Polypharmacy in atrial fibrillation: An analysis of prospective outcomes using the Clinical Practice Research Datalink (CPRD)

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Abstract

Objectives: Observational studies of polypharmacy and the risk of death or ischaemic stroke in individuals with atrial fibrillation (AF) have produced inconsistent findings. The reason for this variation may be due to differences in study designs and populations. By using propensity score matching, the aim of this study was to determine whether polypharmacy (5-9 prescribed medicines) and hyper-polypharmacy (≥10 prescribed medicines) in the three months following AF diagnosis, are associated with an increased risk of death or ischaemic stroke, compared to non-polypharmacy (1-4 prescribed medicines).

Design: Prospective cohort study

Setting: Clinical Practice Research Datalink (CPRD) GOLD (June 2006 to April 2019)

Participants: 33,984 individuals with atrial fibrillation

Main outcome measures: Hazard ratios (HR) and 95% confidence intervals (CI) for the risk of death and ischaemic stroke. Logistic regression and propensity score matching (PSM) (1:1) were implemented in this study. Logistic models were adjusted for age, gender, eleven diagnosed conditions, obesity, alcohol consumption, smoking and wealth. In the PSM models, cases and controls with near identical health profiles were selected from the study pool.

Results: 47.9% (n=16,271) of the participants had polypharmacy, 30.4% (n= 10,355) had hyper-polypharmacy, while 21.7% (n=7, 358) had non-polypharmacy. PSM showed that polypharmacy was significantly associated with an increased risk of death during follow-up (HR 1.32; 95% CI: 1.19-1.47), but not ischaemic stroke (HR 0.84; 95% CI: 0.69-1.02). The

risk of death during follow-up was accentuated in the hyper-polypharmacy group (HR 1.89; 95% CI: 1.65-2.16); however, no significant association was found between hyper-polypharmacy and ischaemic stroke (HR 1.19; 95% CI: 0.91-1.57).

Conclusion: Polypharmacy and hyper-polypharmacy were significantly associated with an increased risk of death during follow-up, but not ischaemic stroke, in individuals with AF. The effect of comorbidity and other confounding factors was minimized by using propensity score matching in this large dataset. Further research conducted at drug class or individual drug level, could identify which medications, or combinations of medications, within polypharmacy and hyper-polypharmacy regimens are associated with an increased risk of death in AF. Identifying these medications could help to inform prescribing decisions and deprescribing practices in AF, and hence this study provides baseline data for future research. Furthermore, this research may develop our understanding regarding the lack of association between polypharmacy, hyper-polypharmacy, and ischemic stroke in AF.

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had no idea that I was working on this thesis most evenings, while you slept- I did it for us, and for our future.

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Abbreviations

ACE – Angiotensin-converting enzyme

ADR – Adverse drug reaction

AF – Atrial fibrillation

AFFIRM – Atrial fibrillation follow-up investigation of rhythm management

ARISTOTLE – Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation

BAFTA – Birmingham atrial fibrillation treatment of the aged

BMI – Body mass index

BMJ – British Medical Journal

BNF – British National Formulary

BP – Blood pressure

CAD – Coronary artery disease

CASP – Critical Appraisal Skills Programme

CCG – Clinical Commissioning Group

CHA2DS2-VASc – Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65 to 74 years, sex category score

CHF – congestive heart failure

CHD – Coronary heart disease

CI – Confidence interval

CIRS – Cumulative illness rating scale

CNS – Central nervous system

COPD – Chronic obstructive pulmonary disease

CPRD – Clinical Practice Research Datalink

CrCl – Creatinine clearance

CV - Cardiovascular

DOAC – Direct-acting oral anticoagulant

DOH – Department of Health

DVT – Deep vein thrombosis

EGFR – Estimated Glomerular Filtration Rate

ELSA – English Longitudinal Study of Ageing

GI - Gastrointestinal

GP – General Practitioner

HAS-BLED –Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage score

HES – Hospital Episode Statistics

HF – Heart failure

HR – Hazard ratio

HR – Heart rate

IHD – Ischaemic heart disease

IMD – Index of Multiple Deprivation

INR – International normalised ratio

ISAC – Independent Scientific Advisory Committee

LVF – Left ventricular function

MAI – Medication Appropriateness Index

MeSH – Medical Subject Headings

MHRA – Medicines and Healthcare products Regulatory Agency

MI – Myocardial infarction

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NIHR – National Institute for Health Research

NOS -Newcastle-Ottawa Scale

NSAID – Non-Steroidal Anti-Inflammatory Drugs

OAC – Oral anticoagulant

OR – Odds ratio

OTC – Over-the-counter

PE – Pulmonary embolism

PHE – Public Health England

PICO – Population, Intervention, Comparator, Outcome

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analyses

PSM – Propensity score matching

QOF – Quality and Outcomes Framework

QOL – Quality of life

REPOSI – Registro Politerapie Simi study

RoBANS – Risk-of-Bias Assessment tool for Non-Randomised Studies

ROCKET AF – Rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation

SD – Standard deviation

SE – Systemic embolism

SES – Socio-economic status

SPSS – IBM Statistical Package for Social Sciences

SSRI – Selective serotonin reuptake inhibitor

START – Screening Tool to Alert doctors to Right indicated Treatments

STOPP – Screening Tool of Older People's potentially inappropriate Prescription

TCA – Tricyclic antidepressant

TIA – Transient ischaemic attack

TTR – Time in therapeutic range

UK – United Kingdom

USA – United States of America

VKA – Vitamin K antagonist

Prologue

While waiting for the main dataset for this thesis from the Clinical Practice Research Datalink (CPRD), the research team conducted analyses on Wave 6 data (2012-2013) and Wave 7 data (2014-2015) from the English Longitudinal Study of Ageing, and the following papers were published in peer-reviewed journals:

Slater, N., White, S., *et al.* (2018) 'Factors associated with polypharmacy in primary care: A cross-sectional analysis of data from the English Longitudinal Study of Ageing (ELSA)', *BMJ Open*, 8(3), pp. 1–9. doi: 10.1136/bmjopen-2017-020270.

This paper aimed to determine whether smoking, alcohol consumption, obesity, and wealth, in addition to increasing age and morbidities, were associated with polypharmacy prevalence, among older people who resided in England. Further information about this study, including research findings are presented in section 1.3.4.

Slater, N., White, S. and Frisher, M. (2020) 'Central nervous system (CNS) medications and polypharmacy in later life: cross-sectional analysis of the English Longitudinal Study of Ageing (ELSA)', *BMJ Open*, 10(9), p. e034346. doi: 10.1136/bmjopen-2019-034346.

This paper identified the most common central nervous system (CNS) drug classes taken by older individuals (≥50 years). Following this, the associations between polypharmacy and the most common CNS drug classes were examined in detail. Further information about this study, including research findings are presented in section 1.6.

Slater, N., Rowley, C., *et al.* (2018) 'Evaluating associations between metabolic health, obesity and depressive symptoms: a prospective analysis of data from the English Longitudinal Study of Ageing (ELSA) with a 2-year follow-up', *BMJ Open*, 8(12), p.

e025394. doi: 10.1136/bmjopen-2018-025394.

The latter paper aimed to determine whether obesity or metabolic health were associated with depression, among older people who resided in England. Although polypharmacy was not the focus of this paper, the statistical methods learnt whilst working on this paper have been helpful when analysing the data for this thesis.

Overview

This thesis presents an analysis of prospective outcomes in 33,984 individuals with atrial fibrillation (AF) using the Clinical Practice Research Datalink (CPRD). The aim of this research was to determine whether polypharmacy (5-9 prescribed medicines) and hyper-polypharmacy (≥10 prescribed medicines) in the three months following AF diagnosis, are associated with an increased risk of death or ischaemic stroke, compared to non-polypharmacy (1-4 prescribed medicines), using logistic regression and propensity score matching. This type of matching ensures that cases and controls are similar at study entry point, thus reducing the effect of confounding factors. Finally, this thesis complements the research team's previously published polypharmacy work (Slater *et al.*, 2018; Slater *et al.*, 2020).

Thesis structure

This thesis is comprised of seven chapters. A description of each chapter is provided below.

Chapter 1 presents a narrative review of the polypharmacy literature and focuses on five key areas: the difficulty in defining polypharmacy (section 1.2), the factors contributing to polypharmacy prevalence (section 1.3), the benefits of 'appropriate' polypharmacy (section 1.4), the consequences of 'inappropriate' polypharmacy (section 1.5) and the composition of polypharmacy regimens (section 1.6).

This narrative review showed that the prevalence of polypharmacy is continuing to rise. A growing ageing population, rising numbers of individuals with chronic conditions and multi-morbidities, preventative prescribing, lower wealth, and obesity, have been identified as some of the contributors towards polypharmacy prevalence (Gorard, 2006; Guthrie *et al.*, 2015; Slater *et al.*, 2018). The narrative review also showed that polypharmacy is often associated with adverse health outcomes, including adverse drug reactions, hospitalisations, falls and mortality (Cadogan *et al.*, 2016). It may be possible to reduce the likelihood of these adverse events, particularly in older people, by deprescribing; however, further research into polypharmacy and hyper-polypharmacy is required.

This thesis examines polypharmacy in atrial fibrillation (AF). The rationale for selecting AF is explained in the final section of Chapter 1 (section 1.7). To summarise, AF is the most common sustained cardiac arrhythmia in England, and like polypharmacy, the prevalence of AF increases with age (Zoni-Berisso *et al.*, 2014; Lacoin *et al.*, 2017). The condition is 'not usually life-threatening'; therefore, it is possible to study mortality as an outcome (NHS, 2021a). Furthermore, individuals with AF may experience polypharmacy or hyper-polypharmacy due to the clinical management of the condition, and the presence of co-morbidities.

Chapter 2 presents a systematic review which examines the adverse outcomes associated with polypharmacy, in individuals with atrial fibrillation

Chapter 3 introduces the thesis aim and objectives. This chapter also discusses the methods used in this research, including the rationale for selecting the CPRD GOLD dataset for the

analyses (section 3.3). To summarise, the size of the dataset enhances the statistical power of the analyses and improves the reliability of conclusions drawn in this thesis (Strongman *et al.*, 2019). The dataset provides a rich source of health data, with 'at least 20 years of follow-up data', for over one-quarter of all patients currently registered with a participating GP surgery (Herrett *et al.*, 2015). The dataset has also been shown to be broadly representative of the UK general population, in terms of age, gender and ethnicity, previously (Bhaskaran *et al.*, 2013; Herrett *et al.*, 2015).

Chapter 4 is the first results chapter. This chapter presents the unadjusted logistic regression results for the associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke). The associations between prognostic factors and study outcomes are also examined in this chapter.

Chapter 5 is the second results chapter. The adjusted logistic regression and propensity score matched results for the associations between polypharmacy, in the first three months following AF diagnosis, and study outcomes (death and ischaemic stroke) are presented in this chapter.

Chapter 6 is the final results chapter. The adjusted logistic regression and propensity score matched results for the associations between hyper-polypharmacy, in the first three months following AF diagnosis, and study outcomes (death and ischaemic stroke) are presented in this chapter.

Chapter 7 discusses the key findings from the three results chapters (Chapter 4, Chapter 5, and Chapter 6). In Chapter 7, the key findings are considered in the context of the thesis objectives (section 7.2), and then discussed in the context of the existing literature (section 7.3). The strengths and limitations of this research (section 7.4), along with the significance of the findings for clinical practice (section 7.5) and opportunities for future research (section 7.6) are also discussed within this chapter. A thesis conclusion is presented in section 7.7.

Chapter 1: Background

1.1 Introduction

This chapter provides a narrative review of the polypharmacy literature by focusing on five key areas: the difficulty in defining polypharmacy (section 1.2), the factors contributing to polypharmacy prevalence (section 1.3), the benefits of 'appropriate' polypharmacy (section 1.4), the consequences of 'inappropriate' polypharmacy (section 1.5) and the composition of polypharmacy regimens (section 1.6). A chapter summary is provided in section 1.7.

1.2 The difficulty in defining polypharmacy

The term polypharmacy has appeared in the literature for over 150 years, and is used to describe the concomitant use of multiple medicines by one individual (Bushardt *et al.*, 2008). However, there is no consensus at present regarding the specific definition of polypharmacy (Duerden *et al.*, 2013).

Masnoon *et al.* (2017) conducted a systematic review to identify literature which defined polypharmacy. A total of 110 articles were eligible for inclusion in the review and 138 definitions of polypharmacy were examined. Most polypharmacy definitions (80.4%, n=111/138) were numerical, with 46.4% of them describing polypharmacy as the concomitant administration of "five or more medications". Fewer definitions

(8.7%, n=12/138) of polypharmacy were descriptive. Findings from this systematic review showed that there was significant heterogeneity in the existing definitions of polypharmacy, and the authors concluded that there is a need for an "internationally agreed" definition.

The numerical definitions provide a threshold to define the concept of polypharmacy; however, clinical considerations, such as an individual's co-morbidities, pharmacokinetic and pharmacodynamic status or the likelihood of adverse drug events are not taken into consideration with this type of polypharmacy definition. Furthermore, Mortazavi *et al.* (2016) showed that the descriptive definitions of polypharmacy are applied in different contexts throughout the literature. In some literature, polypharmacy is used to describe multiple medication use (i.e., many medicines), whereas, in other literature the term is used to describe excessive, inappropriate, or unnecessary medication usage (i.e., too many medicines). Consequently, the variation in polypharmacy definitions can make it difficult to compare research within this subject area.

Cadogan *et al.* (2016) also recognised that there are various definitions of polypharmacy in the literature; however, they acknowledged that it would be a practical impossibility to completely remove the term from the existing literature. Therefore, the authors suggested that this long-term definition issue could be addressed by following Aronson (2006) recommendations to subdivide the term into "appropriate polypharmacy" and "inappropriate polypharmacy" when writing about this topic in the future. Aronson (2006) elaborated on this idea and stated that there is a need to determine whether each medication has been prescribed appropriately or inappropriately, according to guidelines, evidence and patient preference. Aronson (2006) also emphasised the importance of considering each

medication in the context of the whole prescription and within a patient's medication regimen, before deciding on the appropriateness of polypharmacy. One limitation of this approach is that it may be difficult to differentiate between appropriate and inappropriate polypharmacy, without being entirely subjective. Furthermore, it may also be a time-consuming task, as the appropriateness of polypharmacy would need to be considered separately for each individual. The benefits of appropriate polypharmacy are discussed in a subsequent section (section 1.4). This section also includes information about the tools which are currently available to determine medication appropriateness.

1.3 The factors contributing to polypharmacy

A number of different factors have been identified as contributors towards the rising prevalence of polypharmacy, including an ageing population (section 1.3.1), increasing numbers of individuals with chronic conditions and multi-morbidities (section 1.3.2) and rising levels of preventative prescribing (section 1.3.3) (Gorard, 2006). Each of these factors will be discussed in more detail within this section. Furthermore, our analysis of the English Longitudinal Study of Ageing data identified other factors that were associated with polypharmacy prevalence, and these factors will be discussed in section 1.3.4 (Slater *et al.*, 2018).

1.3.1 An ageing population

By 2045, the number of individuals aged over 65 years will equate to almost one quarter (24.6%) of the entire UK population (Office for National Statistics, 2017). At present,

60.4% of all medicines prescribed in the UK are supplied to older individuals; however, this percentage is anticipated to rise as the population continue to live longer (Prescribing and Medicines Team and Health and Social Care Information Centre, 2016).

An ageing population is also associated with an increased prevalence of chronic conditions (Maresova *et al.*, 2019). Analysis of Wave 1-7 data from the English Longitudinal Study of Ageing (ELSA) showed that the prevalence of chronic health conditions increased with age, in both men and women (Banks *et al.*, 2014). In this study, ELSA data were analysed and stratified according to the participant's age group in 2002 (the year ELSA commenced). Of the male participants, who were aged between 55 and 59 years in 2002, 7.4% had received a diagnosis of coronary heart disease (CHD) at Wave 1 (2002-2003). By Wave 7 (2014-2015), 21.6% of these male participants had received a CHD diagnosis. The increasing prevalence of CHD diagnoses over time was observed in all male age groups. Similarly, 3.4% of women participants, who were aged between 55 and 59 years in 2002, had received a diagnosis of coronary heart disease (CHD) at Wave 1 (2002-2003), and this percentage had increased to 10.4% by Wave 7 (2014-2015) (Banks *et al.*, 2014). The increasing prevalence of CHD diagnoses over time was observed in all female age groups too. Similar trends were seen with other chronic conditions, including diabetes mellitus, cancer, and respiratory illnesses (Banks *et al.*, 2014). One conclusion derived from the ELSA analyses was that most older people (≥65 years) in England are living with at least one chronic condition (Banks *et al.*, 2014). This conclusion is supported by a Department of Health report which incorporated data from the General Lifestyle Survey (Department of Health, 2012; Office for National Statistics, 2013). Both sources showed that the number of people with chronic conditions increased as the population became older. Consequently,

these individuals are likely to be prescribed more medications to manage their conditions, thus contributing towards an increase in polypharmacy prevalence.

1.3.2 Increasing morbidities and multi-morbidities

Over 15 million people in the UK have been diagnosed with a chronic condition, such as diabetes mellitus, hypertension, or arthritis (Department of Health, 2012; Morrison *et al.*, 2016). The National Health Service (NHS) currently allocates 70% of the overall budget to the management of chronic conditions; however, an additional £5 billion per year (equating to 3.9% of the overall NHS budget), is required to accommodate the rising numbers of patients with multiple chronic conditions (multi-morbidity) over the next few years (Department of Health, 2012; The Kings Fund, 2021).

Multi-morbidities are commonly associated with adverse outcomes including worsening quality of life, increased NHS utilisation, and increased mortality rates (Koné Pefoyo *et al.*, 2015). A number of factors have been identified as contributors to the rising prevalence of multi-morbidities in the UK, including increasing age, female gender, and lower socio-economic status (Abad-Díez *et al.*, 2014; Roman Lay *et al.*, 2020).

Marengoni *et al.* (2011) conducted a systematic review to identify literature which examined the association between age and multi-morbidities. There were 41 articles eligible for inclusion in the review. The prevalence of multi-morbidities in older individuals varied throughout the literature, ranging from 55% to 98%. Marengoni *et al.* (2011) suggested that

the differing figures may have been influenced by data collection methods, for example some data were collected using structured interviews, while other studies analysed data in clinical databases or obtained data during clinical examinations. Another possible explanation for the varying figures could be that older people tend to be less accurate when they are asked to self-report information about their medical conditions (Short *et al.*, 2009). Despite the variations in multi-morbidity data reported in their systematic review, Marengoni *et al.* (2011) concluded that an increasing prevalence of multi-morbidities is associated with an ageing population. Barnett *et al.* (2012) supported this conclusion, following their analysis of Scottish primary care data. In the latter study, 64.9% of all adults aged between 65 and 84 years had multi-morbidities. This percentage increased to 81.5% in adults aged over 85 (Barnett *et al.*, 2012).

Gender has also been shown to be another determinant of multi-morbidity prevalence. Violan *et al.* (2014) conducted a systematic review of observational studies and reported an association between female sex and an increasing prevalence of multi-morbidities. The same conclusion was reached by researchers in Iran when they conducted a large population-based study, involving 49,946 participants (Alimohammadian *et al.*, 2017). In the latter study, the prevalence of multi-morbidities was calculated for both genders and the results showed a statistically significant difference between the prevalence of multi-morbidities in women (25.0%), compared to men (13.4%) (Alimohammadian *et al.*, 2017). However, there are several limitations which need to be taken in account when considering the findings of the latter study. First, all participants were asked to provide information about their medical history. This method relies on all participants being able to accurately recall information, otherwise the study results may be influenced by recall bias. Furthermore, the results may have been overstated as previous research has shown that

women tend to share more information about their medical conditions when asked to self-report, compared to men (Murtagh and Hubert, 2004).

The association between an individual's socio-economic status and the prevalence of multi-morbidities has been examined previously. Uijen and van de Lisdonk (2008) examined the trends in multi-morbidities over a 20-year period. Findings showed that individuals who resided in economically deprived areas were more susceptible to developing multi-morbidities, compared to those living in affluent areas. Macleod *et al.* (2004) supported this conclusion following their analyses of primary care data for 7,286 participants. The findings from these studies (Macleod *et al.*, 2004; Uijen and van de Lisdonk, 2008) were supported by a Department of Health (DoH) report which showed that there was a higher prevalence (60%) of chronic conditions in individuals who resided in economically deprived areas, compared to individuals living in affluent areas (Department of Health, 2012). The DoH report also stated that there was an increased likelihood that an individual who lived in an economically deprived area would experience a more severe form of a chronic condition (30% more severe), compared to an individual who resided in an affluent area (Department of Health, 2012).

Few studies have investigated whether polypharmacy is associated with specific chronic conditions or multi-morbidities previously (Barnett *et al.*, 2012; Payne *et al.*, 2014). To address this gap in the literature, Aubert *et al.* (2016) analysed prescribing data and calculated adjusted odds ratios for the association between polypharmacy and specific chronic conditions, with 95% confidence intervals. Statistically significant associations were reported between polypharmacy and hypertension (OR 8.49; 95% CI, 5.25-13.73);

polypharmacy and diabetes mellitus (OR 4.47; 95% CI, 3.23-6.20); and polypharmacy and cardiovascular diseases, including angina, coronary artery disease and congestive heart failure (OR 3.74; 95% CI, 2.76-5.08) (Aubert *et al.*, 2016). No statistically significant associations were found between polypharmacy and chronic pulmonary diseases (OR 1.29; 95% CI, 0.94-1.76); polypharmacy and psychiatric disorders (OR 1.14; 95% CI, 0.83-1.59); or polypharmacy and dementia (OR 0.83; 95% CI, 0.35-2.01) (Aubert *et al.*, 2016). Similar findings were reported during the Registro Politerapie SIMI (REPOSI) study, which showed that polypharmacy was independently associated cardiovascular conditions, including hypertension ($p<0.01$), ischaemic heart disease ($p<0.01$) and atrial fibrillation ($p<0.01$) (Nobili *et al.*, 2011).

Payne *et al.* (2014) also examined the associations between polypharmacy, specific chronic conditions, and multi-morbidities. Findings showed that 20.8% of individuals with two chronic conditions were prescribed between four and nine regular medicines, and 1.1% were prescribed 10 or more regular medications; whereas, 47.7% of individuals with six or more chronic conditions were prescribed between four and nine regular medicines and 41.7% were prescribed 10 or more regular medications (Payne *et al.*, 2014). Furthermore, findings showed that prescribing patterns varied between chronic conditions. Cardiovascular conditions, including atrial fibrillation, ischaemic heart disease and heart failure, were most frequently associated with polypharmacy, after the statistical models were adjusted for age, gender, and wealth (Payne *et al.*, 2014).

One possible explanation for the latter finding could be that most of the clinical guidelines used in the management of cardiovascular diseases recommend the use of multiple

medications, for example the National Institute for Health and Care Excellence (NICE) guidelines for chronic heart failure management recommends that a minimum of three different drug classes (loop diuretics, angiotensin-converting enzyme inhibitors and beta-blockers) should be initiated, if considered clinically appropriate, thus increasing the likelihood of polypharmacy for an individual with heart failure (NICE, 2017).

While guidelines for the management of cardiovascular conditions may increase the prevalence of polypharmacy, there are other clinical guidelines which may reduce the prevalence of polypharmacy, for example, in the management of psychiatric conditions. Current guidelines recommend that a medication (e.g., an antipsychotic) is stopped, if deemed ineffective, before initiating a new medication (NICE, 2021d). These guidelines differ from previous practice as new medications would have been added into a regimen to treat a psychiatric condition, without deprescribing the medications which were considered ineffective.

At present, the clinical guidelines, published by NICE, focus on single diseases; however, there are growing concerns that these guidelines may not be sufficient or effective when treating patients with multi-morbidities (Barnett *et al.*, 2012). Hughes *et al.* (2013) investigated this concern by evaluating a selection of NICE guidelines, to determine whether these guidelines were appropriate for managing individuals with multi-morbidities. The NICE guidelines were applied synergistically to two hypothetical patients, and the authors concluded that this approach, which is currently standard practice in the UK, increased pill burden and the likelihood of polypharmacy, and did not provide any guidance about the prioritisation of recommendations from different clinical guidelines (Hughes *et*

al., 2013). Koné Pefoyo *et al.* (2015) and Ong *et al.* (2020) supported these conclusions. Furthermore, Ong *et al.* (2020) reported that the application of multiple clinical guidelines increased an individual's treatment burden, thus resulting in poorer adherence to treatment plans and worsening clinical outcomes.

There have been several strategies suggested to address the issue of multi-morbidity management within the current clinical guidelines. One strategy could be to cross-reference guidelines for conditions which commonly occur together, for example type 2 diabetes mellitus and hypertension. This would enable serious medication interactions to be identified (Hughes *et al.,* 2013). However, this approach has the potential to make patient care very complex, and it may not be practically possible to cross-reference all disease guidelines, particularly for rare diseases or diseases that are not commonly associated with other conditions (Boyd *et al.*, 2005). Further research would also be required to determine which specific diseases cluster together in individuals with multi-morbidities.

Another strategy to address the issue of multi-morbidity management in clinical guidelines, could be to develop patient-centered guidelines, which consider treatment burden, adherence and patient preference, in addition to the management of multiple chronic conditions (Du Vaure *et al.*, 2016). The latter strategy has been partially implemented by NICE.

In 2016, NICE published some general guidance about optimising care for individuals with multi-morbidities (NICE, 2016a). This guidance advocates shared decision making, while also encouraging practitioners to holistically consider the impact of diseases, treatment, and

guideline recommendations, on an individual's quality of life (NICE, 2016a). The main purpose of this guidance was to reduce 'treatment burden (polypharmacy and multiple appointments) and unplanned care'. While this guidance acknowledges that polypharmacy is associated with multi-morbidities, the suggestion that it should be reduced implies that polypharmacy is always harmful to an individual. However, there are occasions when polypharmacy may be beneficial for an individual, for example in the management or prevention of cardiovascular conditions (Allan *et al.*, 2019). The appropriateness of polypharmacy will be discussed in more detail in section 1.4.

