2. 17% were anticoagulated, but a risk based decision support aid suggested that 70% should be.</td>
</tr>
<tr>
<td>Perera 2009</td>
<td>Prospective cohort</td>
<td>Inpatients with AF</td>
<td>≥70</td>
<td>1</td>
<td>Australia</td>
<td>Modified EFS</td>
<td>207</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Description</td>
<td>Age (years)</td>
<td>Country</td>
<td>Index</td>
<td>N</td>
<td>Findings</td>
<td></td>
</tr>
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</tr>
<tr>
<td>Pilotto 2016 191</td>
<td>Retrospective cohort</td>
<td>Community-dwelling adults with previous hospitalisation for AF</td>
<td>≥65</td>
<td>Italy</td>
<td>MPI</td>
<td>1287</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Polidoro 2013 198</td>
<td>Prospective cross-sectional</td>
<td>Consecutive admissions to geriatric unit.</td>
<td>1</td>
<td>Italy</td>
<td>Frailty index&lt;sup&gt;37&lt;/sup&gt;</td>
<td>140</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**

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.\textsuperscript{236} Observational data may allow researchers to evaluate ‘real world’ experience, generate hypotheses, and develop an understanding of the associations between exposures and outcomes.\textsuperscript{237, 238} However, care must be taken to consider confounding and other forms of bias, and due regard given to governance and consent.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{239} In particular, there are risks of patient privacy violations associated with data breaches.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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,\textsuperscript{249} and 96\% of practices have been using EHR since 1996.\textsuperscript{250, 251} The use of EHR has a range of advantages including improved quality of care, guideline adherence, and financial efficiencies.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{254} and the Snow Agent surveillance system for infectious diseases in Norway,\textsuperscript{255} amongst others.\textsuperscript{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. 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 eFl was developed using ResearchOne, and validated using the THIN database. 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. 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. 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). 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).
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. 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. 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. The THIN database contains anonymised primary care records from 562 general practices covering 6.5% of the UK population. 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.

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). 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. 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.
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. 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. 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. 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, and patients that are not included may be systematically different from those that are.

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. 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. 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. 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$_2$DS$_2$-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.

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), 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. 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.

The Read clinical classification was purchased by the UK Department of Health in 1990, which gave the opportunity for comprehensive and standardised clinical coding. 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’.

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.\textsuperscript{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.\textsuperscript{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 using 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. 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.

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. 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,\textsuperscript{275} and that it was used in the development of the eFI.\textsuperscript{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.

**Abbreviations**

LIDA: Leeds Institute for Data Analytics  
VRE: Virtual Research Environment  
SQL: Structured Query Language  
CSV: Comma-Separated Values

![Figure 6: Chart to illustrate data flow](image-url)
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. 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>
<thead>
<tr>
<th>Table 16: Summary of data tables that were supplied by ResearchOne</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table name</strong></td>
</tr>
<tr>
<td>Patient details</td>
</tr>
<tr>
<td>Address</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>GP registration history</td>
</tr>
<tr>
<td>Repeatability of medications</td>
</tr>
<tr>
<td>Additional coded data</td>
</tr>
<tr>
<td>Address details</td>
</tr>
</tbody>
</table>
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).

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

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, 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

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

### 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

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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.\textsuperscript{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.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Example of the ‘parent’ and ‘child’ structure of CTV-3 codes}
\end{figure}

\textsuperscript{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>
<thead>
<tr>
<th>Ethnic category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>British, Irish</td>
</tr>
<tr>
<td>Mixed</td>
<td>White and black Caribbean, white and black</td>
</tr>
<tr>
<td></td>
<td>African, white and Asian</td>
</tr>
<tr>
<td>Asian or Asian British</td>
<td>Indian, Pakistani, Bangladeshi</td>
</tr>
<tr>
<td>Black or black British</td>
<td>Caribbean, African</td>
</tr>
<tr>
<td>Other ethnic groups</td>
<td>Chinese</td>
</tr>
</tbody>
</table>

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. 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

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

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.\textsuperscript{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 CHA2DS2-VASc score of two or above, taking bleeding risk into account.’ On this basis, patients with AF were further grouped into those with a CHA2DS2-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 \( \text{CHA}_2 \text{DS}_2 \)-\text{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 \( \text{CHA}_2 \text{DS}_2 \)-\text{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. 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. 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.

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 which may not be well reflected in primary care coding; both carry an elevated stroke risk; and the two have been previously grouped in a trial setting.

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

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

**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\(^c\), 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**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>warfarin</td>
</tr>
<tr>
<td>Apixaban</td>
<td>apixaban, eliquis</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>edoxaban, lixiana</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>rivaroxaban, xarelto</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>dabigatran, pradaxa</td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>acenocoumarol, sinthrome</td>
</tr>
<tr>
<td>Phenindione</td>
<td>phenindione</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>British national formulary indications$^{154}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban</strong></td>
<td>Stroke and systemic embolism prophylaxis in NVAF, in patients with 2 or more of: age ≥ 80 years, body-weight &lt; 61 kg, or serum creatinine ≥ 133 mmol/L. Alternative indications: VTE prophylaxis following knee or hip replacement surgery; recurrent DVT or PE prophylaxis.</td>
</tr>
<tr>
<td>2.5mg BD</td>
<td>Stroke and systemic embolism prophylaxis in NVAF in patients with body weight &lt; 61kg. Alternative indications: treatment or prophylaxis of DVT or PE in patients with body weight &lt; 61kg.</td>
</tr>
<tr>
<td>5mg BD</td>
<td>Stroke and systemic embolism prophylaxis in NVAF</td>
</tr>
<tr>
<td>30mg OD</td>
<td>Stroke and systemic embolism prophylaxis in NVAF</td>
</tr>
<tr>
<td>60mg OD</td>
<td>Stroke and systemic embolism prophylaxis in NVAF. Alternative indications: treatment or prophylaxis of DVT or PE</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>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</td>
</tr>
<tr>
<td>15mg OD</td>
<td>Stroke and systemic embolism prophylaxis in NVAF</td>
</tr>
<tr>
<td>20mg OD</td>
<td>Stroke and systemic embolism prophylaxis in NVAF. Alternative indications: treatment or prophylaxis of DVT or PE</td>
</tr>
<tr>
<td>15mg BD</td>
<td>Initial treatment of DVT or PE</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>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</td>
</tr>
<tr>
<td>110mg BD</td>
<td>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</td>
</tr>
<tr>
<td>150mg BD</td>
<td>Treatment of DVT or PE or prophylaxis of recurrent DVT or PE.</td>
</tr>
</tbody>
</table>

**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). 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, although most gaps between medication renewals were shorter than 30 days. 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).

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. 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), this has precedent in other recent studies and represents a more rigorous approach using the maximum granularity that is possible within the limitations of the data.
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Design</th>
<th>Persistence definition</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinogradova, 2018</td>
<td>UK primary care: CPRD and Q-research</td>
<td>Retrospective, new-users</td>
<td>Gap of less than 30 days between prescriptions.</td>
<td>Persistence not quantified – patients censored when OAC discontinued or changed.</td>
</tr>
<tr>
<td>Johnson, 2016</td>
<td>UK primary care: CPRD</td>
<td>Retrospective, new-users</td>
<td>Gap of less than twice the median prescription duration between prescriptions.</td>
<td>Proportion of patients who were persistent over the course of follow-up.</td>
</tr>
<tr>
<td>Beyer-Westendorf, 2015</td>
<td>Dresden, Germany: OAC registry</td>
<td>Prospective cohort</td>
<td>Gap less than four weeks between prescriptions.</td>
<td>Discontinuation rates and time-to-event analysis for discontinuation.</td>
</tr>
<tr>
<td>Willey, 2015</td>
<td>USA: pharmacy claims data</td>
<td>Retrospective, new-users</td>
<td>Gap less than 30 days between prescriptions. For warfarin gap between prescriptions of 60 days, and less than 42 days between INR tests.</td>
<td>Discontinuation rates and mean time to discontinuation.</td>
</tr>
<tr>
<td>Go, 2003</td>
<td>Northern California, USA: ATRIA cohort</td>
<td>Prospective cohort</td>
<td>Gap of less than 60 days between warfarin prescriptions, unless an intervening INR measurement was obtained at least every 42 days.</td>
<td>Multivariable Cox models, incorporated time-dependent warfarin use data.</td>
</tr>
</tbody>
</table>

**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. 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, and in previous observational cohort work comparing the efficacy and safety of DOAC agents and warfarin. 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. 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.

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'.

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.

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, whereas in HEMORR²HAGES, bleeding in any site requiring hospital admission was included. 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. 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. 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.

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. A tendency to experience falls is associated with an increased risk of major bleeding in patients that are prescribed OAC, 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, 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.\textsuperscript{300, 301}

**4.10.4.5 Censoring**

For all participants, outcome data were right-censored, with the last death recorded in ResearchOne on 1\textsuperscript{st} April 2017. The last recorded event in the data was on 10\textsuperscript{th} April 2017. The date of censor was therefore set to 11\textsuperscript{th} 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](image-url)
Baseline characteristics and co-variates

Potential confounders were identified \textit{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,\textsuperscript{302} those that may influence prescribing decision, or because they increase the risk of bleeding.\textsuperscript{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.

\textbf{Age}

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

\textbf{Sex}

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

\textbf{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),\textsuperscript{304} and an increased risk of stroke.\textsuperscript{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.\textsuperscript{306}

**Socioeconomic status**

Higher levels of deprivation are associated with an increased incidence (and severity) of stroke,\textsuperscript{305} and all-cause mortality.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{251, 308}

4.10.5.1.1 Risk scores

**Stroke risk: CHA\textsubscript{2}DS\textsubscript{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,\textsuperscript{309} I was sent a list of CTV-3 parent codes that is used within SystmOne to calculation the CHA\textsubscript{2}DS\textsubscript{2}-VASc score.
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. 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>
<thead>
<tr>
<th>ATRIA risk score</th>
<th>Risk category</th>
<th>Annual risk of haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>Low</td>
<td>0.76%</td>
</tr>
<tr>
<td>4</td>
<td>Intermediate</td>
<td>2.6%</td>
</tr>
<tr>
<td>&gt;4</td>
<td>High</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

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) or HEMORR\textsubscript{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) were considered, and whilst there is evidence that HAS-BLED has been shown to have the best predictive and discriminative performance of the three, 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. Any condition coded as a “child” of the term ‘bleeding disorder’ in the CTV-3 hierarchy within TRUD was also included. 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. 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. 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. This may affect clinical decision-making. The eFI code list was used to identify a history of falls.
Hypertension
Hypertension is a major risk factor for stroke and all-cause mortality. 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.

Hyperthyroidism
Hyperthyroidism is an established risk factor for AF, 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, and is also a potential indication for alternative antiplatelet or anticoagulant therapy, particularly following an acute coronary syndrome. 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. 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. 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>
<thead>
<tr>
<th>Drug class</th>
<th>Drug name</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>Aspirin</td>
<td>aspirin, micropirin, nu-seals, danamep, disprin, mandaprin</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>clopidogrel, plavix</td>
</tr>
<tr>
<td></td>
<td>Ticagrelor</td>
<td>ticagrelor, brilique</td>
</tr>
<tr>
<td></td>
<td>Prasugrel</td>
<td>prasugrel, efient</td>
</tr>
<tr>
<td></td>
<td>Dipyridamole</td>
<td>dipyridamole, attia, ofcram pr, persantin retard, trolactin, persantin</td>
</tr>
<tr>
<td>Proton pump</td>
<td>Omeprazole</td>
<td>omeprazole, losec, mepradec, mezzopram</td>
</tr>
<tr>
<td>inhibitor</td>
<td>Esomeprazole</td>
<td>esomeprazole, emozul, ventra, nexion</td>
</tr>
<tr>
<td></td>
<td>Pantoprazole</td>
<td>pantoprazole, pantoloc</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole</td>
<td>rabeprazole, pariet</td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>lansoprazole, zoton fastab</td>
</tr>
<tr>
<td>Macrolide</td>
<td>Azithromycin</td>
<td>azithromycin, zithromax, zedbac</td>
</tr>
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<td>antibiotics</td>
<td>Clarithromycin</td>
<td>clarithromycin, klaricid, xetinin</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>erythromycin, erythrolar, erythrocin, erythroped</td>
</tr>
<tr>
<td>NSAID</td>
<td>Aceclofenac</td>
<td>aceclofenac, preservex</td>
</tr>
<tr>
<td></td>
<td>Celecoxib</td>
<td>celecoxib, celebrex</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
<td>diclofenac , voltarol, dicloflex, econac, fenactol , volsaid, enstar, arthrotec, misofen, masidemen</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
<td>diclofenac , voltarol, dicloflex, econac, fenactol , volsaid, enstar, arthrotec, misofen, masidemen</td>
</tr>
<tr>
<td></td>
<td>Etodolac</td>
<td>etodolac, etolyn, etopan, lodine, eccoxolac</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>flurbiprofen, strefen</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>ibuprofen, brufen, brufen, anadin, feminax express, ibucalm, nurofen</td>
</tr>
<tr>
<td></td>
<td>Indometacin</td>
<td>indomethacin, indocid, berlind</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>ketoprofen, oruvail, tiloket cr, larafen cr, valket</td>
</tr>
<tr>
<td></td>
<td>Mefenamic Acid</td>
<td>mefenamic acid, ponstan</td>
</tr>
<tr>
<td></td>
<td>Meloxicam</td>
<td>meloxicam</td>
</tr>
<tr>
<td></td>
<td>Nabumetone</td>
<td>nabumetone, relifex</td>
</tr>
<tr>
<td></td>
<td>Naprofen</td>
<td>naprofen, feminax ultra, naprosyn ec, vimovo</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
<td>dexketoprofen, skudexa</td>
</tr>
<tr>
<td></td>
<td>Piroxicam</td>
<td>piroxicam, feldene</td>
</tr>
<tr>
<td></td>
<td>Sulindac</td>
<td>sulindac</td>
</tr>
<tr>
<td></td>
<td>Tenoxicam</td>
<td>tenoxicam, mobiflex</td>
</tr>
<tr>
<td></td>
<td>Tiaprofenic Acid</td>
<td>tiaprofenic acid, surgam</td>
</tr>
<tr>
<td></td>
<td>Tolafenamic Acid</td>
<td>tolafenamic acid, clotam rapid</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Hydrocortisone</td>
<td>hydrocortisone, plenadren,</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>dexamethasone, glensoludex, neofordex, dexsol, martapan</td>
</tr>
<tr>
<td></td>
<td>Betamethasone</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>Atorvastatin</td>
<td>atorvastatin, lipitor</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin</td>
<td>fluvastatin, dorisin xl, lescal xl, nandovar xl</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>pravastatin</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin</td>
<td>rosuvastatin, crestor</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>simvastatin, simvador, zocor, inegy, cholib</td>
</tr>
<tr>
<td>Anti-epileptic</td>
<td>Phenytoin</td>
<td>phenytoin, epanutin</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>carbamazepine, carbagen, tegretol</td>
</tr>
</tbody>
</table>

**Abbreviation** NSAID: non-steroidal anti-inflammatory drug

**Source:** British National Formulary
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.\textsuperscript{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\textsubscript{2}DS\textsubscript{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\textsubscript{2}DS\textsubscript{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
- CHA2DS2-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. 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. 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.
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](image-url)
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.

![Histogram of frailty categories for the complete cohort, n=536,955](image)

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.
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

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

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

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](image)
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

<table>
<thead>
<tr>
<th></th>
<th>All n=536,955</th>
<th>No history of AF n=475,778</th>
<th>History of AF n=61,177</th>
<th>p-value for difference between AF and non AF cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age. Median (IQR)</strong></td>
<td>73.8 (69.0-80.5)</td>
<td>73.1 (68.8-79.6)</td>
<td>79.7 (73.3–85.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Female. n (%)</strong></td>
<td>290,764 (54.2)</td>
<td>262,777 (55.2)</td>
<td>27,987 (45.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>IMD. n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most deprived quintile</td>
<td>65,337 (13.0)</td>
<td>57,898 (13.0)</td>
<td>7,439 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Least deprived quintile</td>
<td>122,726 (24.3)</td>
<td>109,281 (24.5)</td>
<td>13,445 (23.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of eFI deficits, median (IQR)</strong></td>
<td>5 (3-8)</td>
<td>5* (3-8)</td>
<td>9 (6-12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Frailty category. n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>218,865 (40.8)</td>
<td>212,422 (44.7)</td>
<td>6,443 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild</td>
<td>181,986 (33.9)</td>
<td>161,634 (34.0)</td>
<td>20,352 (33.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>91,411 (17.0)</td>
<td>71,086 (14.9)</td>
<td>20,315 (33.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>44,693 (8.3)</td>
<td>30,626 (6.4)</td>
<td>14,067 (23.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>71,418 (13.3)</td>
<td>61,193 (12.9)</td>
<td>10,225 (16.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong></td>
<td>102,529 (19.1)</td>
<td>82,204 (17.3)</td>
<td>20,325 (33.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>92,146 (17.2)</td>
<td>77,915 (16.4)</td>
<td>14,231 (23.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>25,553 (4.8)</td>
<td>13,103 (2.8)</td>
<td>12,450 (20.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>283,517 (52.8)</td>
<td>242,177 (51.0)</td>
<td>41,340 (67.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hyperthyroid</strong></td>
<td>10,875 (2.0)</td>
<td>8,873 (1.9)</td>
<td>2,002 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ischaemic heart disease</strong></td>
<td>84,237 (15.7)</td>
<td>64,651 (13.6)</td>
<td>19,586 (32.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32,802 (6.1)</td>
<td>25,383 (5.3)</td>
<td>7,419 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>9,597 (1.8)</td>
<td>7,718 (1.6)</td>
<td>1,879 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stroke</strong>†</td>
<td>25,412 (4.7)</td>
<td>18,173 (3.8)</td>
<td>7,239 (11.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infarct</td>
<td>10,593 (2.0)</td>
<td>7,414 (1.6)</td>
<td>3,179 (5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unspecified</td>
<td>17,982 (3.4)</td>
<td>12,939 (2.7)</td>
<td>5,043 (8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td>56,407 (12.2)</td>
<td>53,649 (11.3)</td>
<td>11,758 (19.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>23,003 (4.3)</td>
<td>14,263 (3.0)</td>
<td>8,740 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of smoking</td>
<td>378,646 (70.7)</td>
<td>333,277 (70.3)</td>
<td>45,376 (74.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

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).

![Kaplan-Meier graph showing all-cause mortality by frailty category](image)

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

**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.

![Kaplan-Meier graph showing incidence of first stroke event by frailty category, with 95% confidence interval. n=536,955](image)

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.

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.