Further guidance on shared decision making has been published recently by NICE. The newest guidance outlines how shared decision making can be implemented into everyday healthcare practices (NICE, 2021e). In addition to this new guidance, a learning package has been created for healthcare professionals to develop their shared decision-making knowledge and skills (NICE, 2021f).

In summary, the prevalence of multi-morbidities is continuing to rise across the UK and there are certain group of individuals who are more susceptible to experiencing multi-morbidities, for example older individuals or those who reside in economically deprived areas. These individuals will often have complex care needs and their chronic conditions will be managed using a number of different disease guidelines. Prescribing multiple medications is often advocated by the guidelines, thus contributing to an increase in polypharmacy prevalence. Furthermore, there is evidence to suggest that polypharmacy is independently associated with cardiovascular conditions; however, this association has not been established with other chronic conditions and requires further investigation.

1.3.3 Rising levels of preventative prescribing

One key element of the 'NHS Long Term Plan' is to prevent illness. At NHS level, this plan aims to reduce the pressure on healthcare services and provide cost-effective treatments. At an individual level, this plan aims to improve longevity and quality of life, by encouraging individuals to make informed, healthy lifestyle choices (Dohnhammar, 2016; NHS, 2021b). However, this plan has also impacted prescribing practices, with an increased number of medicines being prescribed for preventative purposes in recent years. For example, NICE guidelines recommend that different types of medications, including antiplatelets, anticoagulants, antihypertensives and lipid-lowering drugs, should be initiated to prevent the development of a range of cardiovascular conditions, and mortality, in high-risk individuals (NICE, 2021a).

The effects of preventative prescribing in cardiovascular conditions has been examined previously. A meta-analysis of 287 studies was conducted to determine whether antiplatelet regimens prevented or reduced future cardiovascular events in high risk patients (Antithrombotic Trialists' Collaboration, 2002). Findings showed that the risk of an ischaemic stroke or myocardial infarction was 25.0% lower in the groups who were prescribed antiplatelets, compared to the control groups. The incidence of mortality and non-fatal vascular events were also lower in the treatment groups, compared to the control groups (16.7% and 33.3% respectively) (Antithrombotic Trialists' Collaboration, 2002).

Statins are also commonly prescribed for the primary and secondary prevention of cardiovascular conditions (NICE, 2021a). A systematic review of 18 randomised controlled

trials reported that statins reduced the following: mortality, the development of cardiovascular diseases and the incidence of stroke (Taylor *et al.*, 2013). In 2016, NICE reviewed the evidence in relation to prescribing statins for the prevention of cardiovascular disease, and the threshold for initiating statins was lowered. As a result, there are now over 4 million additional individuals in the UK, who meet the revised criteria for prescribing statins for preventative purposes (NICE, 2016b).

Preventative prescribing is common practice in other conditions too, including migraines, osteoporosis and venous thromboembolisms (Nicolaides *et al.*, 2013; Compston *et al.*, 2017; Silberstein, 2017). Patients who are at high risk of developing osteoporosis are often offered several preventative medications, including calcium supplements, vitamin D supplements and bisphosphonates, when appropriate (Sunyecz, 2008; Compston *et al.*, 2017). Similarly, prophylactic medications are offered to patients who suffer from migraines, once patient preference, co-morbidities and the risk of adverse events have been taken into consideration. Several years ago, topiramate was considered as a third line drug for migraine prevention, due to a lack of scientific evidence relating to the drug's mode of action and efficacy (Silberstein, 2017). However, topiramate is now considered as the drug of choice for migraine prophylaxis in the latest NICE guidelines, based upon the results generated during a large scale, randomised controlled trial involving 3,000 participants .Trial findings showed that topiramate reduced migraine frequency and improved the quality of life for study participants (Silberstein, 2017; NICE, 2020).

The benefits of preventative prescribing have been shown previously; however, this prescribing practice may be a contributory factor to the rising prevalence of polypharmacy.

(Duerden *et al.*, 2013; Hazell and Robson, 2015). Few studies have examined the composition of polypharmacy, and of those, there have been no studies which have separated medications indicated for disease prevention, from medications indicated for disease treatment (Bjerrum *et al.*, 1998; Wastesson *et al.*, 2018; Slater *et al.*, 2020). This has identified an area for future research. Furthermore, preventative prescribing is considered appropriate for the purpose of disease prevention; however, the appropriateness of the medications within a regimen, particularly within a polypharmacy regimen, require further consideration, to minimise the likelihood of adverse outcomes. The adverse outcomes associated with polypharmacy are discussed in more detail in section 1.5.

1.3.4 Other factors identified following the analysis of the English Longitudinal Study of Ageing (ELSA) data

Increasing age and morbidities have been shown to be associated with polypharmacy previously (Department of Health, 2012; Banks *et al.*, 2014; Silveira *et al.*, 2014). However, few studies have sought to determine whether sociodemographic or lifestyle factors are associated with polypharmacy prevalence (Haider *et al.*, 2008; Castioni *et al.*, 2017).

While waiting for the main dataset for this thesis from the Clinical Practice Research Datalink (CPRD), the research team conducted analyses on Wave 6 data (2012-2013), from the English Longitudinal Study of Ageing (Slater *et al.*, 2018). Data from 7730 participants, aged over 50, were included in the analyses. The aim of the analyses was to determine whether smoking, alcohol consumption, obesity, and wealth, in addition to increasing age

and morbidities, were associated with polypharmacy prevalence, among older people who resided in England (Slater *et al.*, 2018).

This study showed that polypharmacy was significantly associated with lower wealth (lowest wealth quintile versus highest wealth quintile, adjusted OR 1.28; 95% CI 1.04-1.69) and obesity (adjusted OR 1.81; 95% CI, 1.53-2.15). Furthermore, an inverse association was found between polypharmacy and very frequent alcohol consumption (defined as consuming alcohol at least five per week) (no alcohol consumption versus very frequent alcohol consumption, adjusted OR 0.64; 95% CI, 0.52-0.78). No statistically significant association was found between smoking and polypharmacy prevalence. Finally, this study confirmed the significant associations between polypharmacy and increasing age (50-59 years versus 70-79 years, adjusted OR 3.42; 95% CI, 2.81-4.77), and polypharmacy and morbidities (adjusted OR 2.94; 95% CI, 2.55-3.39), which have been reported previously (Slater *et al.*, 2018).

Fano (2014) complemented our wealth findings and concluded that individuals who resided in affluent areas were 33% less likely to experience polypharmacy, compared to individuals living in deprived areas. Significant associations between deprivation and the increased prevalence of multi-morbidities have also been established, as discussed in section 1.3.2 (Barnett *et al.*, 2012). Therefore, as UK wealth inequalities continue to broaden, individuals living in deprived areas are more likely to require polypharmacy to manage their multi-morbidities, thus providing support for our research findings (Office for National Statistics, 2015).

Obesity (defined as BMI ≥ 30kg/m^2) was also found to be significantly associated with polypharmacy prevalence in our ELSA analyses (Slater *et al.*, 2018). A similar association has been shown in a study which examined prescribing patterns in normal weight individuals, compared to obese individuals (Counterweight Project Team, 2005). Stratification of results by disease type showed that cardiovascular medications, central nervous system medications and endocrine medications were twice as likely to be prescribed for obese individuals, compared to normal weight individuals (Counterweight Project Team, 2005). One limitation of their study, in relation to this research, was that the data were not stratified according to polypharmacy group. Furthermore, it was not possible to determine the direction of causality, due to the cross-sectional nature of the analyses (Counterweight Project Team, 2005). Our study findings, in relation to obesity and polypharmacy, are important because Public Health England (PHE) have identified obesity as a major public health issue (PHE, 2017). As a consequence of the current obesity epidemic, polypharmacy prevalence in people aged over 50 is likely to rise too (Slater *et al.*, 2018).

An inverse association was found between polypharmacy and frequent alcohol consumption. In our published paper (Slater *et al.*, 2018) we suggested that this finding may be explained by the 'sick quitter hypothesis', whereby individuals with deteriorating health either abstain or reduce their alcohol consumption (Shaper *et al.*,1988; Rimm and Moats, 2007; Frisher *et al.*, 2015). However, the sick quitter hypothesis has been disputed in the literature previously (Rimm and Moats, 2007). Antonelli Incalzi *et al.* (2005) also reported that polypharmacy was inversely associated with increasing alcohol consumption, thus providing support for our findings. The authors attributed the association to bias, by suggesting that individuals with good health were less likely to correct unhealthy lifestyle

decisions, such as excessive alcohol consumption, compared to individuals with poorer health (Antonelli Incalzi *et al.*, 2005). Although it was beyond the scope of our research to explore the association between polypharmacy and alcohol consumption in more detail, it would be prudent to take an individual's alcohol consumption into consideration when analysing polypharmacy data in the future.

Mixed findings have been reported regarding the association between smoking and polypharmacy previously (Rajska-Neumann *et al.*, 2005; Rieckert *et al.*, 2018). Smoking was not found to be associated with polypharmacy prevalence in our ELSA analyses, while an inverse association was reported in another study (Antonelli Incalzi *et al.*, 2005; Slater *et al.*, 2018). There are multiple diseases caused by smoking, for example chronic obstructive pulmonary disease (COPD), ischaemic heart disease and cancer (Wen *et al.*, 2020). Furthermore, individuals who reside in deprived areas are four times more likely to smoke, compared to individuals who reside in affluent areas (Hiscock *et al.*, 2012). While chronic conditions and lower wealth have been shown to be associated with smoking, these factors have also been shown to be associated with polypharmacy prevalence. Despite finding no significant association between polypharmacy and smoking in our ELSA analyses, further research into this association is required.

1.4 The benefits of 'appropriate' polypharmacy

Polypharmacy is often considered to be the prescribing of 'too many drugs' and as a consequence, most of the literature has focused on the negative health outcomes associated with polypharmacy, rather than examining the potential benefits (Cadogan *et al.*, 2016).

However, prescribing ‘many drugs’ for the management of chronic conditions may be beneficial, if all prescribing decisions are evidence based and all drug combinations have been optimised to meet patient needs (Cadogan *et al.*, 2016). The latter is often referred to as ‘appropriate polypharmacy’, and it has been suggested that appropriate polypharmacy has the potential to ‘improve an individual’s quality of life and in some cases, extend their life expectancy’ (Duerden *et al.*, 2013).

Several studies have examined whether interventions, such as regular medication reviews or deprescribing practices (section 1.4.4), can promote medicines optimisation and hence increase the prevalence of ‘appropriate polypharmacy’. Lavan *et al.* (2016) concluded that educational sessions for prescribers had the potential to reduce inappropriate prescribing in elderly patients with multiple chronic conditions. The authors suggested that this intervention should be targeted at newly qualified doctors, particularly those who are working in secondary care, as previous research has shown that this group of professionals make the most prescribing mistakes (Lavan *et al.*, 2016).

Prescriber training, along with medication reviews and patient education were also evaluated in a systematic review which aimed to determine whether these interventions improved appropriate polypharmacy among older people (Cooper *et al.*, 2015). Findings showed that all of these interventions reduced the number of inappropriately prescribed medicines, but it was not possible to determine whether the interventions resulted in clinically beneficial outcomes for the patients. The review also showed that there was significant heterogeneity in how medication appropriateness is measured (Cooper *et al.*, 2015). Some studies opted to use Beers Criteria (Samuel, 2015), while other studies used

the Medication Appropriateness Index (Hanlon and Schmader, 2013) or the Screening Tool of Older People's potentially inappropriate Prescription (STOPP) and Screening Tool to Alert doctors to Right indicated Treatments (START) to determine the appropriateness of prescribed medications (O'Mahony *et al.*, 2015), thus making it difficult to make comparisons between study outcomes. The authors recognised this limitation of their research and identified a need for a globally accepted, standardised tool for determining the appropriateness of prescribing in older people, particularly as the prevalence of polypharmacy is continuing to rise (Cooper *et al.*, 2015). The tools for determining medication appropriateness are discussed in more detail, in the subsequent sections of this chapter (section 1.4.1 Beers Criteria; section 1.4.2 Medication Appropriateness Index and section 1.4.3 the STOPP START criteria).

1.4.1 Beers Criteria

Beers Criteria is an explicit tool which identifies medications that are considered inappropriate for prescribing in older individuals (Samuel, 2015). The American Geriatric Society have been updating the criteria, according to the latest evidence, on a three-yearly basis since 2012 (Fixen, 2019). In 2012, the criteria were modified to include 53 medications which were considered to be harmful to older individuals. These medications were separated into the following three categories: 'medicines to avoid, medicines to avoid in certain diseases and syndromes and medicines which should be used with caution' (Abeyratne and Masud, 2014). In 2015, two new categories ('dose adjustments for drugs used in patients with renal impairment' and 'drug-drug interactions') were introduced (Salbu and Feuer, 2017). The criteria were reviewed in 2019 and 70 modifications were made (Fixen, 2019).

Although Beers criteria is commonly cited in the literature, it is associated with several limitations. First, the tool was developed in the United States of America (USA); therefore, some of the included medications are not available or commonly prescribed in Europe, thus limiting the applicability of the tool to practice in the UK (Laroche *et al.*, 2007; Pasina *et al.*, 2014). Second, the tool identifies medications which are inappropriate for older individuals; however, no alternative medications are suggested. Furthermore, mixed finding have been reported when the association between Beers criteria medications and clinically relevant health outcomes have been examined previously. Onder *et al.*, (2005) reported no significant association between Beers criteria medications and an increased length of hospital stay (OR 1.09; 95% CI: 0.95-1.25), after adjusting for gender, age, chronic conditions and the number of baseline medications, while Budnitz *et al.* (2007) reported that 3.6% of all emergency hospital admissions for adverse drug events were caused by Beers criteria medications. Finally, Lund *et al.* (2011) commented that the criteria only covered a small proportion of inappropriate prescribing practices and hence does not reflect current practice, for example only 17 drug-drug interactions were identified as potentially harmful to older people in the 2015 version of the criteria (Samuel, 2015). Multiple drug-drug interactions could potentially occur within polypharmacy regimens; therefore, the applicability of this tool for determining the appropriateness of polypharmacy is questionable.

1.4.2 Medication Appropriateness Index

Hanlon *et al.*, (1992) developed the Medication Appropriateness Index (MAI) to enhance the quality of prescribing in older people, by identify prescribing issues. The MAI consists of 10 explicit criteria which cover a variety of topics including product details, indications,

interactions, and therapy costs. Clinicians must answer all 10 questions before deciding whether a medication is 'appropriate, marginally appropriate or inappropriate' for an older individual (Hanlon and Schmader, 2013). Each question has a weighted value based on a 3-point Likert scale. Indication or effectiveness issues are given a score of 3, missing directions or dosage issues are given a score of 2 and issues associated with prescription duration and cost are given scores of 1 (Hanlon and Schmader, 2013). The scoring systems allows the level of inappropriateness to be quantified and each medication is given a score between 0 (appropriate) – 18 (inappropriate). The scores given to each medication are summated to provide the individual with an overall MAI score (Hanlon and Schmader, 2013).

The MAI has been predominantly used in hospital and nursing home settings previously (Crotty, 2004; Spinewine *et al.*, 2007; West *et al.*, 2013). West *et al.* (2013) implemented the tool in an Emergency Department of a Maltese hospital. Findings showed that 92% (n=115/125) of the cohort were taking at least one medication which was considered to have been inappropriately prescribed, according to the MAI, while the most common prescribing issues were incorrect dosages (18.5%) and incorrect directions (26%) (West *et al.,* 2013). Fewer studies have used the MAI to assess prescribing practices in primary care (Kassam *et al.,* 2003; Bregnhøj *et al.*, 2005). Kassam *et al.* (2003) suggested that this is because medication data is more readily available from drug charts in hospitals, compared to community settings.

The MAI could be applied to determine the appropriateness of polypharmacy regimens; however, the tool has some limitations. Burt *et al.* (2018) reported that a patient panel

identified drug efficiacy, drug interactions, contra-indications and medication adherence as the most important factors associated with polypharmacy appropriateness. Some of these factors, for example medication adherence and contra-indications, are not covered in the MAI. Underprescribing has also been shown to be associated with polypharmacy; however, this is another factor which is not covered by the existing criteria (Kuijpers *et al.*, 2008; Marcum and Gellad, 2013). Expert opinions were sought when developing the MAI criteria and the weighted scoring system; nevertheless, it is evident that clinicians prioritise different factors, in comparison to patients, when considering prescribing appropriateness in relation to polypharmacy (Volume *et al.*, 2011).

Finally, it is possible to assess the appropriateness of any medication using the MAI. However, it can be a time consuming process, with Whitman *et al.* (2016) estimating that the application of the criteria can take approximately ten minutes per medication. Consequently, this tool may not be practical for assessing the appropriateness of complex polypharmacy regimens.

1.4.3 Screening Tool of Older People's potentially inappropriate Prescription (STOPP) and Screening Tool to Alert doctors to Right indicated Treatments (START)

The STOPP START tool evolved as a result of a collaborative project between two departments at University College Cork, Ireland. The aim of the project was to create a tool which would improve the safety and quality of prescribing among the elderly population (Sreenan *et al.*, 2019).

The first version of this tool was published in 2008 (O'Mahony *et al.*, 2015). It comprised of 87 statements, with 65 clinical statements allocated to STOPP and the remaining 22 evidence-based statements allocated to START (Gallagher *et al.*, 2008). All statements were organised according to physiological systems, similar to the chapters within the British National Formulary (BNF) (Joint Formulary Committee, 2021).

The STOPP START tool was updated in 2015, and the number of clinical statements in STOPP increased to 80, while the number of evidence-based statements in START increased to 34 (O'Mahony *et al.*, 2015). Currently, the criteria only address issues associated with prescribed medications; therefore, excluding any issues associated with over-the-counter (OTC) medicines or herbal products (Herefordshire Clinical Commissioning Group, 2016).

In addition to making recommendations about which prescribed medications should be started or stopped in older people, the tool covers topics such as drug-drug interactions (for example 'stop Non-Steroidal Anti-Inflammatory Drugs with concurrent oral corticosteroids, without concurrent, appropriate gastroprotection'), drug-disease interactions (for example 'stop thiazide diuretic with recent or concurrent gout') and lifestyle advice (for example 'provide activity, fitness or exercise advice for patients with osteoarthritis and lower back pain') (Herefordshire Clinical Commissioning Group, 2016; Aziz *et al.*, 2018). Furthermore, the tool recommends alternative medications in the STOPP criteria, unlike Beers criteria (Whitman *et al.*, 2016).

The superiority of the STOPP/START tool for determining prescribing appropriateness, compared to the Beers criteria, has been shown in several studies. Gallagher and O'Mahony (2008) reported that the STOPP criteria identified a greater proportion of inappropriately prescribed medications associated with hospital admissions, compared to Beers criteria. Findings also showed that the STOPP criteria identified more patients who had an increased risk of falls due to inappropriate prescribing, compared to Beers criteria (Gallagher and O'Mahony, 2008). Hamilton *et al.* (2011) reported similar findings and concluded that the STOPP criteria were better at identifying prescribed medications which caused hospital admissions as a result of adverse drug events, compared to Beers criteria.

In contrast, Verdoorn *et al.* (2015) showed that only a small proportion (19%, n=314/1656) of drug related problems, such as 'inappropriate drug selected' or 'no indication apparent', were identified when the STOPP and START criteria were applied during medications reviews (n=457) conducted by community pharmacists. While these findings demonstrated that the STOPP and START criteria could be easily implemented in practice, it also showed that the criteria do not comprehensively cover all inappropriate prescribing practices or prescribing omissions (Lönnbro and Wallerstedt, 2017).

One strength of the STOPP START tool is that it has been applied across a variety of settings previously, including primary care (Ryan *et al.*, 2009; Yayla *et al.*, 2013), secondary care (Curtin *et al.*, 2019) and nursing homes (Ryan *et al.*, 2013; Khodyakov *et al.*, 2017). However, the tool is also associated with some limitations. First, the proportion of inappropriately prescribed medications and omissions, according to the STOPP/START criteria, have been reported in these studies; however, none of the studies have

prospectively examined whether the criteria are linked to improvements in long-term health outcomes (Whitman *et al.*, 2016; Rakesh *et al.*, 2017). Furthermore, few studies have utilised the STOPP START criteria to examine the appropriateness of polypharmacy regimens, thus identifying a potential area for future research (Verdoorn *et al.*, 2015).

1.4.4 Deprescribing and other interventions to achieve appropriate polypharmacy

Appropriate polypharmacy may be achieved by removing all unnecessary drugs or those with no valid clinical indication from a patient's medication regimen. This practice is often referred to as deprescribing (Thompson and Farrell, 2013). Page *et al.* (2016) conducted a systematic review to determine whether deprescribing reduced mortality in older adults with polypharmacy. Findings showed that deprescribing in polypharmacy was associated with a reduction in mortality (OR 0.32; 95% CI: 0.17-0.60), in non-randomised studies, but no significant association was found in randomised studies (OR 0.82; 95% CI: 0.61-1.11). The difference in findings could be attributed to differences in the medications being deprescribed (type and number), study settings, participant demographics and varying levels of statistical adjustments. Despite the mixed findings reported, the authors concluded that deprescribing may be a beneficial intervention in older people with polypharmacy; however, the longer-term benefits of deprescribing in polypharmacy require further exploration (Page *et al.*, 2016; Chang *et al.*, 2020).

Other studies have also examined whether the application of deprescribing tools can encourage appropriate polypharmacy. McIntyre *et al.* (2017) developed a deprescribing tool to identify five groups of medications (diuretics, proton-pump inhibitors, statins,

alpha-blockers and quinine) which were considered to be inappropriate for haemodialysis patients. All study participants had their medication regimens screened using the deprescribing tool, over a six-month period. Results showed that 71% (n=171/240) of the participants were taking at least one medication which was considered to be inappropriate, and consequently 78% of these medicines were deprescribed during the patients visit. By the end of the study period, over half of the participants (57%) were taking fewer medications compared to baseline. No adverse effects were reported, and the researchers concluded that their results provided evidence to support deprescribing, particularly among polypharmacy patients. However, it was beyond the scope of the study to identify barriers which may hinder deprescribing in individuals with polypharmacy (McIntyre *et al.*, 2017).

Harriman *et al.* (2014) addressed this research gap by conducting a qualitative study, involving prescribers who predominantly cared for older individuals. The prescribers discussed their concerns about deprescribing, including their reluctance to deprescribe a medication if it was started by another practitioner, the influence of organisational factors on deprescribing practices and the fear of causing an adverse drug event by stopping medications. One-quarter of the prescribers reported that they were reluctant to deprescribe medications, while over half of the prescribers felt that the current approach to deprescribing was inconsistent and required improvement. Only 30 prescribers took part in this study; therefore, further research is required to determine whether a larger group of practitioners share the same views about deprescribing practices (Harriman, *et al.*, 2014). Future research could also examine patient perceptions towards deprescribing, as these individuals are often overlooked when deprescribing tools and clinical guidelines are produced (Dowden, 2017).

Recently, researchers in Ireland have been attempting to develop several more interventions to improve the appropriateness of polypharmacy in primary care (Cadogan *et al.*, 2016). Evidence for these interventions has been gathered systematically, and the researchers have incorporated established behavioral theories into their intervention designs. The interventions have been designed to target patients, pharmacists, and general practitioners (GPs) respectively, and each intervention has been tested for feasibility. The results from the feasibility studies are being evaluated, before these interventions are tested on a larger scale (Cadogan *et al.*, 2016). Further research is also required to determine whether these interventions result in clinically beneficial health outcomes for individuals with polypharmacy.

1.5 The consequences of 'inappropriate' polypharmacy

This section will examine some of the consequences associated with 'inappropriate' polypharmacy, including adverse drug reactions (section 1.5.1), an increased risk of falls (section 1.5.2), which can result in hospitalisations (section 1.5.3) and mortality (section 1.5.4), particularly among older individuals and those with multiple chronic conditions (Maher *et al.*, 2014).

1.5.1 Adverse drug reactions

Polypharmacy increases the opportunity for drug-drug interactions to occur and sometimes these interactions can have harmful consequences for an individual. Adverse drug reactions (ADRs) are associated with morbidity, reduced quality of life, and mortality. Furthermore,

ADRs have been shown to increase the pressure on the NHS, in terms of service provision and costs (Patel *et al.*, 2007; Pourpak *et al.*,2008; Frontier Economics, 2014).

Findings from a prospective cohort study showed that individuals with polypharmacy (defined as five or more concomitant medications) were twice as likely to experience ADRs, compared to individuals who took between one and four regular medications (Ahmed *et al.*, 2014). Similarly, Shah and Hajjar (2012) reported that the risk of ADRs increased from 58% in individuals taking five prescribed medications to 82% in individuals taking seven or more prescribed medications.

Pirmohamed *et al.* (2004) investigated which medications were most commonly implicated in ADRs. The authors reported that the administration of diuretics (27.3%, n=334/1225) and non-steroidal anti-inflammatory drugs (NSAIDs) (29.6%, n=363/1225), were most common in ADRs. Other medications implicated in ADRs included anticoagulants (10.5%, n=129/1225), ACE inhibitors (7.7%, n=94/1225), antidepressants (7.1%, n=87/1225), beta-blockers (6.8%, n= 83/1225) and opiates (6.0%, n=73/1225) (Pirmohamed *et al.*, 2004). Similarly, Howard *et al.* (2007) identified four groups of medications (antiplatelets, diuretics, NSAIDs and anticoagulants) which accounted for over 50% of all hospital admissions associated with ADRs, thus providing support for the previous findings.

There are varying percentages reported in the literature regarding the proportion of ADRs which resulted in hospital admissions. These percentages range from 0.16% to 15.7%, with

a median value of 5.3% (Kongkaew *et al.*, 2008). Older people and those with pre-existing conditions are most likely to be admitted to hospital following an ADR (Lavan *et al.*, 2016). The pharmacokinetic and pharmacodynamic changes associated with ageing have been attributed to the increased susceptibility of older people to ADRs. These changes will be examined in more detail in section 1.5.1.1.

1.5.1.1 The pharmacokinetic and pharmacodynamic changes associated with ageing

The literature regarding the impact of ageing on drug absorption is conflicting. Bressler and Bahl (2003) reported that ageing reduces gastric blood flow and gastric motility which may be beneficial because it increases the time for drug absorption, while Russel (2010) stated that ageing causes a decline in drug transporter function, thus reducing overall drug absorption. Other authors have discussed how drug absorption can be influenced by a reduction in gastric acid secretion, which increases gastric pH levels and delays the dissolution and absorption of oral medications, such as anti-epileptics (Popović, *et al.*, 1995; Currie, 2011). One possible explanation for the conflicting literature about the impact of ageing on drug absorption could be that older individuals are often excluded or underrepresented in clinical trials; therefore, there is a lack of evidence regarding the absorption of medications in this group (Shenoy and Harugeri, 2015). Furthermore, it is not always possible to predict all geriatric health outcomes based on the data gathered from adults aged below 65, due to the pharmacokinetic and pharmacodynamic changes associated with ageing (Shenoy and Harugeri, 2015).

Drug distribution also changes with age, due to increased amounts of body fat, a decline in lean body mass and a reduction in total body water (Shi and Klotz, 2011). As a result, water soluble drugs (e.g. theophylline) will have a smaller volume of distribution compared to fat soluble drugs (e.g. diazepam) (Mangoni and Jackson, 2003). Fat soluble drugs will have a longer half-life in older people; therefore, dose adjustments may be required to avoid adverse effects, such as prolonged sedation, which could lead to falls and an increased demand on healthcare services (de Jong *et al.*, 2013).

An association between increasing age and declining hepatic function has been reported in the literature (Anantharaju *et al.*, 2002; Mangoni and Jackson, 2003; Ruskin and Linnebur, 2014). Ruskin and Linnebur (2014) quantified the decline in hepatic function and reported that it reduced by 1% each year, once an individual has reached the age of 40. One posible explanation for the decline in hepatic function could be that hepatic size and perfusion rates reduce with age (Anantharaju *et al.*, 2002). The impact of ageing on first pass metabolism, in relation to specific medications, has also been examined previously. Some medications, such as verapamil (Vogelgesang *et al.*, 2004), propranolol (Lalka *et al.*,1993) and carbamazepine (Shi and Klotz, 2011) require extensive first pass metabolism, while other medications, such as angiotensin-converting enzyme inhibitors require activation by the liver to exert their therapeutic effects (Mangoni and Jackson, 2003). Consequently, medications which have not been successfully metabolised or activated by the liver are likely to accumulate, thus increasing the likelihood of ADRs in older individuals.

In addition to changes in drug distribution and a decline in hepatic function, an age-related decline in glomerular filtration has been reported (Weinstein and Anderson, 2010). This

may affect the renal clearance of many drugs, including lithium (Hewick *et al.*, 1977), methotrexate (Bischoff *et al.*, 1971) and indomethacin (Oberbauer *et al.*, 1993), resulting in an accumulation of these medications in older individuals. An accumulation of methotrexate could induce bone marrow suppression, pulmonary toxicity or hepatic toxicity, while an accumulation of lithium could cause circulatory failure, seizures, coma or mortality (Hewick *et al.*, 1977).

The impact of ageing on pharmacodynamics was examined in a systematic review of 69 studies (Bowie and Slattum, 2007). Findings showed that as individuals age, they become more pharmacodynamically sensitive to medications, in particular to medications which act on the central nervous system (CNS) and the cardiovascular system (Bowie and Slattum, 2007). Mangoni and Jackson (2003) supported these findings. Furthermore, our analyses into the composition of polypharmacy regimens, involving data from 7730 participants from the English Longitudinal Study of Ageing, showed that 90.6% of the participants with polypharmacy were taking cardiovascular medications, while 57.8% of all participants with polypharmacy were taking CNS medications (Slater *et al.*, 2020). Therefore, older people will be more susceptible to the adverse events associated with these medications, due to pharmacodynamic changes, and the likelihood of adverse events may be accentuated in older people with polypharmacy.

1.5.2 Falls

The NHS spends approximately £2.3 billion per annum treating individuals who have fallen (NICE, 2013; Dhalwani *et al.*, 2017). In addition to the financial implications associated with falls, there are psychological and physical consequences for the individual who has fallen. Psychological consequences include a reduction in an individual's quality of life or the loss of self-confidence; while the physical consequences of falls include fractures, morbidity, hospitalisations, and mortality (Hammond and Wilson, 2013).

Older individuals are more susceptible to falls, and the cause is often multifactorial. Issues such as poor balance, visual impairment, environmental hazards, and polypharmacy, have been identified as potential risk factors for falls (PHE, 2020). The association between polypharmacy and falls has been examined previously; however, mixed findings have been reported (Lawlor, 2003; Ziere *et al.*, 2006; Dhalwani *et al.*, 2017; Zia, *et al.*, 2017).

Analysis of wave 6 and wave 7 ELSA data showed that individuals with polypharmacy (5 to 9 concomitant medications) had a 21% higher rate of falls, compared to individuals without polypharmacy (Dhalwani *et al.*, 2017). The rate of falls was accentuated in individuals with excessive polypharmacy (≥10 concomitant medications) (50% higher rate of falls). In this study, data were stratified by polypharmacy status (i.e., the number of concomitant medications), but not by the type of medication. The authors acknowledged this limitation of their research and suggested that future research should examine the specific combinations of medications within polypharmacy regimens, to identify which

combinations most commonly contribute towards falls in older individuals (Dhalwani *et al.*, 2017).

Wong *et al.* (2016) complemented these findings (Dhalwani *et al.*, 2017) and reported an association between polypharmacy and falls. However, other studies have concluded that the association only exists if certain medications are present within polypharmacy regimens (Ziere *et al.*, 2006; Zia, *et al.*, 2017). Ziere *et al.* (2006) reported that medications which acted on the central nervous system (e.g., benzodiazepines), cardiovascular system (e.g., potassium-sparing diuretics) and the musculoskeletal system (e.g., oxicams) increased the risk of falls in older individuals, when prescribed as part of a polypharmacy regimen. Zia *et al.* (2017) reported similar findings. Both studies (Ziere *et al.*, 2006; Zia, *et al.*, 2017) adjusted their analyses for a number of covariates, including morbidities. However, the results may have been influenced by residual confounding because conditions, such as chronic obstructive pulmonary disease (COPD), which has been shown to be associated with falls previously (Lawlor, 2003; Roig *et al.*, 2011), were not included in the adjusted models (Ziere *et al.*, 2006; Zia, *et al.*, 2017). Therefore, it is difficult to determine whether the medications within the polypharmacy regimens were independently associated with falls, or whether the falls were as a result of other morbidities, which were not adjusted for in the analyses.

There may be other explanations for the differing findings reported when the association between polypharmacy and falls has been examined previously. First, different definitions were used to define the study outcome. For example, Lawlor (2003) and Zia *et al.* (2017) defined falls as ‘two or more falls’ in the past year, whereas Ziere *et al.* (2006) defined falls

as ‘one or more falls’ in the past year. Furthermore, Dhalwani *et al.* (2017) used a different time frame to define falls, and asked participants to self-report if they had fallen within a specified two-year period.

Different definitions of polypharmacy were also used in these studies (Lawlor, 2003; Ziere *et al.*, 2006; Roig *et al.*, 2011; Dhalwani *et al.*, 2017; Zia, *et al.*, 2017). Most studies (Lawlor, 2003; Dhalwani *et al.*, 2017; Zia *et al.*, 2017) defined polypharmacy as ‘5 or more’ medications, while Ziere *et al.* (2006) defined polypharmacy as ‘four or more medications’. When different definitions of polypharmacy are used in research, different rates of falls are reported (Dhalwani *et al.*, 2017). Polypharmacy (defined as ≥4 medications) was associated with an 18% higher rate of falls in older individuals, compared to non-polypharmacy. However, the reported rate of falls increased to 21%, 31% and 39%, when the definition of polypharmacy was changed to ≥ 5 medications, ≥ 6 medications and ≥ 7 medications, respectively (Dhalwani *et al.*, 2017).

Consequently, it is difficult to make comparisons between study results when different criteria have been used to assess the outcome of interest (i.e., the incidence of falls), and different definitions have been used to define polypharmacy. Further research is also needed to establish whether polypharmacy is independently associated with falls, or whether the presence of certain medications or combinations within a polypharmacy regimen is a better predictor for determining an older individual’s risk of falling.

1.5.3 Hospitalisations

Hospitalisations are one of the most commonly studied adverse outcomes in polypharmacy research, and most studies have reported a significant association (Fried *et al.*, 2014). One explanation offered for the association is that polypharmacy increases the opportunity for prescribing errors, high risk prescribing and drug-drug interactions to occur, thus increasing the likelihood of hospital admissions or readmissions (Wise, 2013; Abe *et al.*, 2016).

Despite reporting a positive association between polypharmacy and hospital admissions, there is heterogeneity in the samples used to examine the association, in terms of sample size and participant demographics (Fried *et al.*, 2014). For example, Beer *et al.* (2011) conducted a prospective cohort study to determine whether polypharmacy was associated with adverse outcomes, including hospital admissions, in men. Data from 4,260 male participants were analysed, and polypharmacy was found to be significantly associated with hospital admissions (HR 1.04, 95% CI; 1.03-1.06, $p<0.01$), after adjusting for age, body mass index, education, smoking, hypertension, and level of physical activity. However, these findings may not be generalisable to women, as gender differences in hospital admissions rates have been reported previously (Baibergenova *et al.*, 2006; Rodenburg, *et al.*,2011).

Other studies have examined hospital readmissions, in relation to polypharmacy. Logue *et al.* (2016) reported that individuals who took more than six regular medications when admitted to hospital were twice as likely to be readmitted in the 30-days following discharge, compared to individuals who took fewer regular medications. Abe *et al.* (2016)

also reported that polypharmacy was associated with a two-fold increased risk of hospital readmissions (adjusted OR 2.12, 95% CI: 1.03-4.43, p=0.04). Although Picker *et al.* (2015) supported these findings, a lower adjusted odds ratio was reported (adjusted OR 1.26; 95% CI: 1.17-1.36).

There were differing levels of adjustments in the statistical models, in the studies (Picker *et al.*, 2015; Abe *et al.*, 2016; Logue *et al.*, 2016), and this may have contributed to the differing odds ratios reported. For example, Abe *et al.* (2016) and Logue *et al.* (2016) adjusted their models for age, gender, in addition to other covariates and reported similar findings, whereas Picker *et al.* (2015) adjusted their models for 'congestive heart failure, peripheral valvular disease, metastatic cancer, cirrhosis, haemoglobin levels and previous emergency department admissions', but did not adjust for participant age or gender. These studies were also cross-sectional; therefore, it is not possible to determine the direction of causality from the data, nor is it possible to determine whether polypharmacy is a marker of ill health, rather than the underlying cause of hospitalisations (Chang *et al.*, 2020).

Chang *et al.* (2020) recognised some of the limitations associated with the previous research in this subject area, such as the varying levels of adjustments in the statistical models and the heterogeneous study populations. To advance the literature, the authors examined the association between polypharmacy and hospital admissions, using two different statistical approaches, in over 3 million individuals aged over 65 (Chang *et al.*, 2020). First, logistic regression models were adjusted for participant age, gender, geographical location and co-morbidities, and polypharmacy (≥5 prescribed medications) was found to be associated with hospital admissions (adjusted HR 1.18; 95% CI; 1.18-1.19) (Chang *et al.*, 2020).

Following this, the authors used propensity score matching, to match study participants by baseline characteristics. Polypharmacy status was the only measured difference between each matched pair. Over one million (n=1,070,337) matched pair data were analysed, and the hazard ratio for the association between polypharmacy and hospital admissions reduced to 1.16 (95% CI: 1.16-1.17) (Chang *et al.*, 2020).

This large-scale study (Chang *et al.*, 2020) showed that polypharmacy was associated with hospital admissions, in older individuals; however, further research is needed to determine whether all polypharmacy regimens are associated with hospitalisations, or whether the presence of certain medications within a polypharmacy regimen increases the likelihood of an admission or readmission. Furthermore, individuals are admitted to hospitals for a variety of reasons, such as planned operations or emergency treatment, so research is needed to determine whether polypharmacy is associated with all-cause hospital admissions, or only specific types of admissions.

1.5.4 Mortality

Mortality is another commonly studied outcome in polypharmacy research. Previously, most studies have reported significant associations between polypharmacy and mortality, although several studies have found no association (Fried *et al.*, 2014).

Leelakanok *et al.* (2017) conducted a systematic review and meta-analysis to examine the association between polypharmacy and mortality. Overall, there were 47 studies eligible for

inclusion in the review. In comparison to participants who were prescribed between one and four medications, participants who were prescribed five medications were 31% more likely to die. The risk of mortality increased to 59% in participants prescribed between six and nine medications and was greatest (96%) in participants who had been prescribed ten or more medications. Based upon their findings, Leelakanok *et al.* (2017) concluded that polypharmacy was associated with increased risk of mortality; however, the authors also commented that this conclusion should be cautiously interpreted, as individuals with poor health are often prescribed more medications to manage their conditions, so polypharmacy may be a marker of ill health, rather than the cause of mortality.

The limitations of the included literature should also be considered when interpreting the findings from the systematic review and meta-analysis (Leelakanok *et al.*, 2017). First, there were different definitions of polypharmacy used in the studies, including '4 medicines, 5 medicines or between 6 and 9 medicines'. This may have impacted the results reported, as discussed previously in section 1.5.2 (Dhalwani *et al.*, 2017). Furthermore, polypharmacy data were often obtained by asking participants to self-report; however, this approach may have resulted in the provision of inaccurate information due to recall bias, and the resultant effect may have been the misclassification of data (Drieling *et al.*, 2016). Finally, there were differences in statistical adjustments in the included studies. Most studies adjusted their models for age and gender, but the level of adjustment varied for morbidities, and hence it is not possible to determine whether it is the underlying morbidities, or polypharmacy, that is associated with mortality.

To address the issue of confounding, a recent study examined the association between polypharmacy and mortality in older individuals, using propensity score matching. Participants were matched by baseline characteristics, including morbidities, and the results showed that individuals with polypharmacy had a 25% greater risk of mortality, compared to participants with no polypharmacy, in the matched sample (Chang *et al.*, 2020).

In contrast to the literature, Pozzi *et al.* (2010) initially reported that participants with polypharmacy were twice as likely to die, compared to participant with no polypharmacy (unadjusted HR 2.21; 95% CI 1.69-2.91, $p<0.01$), following their unadjusted analyses. However, the significant hazard ratio diminished (adjusted HR 1.2; 95% CI 0.89-1.6, $p=0.24$), when the models were adjusted for participant age, gender, chronic conditions, and functional status. Pozzi *et al.* (2010) acknowledged that their mortality findings were conflicting, in comparison to the literature, and several explanations were suggested. First, it is possible that previous studies may have found an association due to residual confounding. Second, data were provided by participants living in a rural area in Tuscany, Italy, so it is possible that their findings may not be generalisable to a wider population. Finally, the 'small sample size (n=568) and low statistical power' may have impacted the interpretation and reliability of the results (Button *et al.*, 2013).

Most studies have reported that polypharmacy is associated with mortality in older individuals (Fried *et al.*, 2014; Leelakanok *et al.*, 2017; Chang *et al.*, 2020). One common limitation of the previous research is the issue of confounding, particularly in relation to morbidity. To minimise the effect of this limitation in future polypharmacy research, statistical methods, such as propensity score matching, could be implemented. This thesis

used propensity score matching to reduce the risk of confounding, and this has been discussed in section 3.11.

1.6 The composition of polypharmacy

Few studies have examined the composition of polypharmacy regimens (Bjerrum *et al.*, 1998; Wastesson *et al.*, 2018; Slater *et al.*, 2020). Wastesson *et al.* (2018) conducted a cross-sectional analysis to examine the composition of polypharmacy regimens taken by older individuals (≥75 years), in Sweden. The ten most commonly prescribed drug classes in polypharmacy regimens were identified. Of the participants with polypharmacy (n=376,412), 61.1% were prescribed antithrombotics, while 51.9% were prescribed beta-blockers. Other cardiovascular medicines were common in polypharmacy regimens, including lipid regulating drugs (38.5%), calcium channel blockers (28.8%), diuretics (28.1%) and angiotensin converting enzyme inhibitors (25.4%). Other types of medicines, including analgesics (32.3%), hypnotics (27.6%), and gastro-protective drugs (27.8%) were also commonly prescribed for older people with polypharmacy (Wastesson *et al.*, 2018). One conclusion derived from this study was that only a few drug classes make a significant contribution to the nationwide prevalence of polypharmacy. To address the issue of polypharmacy prevalence in older people, the authors suggested that these drug classes could be deprescribed (Wastesson *et al.*, 2018). However, this suggestion may be clinically inappropriate, and challenging to implement at a nationwide level.

The findings from this study (Wastesson *et al.*, 2018) have been supported by several studies previously. Linjakumpu *et al.* (2002) reported that cardiovascular medications, in

addition to CNS medications, are the most commonly prescribed medications in polypharmacy regimens. Similarly, Bjerrum *et al.* (1998) conducted a cross-sectional study to examine the types of medications associated with polypharmacy regimens. There were 5,443 participants with polypharmacy, and 85% (n=4,630) were taking cardiovascular medicines. These medications were often co-prescribed with analgesics and respiratory medicines. Analgesics were the second most commonly prescribed group of drugs for participants with polypharmacy (37.5%, n=2,045), and these medications were often prescribed alongside respiratory medications and anti-rheumatic medications.

Bjerrum *et al.* (1998) also examined the combinations of medications in polypharmacy regimens, at drug class level. A total of 3,980 different drug class combinations were recorded. The ten most frequent drug class combinations accounted for only 3% of all combinations. The latter finding suggested that there was significant heterogeneity in the combination of drug classes within polypharmacy regimens; however, no explanation for the heterogeneity was offered by the authors (Bjerrum *et al.*, 1998). Furthermore, it is not possible to compare these findings to the literature, as no other data are available. The research team have identified that there is a need to explore medication combinations in polypharmacy regimens, and research is currently being planned to address the gap in the literature.

The research team conducted another study (Slater *et al.*, 2020), alongside this thesis, to advance the literature regarding the composition of polypharmacy. The purpose of this research was to identify the most common central nervous system (CNS) drug classes taken

by older individuals (≥50 years). Following this, the associations between polypharmacy and the most common CNS drug classes were examined in detail (Slater, *et al.*, 2020).

Data from 7,730 participants in Wave 6 (2012-2013) of the English Longitudinal Study of Ageing were analysed (Slater *et al.*, 2020). Findings showed that 'non-opioid analgesics, opioid analgesics, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)' were the most common CNS drug classes taken by individuals aged over 50. Medication data in ELSA are coded according to the British National Formulary (BNF) chapters and subsections; however, the coding does not differentiate between specific medications within a drug class (Joint Formulary Committee, 2021). This limitation may need to be considered in future research which examines the composition of medication regimens taken by older individuals (Slater *et al.*, 2020).

Our analyses also showed that polypharmacy was significantly associated with opioid analgesics (adjusted OR 5.71; 95% CI: 4.29-7.61) and non-opioid analgesics (adjusted OR 3.80; 95% CI: 3.25-4.44) (Slater *et al.*, 2020). Although an association between polypharmacy and analgesics has been reported previously, this was the first study to quantify the extent of the association. This association is often attributed to pain co-existing with other long-term conditions; however, this may not entirely explain why there is a three to four-fold difference in the likelihood of taking analgesics in polypharmacy regimens, compared to non-polypharmacy regimens (Gerlach *et al.*, 2017; Wastesson *et al.*, 2018).

Polypharmacy was significantly associated with TCAs (adjusted OR 3.11; 95% CI: 2.43-3.98), and SSRIs (adjusted OR 2.30; 95% CI: 1.83-2.89) (Slater *et al.*, 2020).

However, it was not possible to compare the polypharmacy and antidepressant findings in our study, to the literature, as a recent systematic review (Stuhec and Serra-Mestres, 2018) showed that 'there is almost no data available on antidepressant prescribing in older adults treated with polypharmacy'. This highlights an area for future research, and thus, our findings could be used as a baseline for the research.

1.7 Chapter Summary

Polypharmacy prevalence has been increasing over the past decade, due to a growing ageing population and rising numbers of individuals with chronic conditions and multi-morbidities (Guthrie *et al.*, 2015). Despite the increasing prevalence, there is significant heterogeneity in the definitions of polypharmacy used within the literature (Duerden *et al.*, 2013; Masnoon *et al.*, 2017). Most studies have opted for an arbitrarily selected numeric threshold to define polypharmacy; however, these thresholds are not suitable for determining the clinical appropriateness of the medications within polypharmacy regimens (Masnoon *et al.*, 2017). The numeric thresholds used to define polypharmacy also vary between studies, making it difficult to compare study outcomes. Therefore, a globally accepted definition of polypharmacy is required.

Polypharmacy is often considered to be the prescribing of 'too many drugs' and as a consequence, most of the literature has focused on the negative health outcomes associated with polypharmacy (for example adverse drug reactions, hospitalisations, falls and mortality), rather than examining the potential benefits of 'appropriate' polypharmacy (Cadogan *et al.*, 2016). At present, there is no gold-standard approach to reliably determine

the appropriateness of polypharmacy, although several tools are available to assess the appropriateness of individual medications within polypharmacy regimens.

Few studies have examined the composition of polypharmacy regimens in detail. Medications which act on the central nervous system and cardiovascular system have been shown to be commonly prescribed within these regimens (Bjerrum *et al.*, 1998; Linjakumpu *et al.*, 2002; Wastesson *et al.*, 2018; Slater *et al.*, 2020). Furthermore, these types of medications have been shown to be independently associated with adverse outcomes, for example cardiovascular medications are frequently implicated in falls, and hospital admissions (Pirmohamed *et al.*, 2004; Howard *et al.*, 2007; Gribbin *et al.*, 2010).

The literature also showed that polypharmacy is associated with some chronic conditions, including cardiovascular conditions. However, the term 'cardiovascular conditions' is broad and is often used by authors to encompass a wide range of conditions, for example Aubert *et al.* (2016) excluded hypertension in their definition of cardiovascular conditions, while Nobili *et al.* (2011) included hypertension in their definition. To address the heterogeneity surrounding the term 'cardiovascular conditions', this thesis will focus on one cardiovascular condition, atrial fibrillation (AF).

1.7.1 Atrial fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia in England, affecting approximately 1.4 million adults (Lacoin *et al.*, 2017). The cause of atrial fibrillation is not fully understood; however, individuals with other morbidities, such as hypertension, thyroid

disorders, and diabetes, have a greater susceptibility to developing the condition (NHS, 2021a). Atrial fibrillation is also an independent risk factor for adverse outcomes, including ischemic stroke, congestive heart failure and other cardiovascular related complications (Lacoin *et al.*, 2017). The most reported symptoms of AF are palpitations, chest pain, shortness of breath, fatigue and feeling faint; however, some individuals with AF will be asymptomatic (NHS, 2021a). When an AF diagnosis is made, it will be classified according to the frequency and pattern of arrythmias. There are several different AF classifications: paroxysmal AF (the episode lasts for less one week and sinus rhythm resumes without treatment), persistent AF (the episode lasts for over one week and requires cardioversion treatment), and permanent AF (the episode does not resolve following cardioversion interventions) (NICE, 2021g). The treatment options available for individuals with AF, are discussed in the subsequent paragraphs of this section.

Atrial fibrillation was selected for this research, for several reasons. First, it is the most common sustained cardiac arrhythmia in England. The condition is most prevalent among males and like polypharmacy, the prevalence of AF rises with increasing age (3.7%-4.2% AF prevalence in individuals aged 60-70 years versus 10.0% to 17.0% prevalence in individuals aged above 80 years) (Zoni-Berisso *et al.*, 2014). As a result of the rising prevalence of AF, the NHS is facing an increased demand on resources (Morillo *et al.*, 2017). Second, AF is 'not usually life-threatening'; therefore, it is possible to study mortality as an outcome (NHS, 2021a). Furthermore, there are a variety of pharmacological treatment options available which can improve an individual's AF prognosis. Anticoagulants, including oral direct factor Xa inhibitors (e.g., apixaban) and oral direct thrombin inhibitors (e.g., rivaroxaban), can be prescribed for stroke prevention. Beta-blockers (e.g., atenolol) or rate-limiting calcium channel blockers (e.g., verapamil) can be prescribed to control ventricular rate, while antiarrhythmics (e.g., flecainide or

amiodarone) can be prescribed to restore and maintain regular sinus rhythm (NICE, 2021a). However, the use of multiple drug classes in the management of AF increases the likelihood of polypharmacy. Other treatment options are also available for the management of AF, including catheter ablation and electrical cardioversion (NHS, 2021a). Finally, atrial fibrillation was selected because it commonly co-exists with other conditions, thus further increasing the likelihood that individuals with AF will experience polypharmacy or hyper-polypharmacy (LaMori *et al.*, 2013; Sankaranarayanan *et al.*, 2015).

In the next chapter of this thesis (Chapter 2), a systematic review will be presented which examines the adverse outcomes associated with polypharmacy, in individuals with atrial fibrillation (AF).