**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.
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n=61,177</th>
<th>Robust n=6,443</th>
<th>Mild frailty n=20,352</th>
<th>Moderate frailty n=20,315</th>
<th>Severe frailty n=14,067</th>
<th>p value for difference across categories</th>
<th>p value for trend across categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age. Median (IQR)</td>
<td>79.7 (73.3-</td>
<td>72.7 (68.8-</td>
<td>77.1 (71.6-</td>
<td>81.0 (75.4-86.2)</td>
<td>84.3 (79.1-89.0)</td>
<td>&lt;0.001a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>85.5)</td>
<td>78.2)</td>
<td>82.7)</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>27,987 (45.8)</td>
<td>2,293 (35.6)</td>
<td>8,355 (41.1)</td>
<td>9,569 (47.1)</td>
<td>7,770 (55.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Most deprived quintile</td>
<td>7,439 (12.9)</td>
<td>532 (8.8)</td>
<td>2,064 (10.8)</td>
<td>2,619 (13.6)</td>
<td>2,224 (16.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Least deprived quintile</td>
<td>13,445 (23.3)</td>
<td>1,620 (26.9)</td>
<td>4,672 (24.4)</td>
<td>4,402 (22.9)</td>
<td>2,751 (20.6)</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Living in a nursing home</td>
<td>5,276 (8.6)</td>
<td>66 (1.0)</td>
<td>729 (3.6)</td>
<td>1,763 (8.7)</td>
<td>2,718 (19.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of AF, years</td>
<td>4.8 (2.1-9.4)</td>
<td>3.9 (1.8-7.7)</td>
<td>4.2 (1.9-8.6)</td>
<td>4.9 (2.2-9.7)</td>
<td>5.8 (2.6-10.7)</td>
<td>&lt;0.001a</td>
<td></td>
</tr>
<tr>
<td>Prior to study start</td>
<td></td>
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<td><strong>Risk scores</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-Vasc Mean (SD)</td>
<td>3.8 (1.5)</td>
<td>2.2 (0.98)</td>
<td>3.2 (1.2)</td>
<td>4.0 (1.3)</td>
<td>5.0 (1.4)</td>
<td>&lt;0.001b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATRIA Median (IQR)</td>
<td>3 (2-6)</td>
<td>1 (0-2)</td>
<td>3 (1-5)</td>
<td>4 (3-6)</td>
<td>6 (4-8)</td>
<td>&lt;0.001a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Past medical history, n (%)</strong></td>
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<tr>
<td>Alcohol excess</td>
<td>1,855 (3.0)</td>
<td>163 (2.5)</td>
<td>649 (3.2)</td>
<td>616 (3.0)</td>
<td>427 (3.0)</td>
<td>0.065</td>
<td>0.404</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12,145 (19.9)</td>
<td>193 (3.0)</td>
<td>2,018 (9.9)</td>
<td>4,552 (22.4)</td>
<td>5,382 (38.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Bleeding disorder</td>
<td>945 (1.5)</td>
<td>50 (0.8)</td>
<td>256 (1.3)</td>
<td>329 (1.6)</td>
<td>310 (2.2)</td>
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<tr>
<td>Cancer</td>
<td>10,225 (16.7)</td>
<td>695 (10.8)</td>
<td>3,071 (15.1)</td>
<td>3,656 (18.0)</td>
<td>2,803 (19.9)</td>
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<td>&lt;0.001</td>
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<tr>
<td>Cirrhosis</td>
<td>261 (0.43)</td>
<td>16 (0.25)</td>
<td>73 (0.36)</td>
<td>75 (0.37)</td>
<td>97 (0.69)</td>
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<tr>
<td>Chronic kidney disease</td>
<td>20,325 (33.2)</td>
<td>318 (4.9)</td>
<td>4,334 (21.3)</td>
<td>7,888 (38.8)</td>
<td>7,785 (55.3)</td>
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<td>&lt;0.001</td>
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<tr>
<td>Diabetes mellitus</td>
<td>14,231 (23.3)</td>
<td>127 (2.0)</td>
<td>2,661 (13.1)</td>
<td>5,536 (27.3)</td>
<td>5,907 (42.0)</td>
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<td>&lt;0.001</td>
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<tr>
<td>Falls</td>
<td>11,758 (19.2)</td>
<td>109 (1.7)</td>
<td>1,489 (7.3)</td>
<td>3,928 (19.3)</td>
<td>6,262 (44.3)</td>
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<td>Gastrointestinal bleed</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Upper</td>
<td>918 (1.5)</td>
<td>16 (0.25)</td>
<td>179 (0.88)</td>
<td>334 (1.6)</td>
<td>389 (2.8)</td>
<td>&lt;0.001</td>
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<td>Lower</td>
<td>6,222 (10.2)</td>
<td>366 (5.7)</td>
<td>1,548 (7.6)</td>
<td>2,205 (10.9)</td>
<td>2,103 (15.0)</td>
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<tr>
<td>Unspecified</td>
<td>537 (0.88)</td>
<td>13 (0.20)</td>
<td>92 (0.45)</td>
<td>188 (0.93)</td>
<td>244 (1.7)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Variable</td>
<td>All n=61,177</td>
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<td>p value for difference across categories</td>
<td>p value for trend across categories</td>
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<td>-------------------------------------</td>
</tr>
<tr>
<td>Haematuria</td>
<td>7,535 (12.3)</td>
<td>357 (5.5)</td>
<td>2,082 (10.2)</td>
<td>2,738 (13.5)</td>
<td>2,358 (16.8)</td>
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<tr>
<td>Haemoptysis</td>
<td>1,772 (2.9)</td>
<td>69 (1.1)</td>
<td>346 (1.7)</td>
<td>660 (3.3)</td>
<td>697 (5.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Heart failure</td>
<td>12,450 (20.4)</td>
<td>230 (3.6)</td>
<td>2,155 (10.6)</td>
<td>4,623 (22.8)</td>
<td>5,442 (38.7)</td>
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<td>&lt;0.001</td>
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<tr>
<td>Hypertension</td>
<td>41,340 (67.6)</td>
<td>2,253 (35.0)</td>
<td>12,745 (62.6)</td>
<td>14,931 (73.5)</td>
<td>11,411 (81.1)</td>
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<td>&lt;0.001</td>
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<tr>
<td>Hyperthyroidism</td>
<td>2,002 (3.3)</td>
<td>82 (1.3)</td>
<td>522 (2.6)</td>
<td>703 (3.5)</td>
<td>695 (4.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>982 (1.6)</td>
<td>33 (0.51)</td>
<td>224 (1.1)</td>
<td>330 (1.6)</td>
<td>395 (2.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>19,586 (32.0)</td>
<td>312 (4.8)</td>
<td>3,932 (19.3)</td>
<td>7,425 (36.6)</td>
<td>7,917 (56.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Memory loss</td>
<td>7,880 (12.9)</td>
<td>79 (1.2)</td>
<td>1,095 (5.4)</td>
<td>2,679 (13.2)</td>
<td>4,030 (28.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7,419 (12.1)</td>
<td>78 (1.2)</td>
<td>1,229 (6.0)</td>
<td>2,759 (13.6)</td>
<td>3,353 (23.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>828 (1.4)</td>
<td>28 (0.4)</td>
<td>168 (0.83)</td>
<td>309 (1.5)</td>
<td>323 (2.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Peptic ulcer</td>
<td>3,676 (6.0)</td>
<td>83 (1.3)</td>
<td>709 (3.5)</td>
<td>1,315 (6.5)</td>
<td>1,569 (11.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Varices</td>
<td>86 (0.14)</td>
<td>&lt;10 (&lt;1)</td>
<td>25 (0.11)</td>
<td>29 (0.14)</td>
<td>32 (0.23)</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>7,239 (11.8)</td>
<td>180 (2.8)</td>
<td>1,599 (7.7)</td>
<td>2,570 (12.7)</td>
<td>2,890 (20.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Ischaemic</td>
<td>3,179 (5.2)</td>
<td>111 (1.7)</td>
<td>760 (3.7)</td>
<td>1,157 (5.7)</td>
<td>1,151 (8.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5,043 (8.2)</td>
<td>76 (1.2)</td>
<td>1,024 (5.0)</td>
<td>1,754 (8.6)</td>
<td>2,189 (15.6)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>TIA</td>
<td>6,019 (9.8)</td>
<td>133 (2.1)</td>
<td>1,247 (6.1)</td>
<td>2,192 (10.8)</td>
<td>2,447 (17.4)</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1,879 (3.1)</td>
<td>65 (1.0)</td>
<td>385 (1.9)</td>
<td>717 (3.5)</td>
<td>712 (5.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2,335 (3.8)</td>
<td>107 (1.7)</td>
<td>553 (2.7)</td>
<td>844 (4.2)</td>
<td>831 (5.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a=Kruskal-Wallis; 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$_2$DS$_2$-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 25$^{th}$ and 75$^{th}$ percentile, and the median are shown visually in Figure 25. Of the patients with AF, 95.1% (n=58,204) had a CHA$_2$DS$_2$-Vasc score of 2 or more.

![Box plot showing CHA$_2$DS$_2$-Vasc score at study entry by electronic frailty index category](image)

**Figure 25:** Box plot showing CHA$_2$DS$_2$-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.
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](image-url)
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n=61,177</th>
<th>Robust n=6,443</th>
<th>Mild frailty n=20,352</th>
<th>Moderate frailty n=20,315</th>
<th>Severe frailty n=14,067</th>
<th>p value for difference across categories</th>
<th>p value for trend across categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications in the previous year, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>24,511 (40.1)</td>
<td>1,057 (16.4)</td>
<td>6,676 (32.8)</td>
<td>8,885 (43.7)</td>
<td>7,892 (56.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>427 (0.70)</td>
<td>10 (0.16)</td>
<td>90 (0.44)</td>
<td>167 (0.82)</td>
<td>160 (1.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAID</td>
<td>5,453 (8.9)</td>
<td>284 (4.4)</td>
<td>1,397 (6.9)</td>
<td>900 (4.4)</td>
<td>679 (4.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>1,777 (2.9)</td>
<td>87 (1.4)</td>
<td>566 (2.8)</td>
<td>613 (3.0)</td>
<td>511 (3.6)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>36,498 (59.7)</td>
<td>2,410 (37.4)</td>
<td>11,492 (56.5)</td>
<td>13,102 (64.5)</td>
<td>9,494 (67.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-epileptic drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>235 (0.38)</td>
<td>11 (0.17)</td>
<td>56 (0.28)</td>
<td>87 (0.43)</td>
<td>81 (0.58)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>180 (0.29)</td>
<td>6 (0.09)</td>
<td>47 (0.23)</td>
<td>67 (0.33)</td>
<td>60 (0.43)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medications at the time of study entry, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>OAC at study entry</td>
<td>32,079 (52.4)</td>
<td>2,574 (40.0)</td>
<td>10,730 (52.7)</td>
<td>11,264 (55.5)</td>
<td>7,510 (53.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OAC at sub-therapeutic dose</td>
<td>85 (0.14)</td>
<td>7 (0.11)</td>
<td>24 (0.12)</td>
<td>22 (0.11)</td>
<td>24 (0.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anti-platelet at study entry</td>
<td>3,767 (6.2)</td>
<td>123 (1.9)</td>
<td>812 (4.0)</td>
<td>1,145 (5.7)</td>
<td>1,127 (8.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DOAC at study entry</td>
<td>32,079 (52.4)</td>
<td>2,574 (40.0)</td>
<td>10,730 (52.7)</td>
<td>11,264 (55.5)</td>
<td>7,510 (53.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| Abbreviations: DOAC: direct oral anticoagulants; NSAID: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulation

a=non-parametric test for trend (extension of Wilcoxon rank-sum test). All others: Chi-square

Dose: DOAC at sub-therapeutic dose

Any anti-platelet at study entry

OAC at study entry

Medications in the previous year, n (%)

Medications at the time of study entry, n (%)

Any anti-platelet at study entry

DOAC at sub-therapeutic dose

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.

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

<table>
<thead>
<tr>
<th></th>
<th>All n=61,177</th>
<th>Robust n=6,443</th>
<th>Mild n=20,352</th>
<th>Moderate n=20,315</th>
<th>Severe n=14,067</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>6,143</td>
<td>20.3 (17.5-23.7)</td>
<td>41.5 (39.0-44.1)</td>
<td>86.2 (82.6-89.9)</td>
<td>179.5 (173.0-186.2)</td>
</tr>
<tr>
<td>65&lt;70</td>
<td>244</td>
<td>10.5 (7.3-15.2)</td>
<td>16.4 (13.1-20.4)</td>
<td>34.6 (27.8-43.2)</td>
<td>80.6 (62.5-104.1)</td>
</tr>
<tr>
<td>70&lt;75</td>
<td>447</td>
<td>15.3 (11.1-24.2)</td>
<td>20.2 (16.8-24.3)</td>
<td>48.5 (41.9-56.2)</td>
<td>88.0 (73.6-105.4)</td>
</tr>
<tr>
<td>75&lt;80</td>
<td>817</td>
<td>18.6 (12.8-26.9)</td>
<td>31.0 (26.8-35.8)</td>
<td>55.3 (49.4-62.0)</td>
<td>111.0 (99.3-124.1)</td>
</tr>
<tr>
<td>80&lt;85</td>
<td>1317</td>
<td>26.9 (18.2-39.8)</td>
<td>49.4 (43.5-56.1)</td>
<td>75.3 (68.7-82.6)</td>
<td>147.8 (136.4-160.2)</td>
</tr>
<tr>
<td>85&lt;90</td>
<td>1668</td>
<td>71.9 (49.9-103.4)</td>
<td>81.3 (71.4-92.5)</td>
<td>128.4 (118.3-139.2)</td>
<td>206.4 (192.8-221.0)</td>
</tr>
<tr>
<td>90&lt;95</td>
<td>1248</td>
<td>131.3 (77.7-221.6)</td>
<td>154.2 (132.0-180.2)</td>
<td>185.5 (167.5-205.4)</td>
<td>300.0 (278.7-323.0)</td>
</tr>
<tr>
<td>95&lt;100</td>
<td>402</td>
<td>150.7 (48.6-467.3)</td>
<td>238.1 (175.3-323.4)</td>
<td>328.8 (227.4-389.8)</td>
<td>394.2 (345.9-449.2)</td>
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<tr>
<td><strong>Ischaemic or unspecified stroke</strong></td>
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<td></td>
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</tr>
<tr>
<td>All</td>
<td>617</td>
<td>5.4 (4.0-7.2)</td>
<td>7.2 (6.2-8.3)</td>
<td>9.3 (8.2-10.6)</td>
<td>10.7 (9.2-12.5)</td>
</tr>
<tr>
<td>65&lt;70</td>
<td>48</td>
<td>1.1 (0.4-3.4)</td>
<td>5.5 (3.8-8.1)</td>
<td>5.7 (3.3-9.9)</td>
<td>8.2 (3.7-18.3)</td>
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<tr>
<td>70&lt;75</td>
<td>83</td>
<td>5.6 (3.2-9.6)</td>
<td>4.5 (3.0-6.6)</td>
<td>8.2 (3.3-9.9)</td>
<td>11.2 (6.8-18.6)</td>
</tr>
<tr>
<td>75&lt;80</td>
<td>111</td>
<td>8.0 (4.6-14.1)</td>
<td>6.3 (4.5-8.6)</td>
<td>7.7 (5.7-10.4)</td>
<td>7.6 (5.0-11.7)</td>
</tr>
<tr>
<td>80&lt;85</td>
<td>119</td>
<td>8.7 (4.3-17.3)</td>
<td>7.2 (5.2-10.1)</td>
<td>8.2 (6.2-10.8)</td>
<td>6.7 (4.6-9.8)</td>
</tr>
<tr>
<td>85&lt;90</td>
<td>152</td>
<td>12.4 (5.2-29.9)</td>
<td>12.5 (9.0-12.4)</td>
<td>12.2 (9.3-15.9)</td>
<td>14.3 (11.0-18.6)</td>
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<tr>
<td>90&lt;95</td>
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<td>9.4 (1.3-66.8)</td>
<td>16.7 (10.4-26.9)</td>
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<td>14.1 (10.0-19.9)</td>
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<tr>
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<td>23.3 (16.0-33.9)</td>
<td>51.3 (7.2-360.0)</td>
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<td>27.4 (15.2-49.5)</td>
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<td><strong>Gastrointestinal bleed</strong></td>
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<tr>
<td>All</td>
<td>583</td>
<td>4.5 (3.2-6.2)</td>
<td>5.8 (4.9-6.8)</td>
<td>9.0 (7.9-10.3)</td>
<td>11.8 (10.2-13.6)</td>
</tr>
<tr>
<td>65&lt;70</td>
<td>69</td>
<td>2.6 (1.2-5.4)</td>
<td>7.0 (5.0-9.9)</td>
<td>7.9 (5.0-12.6)</td>
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<tr>
<td>70&lt;75</td>
<td>87</td>
<td>5.6 (3.2-9.6)</td>
<td>4.7 (3.2-6.9)</td>
<td>10.7 (7.9-14.6)</td>
<td>6.7 (3.5-12.9)</td>
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<tr>
<td>75&lt;80</td>
<td>123</td>
<td>4.7 (2.2-9.8)</td>
<td>5.2 (3.7-7.4)</td>
<td>10.5 (8.1-13.7)</td>
<td>10.6 (7.3-15.2)</td>
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<td>80&lt;85</td>
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<td>5.0 (1.2-19.9)</td>
<td>6.1 (3.8-9.8)</td>
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<td>11.1 (8.3-14.9)</td>
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<td>90&lt;95</td>
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<td>All n=61,177</td>
<td>Robust n=6,443</td>
<td>Mild n=20,352</td>
<td>Moderate n=20,315</td>
<td>Severe n=14,067</td>
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<tr>
<td><strong>Events, n</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Intracranial bleed</strong></td>
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<td></td>
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</tr>
<tr>
<td>All ages</td>
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<td>1.2 (0.9-1.8)</td>
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</tr>
<tr>
<td>65-&lt;70</td>
<td>&lt;5</td>
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<td>0.4 (0.1-2.6)</td>
<td>0.4 (0.1-1.7)</td>
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<td>70-&lt;75</td>
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<td>0.9 (0.4-2.2)</td>
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<td>1.2 (0.6-2.5)</td>
<td>2.6 (1.6-4.4)</td>
</tr>
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<td>3.2 (1.0-10.0)</td>
<td>2.1 (1.1-3.4)</td>
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<td>85-&lt;90</td>
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<td>2.5 (0.4-18.0)</td>
<td>1.4 (0.5-3.8)</td>
<td>2.9 (1.7-4.9)</td>
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<tr>
<td>90-&lt;95</td>
<td>17</td>
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<td>2.0 (0.5-7.8)</td>
<td>2.0 (0.8-5.4)</td>
<td>4.7 (2.6-8.5)</td>
</tr>
<tr>
<td>95-&lt;100</td>
<td>&lt;5</td>
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<td><strong>Fall</strong></td>
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<td>5.8 (3.9-8.4)</td>
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</tr>
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<td>70-&lt;75</td>
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<td>3.9 (2.0-7.4)</td>
<td>8.8 (6.7-11.7)</td>
<td>18.9 (14.9-23.9)</td>
</tr>
<tr>
<td>75-&lt;80</td>
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<td>26.8 (24.3-29.5)</td>
<td>6.0 (3.1-11.5)</td>
<td>16.7 (13.7-20.3)</td>
<td>27.3 (23.2-32.5)</td>
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<tr>
<td>80-&lt;85</td>
<td>660</td>
<td>42.6 (39.5-46.0)</td>
<td>8.7 (4.3-17.3)</td>
<td>26.4 (22.1-31.4)</td>
<td>40.8 (36.0-46.3)</td>
</tr>
<tr>
<td>85-&lt;90</td>
<td>758</td>
<td>66.9 (62.3-71.8)</td>
<td>22.6 (11.8-43.4)</td>
<td>59.9 (53.1-67.6)</td>
<td>59.9 (53.1-67.6)</td>
</tr>
<tr>
<td>90-&lt;95</td>
<td>487</td>
<td>93.6 (85.6-102.3)</td>
<td>28.7 (9.3-88.9)</td>
<td>93.8 (81.0-108.6)</td>
<td>93.8 (81.0-108.6)</td>
</tr>
<tr>
<td>95-&lt;100</td>
<td>130</td>
<td>118.6 (99.9-140.8)</td>
<td>105.8 (26.5-423.2)</td>
<td>96.4 (69.8-133.0)</td>
<td>97.0 (69.8-133.0)</td>
</tr>
<tr>
<td><strong>Transient ischaemic attack</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>372</td>
<td>5.1 (4.6-5.6)</td>
<td>3.2 (2.2-4.8)</td>
<td>3.71 (3.0-4.6)</td>
<td>5.5 (4.7-6.6)</td>
</tr>
<tr>
<td>65-&lt;70</td>
<td>31</td>
<td>3.0 (2.1-4.2)</td>
<td>2.6 (1.2-5.4)</td>
<td>3.0 (1.8-5.0)</td>
<td>3.5 (1.8-7.1)</td>
</tr>
<tr>
<td>70-&lt;75</td>
<td>57</td>
<td>4.4 (3.4-5.7)</td>
<td>2.6 (1.2-5.7)</td>
<td>4.0 (2.6-6.0)</td>
<td>6.3 (4.2-9.4)</td>
</tr>
<tr>
<td>75-&lt;80</td>
<td>65</td>
<td>4.2 (3.3-5.3)</td>
<td>2.0 (0.6-6.2)</td>
<td>4.1 (2.7-6.0)</td>
<td>3.6 (2.6-5.6)</td>
</tr>
<tr>
<td>80-&lt;85</td>
<td>95</td>
<td>6.0 (4.9-7.4)</td>
<td>6.5 (2.9-14.5)</td>
<td>3.1 (1.9-5.1)</td>
<td>7.0 (5.2-9.5)</td>
</tr>
<tr>
<td>85-&lt;90</td>
<td>78</td>
<td>6.7 (5.3-8.3)</td>
<td>5.0 (1.2-19.9)</td>
<td>4.6 (2.7-8.0)</td>
<td>5.5 (3.7-8.2)</td>
</tr>
<tr>
<td>90-&lt;95</td>
<td>34</td>
<td>6.2 (4.5-8.7)</td>
<td>19.1 (4.8-76.2)</td>
<td>2.9 (1.0-9.1)</td>
<td>6.0 (3.4-10.6)</td>
</tr>
<tr>
<td>95-&lt;100</td>
<td>12</td>
<td>10.3 (5.9-18.2)</td>
<td>0</td>
<td>11.7 (2.9-46.8)</td>
<td>12.5 (5.2-29.9)</td>
</tr>
</tbody>
</table>
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.
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.