Chapter 2: Systematic Literature Review

2.1 Introduction

This chapter presents a systematic literature review which examines the adverse outcomes associated with polypharmacy, in individuals with atrial fibrillation (AF). The aim of this systematic review is presented in section 2.2, along with the review objectives, research question and rationale for research. All preliminary research is discussed in section 2.3. The systematic literature review methodology is presented in section 2.4 and includes information about the search strategy (section 2.4.1), the literature inclusion and exclusion criteria (section 2.4.2), literature screening (section 2.4.3), data extraction (section 2.4.4), the quality and risk of bias assessments (section 2.4.5) and Google Alerts (section 2.4.6). The systematic review results are presented in section 2.5. A narrative review of the key findings is provided in section 2.6. The quality and risk of bias assessment results are presented in section 2.7. Key findings from the systematic review are discussed in section 2.8. Finally, a chapter summary is provided in section 2.9.

2.2 Aim, objectives and research question

The aim of this systematic review was to answer the following research question:

Is polypharmacy associated with adverse outcomes in individuals with atrial fibrillation?

To achieve the aim, this systematic review had the following objectives:

1. To search a variety of sources, for example bibliographic databases, websites, and reference lists, to identify all literature which has sought to determine whether polypharmacy is associated with adverse outcomes in individuals with AF, and to extract the relevant information.
2. To determine the quality and risk of bias of all literature included within the systematic review, using validated tools.
3. To discuss the key findings of the literature, whilst taking methodological strengths and limitations into account.

There have been several systematic reviews previously, which have examined the associations between polypharmacy and adverse outcomes, such as mortality (Leelakanok *et al.*, 2017) and recurrent falls (Ming and Zecevic, 2018). However, these reviews have examined polypharmacy and adverse outcomes in the general population, rather than focusing on individuals with atrial fibrillation.

A search of the Cochrane Database of Systematic Reviews identified five systematic reviews which examined outcomes in individuals with AF. One review evaluated the effect

of educational interventions on anticoagulation control in individuals with AF (Clarkesmith *et al.*, 2017), while another review examined the risk of bleeding associated with Direct-Acting Oral Anticoagulants (DOACs) and vitamin k antagonists (VKA) when prescribed for individuals with AF (Sharma *et al.*, 2015).The remaining three systematic reviews focused on the efficacy of catheter ablation, compared to pharmacological management in AF (Chen *et al.*, 2012; Nyong *et al.*, 2016; Huffman *et al.*, 2017). Despite examining outcomes in individuals with AF, these reviews did not examine the outcomes in relation to polypharmacy.

The UK population is growing, and individuals are living longer (Angele, 2018). Our previous research into the factors associated with polypharmacy showed that polypharmacy prevalence increases with age (Slater *et al.*, 2018). The prevalence of AF has also been shown to increase with age (Wasmer *et al.*, 2017).Therefore, it is important to understand the outcomes associated with polypharmacy, in individuals with AF, as these outcomes may place increasing demand on healthcare services across the UK.

2.3 Preliminary research

Several preliminary searches were conducted prior to this systematic review. The purpose of this preliminary work was to develop search terms, identify appropriate databases for literature searching and to pilot the quality assessment and risk of bias tools prior to conducting the systematic review.

2.3.1 Developing search terms

The following three search terms were initially identified from the research question: polypharmacy, atrial fibrillation, and outcomes. Synonyms for each of the terms were listed, along with any commonly used acronyms, for example AF. Other search terms were identified through literature searching, for example the different terms used to describe polypharmacy were detailed in a systematic review by Masnoon *et al.* (2017). The U.S National Library of Medicine catalogue was also accessed to identify Medical Subject Headings (MeSH) terms for polypharmacy, atrial fibrillation and outcomes (National Library of Medicine, 2018). The preliminary literature searches were conducted using MEDLINE- EBSCO to refine the list of search terms for this systematic review (Appendix 1).

2.3.2 Database selection

Bramer *et al.* (2017) recommended that multiple electronic bibliographic databases should be searched during a systematic review to obtain the maximum number of relevant records. This recommendation is supported by other authors (Stevinson and Lawlor, 2004; Lemeshow *et al.*, 2005). The following databases were searched in this systematic review: MEDLINE- EBSCO, PubMed, Web of Science and Cochrane Library. These databases were selected because they all offer access to literature in a wide variety of medical fields. In addition to searching multiple databases, reference list searching and website searching was conducted to locate other relevant literature, as recommended by Levay *et al.* (2015).

2.3.3 Selecting quality and risk-of-bias assessment tools

The lead researcher sought advice from a Librarian working in Keele Health Library, to identify validated tools for assessing the quality and risk of bias of all literature included within a systematic review. The Critical Appraisal Skills Programme (CASP, 2018) was suggested because it provides checklists for a variety of different study types. The lead researcher piloted this tool on ten randomly selected cohort studies; however, it was difficult to determine whether the literature was high quality or low quality based on the results generated from the CASP checklist. The CASP checklist comprised of questions about study design, methodological approaches, results, and the impact of results, but there was no specific question about the quality of the study. Instead, quality would have been determined based on the answers to the other questions, and the lead researcher decided that this approach was too subjective. Consequently, further research was conducted to find alternative tools which could assess the quality of the literature.

Harrison *et al.* (2017) identified The Newcastle-Ottawa Scale as a tool for determining the quality of literature included within systematic reviews. The Newcastle-Ottawa Scale categorises the literature as 'good quality', 'fair quality' or 'poor quality' using a scoring system (Wells *et al.*, 2009). The lead researcher piloted this tool on the same ten randomly selected cohort studies, and each study was given an overall rating of quality. For this reason, the Newcastle-Ottawa Scale was preferred, and selected to assess the quality of the literature included in this systematic review.

Further research was conducted to identify a validated tool which could be applied to determine the risk of bias in the systematic review. The Critical Appraisal Skills Programme (CASP, 2018) was deemed inappropriate for determining the quality of literature in this systematic review; however, it was considered for the risk of bias assessment. By applying the CASP tool, it was possible to identify two types of bias (selection bias and classification bias). Nevertheless, other sources of bias may exist in the literature. The Risk-of-Bias Assessment tool for Non-Randomised Studies (RoBANS) was selected for this systematic review. This tool identifies the following types of bias in the literature: selection bias, performance bias, detection bias, attrition bias and reporting bias (Harrison *et al.*, 2017). Furthermore, RoBANS categorises the different types of bias as 'high risk', 'low risk' or 'unclear risk', according to a pre-defined criteria (Kim *et al.*, 2013).

2.4 Methodology

The aim of this systematic review was to answer the following research question: *Is polypharmacy associated with adverse outcomes in individuals with atrial fibrillation?*

2.4.1 Search Strategy

The following electronic bibliographic databases were searched: MEDLINE- EBSCO, PubMed, Web of Science and Cochrane Library, between 24th July 2018 and 31st August 2018, to locate all literature which examined the outcomes associated with polypharmacy, in individuals with AF.

All database searches were limited to identify publications which were written in English and involved human participants. To ensure that all literature identified during the searches was recent and relevant, the searches were also limited by publication dates (1st January 1998 and 31st August 2018). The searches were not limited by publication type; therefore, clinical trial information, case studies, conference presentations, and government publications were identified, in addition to peer-reviewed journal articles.

Other sources were searched during this systematic review including professional body websites (Royal Pharmaceutical Society and General Medical Council), organisation websites (The King's Fund and The National Institute for Health and Care Excellence), and the web-based search engine, Google Scholar. To determine whether other theses had been previously published in this subject area, the British Library EThOS catalogue was also searched. In addition, reference lists for all included studies were screened by the lead researcher to identify other relevant sources of literature.

This search strategy utilised the PICO framework to identify all relevant literature for this systematic review. The PICO framework was chosen because it has been shown to improve the precision and focus of a literature search (Schardt *et al.*, 2007). The search terms used in the PICO framework are presented in Table 2-1. Search terms were linked using two Boolean operators (OR and AND). The Boolean operator OR was used to join all search terms in one column together, for example 'atrial fibrillation OR AF'; whilst the Boolean operator AND was used to join the search terms in all columns together, for example 'atrial fibrillation AND polypharmacy AND outcome*'. Medical Subject Headings (MeSH) terms

were also included in the search, and several terms were truncated, for example 'outcome*' and 'event*'.

Table 2-1: PICO framework and search terms utilised in this systematic review

Population (P)	**Intervention (I)**	**Comparator (C)**	**Outcome (O)**
Atrial fibrillation	Polypharmacy	Not applicable	Outcome*
AF	*polypharmacy		Effect*
Arrhythmia*	Multiple medication*		Impact
	Multiple medicine*		Consequence
	Multiple drug*		Event*
	Many medication*		
	Many medicine*		
	Many drug*		

The 'advanced search' function was used in the MEDLINE- EBSCO, PubMed, Web of Science and Cochrane Library searches.

For the MEDLINE- EBSCO, PubMed and Web of Science, the following search terms were used:

Polypharmacy OR **polypharmacy* OR *multiple medic** OR *many medic** OR *multiple drug** OR *many drug** (to find literature about polypharmacy)

AND

Atrial fibrillation OR *AF* OR *arrythmia** (to find all literature about atrial fibrillation)

AND

*Outcome** OR *effect** OR *impact* OR *consequence* OR *event* (to find all literature about outcomes)

Once the search terms had been entered, the text availability filters were applied, and abstracts and full-text articles were searched for these terms.

For the Cochrane Library search, the following search terms were used:

Polypharmacy AND *atrial fibrillation*

The 'search filter option' was set to search 'title, abstract and keywords'

2.4.2 Inclusion and exclusion criteria

All literature had to meet the following criteria to be eligible for inclusion in this systematic review:

1. Must be written in English.
2. Published between 1st January 1998 and 31st August 2018.
3. Must involve human participants, aged over 18 years.
4. Study participants must have atrial fibrillation.
5. Outcomes associated with polypharmacy must have been examined; however, the nature of the outcome was not predefined.
6. A title, abstract and full-text article must be available for screening.

2.4.3 Literature screening

All literature which met the inclusion criteria for this systematic review (section 2.4.2) were screened in several stages. First, the lead researcher screened all titles and abstracts and categorised the literature into the following two groups: 'accepted sources' or 'rejected sources'. Information about the authors, title, digital object identifier, and the reason for rejection (if appropriate) were recorded in a Microsoft Excel spreadsheet. Following this, a second reviewer was asked to verify whether the lead researcher had applied the inclusion criteria appropriately. The second reviewer was provided with 15 titles and abstracts (equating to approximately 1.5% of all results), which had been randomly selected from the Microsoft Excel spreadsheet, and was asked to independently determine whether the sources should be accepted or rejected, according to the inclusion criteria. (Jepson *et al.*, 2000). Any disagreement which arose between the lead researcher and the second reviewer was either resolved by discussion or passed onto a third reviewer if a consensus could not be reached. Both reviewers are registered pharmacists and have experience in teaching AF to undergraduate MPharm students, and thus were considered suitable reviewers for this systematic review.

Once the titles and abstracts which met the inclusion criteria had been identified, the lead researcher screened the full-text articles to determine whether the literature was eligible for inclusion in the systematic review. The lead researcher also extracted key information from the full-text articles and recorded it in a separate Microsoft Excel spreadsheet. Further information about data extraction is presented in section 2.4.4.

2.4.4 Data extraction

The data extraction spreadsheet used in this systematic review was adapted from the "Data Extraction and Assessment Template" published by The Cochrane Public Health Group (The Cochrane Public Health Group, 2011). The lead researcher recorded the following information in the data extraction spreadsheet, for all literature that met the inclusion criteria for this systematic review: author details, year of publication, country/region of study, study sample size, data source, type of study, participant characteristics (gender and age), inclusion criteria for study participants, outcomes measured, main findings (relating to polypharmacy), confounders controlled for in the statistical analyses and the definition of polypharmacy.

2.4.5 Quality and risk-of-bias assessments

The lead researcher conducted a quality assessment using the Newcastle-Ottawa Scale (NOS) on all literature which met the inclusion criteria for this systematic review (Wells *et al.*, 2009). The NOS uses the following three domains: selection, comparability and outcome, along with a point scoring system to determine the methodological quality of the literature (Lo *et al.*, 2014). The literature could be awarded a maximum of 9 points (4 points from the selection domain, 2 points from the comparability domain and 3 points from the outcome domain respectively), and the total points were used to determine whether the literature is "good quality", "fair quality" or "poor quality" (Wells *et al.*, 2009; Harrison *et al.*, 2017).

The Risk-of-Bias Assessment tool for Non-Randomised Studies (RoBANS) was also used in this systematic review to identify the following types of bias in the included literature: selection bias, performance bias, detection bias, attrition bias and reporting bias, and the risk of bias for all literature was categorised as 'high risk', 'low risk' or 'unclear risk', according to a pre-defined criteria (Kim *et al.*, 2013; Harrison *et al.*, 2017).

2.4.6 Google Alerts

This systematic review was conducted between 24th July 2018 and 31st August 2018 and was up to date at the time of writing (September 2018). However, the lead researcher recognised that the review may need to be updated, to include any relevant literature published between September 2018 and the date of thesis submission. Consequently, a Google Alert was created to notify the lead researcher about any newly published literature, which met the inclusion criteria for this review, and any relevant literature has been included in the discussion section (2.8) of this chapter.

2.5 Results

2.5.1 Search strategy results

A total of 942 records were identified, using the search strategy detailed in section 2.4.1. Most of the records (97.2%, n=916/942) were identified through database searches (747 records were identified in MEDLINE; 86 records were identified in PubMed; 74 records were identified in Web of Science and 9 records were identified in Cochrane Library). The

remaining 26 records were identified by screening the reference lists of the literature which met the inclusion criteria for this systematic review. Of the 942 records identified, there were 91 duplicates, and these records were excluded from the systematic review.

The title and abstract for the remaining 851 records were screened and 821 records were excluded as they did not meet the inclusion criteria for this review. The reasons for exclusion are presented in Table 2-2.

Table 2-2: The reasons for excluding records based on title and abstract screening (n=821)

Reasons for exclusion:	**Number of studies:**
Study did not examine polypharmacy in AF patients	154
Study participants did not have AF	190
Study examined the pharmacological management of AF	53
Study examined surgical interventions to manage AF	40
Outcomes associated with polypharmacy in AF patients were not examined	7
Study investigated the causes of AF/arrhythmias	77
Pharmacology based AF experiments	73
Study examined AF guidelines	8
Study involved non-human participants	22
No abstract available to screen	12
Examined outcomes but not in relation to AF and polypharmacy	185
Total number of records excluded	**821**

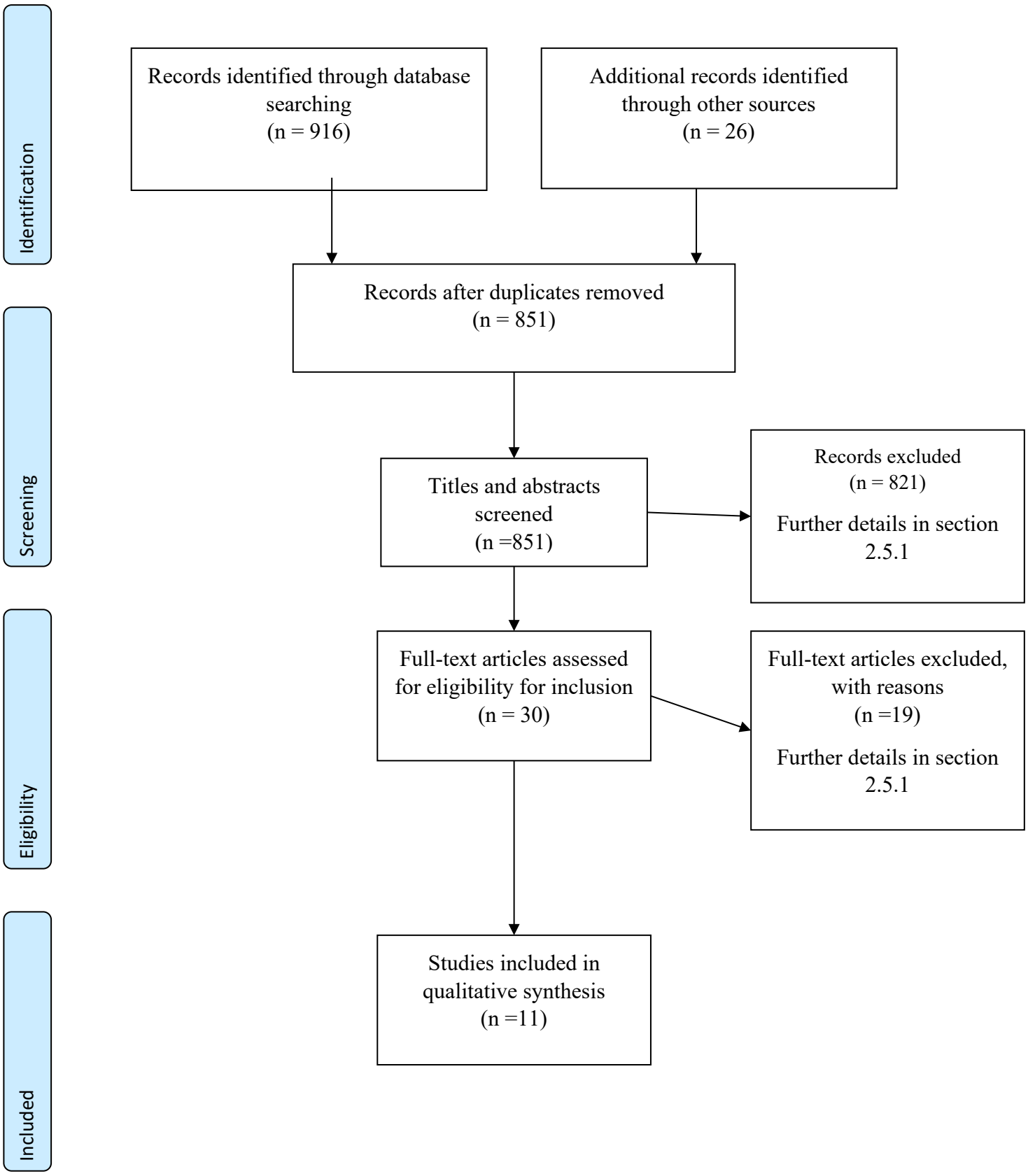
The remaining 30 full-text articles were screened to determine their eligibility for inclusion in the systematic review. Of the 30 full-text articles, 19 were excluded. The reasons for exclusion are presented in Table 2-3.

Table 2-3: The reasons for excluding records following the full-text screening (n=19)

Reasons for exclusion:	**Number of studies:**
Study did not examine outcomes in relation to polypharmacy in AF	9
AF participants not separated from study cohort	4
Study examined the effect of several concurrent medications on outcomes in AF, but did not examine polypharmacy in general	3
Study examined polypharmacy in the management of AF	2
Duplication of work in conference presentation	1
Total number of records excluded	**19**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 2-1) (Moher *et al.*, 2009) provides a schematic representation of the results from this systematic literature search.

Figure 2-1: PRISMA diagram for this systematic review. Adapted from Moher et al. (2009)



2.5.2 Summary of the included literature

There were eleven records which met the inclusion criteria for this systematic review, including seven observational studies (3 retrospective cohort studies; 2 prospective cohort studies and 2 cross-sectional studies) and four post-hoc analyses.

Six studies were conducted in Europe (3 in Spain, 2 in the UK and 1 in Italy), while two studies were conducted internationally across 40 or more different countries. The other three studies were conducted in North America (n=1), Asia (n=1) and Australia (n=1) respectively.

Participant demographics

Collectively, data for 64,260 participants with AF were examined in the eleven studies, and all studies were conducted in populations which had a mean age greater than 60. Most studies (n=8) had a greater proportion of male participants (range 50.4% to 64.5%), compared to female participants; however, three studies had a greater proportion of female participants (range 51.1% to 60.5%), compared to male participants. The number of participants with polypharmacy was explicitly stated in seven studies (66.8%, n=27,277/40,782).

Outcomes

There were seven different outcomes were measured across the included studies. The most commonly measured outcomes were the incidence of major bleeding (n=4), the incidence of stroke (n=4) and mortality (n=4). Other outcomes measured included the impact on quality of life (n=2), anticoagulation control (n=2), the incidence of myocardial infarctions (n=1) and primary non-adherence (n=1).

Additional information about the authors, data source, the inclusion criteria, confounders, key findings, and the definition of polypharmacy, was also extracted from the included studies, and this information is presented in Table 2-4.

Table 2-4: Data extraction from the included studies

	Authors and Publication Date	Country/ Region	Sample Size (n=)	Data Source	Study design	Participant characteristics	Inclusion criteria	Outcomes measured	Confounders	Key findings	Polypharmacy definition
1	Gasse *et al.* (2005)	UK	4,152	General Practice Research Database (1991-2001)	Prospective cohort study	58% male, 57% ≥ 70 years	AF patients, aged 40-84 years, permanently registered to a participating GP surgery and received a warfarin prescription (>90 days) during study period.	Incidence of serious bleed resulting in hospitalisation or death	Age, sex, practice, index date, diabetes, hypertension, heart failure and thyroid disease	OR for the association between polypharmacy and risk of serious bleed was 1.2 (0.4-3.4, p=0.08)	> 4 prescription drugs (including warfarin) in the 30 days preceding the index date.
2	Focks *et al.* (2016)	International (40 countries)	18,201	ARISTOTLE study (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) (2006-2011)	Post-hoc analysis	64.5% male, mean age 69 years ± 10 years	AF patients with ≥1 of : HF, LVF <40%, hypertension, ≥75 years, diabetes, previous stroke, TIA/SE	Incidence of stroke, systemic embolism, death, and major bleeding	Sex, age and country of randomisation	Polypharmacy was associated with stroke/SE (adj HR 1.27; 1.02-1.58), death (adj HR 1.41; 1.23-1.62) and major bleeding (adj HR 1.24; 1.04-1.49).	> 5 concomitant drugs

Table 2-4 (continued): Data extraction from the included studies

Authors and Publication Date		Country/ Region	Sample Size (n=)	Data Source	Study design	Participant characteristics	Inclusion criteria	Outcomes measured	Confounders	Key findings	Polypharmacy definition
3	Piccini *et al. (*2016)	International (45 countries)	14,264	ROCKET AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (2006-2009)	Post-hoc analysis	60.3% males, mean age 73 years (range 64-79)	Nonvalvular AF patients who are at moderate to high risk of stroke. Risk defined as CHADS2 score ≥2	Incidence of stroke, non-CNS embolism, myocardial infarction, death and major bleeding	Age, sex, BMI, region, diabetes, previous stroke, vascular disease, CHF, hypertension, COPD, paroxysmal AF, diastolic BP, CrCl, HR and alcohol use. Additional confounders in bleeding analysis; anaemia, previous GI bleed, platelets, albumin, previous prescribed aspirin, vitamin K antagonists or thienopyridine.	Polypharmacy was not associated with stroke/SE (adj HR 1.07; 0.89-1.29, P=0.78). Polypharmacy was associated with death (adj HR 1.25; 1.09-1.44), major bleeding (adj HR 1.16; 1.07-1.27) and MI (adj HR 1.48; 1.06-2.06).	≥5 concomitant medications
4	Proietti *et al. (*2016)	USA	4,056	AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management) (1995-2002)	Post-hoc analysis	60.7% males, mean age 70 ± 8 years	All participants enrolled into AFFIRM trial. Data about their pharmacological treatments and clinical variables must have been available.	Incidence of death and stroke	Sex (female), diabetes, previous myocardial infarction, and previous stroke	Polypharmacy was associated with death (crude HR 1.47; 1.18-1.82, P<0.001) but it is not associated with stroke (crude HR 1.17; 0.85-1.60, p=0.340).	≥5 prescribed medications

Table 2-4 (continued): Data extraction from the included studies

Authors and Publication Date		Country/ Region	Sample Size (n=)	Data Source	Study design	Participant characteristics	Inclusion criteria	Outcomes measured	Confounders	Key findings	Polypharmacy definition
5	Roalfe *et al.* (2012)	UK	1,762	BAFTA study (Birmingham Atrial Fibrillation Treatment of the Aged study) (2001-2004)	Post-hoc analysis	50.4% males, mean age 82 years (range 76-99)	≥75 years with AF and must have been previously enrolled into BAFTA study.	Quality of life (QOL)	Age, sex (male), disability, diabetes, history of myocardial infarction, heart failure, angina, valve disease, hypertension, stroke and TIA.	Greater medication use is independently associated with lower QOL scores in patients with AF.	No definition of polypharmacy provided
6	Mohammed *et al.* (2017)	Qatar	241	Heart Hospital electronic records (2012-2013)	Retrospective cohort study	50.6% males, mean age 63.5 years ± 12.5 years	Nonvalvular AF patients with a CHADS2 score ≥1	Anticoagulation control (Time in Therapeutic Range - TTR for INR 2-3)	Age and sex	Polypharmacy is associated with worsening anticoagulation control, i.e. lower TTR readings (OR 1.89, 1.03-3.33, p=0.03)	Use of ≥6 medications

Table 2-4 (continued): Data extraction from the included studies

	Authors and Publication Date	Country/ Region	Sample Size (n=)	Data Source	Study design	Participant characteristics	Inclusion criteria	Outcomes measured	Confounders	Key findings	Polypharmacy definition
7	Wang *et al*. (2016)	Australia	367	Database from previous primary care study conducted in NSW, Australia. (2013-2014)	Retrospective cohort study	55.3% males, mean age 77 years ± 7 years	AF patients, aged ≥65 years	Stroke and bleeding risk	COPD, upper GI disease, cognitive impairment and physical function	Polypharmacy was associated with a higher risk of stroke (OR 4.40, 1.23-15.66, P=0.03) and a lower risk of bleeding (OR 10.97, 1.66-72.60, p=0.01).	≥5 regular medications
8	Lobos-Bejarano *et al.* (2017)	Spain	1381	PAULA study database (Feb 2014-Oct 2014)	Retrospective cohort study	39.5% males, mean age 80.3 years li± 7.4 years	Nonvalvular AF patients prescribed a Vitamin K antagonist, minimum of 1 creatinine blood test in last six months and TTR data available	Anticoagulation control (Time in Therapeutic Range - TTR for INR 2-3)	Sex (female), multi-morbidity (≥3 chronic conditions), prescribed amiodarone, dietary habits that influence INR, previous bleed	Polypharmacy is associated with worsening anticoagulation control, i.e. lower TTR readings	≥7 daily medications other than vitamin K antagonist

Table 2-4 (continued): Data extraction from the included studies

Authors and Publication Date		Country/ Region	Sample Size (n=)	Data Source	Study design	Participant characteristics	Inclusion criteria	Outcomes measured	Confounders	Key findings	Polypharmacy definition
9	Rodriguez-Bernal *et al.* (2018)	Spain	18,715	Valencia Health Agency database (2011-2014)	Retrospective cohort study	52.3% males, mean age 74.5 years ± 10.1 years	AF and have been prescribed an oral anticoagulant (OAC) during study period	Primary non-adherence (i.e. not filling a first prescription for an OAC)	Age, sex, country of origin, pharmaceutical costs, baseline comorbidities - CHF, diabetes, hypertension, liver disease, kidney disease, previous stroke, CAD, DVT or PE, bleeding, malignancy, depression, dementia, hospital admissions (<12m), emergency department visits (<12m), ambulatory care visits (<12m), Rx type and OAC prescribed.	Polypharmacy is inversely associated with primary non-adherence (OR 0.59, 95% CI, 0.50-0.70, p ≤0.001)	≥6 prescribed medications
10	Márquez-Contreras *et al.* (2017)	Spain	370	160 Spanish primary or specialised care centres provided data for this study. (May 2013- April 2015)	Prospective cohort study	47.0% males, mean age 75.2 years ± 7.5 years	Nonvalvular AF, treated with rivaroxaban and aged ≥ 18 years	Quality of life (QOL) and compliance	Age, number of co-morbidities, global score, and previous treatment with VKA	Higher numbers of prescribed drugs are associated with lower compliance (OR 0.51; 0.44-0.58) and worsening QOL (OR 0.52, 95% CI, 0.45-0.59).	'higher numbers of prescribed drugs'

Table 2-4 (continued): Data extraction from the included studies

Authors and Publication Date		Country/ Region	Sample Size (n=)	Data Source	Study design	Participant characteristics	Inclusion criteria	Outcomes measured	Confounders	Key findings	Polypharmacy definition
11	Paciullo *et al.* (2018)	Italy	751	REPOSI study- 'Registro Politerapie Simi', (2008-2014)	Post-hoc analysis	48.9% males, median age 81 (IQR 75-85)	AF diagnosis, ≥65 years, treated with either rate or rhythm control strategy	Mortality	Age, sex and cumulative illness rating scale (CIRS)	No significant difference in mortality rates at follow-up between rate and rhythm control strategies (15.9% vs 14.1%, p=0.70).	≥5 medications

2.6 Narrative review of the key findings

The aim of this systematic review was to answer the following research question: *Is polypharmacy associated with adverse outcomes in individuals with atrial fibrillation?* The most commonly measured outcomes in the included studies, were mortality, the incidence of stroke and the incidence of major bleeding. These outcomes will be examined separately within this section.

2.6.1 Polypharmacy and mortality

The association between polypharmacy and mortality, in individuals with AF, was examined in four post-hoc analyses of trial data (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). The adjusted hazard ratios for the association between polypharmacy and mortality were significant and ranged from 1.25 (95% CI; 1.09-1.44) (Piccini *et al.*, 2016) to 1.47 (95% CI; 1.18-1.82) (Proietti *et al.*, 2016). One possible explanation for the slight variation in results could be that differing numeric thresholds were used to define polypharmacy. For example, Proietti *et al.* (2016) defined polypharmacy as '≥5 medicines' and counted cardiovascular medicines only, while Focks *et al.* (2016) defined polypharmacy as '6-8 concomitant medicines' at trial entry but did not differentiate according to the type of medication.

The slight variation in results may have also been caused by the differing numbers of covariates used in the statistical models, in these studies. For example, Focks *et al.* (2016)

adjusted their models for gender, age, and country only; whereas Piccini *et al.* (2016) adjusted their models for the participant demographics, study location, diagnosed conditions, renal function, and several anthropometric measurements, including body mass index.

2.6.2. Polypharmacy and stroke

The association between polypharmacy and stroke, in individuals with AF, was examined in three post-hoc analyses of trial data (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016) and one cross-sectional study (Wang *et al.*, 2016). Differing findings were reported in these studies.

Results from two of the post-hoc analyses (Piccini *et al.*, 2016; Proietti *et al.*, 2016) showed no significant association between polypharmacy at trial entry and ischaemic stroke during follow-up, with Piccini *et al.* (2016) reporting an adjusted hazard ratio of 1.07 (95% CI; 0.89-1.29, p=0.78) and Proietti *et al.* (2016) reporting an adjusted hazards ratio of 1.17 (95% CI; 0.85-1.60, p=0.34). In contrast, Focks *et al.* (2016) reported a significant association between polypharmacy and ischaemic stroke (adjusted HR 1.27; 95% CI 1.02-1.58, p<0.01), in their post-hoc analysis of 'apixaban for reduction of stroke and other thromboembolic events in atrial fibrillation' (ARISTOTLE) trial data. The latter finding is supported by the results from the cross-sectional study (Wang *et al.*, 2016), which reported an unadjusted odds ratio of 4.40 (95% CI: 1.23-15.66, p=0.03), for the association between polypharmacy and ischaemic stroke. There were varying levels of adjustments in the

statistical models in these studies, which may explain the differing findings reported, and this will be examined in more detail in section 2.8.

2.6.3 Polypharmacy and major bleeding

The association between polypharmacy and major bleeding, in individuals with AF, was examined in one prospective cohort study (Gasse *et al.*, 2005), one cross-sectional study (Wang *et al.*, 2016), and two post-hoc analyses of trial data (Focks *et al.*, 2016; Piccini *et al.*, 2016). Differing findings were reported in these studies.

Results from the two post-hoc analyses (Focks *et al.*, 2016; Piccini *et al.*, 2016) showed a significant association between polypharmacy at trial entry and major bleeding during follow-up, with Focks *et al.* (2016) reporting an adjusted hazard ratio of 1.24 (95% CI; 1.04-1.49, $p<0.01$) and Piccini *et al.* (2016) reporting an adjusted hazards ratio of 1.16 (95% CI; 1.07-1.27, $p<0.01$). In contrast, Wang *et al.* (2016) reported that polypharmacy was significantly associated with a lower risk of bleeding, with an unadjusted odds ratio of 10.97 (95% CI: 1.66-72.60, $p=0.01$), while Gasse *et al.* (2005) reported a statistically insignificant adjusted odds ratio of 1.2 (95% CI: 0.4 -3.4, $p=0.08$) when the association between polypharmacy and major bleeding was examined.

2.7 Quality and risk-of-bias assessments of included studies

The Newcastle-Ottawa Scale (NOS) was used to examine the methodological quality of the eleven studies included in this systematic review (Wells *et al.*, 2009). Information about the scale, scoring system and quality thresholds has been presented previously in section 2.4.5. Nine studies were rated as "good quality", whilst the remaining two studies were rated as "fair quality". None of the studies were given a "poor quality" rating; therefore, no studies were excluded from this systematic review based on their methodological quality. Findings from the quality assessment are presented in Table 2-5.

The risk of bias for the eleven included studies was also assessed, using RoBANS (Risk-of-bias assessment tool for non-randomised studies) (Kim *et al.*, 2013). This validated tool assesses the risk of the following biases: selection bias (section 2.7.1), performance bias (section 2.7.2), detection bias (section 2.7.3), attrition bias (section 2.7.4) and reporting bias (section 2.7.5), at study level (Harrison *et al.*, 2017). The key findings are discussed in the narrative below and presented in Table 2-5. The RoBANS assessment of each included study is presented in Appendix 2. No studies were excluded from this systematic review based on their risk of bias assessment.

2.7.1 Selection bias

Most studies (n=10/11) had a low risk of participant selection bias because participants in the exposed groups were selected from the same population as participants in the control

groups; however, one study (Roalfe *et al.*, 2012) selected participants from two different populations which resulted in a high risk of bias judgement.

Another form of selection bias could be introduced if confounders are not adequately adjusted for in the statistical analyses (Kim *et al.*, 2013). All studies included in this systematic review identified potential confounders. However, the number and type of confounders varied between studies, for example Focks *et al.* (2016) adjusted their statistical models for three confounders when examining the association between polypharmacy and stroke, while Piccini *et al.* (2016) adjusted their statistical models for fifteen confounders when they examined the same association. Despite the variation in confounding factors reported in the included studies, six studies had a low risk of selection bias, two studies had an unclear risk of selection bias, while three studies had a high risk of selection bias.

2.7.2 Performance bias

Exposure data were extracted from medical records or during structured interviews in most studies (n=10/11) and thus, these studies were considered to have a low risk of performance bias. One study (Wang *et al.*, 2016) was judged to have an unclear risk of performance bias because the researchers developed their own data collection tool and there was no indication as to whether this tool had been validated or assessed for reliability, prior to the research commencing.

2.7.3 Detection bias

The risk of detection bias varied across the eleven studies. Eight studies had a low risk of detection bias because the assessment of outcomes were blinded, for example Gasse *et al.* (2005) reduced the risk of detection bias by using independent reviewers, who were blinded to participant medication usage, to assess the incidence of serious bleeds. However, it was not possible to determine the risk of detection bias in the remaining studies (n=3/11) because details about the blinding process were either lacking (Márquez-Contreras *et al.*, 2017) or had been omitted from the published manuscript (Roalfe *et al.*, 2012).

2.7.4 Attrition bias

All studies were assessed for the risk of attrition bias. One study had a high risk of attrition bias because follow-up data were available for 55.7% of study participants but no explanation about the missing follow-up data was provided (Paciullo *et al.*, 2018). The risk of attrition bias was unclear in four studies, while six studies were judged to have a low risk of attrition bias because there were no missing data (n=5/6), or the quantity of missing data was negligible (n=1/6) and therefore unlikely to influence study outcomes.

2.7.5 Reporting bias

Most studies (n=10/11) had a low risk of reporting bias because the primary and secondary outcomes were clearly defined, and these studies presented statistically significant results, along with non-significant results for each outcome of interest. One study (Roalfe *et al.*,

2012) was judged to have an unclear risk of reporting bias because the authors defined the primary and secondary outcomes; however, a limited selection of results were presented for some of the outcomes.

Table 2-5: Quality and risk of bias assessment of the included studies (using the Newcastle-Ottawa Quality Assessment Form) (Wells et al., 2009; Kim et al., 2013)

		Selection				Comparability	Outcome				
Study		**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of study**	**Comparability of cohorts on the basis of design or analysis controlled for confounders**	**Assessment of outcome**	**Was length of follow-up long enough for outcomes to occur?**	**Adequacy of follow-up of cohorts**	**Overall quality rating (Good/Fair/Poor)**	**Overall risk-of-bias**
1	Gasse *et al.* (2005)	Truly representative	Drawn from the same community as the exposed cohort	Secure record	Yes	The study controls for age, sex and other confounders	Independent blind assessment	Yes	Complete follow up- all subjects	Good	Low
2	Focks *et al.* (2016)	Somewhat representative	Drawn from the same community as the exposed cohort	Other – trial record	Yes	The study controls for age, sex and other confounders	Record linkage	Yes	No statement	Good	Unclear

Table 2-5 (continued): Quality and risk of bias assessment of the included studies (using the Newcastle-Ottawa Quality Assessment Form) (Wells et al., 2009; Kim et al., 2013)

		Selection				Comparability	Outcome				
Study		**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of study**	**Comparability of cohorts on the basis of design or analysis controlled for confounders**	**Assessment of outcome**	**Was length of follow-up long enough for outcomes to occur?**	**Adequacy of follow-up of cohorts**	**Overall quality rating (Good/Fair/Poor)**	**Overall risk-of-bias**
3	Piccini *et al. (*2016)	Somewhat representative	Drawn from the same community as the exposed cohort	Other – trial record	Yes	The study controls for age, sex and other confounders	Independent blind assessment	Yes	Complete follow up- all subjects	Good	Low
4	Proietti *et al. (*2016)	Somewhat representative	Drawn from the same community as the exposed cohort	Structured interview	No	The study controls for sex and other confounders	Record linkage	Yes	Complete follow up- all subjects	Good	Low

Table 2-5 (continued): Quality and risk of bias assessment of the included studies (using the Newcastle-Ottawa Quality Assessment Form) (Wells et al., 2009; Kim et al., 2013)

		Selection				Comparability	Outcome				
Study		**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of study**	**Comparability of cohorts on the basis of design or analysis controlled for confounders**	**Assessment of outcome**	**Was length of follow-up long enough for outcomes to occur?**	**Adequacy of follow-up of cohorts**	**Overall quality rating (Good/Fair/Poor)**	**Overall risk-of-bias**
5	Roalfe *et al.* (2012)	Somewhat representative	Drawn from a different source	Secure record	No	The study controls for age, sex and other confounders	Self-report	Yes	Complete follow up-all subjects	Fair	Unclear
6	Mohammed *et al.* (2017)	Truly representative	Drawn from the same community as the exposed cohort	Secure record	Yes	The study controls for age and sex	Record linkage	Yes	No statement	Good	Unclear

Table 2-5 (continued): Quality and risk of bias assessment of the included studies (using the Newcastle-Ottawa Quality Assessment Form) (Wells et al., 2009; Kim et al., 2013)

		Selection				Comparability	Outcome				
Study		**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of study**	**Comparability of cohorts on the basis of design or analysis controlled for confounders**	**Assessment of outcome**	**Was length of follow-up long enough for outcomes to occur?**	**Adequacy of follow-up of cohorts**	**Overall quality rating (Good/Fair/Poor)**	**Overall risk-of-bias**
7	Wang *et al*. (2016)	Truly representative	Drawn from the same community as the exposed cohort	Other – researchers designed data collection instruments	No	Study controls for other factors	Record linkage	Yes	No statement	Fair	Unclear
8	Lobos-Bejarano *et al.* (2017)	Somewhat representative	Drawn from the same community as the exposed cohort	Secure record	No	The study controls for sex and other confounders	Record linkage	Yes	No statement	Good	Low

Table 2-5 (continued): Quality and risk of bias assessment of the included studies (using the Newcastle-Ottawa Quality Assessment Form) (Wells et al., 2009; Kim et al., 2013)

		Selection				Comparability	Outcome				
Study		**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of study**	**Comparability of cohorts on the basis of design or analysis controlled for confounders**	**Assessment of outcome**	**Was length of follow-up long enough for outcomes to occur?**	**Adequacy of follow-up of cohorts**	**Overall quality rating (Good/Fair/Poor)**	**Overall risk-of-bias**
9	Rodriguez-Bernal *et al.* (2018)	Truly representative	Drawn from the same community as the exposed cohort	Secure record	Yes	The study controls for age, sex, and other confounders	Record linkage	Yes	Complete follow up-all subjects	Good	Low
10	Márquez-Contreras *et al.* (2017)	Truly representative	Drawn from the same community as the exposed cohort	Structured interview	No	The study controls for age and other confounders	Self-report	Yes	Complete follow up-all subjects	Good	Unclear

Table 2-5 (continued): Quality and risk of bias assessment of the included studies (using the Newcastle-Ottawa Quality Assessment Form) (Wells et al., 2009; Kim et al., 2013)

		Selection				Comparability	Outcome				
Study		**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of study**	**Comparability of cohorts on the basis of design or analysis controlled for confounders**	**Assessment of outcome**	**Was length of follow-up long enough for outcomes to occur?**	**Adequacy of follow-up of cohorts**	**Overall quality rating (Good/Fair/Poor)**	**Overall risk-of-bias**
11	Paciullo *et al.* (2018)	Truly representative	Drawn from the same community as the exposed cohort	Structured interview	Yes	The study controls for age, sex and other confounders	Record linkage	Yes	Follow up rate less than 80% and no description of those lost	Good	Low

2.8 Chapter Discussion

The purpose of this systematic review was to determine whether polypharmacy is associated with adverse outcomes, in individuals with atrial fibrillation. Eleven studies were eligible for inclusion in the review. Polypharmacy was prevalent in over half (66.8%) of the participants with AF, and the most commonly measured outcomes were mortality, the incidence of stroke and the incidence of major bleeding. While a significant association between polypharmacy and mortality was reported in four post-hoc analyses of trial data (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018), conflicting findings were reported when the associations between polypharmacy and ischaemic stroke, and polypharmacy and major bleeding, were examined previously.

All participants in the included studies had AF; however, participants with polypharmacy were at least 25% more likely to die, compared to participants without polypharmacy (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). Cox regression models were used in all of the studies which examined the association between polypharmacy and mortality. The models were adjusted for confounders, to varying degrees (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). Three of the studies adjusted their models for morbidities (Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). However, the authors acknowledged that it was not possible to determine whether it is polypharmacy itself that is associated with mortality, or whether polypharmacy is merely a 'marker' of morbidity and it is the underlying diseases which are associated with mortality, in individuals with AF (Focks *et al.*, 2016; Proietti *et al.*, 2016).

This limitation has been raised in other studies previously (Gomez *et al.*, 2014; Gallagher *et al.*, 2020).

Furthermore, all studies which have previously examined the association between polypharmacy and mortality, in individuals with AF, have been post-hoc analyses of trial data (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). One limitation of the post-hoc analyses is that the results may not be generalisable to all individuals with AF, due to the inclusion criteria utilised in the trials. For example, Piccini *et al.* (2016) analysed polypharmacy data collected during the 'Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)' trial, from participants who had a 'moderate to high risk of a stroke' only. Similarly, Focks *et al.* (2016) analysed data collected during the 'apixaban for reduction of stroke and other thromboembolic events in atrial fibrillation' (ARISTOTLE) trial, from participants with AF, who had at least one additional risk factor for thromboembolism.

Another limitation of the post-hoc analyses is that the available data have been collected specifically for the purpose of the trial, and not for the secondary analyses. Therefore, some data which is essential for examining the associations between polypharmacy and mortality, may not be available. For example, Proietti *et al.* (2016) defined polypharmacy according to cardiovascular medication usage only, as other medication data (i.e., non-cardiovascular medicines) had not been recorded at trial enrolment. Consequently, this may have resulted in an underestimation of polypharmacy prevalence among study participants, and impacted the results reported. If the primary focus of the trial had been to examine the association

between polypharmacy and mortality, all medication data, confounder data and outcome data, would have been recorded; thus, strengthening the conclusions drawn (Curran-Everett and Milgrom, 2013).

Conflicting findings were reported when the association between polypharmacy and ischaemic stroke was examined previously, in individuals with AF (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Wang *et al.*, 2016). In the two post-hoc analyses (Piccini *et al.*, 2016; Proietti *et al.*, 2016), which reported no association between polypharmacy and stroke, the statistical models were adjusted for diabetes mellitus and previous stroke, in addition to other confounders. However, in the two studies (Focks *et al.*, 2016; Wang *et al.*, 2016) which reported a significant association between polypharmacy and stroke, no adjustments were made for diabetes mellitus or previous stroke. Diabetes has been shown to be independently associated with ischaemic strokes, and this risk is enhanced in individuals who have AF as a co-morbidity (Klem *et al.*, 2003; Chen *et al.* 2016). Furthermore, individuals who have experienced an ischaemic stroke previously have an elevated risk of experiencing a subsequent stroke (Scmidt *et al.*, 1988; Amarenco *et al.*, 2018; Chen *et al.*, 2020). Therefore, the inclusion and exclusion of certain confounders in the statistical models, may explain the difference in findings reported.

Similar to the polypharmacy and stroke findings, it is possible that the polypharmacy and major bleeding results differ due to the varying levels of adjustment in the statistical models. There were also different definitions used to define major bleeding. For example, Focks *et al.* (2016) and Piccini *et al.* (2016) defined major bleeding according to the 'International Society on Thrombosis and Heamostasis' criteria (Taylor *et al.*, 2001), and

reported a significant association between polypharmacy and bleeding; whereas Gasse *et al.* (2005) defined major bleeding as bleeds 'that resulted in hospitalisations within 30 days or death within 7 days following the bleeding event', and Wang *et al.* (2016) defined major bleeds using participant HAS-BLED (Pisters *et al.*, 2010) and HEMORR2HAGES (Gage *et al.*, 2006) scores. Consequently, it is difficult to make comparisons between study results when different criteria have been used to assess the outcome of interest (i.e., the incidence of major bleeds).

Different criteria were also used to define polypharmacy in the included studies. Some studies used a threshold of 'five or more medicines'(Piccini *et al.*, 2016; Proietti *et al.*, 2016), while other studies used higher thresholds, for example '6 to 8 concomitant drugs at baseline' (Focks *et al.*, 2016) and 'greater than 7 pills per day, other than a vitamin K antagonist' (Lobos-Bejarano *et al.*, 2017). Only one study defined polypharmacy as '4 or more medicines' (Roalfe *et al.*, 2012). There is still no consensus regarding the definition of polypharmacy; however, Masnoon *et al.* (2017) conducted a systematic review into polypharmacy definitions and concluded that the arbitrarily selected numeric threshold of 'five or more medications' was the most commonly used definition in the literature. If the latter definition of polypharmacy is used in all future research, it may become easier to compare study findings.

The time period for defining polypharmacy also requires consideration when conducting future research. In the post-hoc analyses, polypharmacy was defined at the point of trial entry (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018); however, Focks *et al.* (2016) acknowledged that this approach may result in an

underestimation of polypharmacy prevalence. Furthermore, this approach does not account for changes in prescribing patterns. If polypharmacy prevalence was examined over a greater time period, for example three months, rather than one day, then any fluctuations in prescribing would be taken into account.

In the time period between conducting this systematic review (September 2018) and thesis submission, a systematic review into the outcomes associated with polypharmacy, in individuals with AF, was published (Gallagher *et al.*, 2020). Overall, six studies were included in the systematic review, and the authors concluded that polypharmacy was associated with a number of adverse outcomes including 'all-cause mortality, major bleeding, reduced quality of life, hospitalisations, and poorer physical function; however, no significant association was found between polypharmacy and ischaemic stroke'(Gallagher *et al.*, 2020).

The authors attributed the associations between polypharmacy and adverse outcomes to a range of factors, including 'adverse drug reactions, poor adherence to medication regimens, drug-drug and drug-disease interactions', and question whether it is polypharmacy or the underlying morbidities that are associated with adverse outcomes, in individuals with AF. Similar to this systematic review, the authors acknowledged the heterogeneity in adjustments in the statistical models, of the included studies. The review concluded by suggesting that further research should be conducted in this area, to confirm findings, and to determine whether polypharmacy could be modified, for example by implementing deprescribing strategies, to improve the outcomes for individuals with AF (Gallagher *et al.*, 2020).

Finally, there were several differences between the current systematic review and the aforementioned systematic review (Gallagher *et al.*, 2020). Eleven studies were included in this systematic review, while Gallagher *et al.* (2020) included six studies. One possible explanation for the differing numbers of included papers is that there were different numbers of databases searched in the systematic reviews. Four databases were searched in the current systematic review, while Gallagher *et al.* (2020) searched two databases. Another possible explanation for the differing numbers of included papers is that Gallagher *et al.* (2020) included studies which had a minimum of three months follow-up, whereas the current systematic review did not specify the period of follow-up in the inclusion criteria.

2.9 Chapter Summary

Polypharmacy was associated with the following adverse outcomes: major bleeding, stroke, mortality, reduced quality of life, non-adherence, and worsening anticoagulation control, in individuals with atrial fibrillation.

The association between polypharmacy and mortality has been reported previously in post-hoc analyses. However, these findings may not generalisable to all individuals with AF, due to the inclusion criteria utilised in the trials. To address this limitation, analyses will be conducted using the Clinical Practice Research Datalink (CPRD), which provides 'representative UK population health' data, to examine the association between polypharmacy and mortality, in individuals with AF, and the results will be presented in the subsequent chapters of this thesis (Herrett *et al.*, 2015).

The association between polypharmacy and stroke, in individuals with AF, will also be examined in the subsequent chapters of this thesis, as conflicting results have been reported previously. Varying statistical adjustments may have contributed to the different findings reported. To address this limitation, this study will examine the associations using propensity score matching, in addition to logistic regression (Littnerová *et al.*, 2013). Propensity score matching will enable individuals with AF to be matched according to all measured confounders, so the only difference between the study participants will be the number of medications they had been prescribed in a specified time period (i.e., polypharmacy).

Chapter 3: Methods

3.1 Introduction

The purpose of this chapter is to discuss the methods used in this study. The study aim and objectives are presented in section 3.2. The study design is discussed in section 3.3 and includes information about the data source. To obtain data for this study, an Independent Scientific Advisory Committee (ISAC) application form and protocol were completed, and further information about this application is available in section 3.4. Ethical approval was also required for this research, and details are provided in section 3.5. Study definitions and inclusion criteria are presented in section 3.6 and section 3.7, respectively. Information about feasibility counts and sample sizes are presented in section 3.8. The study exposures and outcomes are detailed in section 3.9, while information about study covariates is provided in section 3.10. Study covariates were included in the propensity score matching analyses and this statistical approach is discussed, in detail, in section 3.11. Information about data extraction and data analysis is presented in section 3.12 and section 3.13, respectively. Finally, a chapter summary is provided in section 3.14.

3.2 Study aim and objectives

The aim of this study was to determine whether polypharmacy and hyper-polypharmacy, in the three months following atrial fibrillation (AF) diagnosis, are associated with death or ischaemic stroke during follow-up. The rationale behind the inclusion of a 3-month time frame is explained in section 3.6.1.