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Frailty category</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.7 (1.3-2.4)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>2.0 (1.4-2.8)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.2 (0.8-1.6)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.2 (0.9-1.8)</td>
</tr>
</tbody>
</table>

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

![Gastrointestinal bleeding event by frailty category](image)

**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.

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Frailty category</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.0 (0.5-2.0)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.5 (0.8-3.0)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>2.5 (1.3-4.9)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.9 (0.4-1.8)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.1 (0.5-2.3)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.6 (0.8-3.5)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, smoking status, IMD quintile, and GP practice ID
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.
Figure 38: Association between frailty status and clinical outcomes, unadjusted, in patients with AF. n=61,177
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frailty category</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.5 (1.3-1.8)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2.4 (2.0-2.8)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>4.0 (3.4-4.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.2 (0.8-1.6)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.2 (0.9-1.8)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2.0 (1.4-2.9)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>2.7 (1.8-4.0)</td>
</tr>
<tr>
<td>IC bleed</td>
<td>Robust</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.9 (0.4-1.8)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.1 (0.5-2.3)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.6 (0.8-3.5)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Frailty Category</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>1.9 (1.3-2.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.6 (1.2-2.2)</td>
</tr>
<tr>
<td>Mild</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>Robust</td>
<td>1.1 (ref)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>2.4 (2.1-2.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.6 (1.5-1.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.5 (1.3-1.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.2 (1.9-2.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.6 (1.5-1.8)</td>
</tr>
<tr>
<td>Robust</td>
<td>1.1 (ref)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.3 (4.1-4.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>3.0 (2.9-3.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.9 (1.8-2.0)</td>
</tr>
<tr>
<td>Robust</td>
<td>1.1 (ref)</td>
</tr>
</tbody>
</table>

HR (95% CI)
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 (CHA₂DS₂-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$_2$DS$_2$-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$_2$DS$_2$-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.

![Diagram showing 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$_2$DS$_2$-Vasc score of two or more, and were considered ‘eligible’ for OAC. OAC was prescribed at study entry in 30,916 (53.1%) of patients with AF and a CHA$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-Vasc points, therefore there was no difference in the number of women after restricting the cohort to patients with AF and CHA$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All patients with AF</th>
<th>Patients with AF and CHA₂DS₂-Vasc score of 2 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n=61,177</td>
<td>Total n=58,204</td>
</tr>
<tr>
<td></td>
<td>Prescribed OAC n=32,079</td>
<td>Prescribed OAC n=30,916</td>
</tr>
<tr>
<td></td>
<td>Not prescribed OAC n=29,098</td>
<td>Not prescribed OAC n=27,288</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, Median (IQR)</td>
<td>79.7 (73.3-85.5)</td>
<td>80.2 (74.3-85.7)</td>
</tr>
<tr>
<td></td>
<td>79.7 (73.8-85.0)</td>
<td>80.1 (74.6-85.2)</td>
</tr>
<tr>
<td></td>
<td>79.7 (72.8-86.1)</td>
<td>80.5 (74.0-86.6)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.087</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>27,987 (45.8)</td>
<td>27,987 (48.1)</td>
</tr>
<tr>
<td></td>
<td>14,285 (44.5)</td>
<td>14,285 (46.2)</td>
</tr>
<tr>
<td></td>
<td>13,702 (47.1)</td>
<td>13,702 (50.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of eFl deficits, median (IQR)</td>
<td>9 (6-12)</td>
<td>9 (7-12)</td>
</tr>
<tr>
<td></td>
<td>9 (6-12)</td>
<td>10 (7-12)</td>
</tr>
<tr>
<td></td>
<td>9 (6-12)</td>
<td>9 (6-12)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMD rank, n (%)</td>
<td>7,439 (12.4)</td>
<td>7,188 (13.1)</td>
</tr>
<tr>
<td></td>
<td>3,756 (12.4)</td>
<td>3,654 (12.5)</td>
</tr>
<tr>
<td></td>
<td>3,683 (13.5)</td>
<td>3,534 (13.7)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living in a nursing home, n (%)</td>
<td>5,276 (8.6)</td>
<td>5,246 (9.0)</td>
</tr>
<tr>
<td></td>
<td>2,021 (6.3)</td>
<td>2,010 (6.5)</td>
</tr>
<tr>
<td></td>
<td>3,255 (11.2)</td>
<td>3,236 (11.9)</td>
</tr>
<tr>
<td>p-value</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Risk scores</strong></td>
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<td></td>
</tr>
<tr>
<td>CHA₂DS₂-Vasc, Mean (SD)</td>
<td>3.8 (1.5)</td>
<td>3.8 (1.4)</td>
</tr>
<tr>
<td></td>
<td>3.9 (1.5)</td>
<td>4.0 (1.4)</td>
</tr>
<tr>
<td></td>
<td>3.6 (1.5)</td>
<td>3.8 (1.4)</td>
</tr>
<tr>
<td>p-value</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>ATRIA, Median (IQR)</td>
<td>3 (2-6)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td></td>
<td>3 (2-6)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td></td>
<td>3 (2-6)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past medical history, n (%)</td>
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<td></td>
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<tr>
<td>Alcohol excess</td>
<td>1,855 (3.0)</td>
<td>1,695 (2.9)</td>
</tr>
<tr>
<td></td>
<td>836 (2.6)</td>
<td>789 (2.6)</td>
</tr>
<tr>
<td></td>
<td>1,019 (3.5)</td>
<td>906 (3.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12,145 (19.9)</td>
<td>11,974 (20.6)</td>
</tr>
<tr>
<td></td>
<td>6,024 (18.8)</td>
<td>5,959 (19.7)</td>
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<tr>
<td></td>
<td>6,121 (21.0)</td>
<td>6,015 (22.0)</td>
</tr>
<tr>
<td>p-value</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td>945 (1.5)</td>
<td>913 (1.6)</td>
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<tr>
<td>Cancer</td>
<td>10,225 (16.7)</td>
<td>9,862 (16.9)</td>
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<td></td>
<td>5,187 (16.2)</td>
<td>5,045 (16.3)</td>
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<tr>
<td></td>
<td>5,038 (17.3)</td>
<td>4,817 (17.7)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*a*: Significant at p < 0.05.

*b*: Significant at p < 0.01.
<table>
<thead>
<tr>
<th>Condition</th>
<th>All patients with AF</th>
<th>Patients with AF and CHA₂DS₂-Vasc score of 2 or more</th>
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</thead>
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<tr>
<td></td>
<td>Total n=61,177</td>
<td>Total n=58,204</td>
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<tr>
<td></td>
<td>Prescribed OAC</td>
<td>Prescribed OAC</td>
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<tr>
<td></td>
<td>n=32,079</td>
<td>n=30,916</td>
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<tr>
<td></td>
<td>Not prescribed OAC</td>
<td>Not prescribed OAC</td>
</tr>
<tr>
<td></td>
<td>n=29,098</td>
<td>n=27,288</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td>p-value*</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>261 (0.43)</td>
<td>253 (0.43)</td>
</tr>
<tr>
<td></td>
<td>112 (0.4)</td>
<td>111 (0.36)</td>
</tr>
<tr>
<td></td>
<td>149 (0.51)</td>
<td>142 (0.52)</td>
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<td></td>
<td>0.002</td>
<td>0.003</td>
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<tr>
<td>CKD</td>
<td>20,325 (33.2)</td>
<td>20,153 (34.6)</td>
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<tr>
<td></td>
<td>11,528 (35.9)</td>
<td>11,435 (37.0)</td>
</tr>
<tr>
<td></td>
<td>8,797 (30.2)</td>
<td>8,718 (32.0)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Falls</td>
<td>11,758 (19.2)</td>
<td>11,637 (20.0)</td>
</tr>
<tr>
<td></td>
<td>5,893 (18.4)</td>
<td>5,843 (18.9)</td>
</tr>
<tr>
<td></td>
<td>5,865 (20.2)</td>
<td>5,794 (21.2)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>918 (1.5)</td>
<td>890 (1.5)</td>
</tr>
<tr>
<td></td>
<td>416 (1.3)</td>
<td>403 (1.3)</td>
</tr>
<tr>
<td></td>
<td>502 (1.7)</td>
<td>487 (1.8)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower</td>
<td>6,222 (10.2)</td>
<td>5,940 (10.2)</td>
</tr>
<tr>
<td></td>
<td>3,185 (9.9)</td>
<td>3,075 (10.0)</td>
</tr>
<tr>
<td></td>
<td>3,037 (10.4)</td>
<td>2,865 (10.5)</td>
</tr>
<tr>
<td></td>
<td>0.038</td>
<td>0.028</td>
</tr>
<tr>
<td>Unspecified</td>
<td>537 (0.88)</td>
<td>524 (0.90)</td>
</tr>
<tr>
<td></td>
<td>232 (0.7)</td>
<td>228 (0.74)</td>
</tr>
<tr>
<td></td>
<td>305 (1.1)</td>
<td>296 (1.1)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematuria</td>
<td>7,535 (12.3)</td>
<td>7,245 (12.5)</td>
</tr>
<tr>
<td></td>
<td>4,226 (13.2)</td>
<td>4,116 (13.3)</td>
</tr>
<tr>
<td></td>
<td>3,307 (11.4)</td>
<td>3,129 (11.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1,772 (2.9)</td>
<td>1,705 (2.9)</td>
</tr>
<tr>
<td></td>
<td>1,042 (3.3)</td>
<td>999 (3.2)</td>
</tr>
<tr>
<td></td>
<td>730 (2.5)</td>
<td>706 (2.6)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertension</td>
<td>41,340 (67.6)</td>
<td>41,146 (70.7)</td>
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<tr>
<td></td>
<td>22,259 (69.4)</td>
<td>22,173 (71.7)</td>
</tr>
<tr>
<td></td>
<td>19,081 (65.6)</td>
<td>18,991 (69.6)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2,002 (3.3)</td>
<td>1,944 (3.3)</td>
</tr>
<tr>
<td></td>
<td>1,068 (3.3)</td>
<td>1,046 (3.4)</td>
</tr>
<tr>
<td></td>
<td>934 (3.2)</td>
<td>898 (3.3)</td>
</tr>
<tr>
<td></td>
<td>0.407</td>
<td>0.535</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>982 (1.6)</td>
<td>972 (1.7)</td>
</tr>
<tr>
<td></td>
<td>304 (0.95)</td>
<td>303 (0.98)</td>
</tr>
<tr>
<td></td>
<td>678 (2.3)</td>
<td>669 (2.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>19,586 (32.0)</td>
<td>19,158 (32.9)</td>
</tr>
<tr>
<td></td>
<td>10,939 (34.1)</td>
<td>10,741 (34.7)</td>
</tr>
<tr>
<td></td>
<td>8,647 (29.7)</td>
<td>8,417 (30.9)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Memory loss</td>
<td>7,880 (12.9)</td>
<td>7,782 (13.4)</td>
</tr>
<tr>
<td></td>
<td>3,513 (11.0)</td>
<td>3,474 (11.2)</td>
</tr>
<tr>
<td></td>
<td>4,367 (15.0)</td>
<td>4,308 (15.8)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7,419 (12.1)</td>
<td>7,400 (12.7)</td>
</tr>
<tr>
<td></td>
<td>3,946 (12.3)</td>
<td>3,939 (12.7)</td>
</tr>
<tr>
<td></td>
<td>3,473 (11.9)</td>
<td>3,461 (12.7)</td>
</tr>
<tr>
<td></td>
<td>0.167</td>
<td>0.835</td>
</tr>
<tr>
<td>Obesity</td>
<td>828 (1.4)</td>
<td>818 (1.4)</td>
</tr>
<tr>
<td></td>
<td>484 (1.5)</td>
<td>481 (1.6)</td>
</tr>
<tr>
<td></td>
<td>344 (1.2)</td>
<td>337 (1.2)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>3,676 (6.0)</td>
<td>3,555 (6.1)</td>
</tr>
<tr>
<td></td>
<td>1,767 (5.5)</td>
<td>1,723 (5.6)</td>
</tr>
<tr>
<td></td>
<td>1,909 (6.6)</td>
<td>1,832 (6.7)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>86 (0.14)</td>
<td>82 (0.14)</td>
</tr>
<tr>
<td></td>
<td>29 (0.09)</td>
<td>28 (0.09)</td>
</tr>
<tr>
<td></td>
<td>57 (0.20)</td>
<td>54 (0.20)</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>7,239 (11.8)</td>
<td>7,239 (12.4)</td>
</tr>
<tr>
<td></td>
<td>4,375 (13.6)</td>
<td>4,375 (14.2)</td>
</tr>
<tr>
<td></td>
<td>2,864 (9.8)</td>
<td>2,864 (10.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unspecified</td>
<td>3,179 (5.2)</td>
<td>3,179 (5.5)</td>
</tr>
<tr>
<td></td>
<td>1,983 (6.2)</td>
<td>1,983 (6.4)</td>
</tr>
<tr>
<td></td>
<td>1,196 (4.1)</td>
<td>1,196 (4.4)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>3,752 (6.1)</td>
<td>5,043 (8.7)</td>
</tr>
<tr>
<td></td>
<td>2,266 (7.1)</td>
<td>3,003 (9.7)</td>
</tr>
<tr>
<td></td>
<td>1,486 (5.1)</td>
<td>2,040 (7.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6,019 (9.8)</td>
<td>6,019 (10.3)</td>
</tr>
<tr>
<td></td>
<td>3,624 (11.3)</td>
<td>3,624 (11.7)</td>
</tr>
<tr>
<td></td>
<td>2,395 (8.2)</td>
<td>2,395 (8.8)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1,879 (3.1)</td>
<td>1,820 (3.1)</td>
</tr>
<tr>
<td></td>
<td>1,346 (4.2)</td>
<td>1,312 (4.2)</td>
</tr>
<tr>
<td></td>
<td>531 (1.8)</td>
<td>508 (1.9)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing IMD data: 3,466 (5.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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\textsubscript{2}DS\textsubscript{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\textsubscript{2}DS\textsubscript{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.

![Box plot showing stroke and bleeding risk](image)

**Figure 43**: Stroke and bleeding risk (CHA\textsubscript{2}DS\textsubscript{2}-VASC and ATRIA) scores by oral anticoagulation prescription status, in patients with CHA\textsubscript{2}DS\textsubscript{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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-VASc score of two or more, n=58,204

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

* 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$_2$DS$_2$-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.
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.
Figure 46: Association between eFI category and OAC prescription at study entry in patients with AF and CHA²DS²-VASc score of two or more. n=58,204
Table 34: Prescription rates of each OAC, of those prescribed OAC at study entry

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

Sin thrombe, 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\(_2\)DS\(_2\)-VASc score, Table 31). The rates for patients with AF and a CHA\(_2\)DS\(_2\)-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\(_2\)DS\(_2\)-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\(_2\)DS\(_2\)-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 39.1, 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\(_2\)DS\(_2\)-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 CHA₂DS₂-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 CHA₂DS₂-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 3: Rates of clinical outcomes (/1000pys) in patients with AF and CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more by frailty status.

<table>
<thead>
<tr>
<th>Frailty Status</th>
<th>n</th>
<th>Person Years follow-up</th>
<th>Rate n</th>
<th>Rate</th>
<th>Rate n</th>
<th>Rate</th>
<th>Rate n</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>58,204</td>
<td>69,610.31</td>
<td>6,085</td>
<td>87.4 (85.3-89.6)</td>
<td>139</td>
<td>22.9 (19.4-27.0)</td>
<td>1,019</td>
<td>43.0 (40.5-45.8)</td>
</tr>
<tr>
<td>Fall</td>
<td>2,662</td>
<td>20,133.18</td>
<td>572</td>
<td>8.3 (7.6-9.0)</td>
<td>36</td>
<td>5.5 (4.3-7.7)</td>
<td>177</td>
<td>3.3 (2.6-4.1)</td>
</tr>
<tr>
<td>IC bleed</td>
<td>133</td>
<td>1,426.03</td>
<td>33</td>
<td>2.5 (1.8-3.4)</td>
<td>4</td>
<td>2.2 (1.4-3.1)</td>
<td>29</td>
<td>1.8 (1.3-2.5)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>605</td>
<td>62,239.84</td>
<td>365</td>
<td>5.8 (5.3-6.3)</td>
<td>21</td>
<td>3.5 (2.8-4.2)</td>
<td>99</td>
<td>1.6 (1.3-2.0)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>334</td>
<td>4,924.52</td>
<td>22</td>
<td>3.5 (2.8-4.2)</td>
<td>0</td>
<td>0.0 (0.0-0.0)</td>
<td>99</td>
<td>1.6 (1.3-2.0)</td>
</tr>
<tr>
<td>Death</td>
<td>1,829</td>
<td>20,133.18</td>
<td>1,829</td>
<td>28.0 (25.5-30.6)</td>
<td>367</td>
<td>5.6 (4.8-6.4)</td>
<td>217</td>
<td>4.4 (3.6-5.3)</td>
</tr>
</tbody>
</table>

**Abbreviations**
- GI: gastrointestinal
- IC: intracranial
- TIA: transient ischemic attack
- AF: atrial fibrillation

**Statistical Note:** n=58,204.

*Table 35: Rates of clinical outcomes (/1000pys) in patients with AF and CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more by frailty status.*
8.5 Oral anticoagulation and clinical outcomes

Overall, the standardised stroke rate for patients with AF and any CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-VASc score of one. There were 12 patients that experienced a stroke event with a CHA₂DS₂-VASc score of one who were not prescribed OAC (rate 5.30, 95% CI 3.01 to 9.33 /1000pys).

For a given CHA₂DS₂-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 CHA₂DS₂-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$_2$DS$_2$-VASc score and OAC status, n=61,177
### Table 36: Stroke rates by OAC status, stratified by CHA\textsubscript{2}DS\textsubscript{2}-VASc score

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc Score</th>
<th>All patients with AF, n=61,177</th>
<th>Not prescribed OAC, n=29,098</th>
<th>Prescribed OAC, n=32,079</th>
<th>Difference between group prescribed OAC and group not prescribed OAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2,973</td>
<td>12</td>
<td>5.30 (3.01-9.33)</td>
<td>0.0003 (0.0002, 0.0005) &lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>9,758</td>
<td>71</td>
<td>5.05 (3.57-7.15)</td>
<td>6.88 (5.03-9.41) -0.0001 (-0.0005, 0.0004) 0.732</td>
</tr>
<tr>
<td>3</td>
<td>15,117</td>
<td>102</td>
<td>7.51 (5.91-9.55)</td>
<td>3.70 (2.66-5.15) 0.0010 (0.0005, 0.0016) &lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>15,678</td>
<td>164</td>
<td>10.61 (8.64-13.03)</td>
<td>7.25 (5.76-9.12) 0.0008 (0.0001, 0.0015) 0.031</td>
</tr>
<tr>
<td>5</td>
<td>9,349</td>
<td>131</td>
<td>14.71 (11.58-18.69)</td>
<td>10.12 (7.92-12.93) 0.0003 (-0.0003, 0.0009) 0.353</td>
</tr>
<tr>
<td>6</td>
<td>5,614</td>
<td>89</td>
<td>14.31 (10.37-19.75)</td>
<td>13.57 (10.34-17.81) -0.0003 (-0.0008, 0.0002) 0.296</td>
</tr>
<tr>
<td>7</td>
<td>2,143</td>
<td>37</td>
<td>23.56 (15.51-35.78)</td>
<td>10.40 (6.27-17.25) 0.0003 (-0.0001, 0.0006) 0.132</td>
</tr>
<tr>
<td>8</td>
<td>485</td>
<td>11</td>
<td>20.45 (7.67-54.48)</td>
<td>21.28 (10.15-44.64) -0.0001 (-0.0002, 0.0001) 0.476</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>0</td>
<td>-</td>
<td>0 (0)</td>
</tr>
<tr>
<td>All</td>
<td>61,177</td>
<td>617</td>
<td>8.45 (7.81-9.14)</td>
<td>9.66 (8.67-10.75) 7.38 (6.57-8.29) 0.0023 (0.0009, 0.0036) 0.001</td>
</tr>
</tbody>
</table>

**Abbreviation** OAC: oral anticoagulation
Overall, in patients with AF and a CHA$_2$DS$_2$-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$_2$DS$_2$-VASc score are also reported in Table 38.
Figure 48: Rates of outcome events by oral anticoagulation status in patients with AF and a CHA₂DS₂-VASc score of 2 or more, n=58,204

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OAC status</th>
<th>Rate (95% CI) per 1000 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>No</td>
<td>9.96 (8.93-11.12)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>7.67 (6.83-8.61)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>No</td>
<td>7.76 (6.85-8.78)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>8.72 (7.82-9.72)</td>
</tr>
<tr>
<td>IC bleed</td>
<td>No</td>
<td>1.58 (1.20-2.08)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.20 (1.77-2.73)</td>
</tr>
</tbody>
</table>
Table 37: Rates of outcome events (per 1000 person-years) by OAC status in patients with AF and a CHA₂DS₂-VASc score of two or more