To achieve the aim, this study had the following objectives:

1. To determine the prevalence of polypharmacy (5-9 prescribed medicines) and hyper-polypharmacy (≥10 prescribed medicines) in the first three months following AF diagnosis, and to stratify prescribed medication data by polypharmacy group at baseline.
2. To investigate whether polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, are associated with death or ischaemic stroke during follow-up, using unadjusted logistic regression.
3. To examine the associations between each prognostic factor and study outcomes (death and ischaemic stroke).
4. To determine whether polypharmacy, in the first three months following AF diagnosis, is associated with death or ischaemic stroke during follow-up, using adjusted logistic regression and propensity score matching (1:1).
5. To determine whether hyper-polypharmacy, in the first three months following AF diagnosis, is associated with death or ischaemic stroke during follow-up, using adjusted logistic regression and propensity score matching (1:1).

3.3 Study Design

This prospective cohort study analysed data recorded in the Clinical Practice Research Datalink (CPRD) dataset, CPRD GOLD, between 1st June 2006 and 4th April 2019.

3.3.1 Data Source – Clinical Practice Research Datalink (CPRD)

The Clinical Practice Research Datalink (CPRD) is an organisation 'sponsored by the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR)' (CPRD, 2021a). The organisation gathers anonymous patient data from over 1,800 GP surgeries, located within the United Kingdom, on a monthly basis (CPRD, 2021a). CPRD data are stored in two datasets, CPRD GOLD and CPRD Aurum. GP surgeries who use Vision® software contribute to the CPRD GOLD dataset, while GP surgeries who use EMIS Web® software contribute to the CPRD Aurum dataset. These two CPRD datasets collectively 'encompass 50 million patients, including 15 million patients' who are currently registered with a GP surgery in the UK (Herrett *et al.*, 2015).

3.3.2 Data Source – Clinical Practice Research Datalink (CPRD) GOLD dataset

The CPRD GOLD dataset is comprised of 10 files, each containing anonymised patient data (CPRD, 2021b). For this thesis, data were extracted from the following six files of the CPRD GOLD dataset: Patient, Practice, Clinical, Additional Clinical Details, Test and Therapy. The Patient file provided demographic data, surgery registration data, transfer out dates and transfer out reasons (if the participant had left the participating surgery), death

dates and information about whether each record was ‘up-to-standard’, according to the CPRD quality checks (CPRD, 2021b). Further ‘up-to-standard’ data were available in the Practice file, along with information about where the participating surgeries were located within the UK. The Clinical file provided clinical event data, including the date of the event (for example, the date of AF diagnosis), diagnoses, signs and symptoms. Further data about each clinical event were available from the Additional Clinical Details file. Blood test data and anthropometric measurement data were available in the Test file. Finally, prescibed medication and appliance data, including issue date, product code, quantity and pack size, were available in the Therapy file (CPRD, 2021b).

The CPRD GOLD dataset was selected for this study for several reasons. First, the size of the dataset enhances the statistical power of the analyses and improves the reliability of conclusions drawn in this thesis (Strongman *et al.*, 2019). Second, the dataset provides a rich source of health data, with ‘at least 20 years of follow-up data’, for over one-quarter of all patients currently registered with a participating GP surgery (Herrett *et al.*, 2015). Information about patient demographics, consultations, diagnosed conditions, test results, prescribed medications and secondary care referrals is available for extraction from the CPRD GOLD dataset (Herrett *et al.*, 2015; CPRD, 2021a). Furthermore, previous research has shown that CPRD GOLD data are broadly representative of the UK general population, in terms of age, gender and ethnicity (Bhaskaran *et al.*, 2013; Herrett *et al.*, 2015). Another reason for selecting the CPRD GOLD dataset was it could be linked to other datasets, including Hospital Episode Statistics (HES), cancer data from Public Health England (PHE) and the English Index of Multiple Deprivation (IMD), thus enhancing the depth of the analyses conducted (National Statistics, 2019). In this thesis, the CPRD GOLD data were linked to Patient Level Deprivation Data (IMD 2015). Finally, atrial fibrillation is one of

the conditions covered by the National Institute for Health and Care Excellence (NICE) Quality and Outcomes Framework (QOF) (NICE, 2021c). This framework specifies that GP practices must 'establish and maintain a register of all AF patients', 'record the percentage of patients with atrial fibrillation in whom stroke risk has been assessed using the CHA2DS2-VASc score risk stratification scoring system in the preceding 12 months' and record 'the percentage of patients who are currently treated with anticoagulation drug therapy', in order to meet the performance indicators and receive QOF payments (NICE, 2014). Consequently, CPRD GOLD has become a rich source of information about AF.

3.4 Independent Scientific Advisory Committee (ISAC) application form and protocol

An Independent Scientific Advisory Committee (ISAC) application form (Appendix 3) and ISAC protocol (Appendix 4) were completed by the lead researcher to obtain CPRD GOLD data for this thesis.

The ISAC application form consisted of 29 questions, while the ISAC protocol required the following information: 'study title; lay summary; technical summary; study aims, objectives and rationale; study background; study design; feasibility counts; sample size considerations; data linkage; study population and the selection of controls; exposures, health outcomes and covariates; statistical analysis; plans for addressing confounding; plans for addressing missing data; patient and user group involvement; plans for disseminating research and limitations of the study design'(CPRD, 2018).

The ISAC protocol for this thesis was given the following title: 'Is polypharmacy associated with death or ischaemic stroke in individuals newly diagnosed with atrial fibrillation? A prognostic cohort study using data from The Clinical Practice Research Datalink (CPRD)', and it was drafted several times by the lead researcher to incorporate supervisory team feedback and input from their colleagues in the School of Medicine, at Keele University.

Read Code lists for AF diagnoses, death, ischaemic stroke, and all prognostic factors, were required to accompany the ISAC application form and ISAC protocol. The Read Code lists were generated by the lead researcher, using the medcode dictionaries provided by CPRD. Following this, two academic General Practitioners (GPs), who have previous experience working with CPRD, were invited to peer review the Read Code lists for this thesis.

On 20th April 2018, the academic GPs suggested several amendments to the Read Code lists. The first suggestion was to add the Read Code for chronic atrial fibrillation to the AF diagnoses Read Code list. The GPs also identified 14 additional Read Codes for ischaemic stroke and suggested that these were added to the respective Read Code list. The Read Code lists were updated accordingly by the lead researcher.

The completed ISAC application form, ISAC protocol, and the following appendices: Read Code lists for AF diagnoses (Appendix 5, table A5-1), ischaemic stroke (Appendix 5, table A5-2), and all prognostic factors (Appendix 5, tables A5-3 to A5-12 respectively); feasibility counts (Appendix 6), and sample size calculations (Appendix 7) were submitted to the ISAC Secretariat for approval on 21st May 2018 (Reference: ISAC Protocol 18_151).

Approval was granted on 9th August 2018 (Appendix 8). Following this, CPRD cut the dataset for ISAC Protocol 18_151 and the data were extracted on 3rd April 2019, by the Data Manager in the School of Medicine, at Keele University. Further details regarding data extraction are available in section 3.12.

On 23rd January 2020, an amendment was made to ISAC Protocol 18_151. This protocol requested both Practice Level IMD data and Patient Level IMD data. It was not possible for CPRD to fulfil this request; therefore, ISAC Protocol 18_151 was amended to only request Patient Level IMD data and was subsequently submitted to the ISAC Secretariat to reapprove. The amended protocol (Reference: ISAC Protocol 18_151A) was approved on 6th February 2020 and following this Patient Level IMD data were supplied by CPRD.

Finally, data for this thesis were due to be destroyed on 31st January 2021, according to the CPRD agreement. The data were still required for analysis; therefore, the lead supervisor completed an Extension Request for Data Use application form (Appendix 9) on 12th November 2020. CPRD approved the extension request on 9th December 2020 and data for this thesis will now be destroyed on 31st January 2022.

3.5 Ethical approval

The Clinical Practice Research Datalink (CPRD) have been granted ethical approval by the Health Research Authority, to provide anonymised patient data for use in observational research (reference number 05/ MRE04/87) (Nissen *et al.*, 2017; CPRD, 2021c). In addition

to this ethical approval, all research involving CPRD data requires approval from the Independent Scientific Advisory Committee (ISAC) before anonymised patient data are provided to researchers (CPRD, 2021c). Further information regarding the approved ISAC application form and ISAC protocol for this thesis are presented in section 3.4. Additional ethical approval was not required for this thesis because no patients or members of the public were involved in this research.

3.6 Definitions

Information about the polypharmacy definition used in this thesis is presented in section 3.6.1, while details about the hyper-polypharmacy and non-polypharmacy definitions are presented in section 3.6.2 and 3.6.3 respectively. The difficulty in defining polypharmacy has been discussed previously in section 1.2.

3.6.1 Polypharmacy

Polypharmacy: 5 to 9 prescribed medications in the three months following AF diagnosis

This polypharmacy definition was selected for several reasons. First, the findings from a systematic review of polypharmacy definitions showed that polypharmacy is most commonly defined numerically, using a threshold of five or more medicines (Masnoon *et al.*, 2017). Second, a three-month time frame was included in the definition to take account of any fluctuations in prescribing, which may have occurred following AF diagnosis. Most

AF diagnoses are made in secondary care, and previous research has shown that 85.7% of medication regimens change, usually due to the addition of new medications, in the initial months following hospital discharge (Viktil *et al.*, 2012). Another reason for including this time frame was that Clinical Commissioning Group (CCG) guidance recommends that prescribers should issue prescriptions which cover 28-day treatment periods, as good practice; however, the guidance also acknowledges that prescribers may need to use their discretion and issue prescriptions which cover longer treatment periods, for example 56-days or 84-days, in exceptional circumstances (Blackpool CCG, 2016). Furthermore, previous research into the outcomes associated with polypharmacy, in individuals with AF, have been post-hoc analyses of clinical trial data; therefore, polypharmacy has been defined according to the number of concomitant medicines taken by participants on the day of trial enrollment (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016); whereas, the definition used in this thesis considers medication usage and polypharmacy over a broader period of time. This thesis did not examine the changes in polypharmacy status during follow-up; however, the proportion of participants with polypharmacy and hyper-polypharmacy may increase during follow-up, as our published work has shown an association between polypharmacy, hyper-polypharmacy and increasing age (Slater *et al.*, 2018; Slater *et al.*, 2020). Subsequent analyses could look at the changes in polypharmacy status, at different time points during follow-up. Finally, the inclusion of a time frame was important from a data extraction perspective, as the Therapy file in CPRD GOLD exceeded the drive space that could be allocated for this thesis (section 3.12).

3.6.2 Hyper-polypharmacy

Hyper-polypharmacy: 10 or more prescribed medications in the three months following AF diagnosis.

The numerical definition of hyper-polypharmacy has been used previously in other studies (Peel *et al.*, 2014; Nishtala and Salahudeen, 2015; Kennel *et al.*, 2019). On occasion, hyper-polypharmacy has been termed 'excessive polypharmacy' in the literature (Walckiers *et al.*, 2015; O'Dwyer *et al.*, 2016). The research team considered the use of both terms and decided that 'excessive polypharmacy' may have some negative connotations and could possibly suggest the presence of inappropriate prescribing. This thesis did not examine the appropriateness of prescribing within each participant's medication regimen; therefore, the research team opted to use the term hyper-polypharmacy to describe participants taking 10 or more prescribed medications. The rationale behind the inclusion of a 3-month time frame in the definition has been explained in section 3.6.1.

3.6.3 Non-polypharmacy

Non-polypharmacy: 1 to 4 prescribed medications in the three months following AF diagnosis.

The term non-polypharmacy was selected for this thesis, as previous studies have used it to describe participants who take fewer than five medications (Skov *et al.*, 2011; Slater *et al.*,

2020). However, this is the first study to specify a time frame within the definition. The rationale behind the inclusion of a 3-month time frame in the definition has been explained in section 3.6.1.

3.7 Participant Inclusion Criteria

The following criteria must have been met for a participant to be eligible for inclusion in this study:

- The participant must have had an AF diagnosis, recorded in the Clinical file of CPRD GOLD, between 1st June 2006 and 4th April 2019. All AF diagnoses were identified using the AF Read Code list (Appendix 5, table A5-1), which had been approved previously by the Independent Scientific Advisory Committee (ISAC) when submitted with Protocol 18_151 (section 3.4). In cases where there were multiple AF diagnosis dates recorded, the earliest recorded date was considered to be the date of AF diagnosis.
- The participant must have been prescribed a minimum of one medicine in the first three months following their AF diagnosis, and this information must have been recorded in the Therapy file of CPRD GOLD
- The participant must have 'acceptable data' according to the CPRD quality standards. This information is recorded in the Patient file of CPRD GOLD. The participant must have also been registered with an 'up-to-standard' GP surgery, for a minimum of two years prior to their AF diagnosis (CPRD, 2020).

3.8 Preliminary Research

Feasibility counts and sample size calculations were conducted prior to requesting the CPRD GOLD data for this thesis. The feasibility count information is presented in section 3.8.1, while the sample size calculations are presented in section 3.8.2.

3.8.1 Feasibility Counts

A CPRD training data set containing data from five GP surgeries was used to determine the feasibility of the study based on the inclusion criteria (section 3.7) In the training dataset, there were 2,091 patients who met the inclusion criteria for this study (section 3.7). The patients were allocated into one of the following three groups: non-polypharmacy, polypharmacy or hyper-polypharmacy. Patient numbers for each group are presented in table 3-1.

Table 3-1: Feasibility counts using the CPRD training dataset

Feasibility Counts	**Number of patients**
All patients in the training dataset with an AF diagnosis	5,893
All patients with an AF diagnosis + acceptable data	2,916
Earliest diagnosis date calculated	2,916
Number of patients prescribed a minimum of one medication in the first three months following their AF diagnosis	2,091
Stratified by polypharmacy group (n=2,091)	
Non-polypharmacy group	1,288
Exposed to polypharmacy at study entry (5-9 different prescribed medicines)	662
Exposed to hyper-polypharmacy at study entry (10 or more different prescribed medicines)	141

Based upon the figures generated during the feasibility counts, it was anticipated that there would be 291,600 patients within the CPRD GOLD dataset (500 GP surgeries) who had acceptable data and had received an AF diagnosis. Of these patients, it was anticipated that there would be 209,100 patients who had been prescribed a minimum of one medication in the first three months following AF diagnosis, which equates to approximately 128,800 patients in the non-polypharmacy group, approximately 66,200 patients in the polypharmacy group and approximately 14,100 patients in the hyper-polypharmacy group.

Outcomes were also examined in the training dataset (Appendix 7). The incidence of mortality was 46.0%, 43.8% and 47.5% in the non-polupharmacy, polypharmacy and hyper-polypharmacy groups respectively. The incidence of ischeamic stroke was 14.2%, 8.6% and

9.9% in the non-polupharmacy, polypharmacy and hyper-polypharmacy groups respectively. Similar percentages of outcomes were expected in the main dataset.

Feasbility count data were submitted to the Independent Scientific Advisory Committee (ISAC) for approval on 21st May 2018, alongside the completed ISAC application form (Appendix 3), and ISAC protocol (Appendix 4), and the other appendices detailed in Section 3.4.

3.8.2 Sample size

The CPRD training dataset (section 3.8.1) was analysed to determine the number of patients who had been exposed to polypharmacy or hyper-polypharmacy in the three months following AF diagnosis. Outcome data (death or ischaemic stroke) were also available in the CPRD training dataset. Following this, data were input into G-Power, a software tool that is designed to determine statistical power and calculate sample sizes (Faul, 2007). The following statistical test was used in these calculations: 'Proportions: Difference between two independent proportions'. To conduct these calculations, alpha was set to 0.05 and power was set to 0.80. ISAC gudiance was followed when calculating sample sizes for this study (CPRD, 2018).

1. **Polypharmacy in the first three months following AF diagnosis and death during follow-up.**

   To examine this association, 8021 participants with polypharmacy and 8021 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference in proportions of 2% between the two groups, at a 95%

confidence level. The difference in proportions was the difference between the incidence of mortality in the non-polypharmacy group (46.0%) and the polypharmacy group (43.8%), in the training dataset.

2. **Polypharmacy in the first three months following AF diagnosis and ischaemic stroke during follow-up**

   To examine this association, 502 participants with polypharmacy and 502 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference in proportions of 5% between the two groups, at a 95% confidence level. The difference in proportions was the difference between the incidence of ischaemic stroke in the non-polypharmacy group (14.2%) and the polypharmacy group (8.6%), in the training dataset.

3. **Hyper-polypharmacy in the first three months following AF diagnosis and death during follow-up**

   To examine this association, 2842 participants with hyper-polypharmacy and 2842 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference in proportions of 2% between the two groups, at a 95% confidence level. The difference in proportions was the difference between the incidence of mortality in the non-polypharmacy group (46.0%) and the hyper-polypharmacy group (47.5%), in the training dataset.

4. **Hyper-polypharmacy in the first three months following AF diagnosis and ischaemic stroke during follow-up**

To examine this association, 896 participants with hyper-polypharmacy and 896 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference in proportions of 4% between the two groups, at a 95% confidence level. The difference in proportions was the difference between the incidence of ischaemic stroke in the non-polypharmacy group (14.2%) and the hyper-polypharmacy group (9.9%), in the training dataset.

3.9 Study Exposures and Outcomes

The number of different prescribed medications in the three months following AF diagnosis was the exposure in this study. Prescribed medication data were obtained from the Therapy file in CPRD GOLD, and the extracted data were linked to a Product dictionary. The latter provided further information about product names (generic or proprietary), product codes, drug substances (active ingredients), strengths, formulations, routes of administration, British National Formulary (BNF) Chapters and BNF codes (CPRD, 2020; Joint Formulary Committee, 2021). For each participant, the number of prescribed medications, in the three months following AF diagnosis, was determined by conducting a count of drug substances. The reason for selecting drug substance, rather than product code, was to ensure that appliances, for example insulin pen needles and catheters, were excluded from the prescribed medication count.

Following the count, participants who had been prescribed between one and four different medicines, in the three months following AF diagnosis, were allocated to the non-polypharmacy group. Participants who had been prescribed between five and nine

different medicines, in the three months following AF diagnosis, were allocated to the polypharmacy group. Finally, participants who had been prescribed a minimum of ten different medicines, in the three months following AF diagnosis, were allocated to the hyper-polypharmacy group.

The incidence of death (defined as a death date ≥ study index date and documented in the Patient file of CPRD GOLD), and the incidence of ischaemic stroke (defined as a record of a Read code for ischaemic stroke, as listed in appendix 5, table A5-2, and documented in the Clinical file in CPRD GOLD, with an event date ≥ study index date) were the primary outcomes for this study.

Study follow-up commenced at three months after the date of AF diagnosis (index date). Participants who experienced a primary outcome (death or ischaemic stroke) or transferred out of the participating GP surgery before the start of follow-up, but after the date of AF diagnosis, were excluded from the analyses. The maximum follow-up period for this study was 10 years; however, follow-up was terminated earlier if any of the following events occurred: death, ischaemic stroke or the patient transferred out of the participating GP surgery. Outcome data for the non-polypharmacy group, polypharmacy group and hyper-polypharmacy group, were examined in detail, using logistic regression and propensity score matching. Further information about data analysis is presented in section 3.13.

3.10 Prognostic factors

The Clinical file, Test file and Additional Clinical Details file in CPRD GOLD, in addition to the English Index of Multiple Deprivation (IMD) linked dataset, were accessed to obtain the prognostic factor data for this study. Prognostic factor data recorded between the index date and two years prior to the index date were extracted and included in the statistical analyses. Previous studies which have examined the adverse outcomes associated with polypharmacy, in individuals with AF, have used a selection of the prognostic factors included in this study (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016). Details about the prognostic factors included in this study are provided below, along with the definitions and the rationale for inclusion:

1. Pre-existing medical conditions

The following pre-existing medical conditions were included as prognostic factors in this study: Chronic obstructive pulmonary disease (COPD), diabetes mellitus, heart failure, hypertension, ischaemic heart disease and other ischaemic cardiovascular conditions, peripheral vascular disease, obstructive sleep apnoea, and thyroid disorders. These medical conditions were defined as Read codes (Appendix 5, tables A5-4 to A5-12) recorded in the participant's Clinical file. For each of these medical conditions, the participant's disease status was recorded using the binary categorical variables of yes or no.

The medical conditions included as prognostic factors in this study are independently associated with ischaemic strokes and mortality, and this risk is enhanced in individuals

who have AF as a co-morbidity (Traube and Coplan, 2011; Ashburner *et al.*, 2016; Chen *et al.*, 2016; Marulanda-Londoño and Chaturvedi, 2017; Verdecchia *et al.*, 2018; Matarese *et al.*, 2019; Ugowe *et al.*, 2019). For example, the mortality rate in individuals with AF and heart failure is doubled, compared to individuals with AF alone. Furthermore, ischaemic strokes are reported to be more severe if heart failure is comorbid with AF (Bordignon *et al.*, 2012).

2. Previous ischaemic stroke

This was defined as a Read code for ischaemic stroke (Appendix 5, table A5-2) recorded in the participant's Clinical file. A participant's ischaemic stroke status was recorded using the binary categorical variables of yes or no. Previous research has shown that the risk of a recurrent ischaemic stroke is greatest in the first year after the initial event, and this risk remains elevated for at least five years (Scmidt *et al.*, 1988; Amarenco *et al.*, 2018; Chen *et al.*, 2020). Furthermore, multiple ischaemic strokes are associated with a greater mortality risk, compared to a single ischaemic stroke episode (Aarnio *et al.*, 2014).

3. Previous myocardial infarction

This was defined as a Read code for myocardial infarction (MI) (Appendix 5, table A5-8) recorded in the participant's Clinical file. A participant's MI status was recorded using the binary categorical variables of yes or no. Findings from a population-based study with 30 years follow-up showed that participants who experienced a MI were three times more

likely to experience an ischaemic stroke in the first year after the MI, compared to the general population. The risk of experiencing an ischaemic stroke following a MI remained elevated in the subsequent years of follow-up (HR 1.6, 95% CI: 1.6-1.6) (Scmidt *et al.*, 1988). Another population-based study, which examined the long-term survival rates of participants following an MI, concluded that these individuals were twice to three times more likely to die in the seven years following the MI, compared to the general population after adjusting for age and gender (Smolina *et al.*, 2012).

4. Renal insufficiency

Renal insufficiency was defined as a record of estimated glomerular filtration rate (eGFR) ≤30ml/min/1.73m^2 in the participant's Test file. If more than eGFR value was available, the latest record (i.e., the most recent eGFR value) was selected. Renal insufficiency has been shown to be independently associated with an increased risk of thromboembolism (Wattanakit and Cushman, 2009). This risk is enhanced among individuals with AF, and as a result, these individuals have an increased susceptibility to experiencing an ischaemic stroke. The co-existence of AF and poor renal function has also been shown the be significantly associated with other adverse outcomes, including mortality (Hijazi and Wallentin, 2016; Kiuchi, 2018; Shin *et al.*, 2018).

5. Obesity

Obesity was defined as a body mass index (BMI) ≥30kg/m^2, recorded in the participant's Clinical file. If more than one BMI record was available for a participant, then the latest

record (i.e., the most recent BMI value) was selected. Obesity status was recorded as either obese or non-obese (BMI< 30kg/m^2). The research team have examined the associations between polypharmacy, hyper-polypharmacy and BMI previously (Slater *et al.*, 2018). No statistically significant associations were found between overweight participants (defined as BMI 25.0-29.9 kg/m^2) and polypharmacy or hyper-polypharmacy prevalence. However, obesity was found to be significantly associated with polypharmacy and hyper-polypharmacy prevalence, respectively (Slater *et al.*, 2018).

Obesity has also been reported to be associated with the outcomes of interest in this study (death and ischaemic stroke) (Flegal *et al.*, 2013; Liu *et al.*, 2018). A systematic review of studies examining the associations between BMI status and all-cause mortality, concluded that obese individuals had the greatest risk of all-cause mortality, compared to overweight or normal weight individuals (Flegal *et al.*, 2013). Similarly, a systematic review into the association between BMI and stroke concluded that the risk of ischaemic stroke rises with increasing BMI (Liu *et al.*, 2018).

6. Smoking

Smoking data were available in the Clinical file in CPRD GOLD. Further information about each participant's smoking status was available in the Additional Clinical file (entity = 4). If more than one smoking record was available for a participant, then the latest record (i.e., the most recent smoking record) was selected. Smoking status was recorded as non-smoker, smoker, or ex-smoker. The association between smoking and mortality is well-established

(Darden *et al.*,2018). Furthermore, individuals who smoke are twice to four times more likely to experience an ischaemic stroke, compared to non-smokers (Shah and Cole, 2010).

Previous research into the associations between polypharmacy, hyper-polypharmacy and smoking has produced conflicting results, with several studies reporting no association (Rajska-Neumann *et al.*, 2005; Henderson *et al.*, 2006), and another reporting an inverse association (Incalzi *et al.*, 2005).

7. Alcohol consumption

Alcohol consumption data were available in the Clinical file in CPRD GOLD. Further information about each participant's alcohol consumption was available in the Additional Clinical file (entity = 5). If more than one alcohol consumption record was available for a participant, then the latest record (i.e., the most recent alcohol consumption record) was selected. Alcohol consumption status was recorded as non-drinker, drinker, or ex-drinker. Regular alcohol consumption has been shown to be associated with an increased risk of ischaemic stroke and mortality previously (Hillbom *et al.*,1999; Mostofsky *et al.*, 2010; Rao and Andrade, 2016). In contrast, polypharmacy and hyper-polypharmacy prevalence has been shown to be inversely associated with frequent alcohol consumption (Incalzi *et al.*, 2005; Slater *et al.*, 2018).