<table>
<thead>
<tr>
<th>Event</th>
<th>All n=58,204</th>
<th>Not prescribed OAC at study start n=27,288</th>
<th>Prescribed OAC at study start n=30,916</th>
<th>Difference in proportions (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Rate</td>
<td>Events Rate</td>
<td>Events Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6,085</td>
<td>87.4 (85.3-89.6)</td>
<td>3,267</td>
<td>101.2 (97.8-104.7)</td>
<td>2,818</td>
</tr>
<tr>
<td>Stroke</td>
<td>605</td>
<td>8.7 (8.1-9.5)</td>
<td>320</td>
<td>10.0 (8.9-11.1)</td>
<td>285</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>271</td>
<td>3.9 (3.5-4.4)</td>
<td>160</td>
<td>5.0 (4.3-5.8)</td>
<td>111</td>
</tr>
<tr>
<td>Unspecified</td>
<td>334</td>
<td>4.81 (4.3-5.4)</td>
<td>160</td>
<td>5.0 (4.3-5.8)</td>
<td>174</td>
</tr>
<tr>
<td>GI bleed</td>
<td>572</td>
<td>8.27 (7.6-9.0)</td>
<td>249</td>
<td>7.8 (6.9-8.8)</td>
<td>323</td>
</tr>
<tr>
<td>IC bleed</td>
<td>133</td>
<td>1.9 (1.6-2.3)</td>
<td>51</td>
<td>1.6 (1.2-2.1)</td>
<td>82</td>
</tr>
<tr>
<td>Falls</td>
<td>2,682</td>
<td>39.4 (37.9-40.9)</td>
<td>1,242</td>
<td>39.4 (37.2-41.6)</td>
<td>1,440</td>
</tr>
<tr>
<td>TIA</td>
<td>361</td>
<td>5.2 (4.7-5.8)</td>
<td>181</td>
<td>5.6 (4.9-6.5)</td>
<td>180</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Event</th>
<th>AF, not prescribed OAC</th>
<th>AF, prescribed OAC</th>
<th>Difference in proportions (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Rate (95%CI)</td>
<td>Events</td>
<td>Rate (95%CI)</td>
</tr>
<tr>
<td>Death</td>
<td>3,302</td>
<td>95.6 (92.4–98.9)</td>
<td>2,841</td>
<td>73.3 (70.6–76.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>332</td>
<td>9.7 (8.7–10.8)</td>
<td>285</td>
<td>7.4 (6.6–8.3)</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>168</td>
<td>4.9 (4.2–5.7)</td>
<td>111</td>
<td>2.9 (2.4–3.5)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>164</td>
<td>4.8 (4.1–5.5)</td>
<td>174</td>
<td>4.5 (3.9–5.2)</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>253</td>
<td>7.4 (6.5–8.3)</td>
<td>330</td>
<td>8.6 (7.7–9.6)</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>53</td>
<td>1.5 (1.2–2.0)</td>
<td>83</td>
<td>2.1 (1.7–2.7)</td>
</tr>
<tr>
<td>Falls</td>
<td>1,258</td>
<td>37.2 (35.2–39.3)</td>
<td>1,449</td>
<td>38.2 (36.3–40.2)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>189</td>
<td>5.5 (4.8–6.3)</td>
<td>183</td>
<td>4.7 (4.1–5.5)</td>
</tr>
</tbody>
</table>
In patients with AF and a CHA$_2$DS$_2$-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$_2$DS$_2$-VASC of $\geq 2$, $n=58,204$

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>p value$\dagger$</th>
<th>No OAC</th>
<th>OAC</th>
<th>p value$\dagger$</th>
<th>p-value for interaction by frailty *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No OAC n=27,288</td>
<td>OAC n=30,916</td>
<td></td>
<td>No OAC</td>
<td>OAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1 (ref)</td>
<td>0.75 (0.71-0.79)</td>
<td>&lt;0.001</td>
<td>1 (ref)</td>
<td>0.81 (0.77-0.85)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>1 (ref)</td>
<td>0.97 (0.69-1.36)</td>
<td>0.857</td>
<td>1 (ref)</td>
<td>0.91 (0.64-1.30)</td>
<td>0.608</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (ref)</td>
<td>0.84 (0.75-0.95)</td>
<td>0.007</td>
<td>1 (ref)</td>
<td>0.88 (0.77-0.99)</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (ref)</td>
<td>0.71 (0.65-0.77)</td>
<td>&lt;0.001</td>
<td>1 (ref)</td>
<td>0.75 (0.69-0.82)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (ref)</td>
<td>0.67 (0.62-0.72)</td>
<td>&lt;0.001</td>
<td>1 (ref)</td>
<td>0.76 (0.71-0.82)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1 (ref)</td>
<td>0.77 (0.66-0.90)</td>
<td>0.001</td>
<td>1 (ref)</td>
<td>0.78 (0.67-0.92)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>1 (ref)</td>
<td>0.70 (0.35-1.39)</td>
<td>0.303</td>
<td>1 (ref)</td>
<td>0.64 (0.31-1.32)</td>
<td>0.230</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (ref)</td>
<td>0.92 (0.69-1.24)</td>
<td>0.598</td>
<td>1 (ref)</td>
<td>0.94 (0.69-1.26)</td>
<td>0.661</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (ref)</td>
<td>0.59 (0.45-0.77)</td>
<td>&lt;0.001</td>
<td>1 (ref)</td>
<td>0.61 (0.47-0.80)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (ref)</td>
<td>0.86 (0.64-1.67)</td>
<td>0.337</td>
<td>1 (ref)</td>
<td>0.88 (0.64-1.21)</td>
<td>0.443</td>
<td></td>
</tr>
<tr>
<td><strong>GI bleed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1 (ref)</td>
<td>1.13 (0.95-1.33)</td>
<td>0.162</td>
<td>1 (ref)</td>
<td>1.10 (0.93-1.30)</td>
<td>0.271</td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>1 (ref)</td>
<td>0.91 (0.45-1.82)</td>
<td>0.783</td>
<td>1 (ref)</td>
<td>0.81 (0.38-1.70)</td>
<td>0.570</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (ref)</td>
<td>1.39 (0.98-1.95)</td>
<td>0.063</td>
<td>1 (ref)</td>
<td>1.33 (0.93-1.89)</td>
<td>0.118</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (ref)</td>
<td>1.07 (0.81-1.39)</td>
<td>0.644</td>
<td>1 (ref)</td>
<td>1.05 (0.80-1.39)</td>
<td>0.727</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (ref)</td>
<td>1.00 (0.75-1.34)</td>
<td>1.000</td>
<td>1 (ref)</td>
<td>0.98 (0.73-1.32)</td>
<td>0.897</td>
<td></td>
</tr>
<tr>
<td>IC bleed</td>
<td>All</td>
<td>1 (ref)</td>
<td>1.39 (0.98-1.97)</td>
<td>0.064</td>
<td>1 (ref)</td>
<td>1.40 (0.97-2.00)</td>
<td>0.069</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>---------</td>
<td>------------------</td>
<td>-------</td>
<td>---------</td>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td>Robust</td>
<td>1 (ref)</td>
<td>2.79 (0.70-11.15)</td>
<td>0.147</td>
<td>1 (ref)</td>
<td>1.98 (0.47-8.28)</td>
<td>0.352</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1 (ref)</td>
<td>1.43 (0.67-3.02)</td>
<td>0.352</td>
<td>1 (ref)</td>
<td>1.47 (0.67-3.21)</td>
<td>0.335</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1 (ref)</td>
<td>1.62 (0.87-3.00)</td>
<td>0.126</td>
<td>1 (ref)</td>
<td>1.68 (0.89-3.20)</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1 (ref)</td>
<td>1.02 (0.58-1.79)</td>
<td>0.946</td>
<td>1 (ref)</td>
<td>1.03 (0.58-1.85)</td>
<td>0.918</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>CTV-3 code</th>
<th>Description</th>
<th>Number of times CTV-3 code used in total</th>
<th>Number of patient EHR the CTV-3 code appears in</th>
<th>Percentage of patient EHR the code appears in</th>
</tr>
</thead>
<tbody>
<tr>
<td>G5730</td>
<td>Atrial fibrillation</td>
<td>101,108</td>
<td>39,966</td>
<td>32.00%</td>
</tr>
<tr>
<td>2432</td>
<td>O/E - pulse irregularly irreg.</td>
<td>46,323</td>
<td>23,716</td>
<td>18.99%</td>
</tr>
<tr>
<td>3272</td>
<td>ECG: atrial fibrillation</td>
<td>27,754</td>
<td>20,836</td>
<td>16.68%</td>
</tr>
<tr>
<td>Xa2E8</td>
<td>Paroxysmal atrial fibrillation</td>
<td>24,671</td>
<td>10,962</td>
<td>8.78%</td>
</tr>
<tr>
<td>G573</td>
<td>Atrial fibrillation and flutter</td>
<td>9,133</td>
<td>4,957</td>
<td>3.97%</td>
</tr>
<tr>
<td>XaLFz</td>
<td>Atrial fibrillation resolved</td>
<td>6,417</td>
<td>5,442</td>
<td>4.36%</td>
</tr>
<tr>
<td>G5731</td>
<td>Atrial flutter</td>
<td>6,346</td>
<td>3,528</td>
<td>2.82%</td>
</tr>
<tr>
<td>XaIT</td>
<td>Atrial fibrillation monitoring</td>
<td>5,458</td>
<td>2,948</td>
<td>2.36%</td>
</tr>
<tr>
<td>XaMGD</td>
<td>Atrial fibrillation annual review</td>
<td>3,699</td>
<td>2,060</td>
<td>1.65%</td>
</tr>
<tr>
<td>XaLFi</td>
<td>Excepted from atrial fibrillation quality indicators: Patient unsuitable</td>
<td>2,405</td>
<td>1,912</td>
<td>1.53%</td>
</tr>
<tr>
<td>XaMDG</td>
<td>Atrial fibrillation monitoring first letter</td>
<td>2,121</td>
<td>1,076</td>
<td>0.86%</td>
</tr>
<tr>
<td>XaDV6</td>
<td>H/O: atrial fibrillation</td>
<td>1,893</td>
<td>1,469</td>
<td>1.18%</td>
</tr>
<tr>
<td>XaLFj</td>
<td>Excepted from atrial fibrillation quality indicators: Informed dissent</td>
<td>1,466</td>
<td>1,173</td>
<td>0.94%</td>
</tr>
<tr>
<td>3273</td>
<td>ECG: atrial flutter</td>
<td>1,429</td>
<td>1,202</td>
<td>0.96%</td>
</tr>
<tr>
<td>G573z</td>
<td>Atrial fibrillation and flutter NOS</td>
<td>933</td>
<td>464</td>
<td>0.37%</td>
</tr>
<tr>
<td>XaEga</td>
<td>Rapid atrial fibrillation</td>
<td>800</td>
<td>712</td>
<td>0.57%</td>
</tr>
<tr>
<td>XaOfa</td>
<td>Persistent atrial fibrillation</td>
<td>557</td>
<td>506</td>
<td>0.41%</td>
</tr>
<tr>
<td>XaMDH</td>
<td>Atrial fibrillation monitoring second letter</td>
<td>416</td>
<td>324</td>
<td>0.26%</td>
</tr>
<tr>
<td>XaOft</td>
<td>Permanent atrial fibrillation</td>
<td>397</td>
<td>368</td>
<td>0.29%</td>
</tr>
<tr>
<td>XaMDF</td>
<td>Atrial fibrillation monitoring administration</td>
<td>321</td>
<td>264</td>
<td>0.21%</td>
</tr>
<tr>
<td>Xa7nl</td>
<td>Controlled atrial fibrillation</td>
<td>291</td>
<td>263</td>
<td>0.21%</td>
</tr>
<tr>
<td>XaXrZ</td>
<td>Referral to atrial fibrillation clinic</td>
<td>277</td>
<td>263</td>
<td>0.21%</td>
</tr>
<tr>
<td>XaMDI</td>
<td>Atrial fibrillation monitoring third letter</td>
<td>135</td>
<td>108</td>
<td>0.09%</td>
</tr>
<tr>
<td>XaaUH</td>
<td>Paroxysmal atrial flutter</td>
<td>114</td>
<td>103</td>
<td>0.08%</td>
</tr>
<tr>
<td>XaMFn</td>
<td>Atrial fibrillation monitoring telephone invite</td>
<td>64</td>
<td>60</td>
<td>0.05%</td>
</tr>
<tr>
<td>X202R</td>
<td>Lone atrial fibrillation</td>
<td>57</td>
<td>56</td>
<td>0.04%</td>
</tr>
<tr>
<td>XaLfh</td>
<td>Exception reporting: atrial fibrillation quality indicators</td>
<td>42</td>
<td>39</td>
<td>0.03%</td>
</tr>
<tr>
<td>XaNRA</td>
<td>History of atrial flutter</td>
<td>58</td>
<td>47</td>
<td>0.04%</td>
</tr>
<tr>
<td>CTV-3 code</td>
<td>Number of times CTV-3 code used in total</td>
<td>Number of patient EHR the CTV-3 code appears in</td>
<td>Percentage of patient EHR the code appears in</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>7936A</td>
<td>13</td>
<td>13</td>
<td>0.01%</td>
<td></td>
</tr>
<tr>
<td>X202S</td>
<td>22</td>
<td>15</td>
<td>0.01%</td>
<td></td>
</tr>
<tr>
<td>XE0Wk</td>
<td>33</td>
<td>28</td>
<td>0.02%</td>
<td></td>
</tr>
<tr>
<td>XaMDK</td>
<td>22</td>
<td>21</td>
<td>0.02%</td>
<td></td>
</tr>
<tr>
<td>XaZdc</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>XaeUP</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>244,782</strong></td>
<td><strong>124,908</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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: Exceptioned from atrial fibrillation quality indicators: Patient unsuitable
- XaLFj: Exceptioned 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](image)

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

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

**Abbreviations**  IQR: interquartile range; OAC: oral anticoagulation

Comparing outcome event rates between the reduced analytical cohort and the excluded group in patients with CHA2DS2-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 CHA2DS2-VASc score of two or more. Rates, /1000pys (95% CI)

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

*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.
### Results shown for the reduced analytical cohort (n=52,605) and the excluded group (n=8,194).

Table 43: Rates of outcome events (1000/ys) in patients with AF and a CHA₂DS₂-VASc score of two or more, by frailty status.

<table>
<thead>
<tr>
<th>Event</th>
<th>Reduced cohort</th>
<th>Excluded group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemic stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5.7 (4.7-6.9)</td>
<td>3.0 (2.4-3.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.5 (2.7-4.4)</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>1.3 (0.5-2.3)</td>
<td>0.3 (0.1-0.6)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>10.9 (8.0-12.6)</td>
<td>6.3 (4.7-8.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7.7 (6.6-9.1)</td>
<td>5.3 (3.7-7.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>3.9 (2.6-4.9)</td>
<td>2.0 (1.4-3.0)</td>
</tr>
<tr>
<td><strong>Gastrointestinal bleed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5.0 (4.9-6.2)</td>
<td>3.2 (2.4-5.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.8 (2.4-3.5)</td>
<td>1.5 (1.1-1.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>1.0 (0.6-1.4)</td>
<td>0.3 (0.2-0.6)</td>
</tr>
<tr>
<td><strong>Ischaemic stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>10.9 (8.0-12.6)</td>
<td>6.3 (4.7-8.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7.7 (6.6-9.1)</td>
<td>5.3 (3.7-7.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>3.9 (2.6-4.9)</td>
<td>2.0 (1.4-3.0)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>5.5 (4.4-6.8)</td>
<td>3.0 (1.5-4.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.6 (2.9-4.8)</td>
<td>1.6 (1.0-2.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>1.4 (0.9-2.0)</td>
<td>0.5 (0.3-0.8)</td>
</tr>
</tbody>
</table>

---

Table 44: Rates of outcome events (1000/ys) in patients with AF and a CHA₂DS₂-VASc score of two or more, by frailty status.

<table>
<thead>
<tr>
<th>Event</th>
<th>Reduced cohort</th>
<th>Excluded group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemic stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5.7 (4.7-6.9)</td>
<td>3.0 (2.4-3.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.5 (2.7-4.4)</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>1.3 (0.5-2.3)</td>
<td>0.3 (0.1-0.6)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>10.9 (8.0-12.6)</td>
<td>6.3 (4.7-8.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7.7 (6.6-9.1)</td>
<td>5.3 (3.7-7.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>3.9 (2.6-4.9)</td>
<td>2.0 (1.4-3.0)</td>
</tr>
<tr>
<td><strong>Gastrointestinal bleed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5.0 (4.9-6.2)</td>
<td>3.2 (2.4-5.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.8 (2.4-3.5)</td>
<td>1.5 (1.1-1.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>1.0 (0.6-1.4)</td>
<td>0.3 (0.2-0.6)</td>
</tr>
<tr>
<td><strong>Ischaemic stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>10.9 (8.0-12.6)</td>
<td>6.3 (4.7-8.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7.7 (6.6-9.1)</td>
<td>5.3 (3.7-7.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>3.9 (2.6-4.9)</td>
<td>2.0 (1.4-3.0)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>5.5 (4.4-6.8)</td>
<td>3.0 (1.5-4.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.6 (2.9-4.8)</td>
<td>1.6 (1.0-2.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>1.4 (0.9-2.0)</td>
<td>0.5 (0.3-0.8)</td>
</tr>
</tbody>
</table>
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\textsubscript{2}DS\textsubscript{2}-VASC score $\geq$ 2, in the reduced analytical cohort. n=50,010**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No OAC n=19,464</td>
<td>OAC n=30,546</td>
</tr>
<tr>
<td>Death</td>
<td>1 (ref)</td>
<td>0.63 (0.60-0.67)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (ref)</td>
<td>0.7 (0.6-0.8)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>1 (ref)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>IC bleed</td>
<td>1 (ref)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
</tbody>
</table>

*p-value for difference in HR associated with prescription of OAC.