8. Wealth

Wealth data were extraced from the English Index of Multiple Deprivation (IMD) linked dataset. Based on their IMD data, participants were allocated to one of five wealth quintiles. Quintile 1 was the wealthiest, while quintile 5 was the poorest. The research team have examined the associations between polypharmacy, hyper-polypharmacy and wealth previously. Findings showed that lower wealth was significantly associated with polypharmacy and hyper-polypharmacy prevalence among older individuals (Slater *et al.*, 2018). Furthermore, this association is likely to become more pronounced as the gap in wealth inequalities continues to broaden across the UK (Office for National Statistics, 2015). Lower wealth, in individual with AF, has also been shown to be associated with an increased risk of adverse outcomes, including mortality, myocardial infarctions and heart failure (LaRosa *et al.*, 2020).

3.11 Propensity Score Matching

Propensity score matching (PSM) was implemented in this study to examine the associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke), in detail. Using the propensity score matching function in SPSS, each participant was given a propensity score. The propensity score is a value between zero and one, which is 'the conditional probability of being exposed/treated, rather than the control, given the observed covariates' (Rosenbaum and Rubin, 1983). This statistical approach is becoming increasing popular in observation studies because it enables multiple confounders to be combined into a single score, and thus is associated with a lower risk of bias, compared to other statistical methods, such as logistic regression (Morgan, 2018).

In this research, the purpose of PSM was to balance the study groups (non-polypharmacy, polypharmacy, and hyper-polypharmacy) based on the following prognostic factors: age,

gender, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, ischaemic heart disease, peripheral vascular disease, obstructive sleep apnoea, thyroid disorders, previous myocardial infarction, previous ischaemic stroke, obesity, smoking, alcohol consumption, and wealth. By using this approach, the impact of confounding is reduced, as the only measured difference between the propensity score matched groups was the number of medications prescribed in the three months following AF diagnosis (Rosenbaum and Rubin, 1983; D'Agostino, 1998).

Propensity score matching was conducted in two stages, as it was not possible to match participants from all three groups in a single step. First, participants in the non-polypharmacy group were propensity score matched (1:1) to participants in the polypharmacy group, and findings are presented in Chapter 5. Following this, participants in the non-polypharmacy group were propensity score matched (1:1) to participants in the hyper-polypharmacy group, and findings are presented in Chapter 6.

3.12 Data Extraction

Data extraction for this study commenced on 4th April 2019 and was carried out by the Data Manager in the School of Medicine, at Keele University. Initially, the Data Manager was requested to extract all data which met the inclusion criteria for this study (section 3.7), for the available time period (1st January 1987 and 4th April 2019). The extracted data file was 5GB when zipped and contained approximately 100GB of data when unzipped. To accommodate the unzipped data file, IT services at Keele University were contacted several

times to increase the drive space in the Pharmacy O drive. IT services increased the drive space to 125GB on 8th May 2019. Despite this, there was still insufficient space to store and process the data file. To address this issue, the lead researcher and lead supervisor decided to reduce the time period for data extraction (1st June 2006 and 4th April 2019). The time period alteration did not change the study follow-up period (10 years) and it was still possible to obtain data for prognostic factors in the two years prior to AF diagnosis.

The Data Manager applied the new time period to the data extraction programme and 124,970 patients, who had an AF diagnosis and 'acceptable data' according to the CPRD quality standards, were identified (CPRD, 2020). Based on the feasibility counts (section 3.8.1), the research team were aware that this number of patients would reduce when the medication criteria (>1 prescribed medication in the three months following AF diagnosis) was applied.

Data for the 124,970 patients were extracted and made available to the lead researcher in multiple tables. Prescribed medication data (extracted from Therapy file in CPRD GOLD) were presented in 33 separate tables, while clinical data (extracted from Clinical file in CPRD GOLD) were presented in 9 different tables. To make these data tables more manageable, in terms of size and to enable the data to be imported into Microsoft Access, which has a limit of 2GB per table, further modifications were required. On 24th June 2019, the following fields were removed from the prescribed medication tables: staff identifier, dosage identifier, total quantity, number of days, number of packs, pack type, and the prescription date (i.e., the event date) was restricted to prescriptions issued on or after 1st

June 2006. Following the removal of these fields, the number of prescribed medication tables was reduced to three.

Similar to the prescribed medication tables, the following fields were removed from the clinical data tables, enabling the clinical data to be imported into Microsoft Access: system date, consultation type, consultation identifier, staff identifier, text identifier, episode, entity type, additional details identifier. The clinical event date was also restricted to include only events that occurred after 1st January 1996. Following the removal of these fields, the number of clinical data tables was reduced to two.

Once all the data tables had been reduced to less than 2GB in size, each table was imported into Microsoft Access (2016). Following this, a series of Access queries were conducted by the lead researcher. All queries were documented in a table created by the lead supervisor. The following information was recorded in the query table: the type of query, the purpose of the query, any variables created, the name of input table, the name of output table, the number of records in the output table and any additional comments. Details of all queries used in this study are presented in Appendix 10 (table A10-1).

3.13 Data Analysis

Participants were allocated to one of three groups according to the number of medications that had been prescribed in the three months following AF diagnosis: non-polypharmacy (1-4 prescribed medicines), polypharmacy (5-9 prescribed medicines) and

hyper-polypharmacy (≥10 prescribed medicines). Descriptive statistics were used initially to profile each group according to participant demographics. Following this, prescribed medication data were analysed for each group, and the results were presented in terms of British National Formulary (BNF) Chapters (Joint Formulary Committee, 2021). Descriptive statistics were also used to examine the associations between polypharmacy and hyper-polypharmacy in the three months following AF diagnosis, and study outcomes (death and ischaemic stroke) during follow-up.

To examine the associations in more detail Cox proportional hazards models were used, and the results are presented as hazard ratios (HR) with 95% confidence intervals. Hazard ratios are estimated ratios of the incidence of an event, in an intervention group compared to the control group, throughout a specified study period, rather than at a specific point in time, like odds ratios. In this research, the HR are estimated ratios of the incidence of death and ischemic stroke, in the intervention groups (polypharmacy and hyper-polypharmacy), compared to the control group (non-polypharmacy group), over a ten-year study period. (Monnickendam *et al*., 2019)

Cox proportional hazard models were considered suitable for examining the outcomes of interest (death and ischaemic stroke) over time, while also accounting for multiple prognostic factors (Bellera *et al.*, 2010). The first set of models were unadjusted for any prognostic factors. The second set of models (examining the association between polypharmacy and study outcomes) and third sets of models (examining the associations between hyper-polypharmacy and study outcomes) were adjusted for age, gender, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, ischaemic heart disease and other ischaemic cardiovascular conditions, peripheral vascular disease,

obstructive sleep apnoea, thyroid disorders, previous myocardial infarction, previous ischaemic stroke, renal insufficency, obesity, alcohol consumption, smoking and wealth. Further information about each prognostic factor, along with the definitions and the rationale for inclusion is presented in section 3.10.

The minimum sample size required for the second set of models (which examined the associations between polypharmacy and study outcomes) was 354, while the minimum sample size required for the third set of models (which examined the associations between hyper-polypharmacy and study outcomes) was 567 (Peduzzi *et al.*, 1996). Results from all Cox proportional hazard models were considered to be statistically significant if $p<0.05$. Missing data were coded as 'missing' and were included (but not reported) as a separate category in all of the Cox proportional hazard models. Finally, the analyses were undertaken using IBM Statistical Package for Social Sciences (SPSS) (V.24.0).

Propensity score matching (PSM) was conducted using a newer version of the SPSS software (V.26.0). The PSM function is not a standard setting in SPSS (V.26.0); therefore, the following two Python-based plug-ins had to be installed: FUZZY (V1.3.0) and PSM (V.1.4.7), before any analyses could be conducted. Further information about PSM, including the matching criteria, is presented in section 3.11.

3.14 Chapter Summary

The aim of this study was to determine whether polypharmacy and hyper-polypharmacy, in the three months following atrial fibrillation (AF) diagnosis, are associated with death or ischaemic stroke during follow-up, by analysing CPRD GOLD data. To achieve this aim, the prevalence of polypharmacy or hyper-polypharmacy in the three months following AF diagnosis was determined. Following this, the associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke) during follow-up were examined in detail, using unadjusted logistic regression, adjusted logistic regression and propensity score matching, as discussed within this chapter. The unadjusted logistic regression results are presented in Chapter 4, while the adjusted logistic regression and propensity score matched results for polypharmacy and hyper-polypharmacy are presented in Chapter 5 and Chapter 6, respectively.

Chapter 4: The associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke): unadjusted analyses

4.1 Introduction

The first objective of this study was to determine the prevalence of polypharmacy (5-9 medicines) and hyper-polypharmacy (≥10 medicines) in the first three months following AF diagnosis, and to stratify prescribed medication data by polypharmacy group at baseline. To meet this objective, demographic data and prescribed medication data were analysed, using descriptive statistics, and the results are presented in section 4.2 and section 4.3, respectively.

The second study objective was to investigate whether polypharmacy and hyper-polypharmacy, in the first three months following AF diagnosis, were associated with an increased risk of death or ischaemic stroke during follow-up. Descriptive statistics and logistic regression models were used to meet this objective, and the results are presented in section 4.4. All analyses undertaken in this chapter were unadjusted for prognostic factors.

The purpose of conducting unadjusted analyses initially was to provide baseline data, enabling comparisons to be made with the adjusted and propensity score matched results, which are presented in chapter 5 and chapter 6.

Another study objective was to investigate whether each prognostic factor was associated with death or ischaemic stroke during follow-up. To meet this objective, further logistic regression models were created. The unadjusted results for the associations between each prognostic factor and death are presented in section 4.5, while the results for the associations between each prognostic factor and ischaemic stroke are presented in section 4.6. The key findings from sections 4.2 to 4.6 are discussed in section 4.7, and a chapter summary is presented in section 4.8.

4.2 Participant Characteristics

There were 33,984 participants eligible for inclusion in this study. In the three months following AF diagnosis, 47.9% (n=16,271) of the participants were prescribed between five and nine medicines concurrently (polypharmacy), 30.4% (n=10,355) were prescribed ten or more medicines concurrently (hyper-polypharmacy), while 21.7% (n=7,358) were prescribed between one and four medicines concurrently (non- polypharmacy) (table 4-1). Participants with hyper-polypharmacy were older (mean age 77 years), compared to participants with polypharmacy (mean age 75 years) and participants with non- polypharmacy (mean age 69 years) (table 4-1). In contrast to the polypharmacy and non-polypharmacy groups, there were more women than men in the hyper-polypharmacy group (table 4-1).

Table 4-1: Age and gender of all participants at study entry (n=33,984)

	1-4 medicines (Non-polypharmacy)	**5-9 medicines (Polypharmacy)**	**≥10 medicines (Hyper-polypharmacy)**
Total (*n=33,984)*	7,358	16,271	10,355
Age and Gender			
Age (mean ± SD)	69 ± 14	75 ± 11	77 ± 10
Age (18-30 years) *n* (%)	59 (0.8%)	17 (0.1%)	4 (0.1%)
Age (31-50 years) *n* (%)	700 (9.5%)	372 (2.3%)	110 (1.1%)
Age (51-70 years) *n* (%)	2921(39.7%)	4628 (28.4%)	2399(23.2%)
Age (71-84 years) *n* (%)	2736 (37.2%)	8157 (50.1%)	5695 (55.0%)
Age (≥85 years) *n* (%)	942 (12.8%)	3097 (19.0%)	2147 (20.7%)
Female Sex *n* (%)	2852 (38.8%)	7748 (47.6%)	5489 (53.0%)

Participants with hyper-polypharmacy had more diagnosed conditions in the two years prior to AF diagnosis, compared to participants in the polypharmacy and non-polypharmacy groups. The most commonly diagnosed conditions among participants with hyper-polypharmacy were diabetes mellitus (21.3%), chronic obstructive pulmonary disease (COPD) (16.2%) and ischaemic heart disease (IHD) (11.2%) (table 4-2). In contrast to the hyper-polypharmacy group, the most commonly diagnosed conditions among participants with polypharmacy were hypertension (11.1%), diabetes mellitus (10.3%) and heart failure

(6.5%) (table 4-2). The prevalence of diagnosed conditions was lowest among participants in the non-polypharmacy group. Hypertension (9.0%) and diabetes mellitus (3.3%) were the most prevalent diagnosed conditions among the latter group of participants (table 4-2).

Table 4-2: Diagnosed conditions in the two years prior AF diagnosis for all study participants (n=33,984)

	1-4 medicines (Non-polypharmacy)	**5-9 medicines (Polypharmacy)**	**≥10 medicines (Hyper-polypharmacy)**
Total (*n=33,984)*	7,358	16,271	10,355
Diagnosed conditions in the 2 years prior to AF diagnosis			
COPD *n* (%)	153 (2.1%)	848 (5.2%)	1682 (16.2%)
Diabetes *n* (%)	244 (3.3%)	1672 (10.3%)	2203 (21.3%)
Heart failure *n* (%)	116 (1.6%)	1058 (6.5%)	1088 (10.5%)
Hypertension *n* (%)	660 (9.0%)	1798 (11.1%)	1003 (9.7%)
IHD and other ischaemic cardiovascular (CV) conditions *n* (%)	155 (2.1%)	1031 (6.3%)	1158 (11.2%)
Myocardial infarction *n* (%)	28 (0.4%)	297 (1.8%)	395 (3.8%)
Previous ischaemic stroke *n* (%)	311 (4.2%)	1077 (6.6%)	711 (6.9%)
Peripheral vascular disease *n* (%)	52 (0.7%)	218 (1.3%)	229 (2.2%)
Sleep apnoea *n* (%)	47 (0.6%)	183 (1.1%)	169 (1.6%)
Thyroid disorders *n* (%)	89 (1.2%)	275 (1.7%)	245 (2.4%)
Poor renal function (eGFR ≤30ml/min/1.73m^2) *n* (%)	28 (0.4%)	143 (0.9%)	283 (2.7%)

There were more obese (BMI ≥ 30kg/m^2) participants in the hyper-polypharmacy group (30.2%), compared to the polypharmacy and non-polypharmacy groups (21.1% and 13.9% respectively) (table 4-3). However, the proportion of non-obese (BMI ≤30kg/m^2) participants in the polypharmacy group and hyper-polypharmacy group were similar (42.4% and 43.2% respectively). Furthermore, there were similar proportions of individuals who smoked and consumed alcohol in each group (table 4-3).

Table 4-3: Lifestyle factors at study entry for all participants (n=33,984)

	1-4 medicines (Non-polypharmacy)	**5-9 medicines (Polypharmacy)**	**≥10 medicines (Hyper-polypharmacy)**
Total (*n=33,984)*	7,358	16,271	10,355
Lifestyle Factors at study entry			
Non-obese (BMI ≤30kg/m^2) *n* (%)	2598 (35.3%)	6891 (42.4%)	4475 (43.2%)
Obese (BMI ≥ 30kg/m^2) *n* (%)	1025 (13.9%)	3437 (21.1%)	3132 (30.2%)
Non-drinker (alcohol) *n* (%)	407 (5.5%)	1555 (9.6%)	1331 (12.9%)
Drinker (alcohol) *n* (%)	2255 (30.6%)	5651 (34.7%)	3649 (35.2%)
Ex-drinker (alcohol) *n* (%)	70 (1.0%)	224 (1.4%)	280 (2.7%)
Non-smoker *n* (%)	2797 (38.0%)	6351 (39.0%)	3756 (36.3%)
Smoker *n* (%)	665 (9.0%)	1423 (8.7%)	1062 (10.3%)
Ex-smoker *n* (%)	2008 (27.3%)	5764 (35.4%)	4472 (43.2%)

Finally, in comparison to participants in the non-polypharmacy group, fewer participants in the polypharmacy and hyper-polypharmacy groups were in the wealth quintile 1 (wealthiest) (13.7% and 10.5% respectively), and more participants in the polypharmacy and hyper-polypharmacy groups were in the wealth quintile 5 (poorest) (7.5% and 10.3% respectively) (table 4-4).

Table 4-4: Wealth at study entry for all participants (n=33,984)

	1-4 medicines (Non-polypharmacy)	**5-9 medicines (Polypharmacy)**	**≥10 medicines (Hyper-polypharmacy)**
Total (*n=33,984)*	7,358	16,271	10,355
Wealth at study entry			
Wealth quintile 1 (wealthiest) *n* (%)	1219 (16.6%)	2227 (13.7%)	1087 (10.5%)
Wealth quintile 2 *n* (%)	1034 (14.1%)	2168 (13.3%)	1193 (11.5%)
Wealth quintile 3 *n* (%)	891 (12.1%)	2006 (12.3%)	1231 (11.9%)
Wealth quintile 4 *n* (%)	652 (8.9%)	1560 (9.6%)	1044 (10.1%)
Wealth quintile 5 (poorest) *n* (%)	406 (5.5%)	1226 (7.5%)	1067 (10.3%)

4.3 Prescribed medications in the three months following AF diagnosis

Prescribed medication data were obtained from the Therapy file in CPRD GOLD and prescribing in the three months following AF diagnosis was examined in detail.

In contrast to the other sections in this chapter, the results presented here represent the number of medicines prescribed, rather than the number of participants. The rationale behind this approach was to examine prescribing at a group level, rather than an individual level, using cross-tabulation.

Overall, 270,018 medications were prescribed for the study participants (n=33,984) in the three months following AF diagnosis. Prescribed medication data were stratified by polypharmacy group at baseline and British National Formulary (BNF) Chapters, and the results are presented in table 4-5 (Joint Formulary Committee, 2021).

Table 4-5: Prescribed medications in the three months following AF diagnosis stratified by polypharmacy group at baseline and British National Formulary (BNF) Chapters (n=270,018 medications) (Joint Formulary Committee, 2021).

	1-4 medicines (Non-polypharmacy) (n= 21,846 items)	**5-9 medicines (Polypharmacy) (n=112,899 items)**	**≥10 medicines (Hyper-polypharmacy) (n= 135,273 items)**
BNF Chapter 1 (Gastrointestinal system)	1,144 (5.2%)	8,979 (8.0%)	14,778 (10.9%)
BNF Chapter 2 (Cardiovascular system)	15,594 (71.4%)	67,287 (59.6%)	57,920 (42.8%)
BNF Chapter 3 (Respiratory system)	464 (2.1%)	4,012 (3.6%)	8,858 (6.6%)
BNF Chapter 4 (Central nervous system)	1,336 (6.1%)	10,050 (8.9%)	16,317 (12.1%)
BNF Chapter 5 (Infections)	648 (3.0%)	3,986 (3.5%)	7,634 (5.6%)
BNF Chapter 6 (Endocrine system)	639 (2.9%)	4,636 (4.1%)	7,180 (5.3%)
BNF Chapter 7 (Obstetrics, gynaecology and urinary tract disorders)	147 (0.7%)	771 (0.7%)	1,007 (0.7%)
BNF Chapter 8 (Malignant disease and immunosuppression)	48 (0.2%)	295 (0.3%)	328 (0.2%)
BNF Chapter 9 (Nutrition and blood)	334 (1.5%)	3,013 (2.7%)	5,359 (4.0%)
BNF Chapter 10 (Musculoskeletal and joint diseases)	342 (1.6%)	2,310 (2.1%)	3,113 (2.3%)
BNF Chapter 11 (Eye)	294 (1.4%)	2,072 (1.8%)	2,889 (2.1%)
BNF Chapter 12 (Ear, Nose and Oropharynx)	167 (0.8%)	871 (0.8%)	1,351 (1.0%)
BNF Chapter 13 (Skin)	434 (2.0%)	2,971 (2.6%)	5,454 (4.0%)
BNF Chapter 14 (Vaccines)	139 (0.6%)	737 (0.7%)	676 (0.5%)

BNF Chapter 15 (Anaesthesia)	11 (0.1%)	60 (0.1%)	145 (0.1%)
Unable to identify from codes	105 (0.5%)	849 (0.8%)	2,264 (1.7%)

Participants in the polypharmacy group were collectively prescribed 112,899 medications in the three months following AF diagnosis, of which 59.6% (n=67,287) were cardiovascular medicines (BNF Chapter 2). Other commonly prescribed medications for participants with polypharmacy included central nervous system (CNS) medicines (BNF Chapter 4) (8.9%), gastrointestinal medicines (BNF Chapter 1) (8.0%) and endocrine medicines (BNF Chapter 6) (4.1%) (table 4-5).

In comparison to the polypharmacy group, there was a greater diversity of prescribing in the hyper-polypharmacy group. The most commonly prescribed medicines for participants in the hyper-polypharmacy group were cardiovascular medicines (BNF Chapter 1) (42.8%), CNS medicines (BNF Chapter 4) (12.1%) and gastrointestinal medicines (BNF Chapter 1) (10.9%) (table 4-5). Finally, 71.4% of the medications prescribed for participants in the non-polypharmacy group, were cardiovascular medicines (BNF Chapter 2) (table 4-5).

4.4 An initial examination of the associations between polypharmacy and hyper-polypharmacy in the three months following AF diagnosis, and study outcomes

Descriptive statistics were initially used to determine whether polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, were associated with an

increased risk of death or ischaemic stroke during follow-up. The mean duration of follow-up varied between the study groups (5.5 years ±3 for the non-polypharmacy group, 5.0 years ±3 for the polypharmacy group and 4.1 years ±3 for the hyper-polypharmacy group respectively) (table 4-6).

Before the end of the study, 38.8% (n=13,181/33,984) of the participants had died, and 9.0% (n=3,064/33,984) had experienced an ischaemic stroke. Outcome data were then stratified by polypharmacy group at baseline. The percentage of deaths during follow-up increased from 24.0% in the non-polypharmacy group to 37.2% in the polypharmacy group, and then increased further to 51.8% in the hyper-polypharmacy group. The percentages of ischaemic strokes during follow-up were similar for all groups (table 4-6).

Table 4-6: Prevalence of death and ischaemic stroke among study participants during follow-up (n=33,984)

	1-4 medicines (Non-polypharmacy) (n=7,358)	**5-9 medicines (Polypharmacy) (n=16,271)**	**≥10 medicines (Hyper-polypharmacy) (n=10,355)**
Follow up (years) (mean ± SD)	5.5 ± 3	5.0 ± 3	4.1 ± 3
Total number of deaths per group *n* (%)	1,769 (24.0%)	6,047 (37.2%)	5,365 (51.8%)
Total number of strokes per group *n* (%)	659 (9.0%)	1447(8.9%)	940 (9.1%)

An unadjusted logistic regression model was used to examine the associations between polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, and the risk of death during follow-up. For participants with polypharmacy, the unadjusted hazard ratio (HR) for death during follow-up was 1.73 (1.64 to 1.82, $p<0.01$). This value increased to 2.92 (2.76 to 3.08, $p<0.01$) in participants with hyper-polypharmacy (table 4-7).

Table 4-7: The associations between polypharmacy, hyper-polypharmacy, and death during follow-up (unadjusted) (n=33,984)

	Unadjusted hazard ratio (HR)	95% CI		Sig.
		Lower	Upper	
1-4 medicines (non- polypharmacy)	Reference			
5-9 medicines (polypharmacy)	1.73	1.64	1.82	<0.01
≥10 medicines (hyper-polypharmacy)	2.92	2.76	3.08	<0.01

A second logistic regression model was created to examine the unadjusted associations between polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, and the risk of ischaemic stroke during follow-up. For participants with polypharmacy, the unadjusted hazard ratio (HR) for ischaemic stroke during follow-up was 1.10 (1.00 to 1. 20, p=0.05). This value increased to 1.34 (1.21 to 1.48, p<0.01) in participants with hyper-polypharmacy (table 4-8).

Table 4-8: The associations between polypharmacy, hyper-polypharmacy, and ischaemic stroke during follow-up (unadjusted) (n=33,984)

	Unadjusted hazard ratio	95% CI		Sig.
		Lower	Upper	
1-4 medicines (non- polypharmacy)	Reference			
5-9 medicines (polypharmacy)	1.10	1.00	1.20	0.05
≥10 medicines (hyper-polypharmacy)	1.34	1.21	1.48	<0.01

4.5 Associations between each prognostic factor and death

Further logistic regression models were created to examine the associations between each prognostic factor and death, and the results are presented in table 4-9. Prognostic factor data were recorded in the two years prior to AF diagnosis. Further details about each prognostic factor is available in Chapter 3, section 3.10.

Table 4-9: The associations between each prognostic factor included in this study, and death during follow-up (n= 33,984) (unadjusted)

	Unadjusted hazard ratio	**95% CI**		**Sig.**
		Lower	**Upper**	
Age				
Age (18-30 years)	Reference			
Age (31-50 years)	0.88	0.36	2.17	0.78
Age (51-70 years)	3.21	1.33	7.71	<0.01
Age (71-84 years)	9.20	3.83	22.11	<0.01
Age (≥85 years)	22.17	9.22	53.29	<0.01
Gender				
Male sex	Reference			
Female Sex	1.12	1.09	1.16	<0.01
Diagnosed conditions in the 2 years prior to AF diagnosis				
COPD	2.14	2.03	2.25	<0.01
Diabetes	1.31	1.25	1.38	<0.01
Heart failure	1.91	1.80	2.02	<0.01
Hypertension	0.84	0.79	0.89	<0.01
IHD or other CV conditions	1.13	1.06	1.20	<0.01
Myocardial infarction	1.26	1.13	1.41	<0.01
Previous ischaemic stroke	1.35	1.26	1.44	<0.01
Peripheral vascular disease	1.69	1.50	1.91	<0.01
Sleep apnoea	1.26	1.08	1.46	<0.01
Thyroid disorders	1.07	0.95	1.22	0.27
Poor renal function (eGFR ≤30ml/min/1.73m^2)	2.74	2.46	3.06	<0.01
Lifestyle Factors				
Non-obese (BMI ≤30kg/m^2)	Reference			
Obese (BMI ≥ 30kg/m^2)	0.67	0.64	0.70	<0.01
Non-drinker (alcohol)	Reference			
Drinker (alcohol)	0.72	0.68	0.76	<0.01
Ex-drinker (alcohol)	1.09	0.95	1.24	0.21
Non-smoker	Reference			
Smoker	1.37	1.29	1.45	<0.01
Ex-smoker	1.23	1.18	1.28	<0.01
Wealth				
Wealth quintile 1 (wealthiest)	Reference			
Wealth quintile 2	1.10	1.03	1.19	<0.01
Wealth quintile 3	1.23	1.14	1.32	<0.01
Wealth quintile 4	1.24	1.15	1.33	<0.01
Wealth quintile 5 (poorest)	1.48	1.37	1.60	<0.01

The associations between increasing age and death during follow-up became statistically significant in participants aged over 50 years (table 4-9). For participants aged between 51 and 70 years, the unadjusted HR for death during follow-up was 3.21 (1.33 to 7.71, p<0.01). This value increased to 9.20 (3.83 to 22.11, p<0.01) in participants aged between 71 and 84 years (table 4-9).