**Abbreviations** OAC: oral anticoagulation; GI: gastrointestinal; IC: intracranial
Figure 50: Sensitivity analysis showing the unadjusted association between OAC and clinical outcomes in patients with AF and CHA$_2$DS$_2$-VASc score of two or more

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleed</td>
<td>1.39 (0.99-2.05)</td>
</tr>
<tr>
<td></td>
<td>OAC, reduced cohort</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
<tr>
<td></td>
<td>Interatrial</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.01 (0.84-1.21)</td>
</tr>
<tr>
<td></td>
<td>OAC, reduced cohort</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
<tr>
<td>Death</td>
<td>1.13 (0.95-1.33)</td>
</tr>
<tr>
<td></td>
<td>OAC, original cohort</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
<tr>
<td>Death</td>
<td>0.71 (0.60-0.84)</td>
</tr>
<tr>
<td></td>
<td>OAC, reduced cohort</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
<tr>
<td>Death</td>
<td>0.77 (0.66-0.90)</td>
</tr>
<tr>
<td></td>
<td>OAC, original cohort</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
<tr>
<td>Death</td>
<td>0.63 (0.50-0.87)</td>
</tr>
<tr>
<td></td>
<td>OAC, reduced cohort</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
<tr>
<td>Death</td>
<td>0.75 (0.71-0.79)</td>
</tr>
<tr>
<td></td>
<td>OAC, original cohort</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
<tr>
<td>Death</td>
<td>* (ref)</td>
</tr>
<tr>
<td></td>
<td>No OAC</td>
</tr>
</tbody>
</table>

Note: HR (95% CI)
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 CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-VASC score ≥ 2, by OAC persistence

<table>
<thead>
<tr>
<th></th>
<th>All n=58,204</th>
<th>Persistent on OAC n=28,356</th>
<th>Not persistent on OAC n=5,674</th>
<th>Not prescribed OAC n=24,174</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, Median (IQR)</td>
<td>80.3 (74.3-85.8)</td>
<td>79.9 (74.5-85.1)</td>
<td>81.3 (75.3-86.4)</td>
<td>80.4 (73.9-86.6)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Electronic frailty index category, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>4,863 (8.4)</td>
<td>1,914 (6.8)</td>
<td>382 (6.7)</td>
<td>2,567 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>19,198 (33.0)</td>
<td>9,532 (33.6)</td>
<td>1,691 (29.8)</td>
<td>7,975 (33.0)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>20,099 (34.5)</td>
<td>10,251 (36.2)</td>
<td>1,990 (35.1)</td>
<td>7,858 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>14,044 (24.1)</td>
<td>6,659 (23.5)</td>
<td>1,611 (28.4)</td>
<td>5,774 (23.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMD rank, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most deprived quintile</td>
<td>7,118 (13.1)</td>
<td>3,299 (12.3)</td>
<td>774 (14.4)</td>
<td>3,115 (13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living in a nursing home</td>
<td>5,246 (9.0)</td>
<td>1,547 (5.5)</td>
<td>782 (13.8)</td>
<td>2,917 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of AF, years prior to study start, Median (IQR)</td>
<td>4.76 (2.2-9.4)</td>
<td>5.4 (2.5-10.2)</td>
<td>4.3 (1.6-8.9)</td>
<td>4.2 (2.0-8.4)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td><strong>Risk scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-Vasc, Mean (SD)</td>
<td>3.9 (1.4)</td>
<td>4.0 (1.4)</td>
<td>4.0 (1.4)</td>
<td>3.8 (1.4)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>ATRIA, Median (IQR)</td>
<td>3 (2-6)</td>
<td>4 (2-6)</td>
<td>4 (2-6)</td>
<td>3 (2-6)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td><strong>Past medical history, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>9,862 (16.9)</td>
<td>4,535 (16.0)</td>
<td>1,048 (18.5)</td>
<td>4,279 (17.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Varices</td>
<td>82 (0.14)</td>
<td>22 (0.08)</td>
<td>10 (0.18)</td>
<td>50 (0.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper gastrointestinal bleed</td>
<td>890 (1.5)</td>
<td>348 (1.2)</td>
<td>118 (2.1)</td>
<td>424 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower gastrointestinal bleed</td>
<td>5,940 (10.2)</td>
<td>2,804 (9.9)</td>
<td>609 (10.7)</td>
<td>2,527 (10.5)</td>
<td>0.040</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>972 (1.7)</td>
<td>269 (0.95)</td>
<td>88 (1.55)</td>
<td>615 (2.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Falls</td>
<td>11,637 (20.0)</td>
<td>5,209 (18.4)</td>
<td>1,28 (22.6)</td>
<td>5,147 (21.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Medications in the previous year n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>1,684 (2.9)</td>
<td>829 (2.9)</td>
<td>166 (2.9)</td>
<td>689 (2.9)</td>
<td>0.872</td>
</tr>
<tr>
<td>NSAID</td>
<td>5,209 (9.0)</td>
<td>2,096 (7.4)</td>
<td>500 (8.8)</td>
<td>2,613 (10.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrolide</td>
<td>402 (0.69)</td>
<td>176 (0.62)</td>
<td>49 (0.86)</td>
<td>177 (0.73)</td>
<td>0.078</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>23,695 (40.7)</td>
<td>10,734 (37.9)</td>
<td>2,526 (44.5)</td>
<td>10,435 (43.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-epileptic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbemazepine</td>
<td>224 (0.38)</td>
<td>100 (0.35)</td>
<td>25 (0.44)</td>
<td>99 (0.41)</td>
<td>0.208</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>176 (0.30)</td>
<td>73 (0.26)</td>
<td>25 (0.44)</td>
<td>78 (0.32)</td>
<td></td>
</tr>
<tr>
<td>Medication at study entry, n (%)</td>
<td>All n=58,204</td>
<td>Persistent on OAC n=28,356</td>
<td>Not persistent on OAC n=5,674</td>
<td>Not prescribed OAC n=24,174</td>
<td>p value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Antiplatelet prescription</td>
<td>3,688 (6.3)</td>
<td>581 (2.1)</td>
<td>453 (8.0)</td>
<td>2,654 (11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medications prescribed during the study period, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet*</td>
<td>1,040 (1.8)</td>
<td>233 (0.82)</td>
<td>237 (4.2)</td>
<td>570 (2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Steroid</td>
<td>1,820 (3.1)</td>
<td>862 (3.0)</td>
<td>227 (4.0)</td>
<td>731 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAID</td>
<td>4,979 (8.6)</td>
<td>1,977 (7.0)</td>
<td>494 (8.7)</td>
<td>2,508 (10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrolide</td>
<td>448 (0.77)</td>
<td>188 (0.66)</td>
<td>53 (0.93)</td>
<td>207 (0.86)</td>
<td>0.014</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>25,058 (43.1)</td>
<td>11,195 (39.5)</td>
<td>2,916 (48.6)</td>
<td>10,947 (45.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* 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.
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
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Frailty category</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No OAC</td>
<td></td>
<td>1 (ref)</td>
</tr>
<tr>
<td>OAC prescribed at entry</td>
<td>Robust</td>
<td>0.70 (0.35-1.39)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.92 (0.69-1.24)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.69 (0.45-0.77)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.86 (0.64-1.17)</td>
</tr>
<tr>
<td>OAC prescribed at entry, adjusted</td>
<td>Robust</td>
<td>0.64 (0.31-1.32)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.94 (0.69-1.26)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.61 (0.47-0.80)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.88 (0.64-1.21)</td>
</tr>
<tr>
<td>OAC persistent</td>
<td>Robust</td>
<td>0.75 (0.33-1.69)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.75 (0.52-1.08)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.56 (0.42-0.76)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.99 (0.70-1.39)</td>
</tr>
<tr>
<td>OAC persistent, adjusted</td>
<td>Robust</td>
<td>0.67 (0.28-1.59)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.76 (0.52-1.10)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.57 (0.42-0.76)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.03 (0.72-1.48)</td>
</tr>
<tr>
<td>OAC persistent, AF reduced cohort</td>
<td>Robust</td>
<td>0.66 (0.27-1.59)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.71 (0.46-1.06)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.55 (0.40-0.77)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.87 (0.61-1.26)</td>
</tr>
<tr>
<td>OAC persistent, AF reduced cohort, adjusted</td>
<td>Robust</td>
<td>0.61 (0.24-1.55)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>0.71 (0.47-1.06)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.55 (0.40-0.77)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.92 (0.63-1.35)</td>
</tr>
</tbody>
</table>

Figure 55: Forest plot showing results of the sensitivity analyses for stroke by electronic frailty index category
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Frailty category</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No OAC</td>
<td></td>
<td>1 (ref)</td>
</tr>
<tr>
<td>OAC prescribed at entry</td>
<td>Robust</td>
<td>0.9 (0.5-1.8)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.4 (1.0-2.0)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.1 (0.8-1.4)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>OAC prescribed at entry, adjusted</td>
<td>Robust</td>
<td>0.8 (0.4-1.7)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.1 (0.8-1.4)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>OAC persistent</td>
<td>Robust</td>
<td>0.8 (0.4-1.7)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.1 (0.8-1.4)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>OAC persistent, adjusted</td>
<td>Robust</td>
<td>0.7 (0.3-1.6)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.3 (0.8-1.8)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.0 (0.8-1.4)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>OAC persistent, AF reduced cohort</td>
<td>Robust</td>
<td>0.7 (0.3-1.7)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.4 (0.9-2.2)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>OAC persistent, AF reduced cohort, adjusted</td>
<td>Robust</td>
<td>0.7 (0.3-1.6)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.4 (0.9-2.2)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.8 (0.5-1.1)</td>
</tr>
</tbody>
</table>

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$_2$DS$_2$-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$_2$DS$_2$-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.\textsuperscript{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.\textsuperscript{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$_2$DS$_2$-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 in 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. 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, 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. 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’, 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.

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) 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. 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. 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. Unlike UK Biobank, ResearchOne, has inclusive enrolment criteria, and is less likely to have the same susceptibility to healthy participant bias. 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. 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. 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. 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, 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%
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. 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.

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. In this dataset, 20% of patients with AF and a CHA2DS2-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).
An influential and highly cited study\textsuperscript{d} that provided support for prescribing OAC to patients with recurrent falls was published in 1999.\textsuperscript{233} Man-Son-Hing \textit{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’.\textsuperscript{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 \textit{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.\textsuperscript{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.\textsuperscript{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

\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

\textbf{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\textsubscript{2}DS\textsubscript{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.\textsuperscript{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.\textsuperscript{242, 294} This may also be true
of stroke, particularly when relying on coded data in the absence of free-text comments. 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. 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. 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. 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. Ischaemic stroke rates in the ENGAGE AF-TIMI 48 were 1.25 per 100 person-years in both the warfarin and Edoxaban arms. 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. 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 CHA2DS2-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 CHADS2
score of two or more.\textsuperscript{145} Of these, OAC was prescribed in 72,211 (54.7%). Although CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc are not equivalent, a score of two in either is deemed 'high risk', and eligible for OAC prescription,\textsuperscript{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\textsubscript{2} score of two or more, 53.0\% were prescribed OAC in 2010.\textsuperscript{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\textsubscript{2}DS\textsubscript{2}-VASc score of two or more, from 49.5\% to 62.4\%.\textsuperscript{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\textsubscript{2}DS\textsubscript{2}-VASc score of two or more is associated with an annual stroke risk of at least 2.2\%.\textsuperscript{157} Cowan et al identified that of those with a CHADS\textsubscript{2} score of two or more, 14,987 (11.3\%) were recorded as having refused or had a contraindication to OAC.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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). 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. 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). 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).

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) 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.

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, 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, 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, and three studies showed no statistically significant association. 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{360} Similar trends have been observed in Sweden,\textsuperscript{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.\textsuperscript{362} This could be related to sub-optimal compliance and difficulties in healthcare access.\textsuperscript{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. 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).
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’. 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. 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 participant 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’. 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. 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. 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. 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). SystmOne has therefore been 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. 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. 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. 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. 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. 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’.

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, 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. 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.\textsuperscript{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)\textsuperscript{e} without a prior stroke.\textsuperscript{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).\textsuperscript{376} Both studies have the same potential for misclassification bias with regard to AF type that was previously discussed.\textsuperscript{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,\textsuperscript{138} and the dynamic and progressive nature of AF which may evolve in pattern from paroxysmal to persistent to permanent.\textsuperscript{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,\textsuperscript{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

\textsuperscript{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.\textsuperscript{126, 153} DOACs are not currently licenced in this clinical situation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{128} These changes increase the burden of atrial substrate, thereby sustaining the arrhythmia,\textsuperscript{127} and left atrial enlargement, in particular, has been associated with an increased risk of thrombus formation.\textsuperscript{125} Thus, the duration of AF prior to study entry could have been included as a potential confounder.

The decision was taken \textit{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). 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. 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.

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. 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. 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. 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.

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, post-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,\textsuperscript{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’,\textsuperscript{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.\textsuperscript{11, 219} As previously discussed, the eFI is based upon the cumulative deficit model of frailty as a theoretical framework.\textsuperscript{10, 36} The phenotype model offers an alternative approach to considering frailty,\textsuperscript{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.  

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. 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. 

In this study, frailty was treated as a categorical variable throughout using the cut-points defined within the eFI. 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. 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. 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. 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. 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. As prescription of parenteral anticoagulation is not recommended in chronic AF, only oral agents were included.

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. 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. 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, 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. 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. 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.

The decision to evaluate time to first event, rather than including multiple events in the analysis is a commonly used 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. 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). 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. 

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. 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. 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. 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.\textsuperscript{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\textsubscript{2}DS\textsubscript{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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283


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Appendix A  \( \text{CHA}_2\text{DS}_2\)-Vasc codes

The correspondence below is from Dr John Parry, the Clinical Director of SystmOne. This definition of \( \text{CHA}_2\text{DS}_2\)-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
  Xa0IV  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

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:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
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<tr>
<td>Covering Letter</td>
<td>Dr Christopher Bates</td>
<td>18 June 2011</td>
</tr>
<tr>
<td>Other: List of Stored Data Items</td>
<td>Dr John Parry (TPP)</td>
<td></td>
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<td>Other: Data Protection Registration</td>
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A Research Ethics Committee established by the Health Research Authority
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
| /764456225560/1964
| 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.

A Research Ethics Committee established by the Health Research Authority
Yours sincerely

L. Dyke (pp)

Mr Chris Turnock
Chair

E-mail: nrecommittee.northeast-newcastleandnorthtyneside1@nhs.net

Enclosures: Approval conditions

Copy to: Ms Samantha Crossfield, TPP

A Research Ethics Committee established by the Health Research Authority
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  Alcohol abuse
- XE1YX  Nondependent alcohol abuse
- XaPty  Brief intervention for excessive alcohol consumptn declined
- XaX4S  Extended intervention 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  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 alcohol: withdrawal 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 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 alcohol: resid & late-onset psychotic 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 syndrome
Eu101 [X]Mental and behav dis due to use of alcohol: harmful use
E011z Wernicke-Korsakoff syndrome
E01y. Other alcoholic psychoses
X00Rk Alcoholic dementia NOS
SM0 Alcohol causing toxic effect
XaLrN Alcohol abuse monitoring
E0111 Korsakoff'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 personal alcohol 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
Pernicious anaemia
Deficiency anaemias
Anaemia unspecified
Microcytic anaemia
Ferritin level low
Cobalamin deficiency
Iron deficiency anaemia NOS
Other vitamin B12 deficiency anaemia NOS
Normocytic anaemia
Vitamin B12-deficient megaloblastic anaemia
Iron deficiency anaemia due to dietary causes
Anaemia of chronic disorder
Microcytic hypochromic anaemia
H/O: anaemia - iron deficient
Other vitamin B12 deficiency anaemias
Vitamin B12 deficiency anaemia due to dietary causes
Anaemia due chron blood loss: [iron defic] or [normocytic]
Acute posthaemorrhagic anaemia
Megaloblastic anaemia due to dietary causes
B12 deficiency anaemia (& other)
Anaemia of renal disease
Macrocytic anaemia
Anaemia secondary to renal failure
Pernicious anaemia (& [Biermers][congen def intrins factor])
Anaemia: [unsp][secondary NOS][normocyt/macrocyt unsp cause]
Iron deficiency anaemia due to chronic blood loss
Other iron deficiency anaemias
Chronic anaemia
Idiopathic hypochromic anaemia
(Kelly-Paterson')/(Plumm-Vinson')/(oth sp iron def anaem)
Secondary anaemia NOS
Megaloblastic anaemia
Folate deficiency anaemia NOS
Other anaemias NOS
Unspecified iron deficiency anaemia
Drug-induced haemolytic anaemia
H/O: Anaemia vit.B12 deficient
Haemolytic anaemia
Recurrent anaemia
Oral iron for iron-deficiency anaemias
Acquired haemolytic anaemia
H/O: haemolytic anaemia
Normocytic anaemia due to unspecified cause
Parenteral iron for iron-deficiency anaemias
Folate-deficient megaloblastic anaemia
H/O: blood disorder (& [anaemia])
Autoimmune haemolytic anaemia
Anaemia: [megaloblastic] or [other deficiency]
Megaloblastic anaemia NOS
Anaemia secondary to chronic renal failure
Refractory anaemia with multilineage dysplasia
Protein-deficiency anaemia
Anaemia in other chronic diseases classified elsewhere
Other specified iron deficiency anaemia NOS
Aplastic anaemia
(Anaem: [iron def][microcyt]) or (Kelly-Pat) or (Plumm-Vins)

Macrocytic anaemia of unspecified cause

Vitamin B12 deficiency anaemia (& pleural)

Sideroblastic anaemia

Other dietary vitamin B12 deficiency anaemia

Combined B12 and folate deficiency anaemia

Vit B12 def anaem: [diet][Imersl-Grasbeck][Imerslund][Vegan]

(Thalassaemia (& Mediterr anaemia)) or (leptocytosis, hered)

Refractory anaemia

Aplastic anaemia due to chronic disease

Haemolytic anaemias due to dietary causes

Other specified iron deficiency anaemia

Anaemia in neoplastic disease

(Autoimmun haemolyt anaemia) or (Coombs positive haemolysis)

Sickle cell anaemia

Warm autoimmune haemolytic anaemia

Refractory anaemia with sideroblasts

Deficiency anaemias NOS

Other specified anaemia NOS

Autoimmune haemolytic anaemia NOS

Microangiopathic haemolytic anaemia

Anaemia: [deficiency excluding iron] or [megaloblastic]

Folate deficiency anaemia due to malabsorption with proteinuria

Other specified anaemias

Refractory anaemia, unspecified

Normocytic anaemia following acute bleed

Nutritional anaemias NOS

Hypoplastic haemolytic and renal anaemia drugs Band 1

Folate deficiency anaemia, drug-induced

Cold autoimmune haemolytic anaemia

Anaemia NOS: [other deficiency] or [megaloblastic]

Sickle cell anaemia of unspecified type

Refractory anaemia with excess blasts

Aplastic anaemia NOS

Haemolytic anaemias NOS

Other specified haemolytic anaemias

Chlorotic anaemia

Other specified deficiency anaemias

Aplastic and other anaemias

Chlororhydic 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
XaIT Atrial fibrillation monitoring
XaMGD Atrial fibrillation annual review
XaLFj Expected 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
XaUH Paroxysmal atrial flutter
XE0Wk (Atrial fibrillation) or (atrial flutter)
G573z Atrial fibrillation and flutter NOS
XaMDG Atrial fibrillation monitoring first letter
XaXiZ 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
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<tr>
<th>Code</th>
<th>Description</th>
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<td>XaMDK</td>
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<td>XaUR</td>
<td>Atypical atrial flutter</td>
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<td>Thrombocytopenia</td>
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<td>Disseminated intravascular coagulation</td>
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<td>Autoimmune thrombocytopenia</td>
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<td>XE146</td>
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<td>Thrombocytopenia NOS</td>
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<td>Idiopathic purpura (&amp; thrombocytopenic)</td>
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<td>von Willebrand's disease</td>
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<td>Idiopathic thrombocytopenia</td>
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<td>Purpura and other haemorrhagic conditions</td>
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<td>Thrombocytopenia due to drugs</td>
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<td>Congenital factor VIII deficiency</td>
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<td>Anticoagulant excess without bleeding</td>
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<td>D3z..</td>
<td>Clotting or bleeding disorder NOS</td>
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<td>D311.</td>
<td>Platelet defects: [qualitative][Bernard-Soulier thrombopathy]</td>
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<td>Protein S deficiency</td>
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<td>Factor XII deficiency</td>
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<td>Factor XIII deficiency</td>
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<td>Haemorrhagic condition NOS</td>
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<td>XE149</td>
<td>Secondary thrombocytopenia NOS</td>
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<td>Factor XI deficiency</td>
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<td>Xa36j</td>
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<td>Congenital deficiency of other clotting factor OS</td>
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<td>X20F5</td>
<td>Acquired platelet disorder</td>
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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
Xa0IB 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
Xalyc 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 neo][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  Extramedullary lymphoma of bone - cell lymphoma
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
Xa0I6  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
XaFrI 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
XE219 (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
Metastasis to head and neck lymph node
Metastasis to peritoneum
Malignant tumour of endocrine gland
Diffuse low grade B-cell lymphoma
Malignant neoplasm of upper-outer quadrant of female breast
Osteosarcoma of bone
Malignant tumour of female genital organ
Malignant tumour of unknown origin
Malignant tumour of caecum
Secondary and unspec malig neop of inguinal and leg LN NOS
Lymphoproliferative disorder
Squamous cell carcinoma of gum
Malignant tumour of penis
IgA myeloma
Malignant tumour of cervix
Malignant tumour of appendix
Malignant renal neoplasm (& [other unspec urinary organs])
Malignant neoplasm of trachea, bronchus and lung
Malignant lymphoma
Squamous cell carcinoma of bronchus
Squamous cell carcinoma of trachea
Squamous cell carcinoma of bronchus in left upper lobe
Malignant melanoma of rectum
Hodgkin's disease, lymphocytic depletion
Metastasis to lymph node of unknown primary
Malignant tumour of hepatic flexure
B-cell chronic lymphocytic leukaemia variant
Malignant neoplasm of lower lobe of lung
Primary malignant tumour of peritoneum
306

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 oesophagus
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.  Malignant 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
XaDbp  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 Malignant neoplasm 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
X78IF 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
XaYjI 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)
B112z 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

308
B303. Malignant neoplasm of ribs, sternum and clavicle
C332. Other paraproteinaemias
B22y. Malignant neoplasm of other sites of bronchus or lung
B22z. Malignant neoplasm of bronchus or lung [NOS] or [lung cancer]
B33eG Carcinoma liver/biliary system NOS
B5z. Malignant neoplasm of other and unspecified site NOS
XaBAu Pseudomyxoma peritonei
X78Q7 Malignant neoplasm of other sites of bronchus or lung
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 Malignant tumour of bronchus
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] Other specified malignant neoplasm of lymphoid, haematopoietic and related 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)
X78Wi Clear cell tumour of ovary
B56z. Secondary and unspecified malignant neoplasms of lymph nodes NOS
XE2vj Malignant hydatidiform mole
B4501 Malignant neoplasm of vaginal vault
X78YR Carcinoma of penis
B142. Malignant neoplasm of anal canal (and anal carcinoma)
XaBLv Malignant neoplasm of epiglottis NOS
B26. Malignant neoplasm, overlap lesion of respiratory and intrathoracic organs
XE1zf Ca penis
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 (reticulosarcoma follicular or nodular)
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
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])
Xa0SL Light chain myeloma
XaELI 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
X78fH Malignant neoplasm 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
XxFrFE 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
B58y 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 Malignant tumour eye: [Ca eye][malign melanoma][retinoblastoma]
XE1wt (Ca gum, + rest of mouth) or (carc: [cheek][mouth][palate])
XE1zb Malign 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 malign 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
XaBi1  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
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>XE1y5</td>
<td>Ca pancreas NOS</td>
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<tr>
<td>B58y6</td>
<td>Metastasis to testis</td>
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<tr>
<td>Xa0Sq</td>
<td>Tumour lysis syndrome</td>
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<td>B5400</td>
<td>Malignant tumour of adrenal cortex</td>
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<td>B6278</td>
<td>Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)</td>
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<td>XE1zt</td>
<td>Ca uterus NOS: [carcinoma] or [cancer]</td>
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<td>X78QT</td>
<td>Pancoast tumour</td>
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<td>XE1wr</td>
<td>Ca major saliv gland) or (carc: [parotid][subling][submand])</td>
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<td>B300B</td>
<td>Malignant neoplasm of turbinate</td>
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<td>B13y.</td>
<td>Malignant neoplasm of other specified sites of colon</td>
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<td>XaB1h</td>
<td>Carcinoma of body of pancreas</td>
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<td>B17z.</td>
<td>Malignant neoplasm of pancreas NOS</td>
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<td>B68z.</td>
<td>Leukaemia NOS</td>
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<td>C333.</td>
<td>Macroglobulinaemia</td>
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<td>X78l5</td>
<td>Metastasis to thyroid</td>
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<td>Clinical stage C chronic lymphocytic leukaemia</td>
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<td>Xa3BH</td>
<td>Metastasis to breast of unknown primary</td>
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<td>Xa0St</td>
<td>Hodgkin's disease, lymphocytic predominance - nodular</td>
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<td>B013.</td>
<td>Malignant neoplasm of ventral surface of tongue</td>
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<td>B627B</td>
<td>Other types of follicular non-Hodgkin's lymphoma</td>
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<td>Lymphosarcoma</td>
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<td>Malignant neoplasm lymphatic or haematopoietic tissue NOS</td>
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<td>ByuDD</td>
<td>[X]Oth and unspecif peripheral &amp; cutaneous T-cell lymphomas</td>
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<td>B512.</td>
<td>Malignant neoplasm of temporal lobe</td>
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<td>Other specified leukaemia</td>
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<td>X78l8</td>
<td>Local tumour spread</td>
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<td>XaB1e</td>
<td>Retropertitoneal sarcoma</td>
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<td>X78QF</td>
<td>Malignant tumour of lung parenchyma</td>
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<td>Xa9FC</td>
<td>Malignant lymphoma, follicular centre cell</td>
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<td>XaEJe</td>
<td>Squamous cell carcinoma of bronchus in left lower lobe</td>
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<td>B543.</td>
<td>Malignant tumour of pineal gland</td>
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<td>B5512</td>
<td>Malignant neoplasm of intrathoracic site NOS</td>
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<tr>
<td>XE1x5</td>
<td>Ca oesophagus NOS</td>
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<td>B552.</td>
<td>Malignant tumour of abdomen</td>
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<td>B063.</td>
<td>Malignant tumour of vallecula</td>
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<tr>
<td>B6151</td>
<td>Hodgkin's mixed cellularity of lymph nodes head, face, neck</td>
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<td>Byu81</td>
<td>[X]Malignant neoplasm/overlapping lesion/male genital organs</td>
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<td>X309D</td>
<td>Cystadenocarcinoma of pancreas</td>
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<td>B4A10</td>
<td>Malignant tumour of renal calyx</td>
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<td>B506.</td>
<td>Malignant tumour of choroid</td>
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<td>B49y.</td>
<td>Malignant neoplasm of other site of urinary bladder</td>
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<tr>
<td>B222z</td>
<td>Malignant neoplasm of upper lobe, bronchus or lung NOS</td>
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<td>Overlapping lesion of other and unspecifed parts of mouth</td>
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<td>B614z</td>
<td>Hodgkin's disease, nodular sclerosis NOS</td>
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<td>Malignant neoplasm of connective and soft tissue of thumb</td>
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<td>XE203</td>
<td>Secondary nodes NOS</td>
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<td>B490.</td>
<td>Malignant tumour of trigone of urinary bladder</td>
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<tr>
<td>B3001</td>
<td>Malignant neoplasm of frontal bone</td>
</tr>
<tr>
<td>B055z</td>
<td>Malignant neoplasm of palate NOS</td>
</tr>
<tr>
<td>XE1va</td>
<td>Malignant tumour of middle ear and mastoid</td>
</tr>
<tr>
<td>Xa0bR</td>
<td>Malignant lymphoma of thyroid gland</td>
</tr>
<tr>
<td>Xa0eC</td>
<td>Erythraemia</td>
</tr>
<tr>
<td>B5000</td>
<td>Malignant tumour of ciliary body</td>
</tr>
<tr>
<td>X78gc</td>
<td>Malignant tumour of exocrine pancreans</td>
</tr>
<tr>
<td>X78l3</td>
<td>Metastasis to choroid</td>
</tr>
<tr>
<td>X78bc</td>
<td>Malignant melanoma of iris</td>
</tr>
<tr>
<td>B571.</td>
<td>Metastasis to mediastinum</td>
</tr>
</tbody>
</table>
B614. Hodgkin's disease, nodular sclerosis
B6214 Mycosis fungoides of lymph nodes of axilla and upper limb
Xa99I 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
XaAOc Adenocarcinoma of ilium
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
X78bo 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. Malignant neop connective and soft tissue other specified site
B3104 Malignant neoplasm of tarsus of eyelid
B4303 Malignant neoplasm of myometrium of corpus uteri
Acute myeloid leukaemia with myelodysplasia-related changes
Malignant tumour of vault of bladder
Malignant neoplasm of nose NOS
Secondary and unspec malign neop axilla and upper limb LN
Metastasis to spleen of unknown primary
Malignant tumour of body of stomach
Malignant neoplasm of male genital organs
Secondary malign neoplasm of resp &/or digest syst (& carc)
Malignant neoplasm of genital organs
Other malignant neoplasm NOS
Malignant neoplasm, overlapping lesion of oesophagus
(Ma, oral, pharynx) or (oral carcinomas)
Ca tail of pancreas
Malignant tumour of nasal sinuses
Malignant neoplasm of supraclavicular fossa NOS
Malignant neoplasm rectum, rectosigmoid junction and anus NOS
Malignant neoplasm of bones of skull and face
Metastasis to adrenal gland of unknown primary
Malignant tumour of conjunctiva
Malignant neoplasm of upper lobe/bronchus/lung: (& [Pancoast synd])
Malignant neoplasm of prepylorus of stomach
Other and unspecified leukaemia
Malignant neoplasm of penis, part unspecified
Malig neop of scapula and long bones of upper arm NOS
Malignant neoplasm of anterior wall of urinary bladder
Secondary malignant neoplasm of unknown site
Malignant tumour of uvula
Secondary malig neop of respiratory and digestive systems
Malignant tumour of pituitary gland
Malignant neoplasm of neck NOS
Local recurrence of malignant tumour of tongue
Malignant neoplasm of greater vestibular (Bartholin's) gland
Malignant neoplasm tonsil NOS
Malignant neoplasm of pharynx unspecified
Malignant neoplasm of middle lobe, bronchus or lung
Malignant tumour of lower gingiva
Malignant tumour of soft tissue of shoulder
Secondary malig neop of respiratory and intrathoracic orga
Metastasis to bladder of unknown primary
(Se Ca sp site) or (metast sp site) or (sec Ca known site)
Malignant neoplasm corpus uteri, excluding isthmus
Malignant neoplasm of pelvic peritoneum
Malign neopl resp tract and intrathor organs (& [carcinoma])
Polikidoderma vasculare atrophicans
Leukaemia of unspecified cell type
Malignant neoplasm of scapula
Metastasis to ureter
Malignant tumour of tonsillar fossa
[X]Malignant neoplasms of lymphoid, haematopoietic and rela
Carcinoma of anterior part of floor of mouth
Malignant neoplasm of hilus of lung
Malignant tumour of soft tissue
Malignant neoplasm of nasal conchae
Malignant neoplasm of penis and other male genital organs
Malignant tumour of ileum
Malignant tumour of pylorus
Teratoma of undescended testis
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 neol 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
X76Zc 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
Byu8. [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
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 malign 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
B12y.  Malignant neoplasm other specified digestive tract and peritoneum
Byu0D0 [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
B115.  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 unspecified malignant neoplasm of 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 unspecified malignant neoplasm of 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
Malignant tumour of acoustic vestibular nerve
Malignant tumour of seminal vesicle
Malignant neoplasm of brainstem NOS
Acute erythraemia and erythroleukaemia
Malignant neoplasm of carotid body
Atypical chronic myeloid leukaemia, BCR/ABL negative
Secondary lymphangitic carcinoma
Acute monocytic leukaemia
Malignant neoplasm of trunk NOS
Malignant neoplasm of cheek NOS
Malignant neoplasm of basal ganglia
Malignant neoplasm of axilla NOS
Combined hepatocellular carcinoma and cholangiocarcinoma
Lymphosarcoma of lymph nodes of head, face and neck
Metastasis to vertebral column of unknown primary
Secondary and unspecified malignant neoplasms of lymph nodes head/face/neck
Secondary malignant neoplasm of liver intrahepatic bile duct
Malignant neoplasm of oropharynx, other specified sites
Malignant neoplasm of other specified site of oropharynx NOS
Malignant neoplasm of primary site of breast
Secondary and unspecified malignant neoplasms of lymph nodes multiple sites
Malignant neoplasm of connective and soft tissue of buttock
Secondary malignant neoplasm of other respiratory organs
Malignant neoplasm of pleura
Malignant neoplasm of ovary
Malignant tumour of pleura
Malignant neoplasm of ill-defined, secondary and unspecified sites
Malignant neoplasm of pelvis, sacrum or coccyx NOS
Secondary malignant neoplasm of rectum
Diffuse follicle centre lymphoma
Malig neop other/ill-defined sites lip, oral cavity, pharynx
Malignant neoplasm of other specified mouth parts
Malignant neoplasm of other site of cervix NOS
Sezary's disease
Malignant neoplasm of vertebral column NOS
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.. Monocyctic 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
B6127 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
321

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
XaYjT Subcutaneous panniculitic T-cell lymphoma
Xa0SH T-cell acute lymphoblastic leukaemia
B017. Malignant overlapping lesion of tongue
B5622 Secondary and unsp malig neop inferior mesenteric LN
B520z Malignant neoplasm of cranial nerves NOS
XaFrG Local recurrence of malignant tumour of liver
B3153 Malignant neop 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 unsp 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
X78Ph Local recurrence of malignant tumour of liver
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
XaAsl Referral to stroke service
662M. Stroke monitoring
XaJYc Referral to stroke clinic
XaJKe 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
G66. 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
XalzF Stroke annual review
Stroke and cerebrovascular accident unspecified

(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 invitation

(XE0VL) Cerebral atherosclerosis

(Gyu6C) [X]Sequela of stroke, not specified as haemorrhage 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

(Xa0MI) 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

- Chronic kidney disease stage 3
- Chronic kidney disease stage 3A without proteinuria
- Chronic kidney disease stage 3 with proteinuria
- Chronic kidney disease stage 3B
- Chronic kidney disease stage 3 without proteinuria
- Urine protein test = ++++
- Chronic kidney disease stage 3B without proteinuria
- Chronic kidney disease stage 3A with proteinuria
- Chronic kidney disease stage 3A without proteinuria
- Chronic kidney disease stage 4 with proteinuria
- Chronic kidney disease stage 4 without proteinuria
- Chronic kidney disease stage 4
- Chronic kidney disease stage 5 with proteinuria
- Chronic kidney disease stage 5 without proteinuria
- Chronic kidney disease stage 5
- Diabetes mellitus with persistent microalbuminuria
- Type II diabetes mellitus with persistent microalbuminuria
- Diabetes mellitus with persistent proteinuria
- Chronic renal impairment
- Chronic kidney disease annual review
- Chronic kidney disease quality indicators: Inform dissen

Chronic obstructive pulmonary disease

- Chronic obstructive lung disease
- COPD self-management plan review
- Acute infective exacerbation chronic obstruct airway disease
- Severe chronic obstructive pulmonary disease
- Acute exacerbation of chronic obstructive airways disease
- Moderate chronic obstructive pulmonary disease
- Mild chronic obstructive pulmonary disease
- Acute non-infective exacerbation of COPD
- Chronic obstruct pulmonary dis wth acute exacerbation, unspec
- Chronic obstructive pulmonary disease 6 monthly review
- Chronic obstructive pulmonary disease 3 monthly review
- Chronic obstructive airways disease NOS
- Seen in chronic obstructive pulmonary disease clinic
- Other specified chronic obstructive pulmonary disease clinic
Referral to COPD community nursing team
Obstructive chronic bronchitis NOS
Admit COPD emergency
End stage chronic obstructive airways disease
Very severe chronic obstructive pulmonary disease
Chronic obstruct pulmonary dis with acute lower resp infectn
Chronic obstructive pulmonary disease rescue pack declined
On chronic obstructive pulmonary disease supprtv cre pathway
Other specified chronic obstructive airways disease

Cirrhosis
Alcoholic cirrhosis of liver
Cirrhosis of liver
Primary biliary cirrhosis
Cirrhosis of liver NOS
Cryptogenic cirrhosis
Primary sclerosing cholangitis
Cirrhosis - non-alcoholic
Fibrosis of liver
Biliary cirrhosis
(Cirrhosis - non alcoholic) or (portal cirrhosis)
Macronodular cirrhosis
Cirrhosis and chronic liver disease
(Liver cirrhos: [named vars] or [NOS]) or (hepat fibrosis)
Cirrhosis: [florid] or [alcoholic]
Micronodular cirrhosis
Non-alcoholic cirrhosis NOS
Cardiac cirrhosis
Oesophageal varices in alcoholic cirrhosis of the liver
Biliary cirrhosis NOS
Hepatic sclerosis
Biliary cirrhosis (& [primary])
Oesophageal varices in cirrhosis of the liver
Hepatic fibrosis with hepatic sclerosis
Congenital hepatic fibrosis
Infectious cirrhosis NOS
Alcoholic fibrosis and sclerosis of liver
Portal cirrhosis unspecified
Toxic liver disease with fibrosis and cirrhosis of liver
Alcoholic hepatic failure
Portal cirrhosis
Secondary biliary cirrhosis
Mixed portal cirrhosis
Diffuse nodular cirrhosis
Unilobular portal cirrhosis

Deep vein thrombosis
Deep vein thrombosis of lower limb
Deep Vein Thrombosis
Ileofemoral deep vein thrombosis
[V] Personal history deep vein thrombosis
Antenatal deep vein thrombosis
Unprovoked deep vein thrombosis
Postoperative deep vein thrombosis
Postnatal deep vein thrombosis
(Deep ven thromb leg)(nonpuer milk-leg)(deep thrombophl leg)
DVT: [postnatal] or [obstetric phlegmasia alba dolens]
On deep vein thrombosis care pathway
Deep venous thrombosis of peroneal vein
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
XalIo  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
X20Sm  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
Xallj  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
XalUE  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
XaLP5  non proliferative diabetic retinopathy
XaJ0i  O/E - right eye preproliferative diabetic retinopathy
XaXZR  H/O: diabetes mellitus type 2
XaJ0k  O/E - right eye proliferative diabetic retinopathy
XaE5V  severe non proliferative diabetic retinopathy
XaJ0j  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
Conversion to insulin
Diabetic monitoring NOS
Mild non proliferative diabetic retinopathy
Excepted from diabetes qual indicators: Patient unsuitable
Diabetic cataract
Type II diabetes mellitus with persistent microalbuminuria
Diabetes with other complications
Hb. A1C > 10% - bad control
Diabetes management plan given
Diabetic patient unsuitable for digital retinal photography
HbA1 - diabetic control
Diabetes mellitus with persistent proteinuria
Diabetic Clinic
Diabetes mellitus with renal complications
Diabetes mellitus: [with renal manifestatn] or [nephropathy]
Type II diabetes mellitus with retinopathy
Diabetes mellitus with persistent proteinuria
O/E - Left diabetic foot - ulcerated
Type I diabetes mellitus
Type II diabetes mellitus with renal complications
Diabetes mellitus: [adult onset] or [noninsulin dependent]
Diabetes autonomic neuropathy
Type I diabetes mellitus with retinopathy
Diabetes mellitus with nephropathy NOS
Type II diabetes mellitus with ulcer
Acute painful diabetic neuropathy
Diabetes mellitus with diabetic cataract
Diabetes mellitus with nephropathy NOS
Symptomatic diabetic peripheral neuropathy
Diabetes mellitus (& [cataract] or [retinopathy])
Steroid-induced diabetes mellitus without complication
Ischaemic ulcer diabetic foot
Type I diabetes mellitus without complication
Diabetic polyneuropathy
Type II diabetes mellitus with ophthalmic complications
Diabetes mellitus with neurological manifestation
Type II diabetes mellitus with neuropathic arthropathy
Diabetes + neuropathy (& [amyotrophy])
Type II diabetes mellitus with multiple complications
Diabetes mellitus autosomal dominant type 2
Type II diabetes mellitus with exudative maculopathy
Diabetic neuropathy &/or diabetic polyneuropathy
Type II diabetes mellitus with neurological complications
Type II diabetes mellitus with nephropathy
Diabetes mellitus with other specified manifestation
Diabetes mellitus maturity onset
Diabetes mellitus, adult onset, + neurological manifestation
Type II diabetes mellitus with polyneuropathy
Diabetic mononeuropathy
Type I diabetes mellitus - poor control
Type I diabetes mellitus with renal complications
Diabetes mellitus NOS with no mention of complication
Diabetes mellitus NOS with unspecified complication
Diabetes mellitus with renal manifestation
Diabetes mellitus NOS with neurological manifestation
Diabetes mellitus with hyperosmolar coma
Type 2 diabetes mellitus with ketoacidosis
Type I diabetes mellitus with ophthalmic complications
Type I diabetes mellitus with gastroparesis
Type 1 diabetes mellitus with exudative maculopathy
Type I diabetes mellitus with nephropathy
Diabetes mellitus with peripheral circulatory disorder
Diabetic chronic painful polyneuropathy
Type 1 diabetes mellitus with persistent proteinuria
Type 1 diabetes mellitus with persistent microalbuminuria
Diabetes mellitus NOS with ketoacidosis
Diabetes acute painful polyneuropathy
Type II diabetes mellitus with gangrene
Type I diabetes mellitus with multiple complications
Type II diabetes mellitus with hypoglycaemic coma
Diabetes mellitus induced by non-steroid drugs
Diabetes mellitus NOS with hyperosmolar coma
Latent autoimmune diabetes mellitus in adult
Diabetic (femoral mononeuropathy) & (Diabetic amyotrophy)
Other specified diabetes mellitus with renal complications
Diabetes mellitus NOS with peripheral circulatory disorder
Type I diabetes mellitus with diabetic cataract
Type II diabetes mellitus with mononeuropathy
Diabetes mellitus NOS with ophthalmic manifestation
Type I diabetes mellitus with neurological complications
Diabetes mellitus with: [gangrene] or [periph circul disord]
Other specified diabetes mellitus with ketoacidosis
Other specified diabetes mellitus with multiple comps
Type I diabetes mellitus with hypoglycaemic coma
Diabetes mellitus with ketoacidotic coma
Diabetes mellitus with gangrene
Type I diabetes mellitus with mononeuropathy
Type II diabetes mellitus with peripheral angiopathy
Diabetic neuropathy treatment [no drugs here]
Diabetes mellitus autosomal dominant
Diabetes mellitus with unspecified complication
Other specified diabetes mellitus with ophthalmic complications
Type I diabetes mellitus with gangrene
Other specified diabetes mellitus with neurological comps
Type I diabetes mellitus with ulcer

Falls
Accidental fall
Recurrent falls
Elderly fall
Accidental falls NOS
Fall on same level from slipping, tripping or stumbling
Referral to falls service
Referral to elderly falls prevention clinic
Observation of falls
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>Y3356</td>
<td>Unable to get off floor</td>
</tr>
<tr>
<td>YA756</td>
<td>Has pendant alarm services</td>
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<tr>
<td>XaN4s</td>
<td>Provision of telecare community alarm service</td>
</tr>
<tr>
<td>J5730</td>
<td>Rectal haemorrhage</td>
</tr>
<tr>
<td>X30Bj</td>
<td>Bleeding per rectum</td>
</tr>
<tr>
<td>XaJuv</td>
<td>Painless rectal bleeding</td>
</tr>
<tr>
<td>J573.</td>
<td>(Haemorrhage of rectum &amp; anus) or (PR - bleeding per rectum)</td>
</tr>
<tr>
<td>XE0d3</td>
<td>Anal &amp;/or rectal haemorrhage</td>
</tr>
<tr>
<td>XaJuu</td>
<td>Painful rectal bleeding</td>
</tr>
<tr>
<td>G8480</td>
<td>Bleeding haemorrhoids NOS</td>
</tr>
<tr>
<td>X76fy</td>
<td>Bleeding pile</td>
</tr>
<tr>
<td>J5731</td>
<td>Anal haemorrhage</td>
</tr>
<tr>
<td>X30Bk</td>
<td>Fresh blood passed per rectum</td>
</tr>
<tr>
<td>G8450</td>
<td>External bleeding haemorrhoids</td>
</tr>
<tr>
<td>X76fR</td>
<td>Bleeding from anus</td>
</tr>
<tr>
<td>X30Bi</td>
<td>Lower gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>G8420</td>
<td>Internal bleeding haemorrhoids</td>
</tr>
<tr>
<td>XE0b0</td>
<td>Haemorrhage of rectum and anus</td>
</tr>
<tr>
<td>J573z</td>
<td>Haemorrhage of rectum and anus NOS</td>
</tr>
<tr>
<td>X30Ct</td>
<td>Stomal bleeding</td>
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<tr>
<td>J68..</td>
<td>Gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>XaB3J</td>
<td>Recurrent gastrointestinal bleeding</td>
</tr>
<tr>
<td>XaB3K</td>
<td>Massive gastrointestinal bleed</td>
</tr>
<tr>
<td>J68z.</td>
<td>Gastrointestinal bleeding (&amp; [unspecified])</td>
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<tr>
<td>XE0bJ</td>
<td>Gastrointestinal haemorrhage unspecified</td>
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<td>J68z1</td>
<td>Intestinal haemorrhage NOS</td>
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<td>J68zz</td>
<td>Gastrointestinal tract haemorrhage NOS</td>
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<tr>
<td>Xa00e</td>
<td>Sepsis-associated gastrointestinal haemorrhage</td>
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<tr>
<td>J680.</td>
<td>Haematemesis</td>
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<tr>
<td>XE0rB</td>
<td>Vomiting blood - fresh</td>
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<tr>
<td>X30Bh</td>
<td>Bleeding duodenal ulcer</td>
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<tr>
<td>X30Be</td>
<td>Upper gastrointestinal haemorrhage</td>
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<td>XaBfG</td>
<td>Haematemesis - cause unknown</td>
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<td>G850.</td>
<td>Bleeding oesophageal varices</td>
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<tr>
<td>J1201</td>
<td>Acute duodenal ulcer with haemorrhage</td>
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<tr>
<td>J68z0</td>
<td>Gastric haemorrhage NOS</td>
</tr>
<tr>
<td>J1211</td>
<td>Chronic duodenal ulcer with haemorrhage</td>
</tr>
<tr>
<td>X30Bg</td>
<td>Bleeding gastric ulcer</td>
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<tr>
<td>J1101</td>
<td>Acute gastric ulcer with haemorrhage</td>
</tr>
<tr>
<td>J1111</td>
<td>Chronic gastric ulcer with haemorrhage</td>
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<tr>
<td>XaB5h</td>
<td>Haemorrhagic oesophagitis</td>
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<tr>
<td>J11y1</td>
<td>Unspecified gastric ulcer with haemorrhage</td>
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<tr>
<td>Xa7TU</td>
<td>Oesophageal bleeding</td>
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<tr>
<td>J1103</td>
<td>Acute gastric ulcer with haemorrhage and perforation</td>
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<tr>
<td>Xa363</td>
<td>Vomiting stale blood</td>
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<tr>
<td>J1113</td>
<td>Chronic gastric ulcer with haemorrhage and perforation</td>
</tr>
<tr>
<td>XaBel</td>
<td>Bleeding stress ulcer of stomach</td>
</tr>
<tr>
<td>J11y3</td>
<td>Unspecified gastric ulcer with haemorrhage and perforation</td>
</tr>
<tr>
<td>760J4</td>
<td>Balloon tamponade of oesophagus</td>
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<tr>
<td>K1972</td>
<td>Microscopic haematuria</td>
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<tr>
<td>XE0e5</td>
<td>Haematuria</td>
</tr>
<tr>
<td>XE0rU</td>
<td>Blood in urine - haematuria</td>
</tr>
</tbody>
</table>
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  Recurrent and persistent haematuria df mesangial prolif glomerulonephritis
K0A20  Recurrent+persistent 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
Xa7vl  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
Xallq  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 unsuitable
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
XaWy1  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
X202l  Right ventricular failure
New York Heart Association classification - class III
Heart failure 6 month review
H/O: heart failure
Congestive heart failure due to valvular disease
Congestive heart failure monitoring
Heart: [weak] or [failure NOS]
(Congest card fail)(dropsy)(card insuf)(R hrt fail)(LV fail)
Referral to heart failure exercise programme declined
Heart disease: [arteriosclerotic] or [chronic ischaemic NOS]
Referred by heart failure nurse specialist
New York Heart Assoc classification heart failure symptoms
Acute cardiac pulmonary oedema
Heart failure care plan discussed with patient
Admit heart failure emergency
Heart failure confirmed
Heart failure monitoring third letter
Heart failure self management plan
Heart failure education
Refractory heart failure
Did not attend practice nurse heart failure clinic
Post cardiac operation heart failure NOS
H/O: Heart failure in last year
Did not attend heart failure clinic
Heart failure information given to patient
Referral to heart failure exercise programme
Heart failure as a complication of care
Vasodilators in heart failure [no drugs here]
Hypertension
Hypertension
Essential hypertension
Excepted from hypertension qual indicators: Patient unsuit
Hypertensive disease
Exception reporting: hypertension quality indicators
Excepted from hypertension qual indicators: Informed dissent
Essential hypertension NOS
Lifestyle advice regarding hypertension
H/O: hypertension
Hypertensive disease NOS
Seen in hypertension clinic
Hypertensive retinopathy
Poor hypertension control
High blood pressure (& [essential hypertension])
Benign essential hypertension
Hypertension secondary to other renal disorders
Hypertension NOS (& [essential])
Secondary hypertension
Systolic hypertension
Hypertension treatm. started
Good hypertension control
Diastolic hypertension
On treatment for hypertension
Labile hypertension
Hypertension clinical management plan
Malignant hypertension
Moderate hypertension control
Hypertension secondary to drug
(Hypertensive disease) or (hypertension)
Malignant essential hypertension
Secondary renovascular hypertension NOS
G244. Hypertension secondary to endocrine disorders
G241. Secondary malignant hypertension
G242. Secondary malignant hypertension NOS
G241z Secondary malignant hypertension NOS
G240z Secondary benign hypertension NOS
G240 Secondary benign hypertension NOS
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
G240 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 multinodular 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 multinodular 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
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>C02y.</td>
<td>Thyrotoxicosis: [other specified origin] or [factitia]</td>
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<tr>
<td>X40H3</td>
<td>Thyroid crisis</td>
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<tr>
<td>C0210</td>
<td>Toxic uninodular goitre with no crisis</td>
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<tr>
<td>X40H4</td>
<td>Thyrotoxicosis due to inappropriate TSH secretion</td>
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<tr>
<td>G613.</td>
<td>Cerebellar haemorrhage</td>
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<tr>
<td>G61z.</td>
<td>Intracerebral haemorrhage NOS</td>
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<tr>
<td>XM0rV</td>
<td>Cerebral haemorrhage</td>
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<tr>
<td>XE0VF</td>
<td>Cerebral parenchymal haemorrhage</td>
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<tr>
<td>Gyu6F</td>
<td>[X] Intracerebral haemorrhage in hemisphere, unspecified</td>
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<td>XaBM4</td>
<td>Left sided intracerebral haemorrhage, unspecified</td>
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<tr>
<td>X00DQ</td>
<td>Brainstem haemorrhage</td>
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<td>G614.</td>
<td>Pontine haemorrhage</td>
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<td>X00DO</td>
<td>Thalamic haemorrhage</td>
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<td>G612.</td>
<td>Basal ganglia haemorrhage</td>
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<td>Cerebral haemorrhage NOS</td>
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<td>G611.</td>
<td>Internal capsule haemorrhage</td>
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<td>G617.</td>
<td>Intracerebral haemorrhage, intraventricular</td>
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<td>XaBM5</td>
<td>Right sided intracerebral haemorrhage, unspecified</td>
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<td>Cortical haemorrhage</td>
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<td>Lobar cerebral haemorrhage</td>
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<td>G616.</td>
<td>External capsule haemorrhage</td>
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<td>X00DN</td>
<td>Subcortical cerebral haemorrhage</td>
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<td>G618.</td>
<td>Intracerebral haemorrhage, multiple localised</td>
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<tr>
<td>G615.</td>
<td>Bulbar haemorrhage</td>
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<td>Acute non-ST segment elevation myocardial infarction</td>
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<tr>
<td>XE2uV</td>
<td>Ischaemic heart disease</td>
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<tr>
<td>G33..</td>
<td>Angina</td>
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<tr>
<td>7928</td>
<td>Percutaneous balloon angioplasty of coronary artery</td>
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<td>X200E</td>
<td>Myocardial infarction</td>
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<tr>
<td>XE0Uh</td>
<td>Acute myocardial infarction</td>
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<td>X2009</td>
<td>Unstable angina</td>
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<td>G33z.</td>
<td>Angina pectoris NOS</td>
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<td>G3z..</td>
<td>Ischaemic heart disease NOS</td>
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<tr>
<td>792..</td>
<td>Coronary artery operations (&amp; bypass)</td>
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<td>14A5.</td>
<td>H/O: angina pectoris</td>
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<tr>
<td>662K0</td>
<td>Angina control - good</td>
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<tr>
<td>X00TE</td>
<td>Coronary artery bypass grafting</td>
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<tr>
<td>X2008</td>
<td>Stable angina</td>
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<tr>
<td>XaIOW</td>
<td>Coronary heart disease review</td>
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<td>G34y1</td>
<td>Chronic myocardial ischaemia</td>
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<tr>
<td>X00TI</td>
<td>Insertion of coronary artery stent</td>
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<td>XaI9h</td>
<td>Coronary heart disease annual review</td>
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<td>G308.</td>
<td>Inferior myocardial infarction NOS</td>
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<td>X2006</td>
<td>Triple vessel disease of the heart</td>
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<tr>
<td>Xa7nH</td>
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<td>XE2aA</td>
<td>Old myocardial infarction</td>
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<td>G30z.</td>
<td>Acute myocardial infarction NOS</td>
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<td>G340.</td>
<td>Coronary (atheroscl or artery dis) or triple vcss dis heart</td>
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<td>G3...</td>
<td>Ischaemic heart disease (&amp; [arteriosclerotic])</td>
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<tr>
<td>Y3657</td>
<td>H/O: Ischaemic heart disease</td>
</tr>
<tr>
<td>G30..</td>
<td>(Myocard inf (&amp; [ac][silent][card rupt])) or (coron thromb)</td>
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<tr>
<td>322..</td>
<td>ECG: myocardial ischaemia</td>
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<tr>
<td>XaNxN</td>
<td>Admit ischaemic heart disease emergency</td>
</tr>
<tr>
<td>14A..</td>
<td>H/O: cardiovasc disease (&amp; [heart disorder][myocard problem])</td>
</tr>
</tbody>
</table>
ECG: shows myocardial ischaemia

ECG: myocardial ischaemia NOS

Myocardial ischaemia

Coronary atherosclerosis

Central crushing chest pain

Ischaemic chest pain

Angina control - worsening

Angina control - poor

Coronary spasm

Cardiac syndrome X

Myocardial infarction (& acute) or coronary thrombosis

H/O: myocardial infarct at greater than 60

Diab mellitus insulin-glucose infus acute myocardial infarct

Crushing chest pain

Other specified ischaemic heart disease

Other acute myocardial infarction NOS

Other acute myocardial infarction

Acute/subacute ischaemic heart disease NOS

[X]Other forms of angina pectoris

Post-infarction ventricular septal defect

Transient myocardial ischaemia

Other chronic ischaemic heart disease NOS

Atrial septal defect/curr comp folow acut myocardial infarct

H/O: myocardial infarct >60

Chronic ischaemic heart disease NOS

Cardiovascular disease annual review declined

Subendocardial ischaemia

Certain current complication follow acute myocardial infarct

Other specified chronic ischaemic heart disease NOS

[V] Vasodilators used in angina pectoris

Other acute and subacute ischaemic heart disease NOS

Alzheimer's disease

Dementia annual review

Referral to memory clinic

Vascular dementia

Confused

H/O: dementia

Poor short-term memory

Dementia monitoring

Memory impairment

Memory disturbance (& amnesia (& symptom))

Dementia in Alzheimer's disease

Seen in memory clinic

Dementia in Alzheimer's dis, atypical or mixed type

Minor memory lapses

Arteriosclerotic dementia NOS

Excepted from dementia quality indicators: Patient unsuitable

Memory lapses

Unspecified dementia

Mild memory disturbance

Confusional state

Excepted from dementia quality indicators: Informed dissent

Senile dementia with paranoia

Mild cognitive disorder

Dementia monitoring second letter
Dementia monitoring third letter
Multi-infarct dementia
Amnesia for recent events
Organic memory impairment
Dementia in Alzheimer's disease with late onset
Lacks capacity to give consent (Mental Capacity Act 2005)
Alcoholic dementia
Age-associated memory impairment
Mixed cortical and subcortical vascular dementia
Lewy body dementia
Senile dementia
Frontotemporal dementia
Dementia in Alzheimer's disease with early onset
Lacks capacity to give consent (Mental Capacity Act 2005)
Alcoholic dementia
Age-associated memory impairment
Lewy body dementia
Senile dementia
Frontotemporal dementia
Memory disturbance: mild
Dementia monitoring telephone invite
Amnesia for remote events
Anti-dementia drug therapy
Dementia monitoring administration
Vascular dementia of acute onset
Dementia in Alzheimer's disease, unspecified
[D]Amnesia (retrograde)
Semantic dementia
Dementia in Parkinson's disease
Other vascular dementia
Cerebral degeneration presenting primarily with dementia
Poor long-term memory
Presenile dementia
Uncomplicated senile dementia
[X] Dementia: [unspecified] or [named variants (& NOS)]
Exception reporting: dementia quality indicators
Alcoholic dementia: [other] or [NOS]
Senile dementia with depression
Arteriosclerotic dementia with delirium
Uncomplicated presenile dementia
Global deterioration scale: assessment of prim deg dementia
Memory: important event not kn
Distortion of memory
Subcortical vascular dementia
Other alcoholic dementia
Memory: count down unsucc.
Memory: present month not knwn
Other senile/presenile dementia
Dementia in conditions EC
Alcoholic dementia NOS
Memory: present place not knwn
Arteriosclerotic dementia (including multi infarct dement)
Uncomplicated arteriosclerotic dementia
Memory: present time not known
Amyotrophic lateral sclerosis with dementia
Dementia in Huntington's disease

Senile dementia with delirium

Presenile dementia NOS

Dementia: [multi-infarct] or [predominantly cortical]

Impairment of registration

Dementia in other specified diseases classified elsewhere

3A10. Memory: own age not known

3A80. Memory: import. person not known

3A50. Memory: own DOB not known

Dementia (& [presenile] or [senile])

Dementia in other diseases classified elsewhere

Senile dementia with depressive or paranoid features

Presenile dementia with depression

Acquired immune deficiency syndrome dementia complex

Patchy dementia

Dementia in Pick's disease

Language disorder of dementia

Disturbance of memory for order of events

Presenile dementia with delirium

Arteriosclerotic dementia with paranoia

Senile dementia with depressive or paranoid features NOS

Presenile dementia with paranoia

Arteriosclerotic dementia with depression

Myocardial infarction

Acute non-ST segment elevation myocardial infarction

Anterior myocardial infarction NOS

Myocardial infarction

Acute myocardial infarction

Unstable angina

Inferior myocardial infarction NOS

H/O: myocardial infarct at less than 60

Other specified anterior myocardial infarction

Acute anterolateral myocardial infarction

Acute myocardial infarction NOS

(Myocard inf (& [ac][silent][card rupt]) or (coron thromb)

Lateral myocardial infarction NOS

ECG: myocardial infarction

Acute subendocardial infarction

Post-myocardial infarction syndrome

Acute inferolateral myocardial infarction

ECG: myocardial infarct NOS

Acute inferoposterior infarction

Myocardial infarction (& [acute]) or coronary thrombosis

H/O: myocardial infarct at greater than 60

Subsequent myocardial infarction

Posterior myocardial infarction NOS

Other acute myocardial infarction NOS

Other acute myocardial infarction

Acute/subacute ischaemic heart disease NOS

Post-infarction ventricular septal defect

Atrial septal defect/curr comp folow acut myocardial infarct

Subsequent myocardial infarction of anterior wall

Thrombosis atrium,auric append&vent/curr comp foll acute MI

[X] Acute transmural myocardial infarction of unspecif site

Subsequent myocardial infarction of inferior wall

Certain current complication follow acute myocardial infarct

Ruptur chordae tendinae/curr comp fol acute myocard infarct
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>G31yz</td>
<td>Other acute and subacute ischaemic heart disease NOS</td>
</tr>
<tr>
<td>XaJJH</td>
<td>Body mass index 40+ - severely obese</td>
</tr>
<tr>
<td>XM00v</td>
<td>Obese build</td>
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<tr>
<td>XabHx</td>
<td>Obese class I (body mass index 30.0 - 34.9)</td>
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<td>222A.</td>
<td>O/E - obese</td>
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<tr>
<td>X76dX</td>
<td>Obese abdomen</td>
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<tr>
<td>XabHy</td>
<td>Obese class II (body mass index 35.0 - 39.9)</td>
</tr>
<tr>
<td>XabHz</td>
<td>Obese class III (BMI equal to or greater than 40.0)</td>
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<tr>
<td>J12..</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>J11..</td>
<td>Gastric ulcer (&amp; [prepyloric] or [pyloric])</td>
</tr>
<tr>
<td>XE0aQ</td>
<td>Gastric ulcer NOS</td>
</tr>
<tr>
<td>J13..</td>
<td>Ulcer: [peptic (PU) site unspecified] or [stress NOS]</td>
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<tr>
<td>J120z</td>
<td>Acute duodenal ulcer NOS</td>
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<tr>
<td>XM0sI</td>
<td>Perforated peptic ulcer</td>
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<tr>
<td>XM1RO</td>
<td>H/O: gastric ulcer</td>
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<tr>
<td>J12z.</td>
<td>Duodenal ulcer NOS</td>
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<tr>
<td>XE0aP</td>
<td>Gastric ulcer</td>
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<tr>
<td>14C1.</td>
<td>H/O: peptic ulcer (&amp; [duodenal] or [gastric])</td>
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<tr>
<td>J120.</td>
<td>Acute duodenal ulcer</td>
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<tr>
<td>X302b</td>
<td>Duodenal ulcer disease</td>
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<tr>
<td>J11z.</td>
<td>Gastric: [erosions] or [multiple ulcers] or [ulcer NOS]</td>
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<tr>
<td>XE0qB</td>
<td>H/O: peptic ulcer</td>
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<tr>
<td>J1202</td>
<td>Acute duodenal ulcer with perforation</td>
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<tr>
<td>X30Bh</td>
<td>Bleeding duodenal ulcer</td>
</tr>
<tr>
<td>XaELE</td>
<td>Multiple gastric ulcers</td>
</tr>
<tr>
<td>1956</td>
<td>Peptic ulcer symptoms</td>
</tr>
<tr>
<td>X302Q</td>
<td>Perforation of duodenal ulcer</td>
</tr>
<tr>
<td>XM0BZ</td>
<td>Peptic ulcer disease</td>
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<tr>
<td>J13z.</td>
<td>Peptic ulcer NOS</td>
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<td>J1020</td>
<td>Gastro-oesophageal reflux disease with ulceration</td>
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<td>J121.</td>
<td>Chronic duodenal ulcer</td>
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<td>XaMO7</td>
<td>Non steroidal anti inflammatory drug induced duodenal ulcer</td>
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<tr>
<td>XaMO5</td>
<td>Non steroidal anti inflammatory drug induced gastric ulcer</td>
</tr>
<tr>
<td>J1301</td>
<td>Acute peptic ulcer with haemorrhange</td>
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<tr>
<td>XaB9d</td>
<td>Repair of perforated pyloric ulcer</td>
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<tr>
<td>J131.</td>
<td>Chronic peptic ulcer</td>
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<td>Xa6ot</td>
<td>Prepyloric gastric ulcer</td>
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<td>J111.</td>
<td>Chronic gastric ulcer</td>
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<tr>
<td>76270</td>
<td>Closure of perforated duodenal ulcer</td>
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<tr>
<td>XM1RN</td>
<td>H/O: duodenal ulcer</td>
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<tr>
<td>J124.</td>
<td>Recurrent duodenal ulcer</td>
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<tr>
<td>Xa84h</td>
<td>Pyloric ulcer</td>
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<td>XE0aS</td>
<td>Gastrojejunal ulcer</td>
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<tr>
<td>J110.</td>
<td>Acute gastric ulcer</td>
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<tr>
<td>J12y1</td>
<td>Unspecified duodenal ulcer with haemorrhage</td>
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<tr>
<td>J12y.</td>
<td>Unspecified duodenal ulcer</td>
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<td>X302c</td>
<td>Peptic ulcer of duodenum</td>
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<tr>
<td>J1201</td>
<td>Acute duodenal ulcer with haemorrhage</td>
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<tr>
<td>J130.</td>
<td>Acute peptic ulcer</td>
</tr>
<tr>
<td>X302F</td>
<td>Chronic peptic ulcer of duodenum</td>
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<tr>
<td>J13y.</td>
<td>Unspecified peptic ulcer</td>
</tr>
<tr>
<td>X302X</td>
<td>Peptic ulcer of stomach</td>
</tr>
<tr>
<td>X20VN</td>
<td>Oversewing perforated gastric ulcer</td>
</tr>
<tr>
<td>X301o</td>
<td>Perforation of gastric ulcer</td>
</tr>
<tr>
<td>J12y2</td>
<td>Unspecified duodenal ulcer with perforation</td>
</tr>
<tr>
<td>J110z</td>
<td>Acute gastric ulcer NOS</td>
</tr>
<tr>
<td>J1211</td>
<td>Chronic duodenal ulcer with haemorrhage</td>
</tr>
</tbody>
</table>
Healed gastric ulcer leaving a scar

Peptic ulcer - (PU) site unspecified

Acute duodenal ulcer without mention of complication

Acute gastric ulcer without mention of complication

Bleeding gastric ulcer

Chronic duodenal ulcer with perforation

Unspecified duodenal ulcer without mention of complication

Unspecified peptic ulcer NOS

Chronic duodenal ulcer without mention of complication

Other specified operation on gastric ulcer

Closure of perforated gastric ulcer

Unspecified duodenal ulcer without mention of complication

Chronic duodenal ulcer unspecified

Gastric ulcer operation

Oversewing perforated duodenal ulcer

Perforated DU (& acute)

Chronic peptic ulcer of stomach

[V]Pers hist digest syst disease (& pept ulcer (& [pept ulcer (& [duod]))]

Chronic duodenal ulcer NOS

Bleeding peptic ulcer

Oversewing of bleeding duodenal ulcer

Acute gastric ulcer with perforation

Operation on duodenal ulcer NOS

Acute gastric ulcer with haemorrhage

Acute peptic ulcer of stomach

Unspecified gastric ulcer NOS

Duodenal ulcer operation

Anti-platelet induced gastric ulcer

Chronic gastric ulcer with haemorrhage

Chronic gastric ulcer NOS

Oversew of blood vessel of duodenal ulcer

Unspecified peptic ulcer with perforation

Acute peptic ulcer NOS

Acute duodenal ulcer with haemorrhage and perforation

Suture of duodenal ulcer not elsewhere classified

Chronic peptic ulcer unspecified

Operation on gastric ulcer NOS

Perforated GU (& [acute])

Unspec duodenal ulcer; unspec haemorrhage and/or perforation

Suture of duodenal ulcer

Ulcer: [peptic NOS]/[gastrojejunal]/[stomal]/[anastomotic]

Non steroidal anti inflammatory drug induced gastric ulcer NOS

Endoscopic injection haemostasis of duodenal ulcer

Acute peptic ulcer with perforation

Omental patch repair of perforated pyloric ulcer

[V] Personal history of gastric ulcer

Unspecified gastric ulcer without mention of complication

Chronic gastric ulcer with obstruction

Chronic peptic ulcer without mention of complication

Gastrojejunal ulcer NOS

Chronic peptic ulcer NOS

Acute peptic ulcer unspecified
Gastric ulcer sample

Acute peptic ulcer without mention of complication

Other specified operation on duodenal ulcer

Laparoscopic closure of perforated gastric ulcer

Unspecified peptic ulcer with haemorrhage

Chronic gastric ulcer with perforation

Chronic gastric ulcer without mention of complication

Endoscopic injection haemostasis of gastric ulcer

Non steroidal anti inflammatory drug induced duodenal ulcer

Anti-platelet induced duodenal ulcer

Acute drug-induced ulcer of stomach

Acute gastrojejunal ulcer with haemorrhage

Chronic peptic ulcer with perforation

Perforated peptic ulcer closure

Chronic peptic ulcer unspecified

Unspecified duodenal ulcer with haemorrhage and perforation

Unspecified duodenal ulcer with haemorrhage and perforation

Stomach ulcer excision

Bleeding stress ulcer of stomach

Stress ulcer of stomach

Primary ulcer of intestine

Unspecified gastrojejunal ulcer

Unspecified gastrojejunal ulcer

Acute gastric ulcer with haemorrhage and perforation

Perforated peptic ulcer closure

Acute gastric ulcer with haemorrhage and perforation

Acute duodenal ulcer with haemorrhage and perforation

Acute peptic ulcer of duodenum

Unspecified duodenal ulcer with haemorrhage and perforation

Closure of gastric ulcer NEC

Chronic gastric ulcer unspecified

Unspecified duodenal ulcer with perforation

Chronic duodenal ulcer with obstruction

Chronic duodenal ulcer with haemorrhage and perforation

Peripheral vascular disease

Absent right foot pulses

L. dorsalis pedis absent

R. dorsalis pedis absent

Lower limb ischaemia

Right dorsalis pedis abnormal

Peripheral vascular disease NOS

Peripheral ischaemia

Upper limb ischaemia

(Peri vasc dis (& [isch][oth])) or (isch leg) or (peri isch)

History of peripheral vascular disease

Critical upper limb ischaemia

Critical lower limb ischaemia

Critical ischaemia of foot

Ischaemic ulcer diabetic foot

Arterial ischaemia

Consistencies

Diabetes mellitus with peripheral circulatory disorder

Diabetes mellitus with: [gangrene] or [periph circul disord]

Diabetes mellitus with gangrene

Atherosclerosis: [precerebral] or [cerebral]

Type II diabetes mellitus with peripheral angiopathy

Type I diabetes mellitus with gangrene

Pulmonary embolus

Postoperative pulmonary embolus

Pulmonary thromboembolism
Recurrent pulmonary embolism
Acute massive pulmonary embolism
Obstetric pulmonary embolism
Subacute massive pulmonary embolism
Obstetric pulmonary embolism NOS - delivered
Obstetric pulmonary embolism NOS, unspecified
Obstetric blood-clot pulmonary embolism
Obstetric pulmonary embolism NOS

Smoking
Non-smoker
Never smoked tobacco
Non-smoker (& [never smoked tobacco])
Ex smoker
Non-smoker annual review
Ex-cigarette smoker amount unknown
Cigarette consumption
Ex-smoker
Cigarette smoker
Ex-cigarette smoker
Stopped smoking
Ex-moderate smoker (10-19/day)
Moderate cigarette smoker (10-19 cigs/day)
Trying to give up smoking
Age at starting smoking
Keeps trying to stop smoking
Negotiated date for cessation of smoking
[Tobacco consumption] or [smoker - amount smoked]
Rolls own cigarettes
Smoking status at 4 weeks
Smoking restarted
Heavy cigarette smoker (20-39 cigs/day)
Ex-heavy smoker (20-39/day)
Pipe smoker
Ex-smoker - amount unknown
Ex-light smoker (1-9/day)
Wants to stop smoking
Smoking cessation programme start date
Smoking status between 4 and 52 weeks
Ex-very heavy smoker (40+/day)
Ex-cigar smoker
Not interested in stopping smoking
Cigar smoker
Cigar consumption
Ex-trivial smoker (<1/day)
Date ceased smoking
Current non-smoker
Thinking about stopping smoking
Time since stopped smoking
Pipe tobacco consumption
Light cigarette smoker (1-9 cigs/day)
(Trivial smoker - < 1 cig/day) or (occasional smoker)
Tobacco smoking behaviour
Tobacco consumption NOS
Contented smoker
Tobacco smoking consumption
Carbon monoxide reading at 4 weeks
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)
Ub1IT  Moderate cigarette smoker
XaQ8V  Ex roll-up cigarette smoker
1376  Very heavy cigarette smoker (40+ cigs/day)
XalkX  Ready to stop smoking
XaQzw  Recently stopped smoking
Ub0p2  Total time smoked
Xalr7  Smoking free weeks
Ub1IV  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
Ub1IS  Light cigarette smoker
XalQi  Smoking cessation milestones
137P.  Smoker (& cigarette)
XaW0h  Practice based smoking cessation programme start date
Xaltg  Reason for restarting smoking
XalQm  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
Ub1IW  Chain smoker
XaXPX  Smoking status at 12 weeks
XaluQ  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**

Xa00l  Occipital cerebral infarction
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>X00DA</td>
<td>Lacunar infarction</td>
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<tr>
<td>Xa0kZ</td>
<td>Cerebral infarction</td>
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<tr>
<td>X00DI</td>
<td>Haemorrhagic cerebral infarction</td>
</tr>
<tr>
<td>X00D8</td>
<td>Posterior cerebral circulation infarction</td>
</tr>
<tr>
<td>X00D7</td>
<td>Partial anterior cerebral circulation infarction</td>
</tr>
<tr>
<td>Xa00K</td>
<td>Brainstem infarction</td>
</tr>
<tr>
<td>G640</td>
<td>Cerebral thrombosis</td>
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<tr>
<td>X00D3</td>
<td>CVA - cerebral artery occlusion</td>
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<td>X00D6</td>
<td>Total anterior cerebral circulation infarction</td>
</tr>
<tr>
<td>Xa00J</td>
<td>Cerebellar infarction</td>
</tr>
<tr>
<td>XaBED</td>
<td>Right sided cerebral infarction</td>
</tr>
<tr>
<td>XaBEC</td>
<td>Left sided cerebral infarction</td>
</tr>
<tr>
<td>XaJgQ</td>
<td>Infarction of basal ganglia</td>
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<tr>
<td>XaB4Z</td>
<td>Multiple lacunar infarcts</td>
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<tr>
<td>XE0VJ</td>
<td>Cerebral infarction NOS</td>
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<tr>
<td>X00DC</td>
<td>Pure sensory lacunar infarction</td>
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<tr>
<td>XaQbK</td>
<td>Pure motor lacunar syndrome</td>
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<tr>
<td>X00D5</td>
<td>Anterior cerebral circulation infarction</td>
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<tr>
<td>G6410</td>
<td>Cerebral infarction due to embolism of cerebral arteries</td>
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<tr>
<td>G64z.</td>
<td>Infarct (&amp; [cerebell] or [cerebral NOS] or [brainstem NOS])</td>
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<tr>
<td>Gyu64</td>
<td>[X]Other cerebral infarction</td>
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<td>G6400</td>
<td>Cerebral infarction due to thrombosis of cerebral arteries</td>
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<tr>
<td>X00D9</td>
<td>Brainstem infarction NOS</td>
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<td>Xa00M</td>
<td>Wallenberg syndrome</td>
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<tr>
<td>Gyu63</td>
<td>[X]Cerebral infarct due/unspocclus/sten/cerebral artrs</td>
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<td>G6760</td>
<td>Cerebral infarct due cerebral venous thrombosis, non-pyogenic</td>
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<td>X00DK</td>
<td>Posterior cerebral circulation haemorrhagic infarction</td>
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<tr>
<td>Gyu6G</td>
<td>[X]Cerebral infarct due unspocclus/stenos precerebral arteries</td>
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<td>Cerebral infarction due to embolism of precerebral arteries</td>
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<td>X00DJ</td>
<td>Anterior cerebral circulation haemorrhagic infarction</td>
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<td>G63y0</td>
<td>Cerebral infarct due to thrombosis of precerebral arteries</td>
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<tr>
<td>X00DB</td>
<td>Pure motor lacunar infarction</td>
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<td>X00DD</td>
<td>Pure sensorimotor lacunar infarction</td>
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<td>Xa00P</td>
<td>Weber syndrome</td>
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<td>X00D4</td>
<td>Infarction - precerebral</td>
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**Stroke - unspecified**

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<tbody>
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<td>XaEGq</td>
<td>Stroke NOS</td>
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<tr>
<td>X00D1</td>
<td>Cerebrovascular accident</td>
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<td>G66..</td>
<td>CVA - cerebrovascular accident (&amp; unspecified &amp; stroke)</td>
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<td>XE2aB</td>
<td>Stroke and cerebrovascular accident unspecified</td>
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<tr>
<td>XE0X2</td>
<td>(Cereb infarc)(cerebrovas acc)(undef stroke/CVA)(stroke NOS)</td>
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<tr>
<td>G667.</td>
<td>Left sided cerebral hemisphere cerebrovascular accident</td>
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<tr>
<td>X00DR</td>
<td>Stroke of uncertain pathology</td>
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<tr>
<td>G668.</td>
<td>Right sided cerebral hemisphere cerebrovascular accident</td>
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<tr>
<td>X00DT</td>
<td>Posterior circulation stroke of uncertain pathology</td>
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<tr>
<td>G664.</td>
<td>Cerebellar stroke syndrome</td>
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<tr>
<td>X00DE</td>
<td>Lacunar ataxic hemiparesis</td>
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<tr>
<td>X00DS</td>
<td>Anterior circulation stroke of uncertain pathology</td>
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<tr>
<td>G663.</td>
<td>Brainstem stroke syndrome</td>
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<tr>
<td>Xa00L</td>
<td>Benedict syndrome</td>
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<tr>
<td>X00DF</td>
<td>Dysarthria-clumsy hand syndrome</td>
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<tr>
<td>Xa1hE</td>
<td>Extension of cerebrovascular accident</td>
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<tr>
<td>XaQbM</td>
<td>Pure sensory lacunar syndrome</td>
</tr>
</tbody>
</table>

**Sub-dural haematoma**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xa0AB</td>
<td>Subdural haematoma</td>
</tr>
<tr>
<td>XA0BD</td>
<td>Traumatic subdural haematoma</td>
</tr>
<tr>
<td>XaA99</td>
<td>Chronic intracranial subdural haematoma</td>
</tr>
</tbody>
</table>
Subdural haemorrhage

- Subdural haemorrhage
- Traumatic subdural haemorrhage
- Non-traumatic subdural haematoma
- Traumatic intracranial subdural haematoma
- Subdural haemorrhage NOS
- Closed traumatic subdural haemorrhage
- Subdural h'ge inj no open intracran wnd+LOC unspec duration
- Non-traumatic intracranial subdural haematoma
- Traumatic subdural haematoma without open intracranial wound
- Traumatic subdural haematoma with open intracranial wound
- Subdural h'ge inj no open intracranial wound+no loss consc

Subarachnoid haemorrhage

- Subarachnoid haemorrhage
- Subarachnoid haemorrhage NOS
- Traumatic subarachnoid haemorrhage
- Other subarachnoid haemorrhage
- Spontaneous subarachnoid haemorrhage
- Subarachnoid haemorrhage from post communic artery aneurysm
- Subarachnoid haemorrhage from basilar artery aneurysm
- Subarachnoid haemorrhage from multiple aneurysms
- Subarachnoid haemorrhage from ant communicat artery aneurysm
- Subarachnoid haemorrhage from post cerebral artery aneurysm
- Subarachnoid haemorrhage due to ruptured aneurysm
- Subarachnoid haemorrhage from post inf cerebell artery aneur
- Subarachnoid haemorrhage from ant cerebral artery aneurysm
- Closed traumatic subarachnoid haemorrhage
- Open traumatic subarachnoid haemorrhage
- Subarachnoid haemorrhage from carotid siphon and bifurcation
- Subarachnoid haemorrhage from vertebral artery
- Subarachnoid haemorrhage from carotid artery aneurysm
- Subarachnoid haemorrhage from other intracranial arteries

Transient ischaemic attack

- Transient ischaemic attack
- Transient cerebral ischaemia NOS
- (Drop attack) or (trans cereb isch) or (verteb-basil insuff)
- Carotid territory transient ischaemic attack
- Vertebrobasilar insufficiency
- Transient ischaemic attacks
- Amaurosis fugax
- Anterior cerebral artery syndrome
- [X]Other transnt cerebral ischaemic attacks+related syndroms
- Middle cerebral artery syndrome
- Other transient cerebral ischaemia
- Vertebrobasilar territory transient ischaemic attack
- Posterior cerebral artery syndrome
- Vertebrobasilar artery syndrome
- Vertebrobasilar artery syndrome
- (Trans isch attacks) or (vert-basil insuf) or (drop attacks)
- Basilar artery syndrome
Valvular disease

G654. Multiple and bilateral precerebral artery syndromes
G653. Carotid artery syndrome hemispheric
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
X77wl 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
Xal9k 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
Isolated aortic stenosis
Mitral stenosis with insufficiency
Rheumatic aortic regurgitation
Aortic valve dysplasia
Rheumatic aortic stenosis
Pulmonary stenosis, non-rheumatic
Papillary muscle degeneration
Congenital tricuspid atresia and stenosis
Pulmonary valve disease
Pulmonary incompetence, cause unspecified
Rheumatic aortic valve disease
Tricuspid valve disease NEC
Congenital pulmonary stenosis NOS
Pulmonary valve disorders NOS
Non-rheumatic mitral valve stenosis
Pulmonary incompetence, non-rheumatic
Rheumatic mitral disease NOS
Rheumatic aortic valve disease (& [chronic])
Papillary muscle atrophy
Rheumatic tricuspid regurgitation
Tricuspid valve disorders, non-rheumatic
Pulmonary regurgitation (& [non-rheumatic])
Rheumatic mitral insufficiency (& [stenosis with])
Other mitral valve diseases
Rheumatic mitral valve changes
Mitral valve dysplasia
Ebstein's anomaly of tricuspid valve
Mitral leaflet dysplasia
Congenital aortic valve abnormality
Tricuspid incompetence (& [non-rheumatic])
Other aortic valve disorders
Congenital tricuspid regurgitation
Aortic valve cusp abnormality
Congenital mitral valve stenosis
Supravalvar aortic stenosis
Prosthetic mitral valve regurgitation
Tricuspid stenosis
Rheumatic aortic valve disease NOS
Aortic valve disorders in diseases classified elsewhere
Pulmonary valve anomaly, unspecified
Accessory tissue on aortic valve cusp
Post-infarction mitral papillary muscle rupture
Congenital pulmonary valve abnormality
Parachute malformation of mitral valve
Rheumatic pulmonary valve disease
Mitral chordae rupture
Congenital pulmonary regurgitation
Tricuspid valve disorders NOS
Torn mitral leaflet
Congenital aortic valve insufficiency NOS
Rheumatic pulmonary valve disease NOS
Tricuspid valve dysplasia
Aortic stenosis with doming
Rheumatic mitral valve leaflet changes
Tricuspid valve prolapse
Rheumatic aortic stenosis with insufficiency
Pulmonary valve stenosis with insufficiency
Congenital mitral regurgitation
Aortic valve fibrosis
Tricuspid stenosis, cause unspecified
Tricuspid stenosis, non-rheumatic
Mitral regurgitation due to dysfunct subvalvular apparatus
[X] Mitral valve disorders in diseases classified elsewhere
Other rheumatic aortic valve diseases
Fused commissure of the mitral valve
Fusion of mitral valve cusps
Rheumatic tricuspid valve disease NOS
Aortic regurgitation due to cystic medial necrosis of aorta
[X] Tricuspid valve disorders/diseases CE
[X] Other pulmonary valve disorders
Rheumatic tricuspid stenosis and insufficiency
Ruptur chordae tendinae/curr comp fol acute myocard infarct
Other non-rheumatic tricuspid valve disorders
Rheumatic pulmonary valve stenosis
Tricuspid leaflet abnormality
Congenital aortic valve insufficiency
Aortic valve cusp prolapse
Non-rheumatic tricuspid valve disorder, unspecified
Tricuspid valve vegetations
[X] Other non-rheumatic mitral valve disorders
Other pulmonary valve anomaly NOS
Oesophageal varices
Operation on oesophageal varices
Gastric varices
Bleeding oesophageal varices
Fibreoptic oesophagoscopy and banding of oesophageal varices
Oesophageal varices NOS
Rigid oesophagoscopy and banding of oesophageal varices
Open injection sclerotherapy to oesophageal varices
Oesophageal varices with bleeding in diseases EC
Fibreoptic oesophagoscopy & injection sclerotherapy varices
Open operation on oesophageal varices NOS
Oesophageal varices in alcoholic cirrhosis of the liver
Oesophageal varices without bleeding
Oesophageal varices in diseases EC
[X] Oesophageal varices in diseases classified elsewhere
Oesophageal varices in cirrhosis of the liver
Local ligation of oesophageal varices
Duodenal varices
Sclerotherapy of oesophageal varices
Open operations on oesophageal varices
Oesophageal varices without bleeding in diseases EC
Oesophageal varices in diseases EC NOS
Ruptured varix