Hypertension was inversely associated with death during follow-up (HR 0.84; 95% CI: 0.79 to 0.89, p <0.01) (table 4-9). However, the other diagnosed conditions, included as prognostic factors in this study, were associated with an increased risk of death during follow-up. Poor renal function (HR 2.74; 95% CI: 2.46 to 3.06, p<0.01) and COPD (HR 2.14; 95% CI: 2.03 to 2.25, p<0.01) had the highest unadjusted hazard ratios for death during follow-up (table 4-9).

Obesity (BMI ≥ 30kg/m^2) was found to be inversely associated with death during follow-up (HR 0.67;95% CI: 0.64 to 0.70, p <0.01) (table 4-9). Similarly, alcohol consumption was inversely associated with death during follow-up (unadjusted HR 0.72; 95% CI: 0.68 to 0.76, p<0.01) (table 4-9). In contrast to the obesity and alcohol consumption findings, the unadjusted HR for death and smoking was 1.37 (1.29 to 1.45, p<0.01). This value reduced to 1.23 (1.18 to 1.28, p<0.01) in ex-smokers (table 4-9).

Wealth was moderately associated with death during follow-up. The unadjusted hazard ratio for death increased from 1.10 (1.03 to 1.19, p<0.01) in wealth quintile 2, to 1.48 (1.37 to

1.60, p<0.01) in wealth quintile 5 (poorest). All findings in relation to wealth were statistically significant (table 4-9).

4.6 Associations between each prognostic factor and ischaemic stroke

Logistic regression models were also used to examine the associations between each prognostic factor and ischaemic stroke, and the results are presented in table 4-10.

Table 4-10: The associations between each prognostic factor included in this study, and ischaemic stroke during follow-up (n= 33,984) (unadjusted)

	Unadjusted hazard ratio	**95% CI**		**Sig.**
		Lower	**Upper**	
Age				
Age (18-30 years)	Reference			
Age (31-50 years)	2.58	0.36	18.73	0.35
Age (51-70 years)	5.96	0.84	42.39	0.07
Age (71-84 years)	10.12	1.42	71.86	0.02
Age (≥85 years)	15.33	2.16	109.03	<0.01
Gender				
Male sex	Reference			
Female Sex	1.21	1.13	1.30	<0.01
Diagnosed conditions in the 2 years prior to AF diagnosis				
COPD	0.90	0.77	1.05	0.17
Diabetes	1.15	1.03	1.28	0.01
Heart failure	0.78	0.66	0.93	<0.01
Hypertension	1.11	0.99	1.24	0.08
IHD or other CV conditions	1.11	0.97	1.27	0.12
Myocardial infarction	0.92	0.71	1.20	0.55
Previous ischaemic stroke	2.46	2.20	2.74	<0.01
Peripheral vascular disease	1.73	1.35	2.23	<0.01
Sleep apnoea	1.22	0.89	1.67	0.23
Thyroid disorders	1.07	0.82	1.40	0.61
Poor renal function (eGFR ≤30ml/min/1.73m^2)	1.32	0.97	1.81	0.08
Lifestyle Factors				
Non-obese (BMI ≤30kg/m^2)	Reference			
Obese (BMI ≥ 30kg/m^2)	0.74	0.68	0.82	<0.01
Non-drinker (alcohol)	Reference			
Drinker (alcohol)	0.90	0.79	1.02	0.11
Ex-drinker (alcohol)	1.12	0.84	1.49	0.46
Non-smoker	Reference			
Smoker	1.06	0.93	1.20	0.42
Ex-smoker	1.01	0.93	1.09	0.89
Wealth				
Wealth quintile 1 (wealthiest)	Reference			
Wealth quintile 2	1.04	0.91	1.20	0.54
Wealth quintile 3	1.02	0.89	1.18	0.74

Wealth quintile 4	0.95	0.81	1.11	0.50
Wealth quintile 5 (poorest)	0.95	0.80	1.12	0.53

The association between increasing age and ischaemic stroke during follow-up was only statistically significant in participants aged between 71 and 84 years (HR 10.12; 95% CI:1.42-71.86, p=0.02) and in participants aged over 85 years (HR 15.33; 95% CI: 2.16-109.03, p<0.01) (table 4-10). Furthermore, participants who had experienced an ischaemic stroke, in the two years prior to AF diagnosis, were almost 2.5 times more likely to experience another ischaemic stroke during follow-up, compared to participants who had not experienced an ischaemic stroke in the two years prior to AF diagnosis (HR 2.46; 95% CI: 2.20 to 2.74, p<0.01) (table 4-10).Other diagnosed conditions associated with ischaemic stroke during follow-up included peripheral vascular disease (HR 1.73; 95% CI: 1.73 to 2.23, p<0.01) and diabetes mellitus (HR 1.15; 95% CI: 1.03 to 1.28, p<0.01) (table 4-10).

Obesity (BMI ≥ 30kg/m^2) was found to be inversely associated with ischaemic stroke during follow-up (HR 0.74; 95% CI: 0.68 to 0.82, p <0.01) (table 4-10). However, the model failed to produce any statistically significant results when the associations between alcohol consumption and smoking were examined, in relation to ischaemic stroke during follow-up (table 4-10).

Lower wealth was not associated with ischaemic stroke during follow-up. In the poorer wealth quintiles (quintile 4 and 5), the unadjusted HR for ischaemic stroke was 0.95 (0.81 to 1.11, p=0.50) in wealth quintile 4 and 0.95 (0.80 to 1.12, p=0.53) in wealth quintile 5 (poorest) (table 4-10).

4.7 Chapter Discussion

Overall, 47.9% (n=16,271) of the participants were prescribed between five and nine medications concurrently (polypharmacy), while 30.4% (n=10,355) were prescribed ten or more medications concurrently (hyper-polypharmacy), in the three months following AF diagnosis. Other studies have reported a similar prevalence of polypharmacy and hyper-polypharmacy in individuals with AF previously (Piccini *et al.*, 2016; Proietti *et al.*, 2016). In this study, logistic regression (unadjusted) showed that polypharmacy and hyper-polypharmacy were associated with an increased risk of death and ischaemic stroke during follow-up. Furthermore, the unadjusted associations between death and hyper-polypharmacy (HR 2.92; 95% CI: 2.76-3.08, $p<0.01$), and ischaemic stroke and hyper-polypharmacy (HR 1.34; 95% CI: 1.21-1.48, $p<0.01$), were accentuated, in comparison to the associations between death and polypharmacy (HR 1.73; 95% CI; 1.64 to 1.82, $p<0.01$), and ischaemic stroke and polypharmacy (HR 1.10; 95% CI; 1.00 to 1.20, $p=0.05$).

The prevalence of diagnosed conditions in the two years prior to AF diagnosis increased simultaneously with the number of prescribed medications, for example 3.3% of the participants in the non-polypharmacy group had been diagnosed with diabetes mellitus, while 10.3% of participants with polypharmacy and 21.3% of participants with hyper-polypharmacy had been diagnosed with diabetes mellitus, respectively. Furthermore, detailed analysis of prescribing data showed that participants in the non-polypharmacy

group were predominantly prescribed cardiovascular medicines (BNF Chapter 2) in the three months following AF diagnosis. In contrast to the non-polypharmacy group, the proportion of cardiovascular medicines, in relation to overall prescribing, was lower in the polypharmacy and hyper-polypharmacy groups, but there were more medicines prescribed from other BNF chapters (Joint Formulary Committee, 2021). Each BNF chapter represents a different diseased organ system; therefore, by proxy, these findings show that polypharmacy and hyper-polypharmacy are associated with multi-morbidity (Duerden *et al.*, 2013; Payne *et al.*, 2014; Payne, 2016).

All diagnosed conditions recorded in the two years prior to AF diagnosis, with the exception of hypertension and thyroid disorders, were associated with death during follow-up, to a varying extent. Participants with poor renal function (defined as eGFR ≤30ml/min/1.73m^2) were almost three times more likely to die during follow-up, compared to participants in the reference category (eGFR >30ml/min/1.73m^2). Similar hazard ratios have been reported when the association between severe renal impairment and mortality, in participants with other cardiovascular conditions, has been examined previously (van Domburg *et al.*, 2008). In the current study, hypertension was found to be inversely associated with death. This finding requires further investigation as hypertension rarely exists in isolation (Noh *et al.*, 2016). Instead, hypertension is often a precursor to the development of other chronic diseases, including renal failure, ischaemic heart disease and heart failure, which have been shown to be independently associated with an increased risk of mortality (Mohamed *et al.*, 2020).

The associations between lifestyle factors, wealth, and study outcomes (death and ischaemic stroke) were also examined in this study. Obesity was found to be inversely associated with death and ischaemic stroke during follow-up. Few studies support our obesity findings, in relation to mortality (Romero-Corral *et al.*, 2006; Hamer and Stamatakis, 2012; Kuk *et al.*, 2018). Instead, most studies report an association between obesity and death, and attribute the association to metabolic disturbances (for example, hypertension, impaired glucose metabolism and hypercholesterolaemia), resulting in the development of cardiovascular diseases and death (Faeh *et al.*, 2011; Slater *et al.*, 2018; Tobias and Hu, 2018; Xu *et al.*, 2018). Metabolic disturbances have also been linked to the reported association between obesity and ischaemic stroke previously (Kernan *et al.*, 2013; Li *et al.*, 2016). It was beyond the scope of the current study to analyse metabolic data, such as blood test results; however, this could be an area for future research within the AF population.

Polypharmacy and hyper-polypharmacy were most prevalent among participants in the poorer wealth quintiles (quintiles 4 and 5), thus supporting the existing literature (Slater *et al.*, 2018). Furthermore, this study showed that participants living in the lowest wealth quintile (wealth quintile 5) were 48% more likely to die during follow-up, compared to participants living in the highest wealth quintile. This finding is important because wealth inequalities are continuing to broaden across England; therefore, the risk of mortality is likely to be further enhanced in individuals with AF, who are living in the poorer wealth quintiles (Phillips and Agrawal, 2020).

The association between lower wealth and ischaemic stroke was also examined in this study; however, no statistically significant association was found. While these stroke

findings are supported by Avendano and Glymour, (2008), conflicting findings have been reported in other studies previously. Grimaud *et al.* (2011) concluded that individuals with a higher socio-economic status (SES) were more likely to experience an ischaemic stroke, compared to individuals with a lower SES; whereas, McFadden *et al.* (2009) reported that the incidence of ischaemic stroke was greatest among those in lower socio-economic groups. Despite the differing findings, both studies (McFadden *et al.*, 2009; Grimaud *et al.*, 2011) acknowledged that the underlying reasons for the reported associations between wealth and ischaemic stroke are not fully understood.

Finally, alcohol consumption was inversely associated with death during follow-up, but not ischaemic stroke. Conclusions drawn from a meta-analysis of 34 prospective studies, which examined the association between mortality and alcohol consumption, partially support our findings (Di Castelnuovo, 2006). Moderate alcohol consumption was found to be inversely associated with mortality; however, excessive alcohol consumption was associated with an increased risk of mortality. In the current study, participants were only categorised as drinkers, ex-drinkers, or non-drinkers; therefore, it is possible that a different conclusion may have been reached if participants had been subdivided further, according to their level of alcohol consumption.

4.8 Chapter Summary

The unadjusted logistic regression models showed that polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, were associated with an increased risk of death and ischaemic stroke during follow-up. Furthermore, the unadjusted

associations between hyper-polypharmacy and death, and hyper-polypharmacy and ischaemic stroke were accentuated, in comparison to the associations between polypharmacy and death, and polypharmacy and ischaemic stroke.

When the associations between prognostic factors and study outcomes were examined, some statistically significant associations were observed. It is possible that these associations may affect the associations observed between polypharmacy, hyper-polypharmacy, and the study outcomes. Therefore, to minimise confounding, all statistical models in the subsequent chapters (chapter 5 and chapter 6) were adjusted for the prognostic factors and propensity score matched (1:1).

Chapter 5: The associations between polypharmacy and study outcomes (death and ischaemic stroke): adjusted and propensity score matched analyses

5.1 Introduction

One study objective was to determine whether polypharmacy, in the first three months following AF diagnosis, is associated with an increased risk of death or ischaemic stroke during follow-up, using adjusted logistic regression and propensity score matching (1:1). The adjusted logistic regression results for the association between polypharmacy and death during follow-up are presented in section 5.2, while the adjusted logistic regression results for the association between polypharmacy and ischaemic stroke during follow-up are presented in section 5.3.

Following the adjusted analyses, propensity score matching (1:1) was implemented, and the results are presented in section 5.4 and section 5.5, respectively. The associations between polypharmacy and study outcomes (death and ischaemic stroke) were also examined in the propensity score matched groups, and the results are presented in section 5.6.

The association between polypharmacy in the first three months following AF diagnosis and study outcomes (death and ischaemic stroke) has been examined using unadjusted logistic

regression (Chapter 4, section 4.4), adjusted logistic regression and propensity score matching. A summary of results is provided in section 5.7.

The key findings from sections 5.2 to 5.7 are discussed in section 5.8, and a chapter summary is presented in section 5.9.

5.2 Polypharmacy and death: adjusted analyses

The method for the adjusted analyses is presented in section 3.13. Logistic regression showed that polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death during follow-up (unadjusted HR 1.73; 95% CI; 1.64 to 1.82, p<0.01) (table 5-1). After adjusting for participant age, the hazard ratio (HR) reduced to 1.34 (95% CI: 1.27 to 1.42, p<0.01) (table 5-1). The HR reduced further to 1.30 (95% CI: 1.24 to 1.38, p<0.01) when the model was adjusted for diagnosed conditions, lifestyle factors and wealth, in addition to participant age and gender (table 5-1).

Table 5-1: Logistic regression to examine the association between polypharmacy and death during follow-up (n= 33,984). Duration of follow-up data is presented in table 4-6.

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Polypharmacy	1.73	1.64	1.82	<0.01
Polypharmacy Adjusted for gender	1.72	1.63	1.81	<0.01
Polypharmacy Adjusted for age	1.34	1.27	1.42	<0.01
Polypharmacy Adjusted for age, gender and diagnosed conditions	1.30	1.23	1.37	<0.01
Polypharmacy Adjusted for age, gender, diagnosed conditions and lifestyle factors	1.31	1.24	1.38	<0.01

Polypharmacy Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	1.30	1.24	1.38	<0.01

5.3 Polypharmacy and ischaemic stroke: adjusted analyses

Logistic regression was also used to examine the association between polypharmacy and ischaemic stroke. The method for the adjusted analyses is presented in section 3.13. The unadjusted results showed that polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of ischaemic stroke during follow-up (unadjusted HR 1.10, 95% CI: 1.00 to 1.20, p<0.05) (table 5-2). However, when the models were adjusted in a stepwise manner, for participant gender, age, diagnosed conditions, lifestyle factors and wealth, the HR reduced to 0.91 (95% CI; 0.83 to 1.01, p<0.07) and became statistically insignificant (table 5-2).

Table 5-2: Logistic regression to examine the association between polypharmacy and ischaemic stroke during follow-up (n= 33,984). Duration of follow-up data is presented in table 4-6.

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Polypharmacy	1.10	1.00	1.20	0.05
Polypharmacy Adjusted for gender	1.08	0.98	1.18	0.11
Polypharmacy Adjusted for age	0.94	0.85	1.03	0.16
Polypharmacy Adjusted for age, gender and diagnosed conditions	0.90	0.83	1.00	0.05
Polypharmacy Adjusted for age, gender, diagnosed conditions and lifestyle factors	0.91	0.83	1.00	0.06

Polypharmacy Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	0.91	0.83	1.01	0.07

5.4 Participant characteristics in the propensity score matched groups

The adjusted logistic regression results presented in sections 5.2 and 5.3 showed that polypharmacy, in the first three months following AF diagnosis, is associated with an increased risk of death during follow-up, but not ischaemic stroke. To investigate these associations further, propensity score matching (PSM) was implemented (Rosenbaum and Rubin, 1983). The purpose of PSM was to balance the non-polypharmacy group and polypharmacy group based on their prognostic factors, and thus reduce the impact of confounding in this study (Littnerová *et al.*, 2013).

Overall, 2,451 participants in the non-polypharmacy group were propensity score matched (1:1) by age, gender, diagnosed conditions in the two years prior to AF diagnosis, lifestyle factors and wealth, to 2,451 participants in the polypharmacy group. Demographic data for the propensity score matched groups are presented in table 5-3, while demographic data for all study participants has been presented previously in Chapter 4 (section 4.2).

Table 5-3: Demographic data for the propensity score matched groups (non-polypharmacy and polypharmacy) (n=4,902)

	1-4 medicines (Matched non-polypharmacy)	**5-9 medicines (Matched polypharmacy)**
Total (*n*)	**2,451**	**2,451**
Age and Gender		
Age (18-30 years) *n* (%)	0 (0.0%)	0 (0.0%)
Age (31-50 years) *n* (%)	60 (2.4%)	60 (2.4%)
Age (51-70 years) *n* (%)	877 (35.8%)	877 (35.8%)
Age (71-84 years) *n* (%)	1,204 (49.1%)	1,204 (49.1%)
Age (≥85 years) *n* (%)	310 (12.6%)	310 (12.6%)
Female Sex *n* (%)	1,019 (41.6%)	1,019 (41.6%)
Diagnosed conditions at study entry		
COPD *n* (%)	9 (0.4%)	9 (0.4%)
Diabetes *n* (%)	32 (1.3%)	32 (1.3%)
Heart failure *n* (%)	5 (0.2%)	5 (0.2%)
Hypertension *n* (%)	51 (2.1%)	51 (2.1%)
IHD or other CV conditions *n* (%)	3 (0.1%)	3 (0.1%)
Myocardial infarction *n* (%)	0 (0.0%)	0 (0.0%)
Previous stroke *n* (%)	19 (0.8%)	19 (0.8%)
Peripheral vascular disease *n* (%)	1 (0.0%)	1 (0.0%)
Sleep apnoea *n* (%)	0 (0.0%)	0 (0.0%)
Thyroid disorders *n* (%)	1 (0.0%)	1 (0.0%)
Poor renal function (EGFR ≤30ml/min/1.73m^2) *n* (%)	0 (0.0%)	0 (0.0%)
Lifestyle Factors at study entry		
Obese (BMI ≥ 30kg/m^2) *n* (%)	220 (9.0%)	220 (9.0%)
Non-obese (BMI ≤30kg/m^2) *n* (%)	813 (33.2%)	813 (33.2%)
Non-drinker (alcohol) *n* (%)	64 (2.6%)	64 (2.6%)
Drinker (alcohol) *n* (%)	692 (28.2%)	692 (28.2%)
Ex-drinker (alcohol) *n* (%)	2 (0.1%)	2 (0.1%)
Non-smoker *n* (%)	887 (36.2%)	887 (36.2%)
Smoker *n* (%)	102 (4.2%)	102 (4.2%)
Ex-smoker *n* (%)	709 (28.9%)	709 (28.9%)
Wealth at study entry		

Wealth quintile 1 (wealthiest) *n* (%)	387 (15.8%)	387 (15.8%)
Wealth quintile 2 *n* (%)	278 (11.3%)	278 (11.3%)
Wealth quintile 3 *n* (%)	256 (10.4%)	256 (10.4%)
Wealth quintile 4 *n* (%)	126 (5.1%)	126 (5.1%)
Wealth quintile 5 (poorest) *n* (%)	60 (2.4%)	60 (2.4%)

5.5 Prescribed medications in the three months following AF diagnosis, in the propensity score matched groups

Prescribed medication data for the propensity score matched groups were obtained from the Therapy file in CPRD GOLD and prescribing in the three months following AF diagnosis was examined in detail.

In contrast to the other sections in this chapter, the results presented here represent the number of medicines prescribed, rather than the number of participants. The rationale behind this approach has been discussed in section 4.3.

In the propensity score matched sample, there were 7,287 medications prescribed for the participants in the non-polypharmacy group (n= 2,451), while there were 16,567 medications prescribed for the participants in the polypharmacy group (n=2,451), in the three months following AF diagnosis. Prescribed medication data for the matched groups were stratified by British National Formulary (BNF) Chapters, and the results are presented in table 5-4 (Joint Formulary Committee, 2021).

Table 5-4: Prescribed medications in the three months following AF diagnosis stratified by British National Formulary (BNF) Chapters for the propensity score matched groups (n=23,854 medications) (Joint Formulary Committee, 2021).

	1-4 medicines (Matched non-polypharmacy) **(n= 7,287 items)**	**5-9 medicines (Matched Polypharmacy)** **(n=16,567 items)**
BNF Chapter 1 (Gastrointestinal system)	408 (5.6%)	1,417 (8.6%)
BNF Chapter 2 (Cardiovascular system)	5,149 (70.7%)	9,714 (58.6%)
BNF Chapter 3 (Respiratory system)	137 (1.9%)	450 (2.7%)
BNF Chapter 4 (Central nervous system)	431 (5.9%)	1,585 (9.6%)
BNF Chapter 5 (Infections)	214 (2.9%)	667 (4.0%)
BNF Chapter 6 (Endocrine system)	195 (2.7%)	497 (3.0%)
BNF Chapter 7 (Obstetrics, gynaecology and urinary tract disorders)	60 (0.8%)	134 (0.8%)
BNF Chapter 8 (Malignant disease and immunosuppression)	15 (0.2%)	35 (0.2%)
BNF Chapter 9 (Nutrition and blood)	124 (1.7%)	476 (2.9%)
BNF Chapter 10 (Musculoskeletal and joint diseases)	112 (1.5%)	393 (2.4%)
BNF Chapter 11 (Eye)	121 (1.7%)	317 (1.9%)
BNF Chapter 12 (Ear, Nose and Oropharynx)	59 (0.8%)	141 (0.9%)
BNF Chapter 13 (Skin)	183 (2.5%)	492 (3.0%)
BNF Chapter 14 (Vaccines)	46 (0.6%)	115 (0.7%)

BNF Chapter 15 (Anaesthesia)	4 (0.1%)	16 (0.1%)
Unable to identify from codes	29 (0.4%)	118 (0.7%)

Over half (58.6%) of the medications prescribed for the matched polypharmacy group, in the three months following AF diagnosis, were cardiovascular medicines (BNF Chapter 2) (table 5-4). Other commonly prescribed medications for the matched polypharmacy group included central nervous system (CNS) medicines (BNF Chapter 4) (9.6%) and gastrointestinal medicines (BNF Chapter 1) (8.6%) (table 5-4).

Prescribing in the matched non-polypharmacy group was less diverse, compared to the matched polypharmacy group. Cardiovascular medicines (BNF Chapter 2) accounted for 70.7% of all medicines prescribed in the matched non-polypharmacy group, in the three months following AF diagnosis. Other commonly prescribed medicines for the matched non-polypharmacy group included CNS medicines (BNF Chapter 4) (5.9%) and gastrointestinal medicines (BNF Chapter 1) (5.6%) (table 5-4).

The results presented in this section for the propensity score matched groups, were compared to the results from the analysis of prescribing data for all study participants (Chapter 4, section 4.3). The most commonly prescribed medicines for participants in the polypharmacy groups (complete and matched) were cardiovascular medicines (BNF Chapter 2), CNS medicines (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1). The proportion of these medicines, in relation to overall prescribing in the three months

following AF diagnosis, were similar in both polypharmacy groups (complete and matched) (table 5-5).

Table 5-5: The most commonly prescribed medications in the three months following AF diagnosis stratified by British National Formulary (BNF) Chapters, for the polypharmacy groups (complete and propensity score matched) (Joint Formulary Committee, 2021).

	Complete polypharmacy group (n=112,899 items prescribed for 16,271 participants)	**Matched polypharmacy group (n=16,567 items prescribed for 2,451 participants)**
BNF Chapter 1 (Gastrointestinal system)	8,979 (8.0%)	1,417 (8.6%)
BNF Chapter 2 (Cardiovascular system)	67,287 (59.6%)	9,714 (58.6%)
BNF Chapter 4 (Central nervous system)	10,050 (8.9%)	1,585 (9.6%)

Similarly, the most commonly prescribed medicines for participants in the non-polypharmacy groups (complete and matched) were cardiovascular medicines (BNF Chapter 2), CNS medicines (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1). The proportion of these medicines, in relation to overall prescribing in the three months following AF diagnosis, were also similar in both non-polypharmacy groups (complete and matched) (table 5-6).

Table 5-6: The most commonly prescribed medications in the three months following AF diagnosis stratified by British National Formulary (BNF) Chapters, for the non-polypharmacy groups (complete and propensity score matched) (Joint Formulary Committee, 2021).

	Complete non-polypharmacy group (n=21,846 items prescribed for 7,358 participants)	Matched non-polypharmacy group (n=7,287 items prescribed for 2,451 participants)
BNF Chapter 1 (Gastrointestinal system)	1,144 (5.2%)	408 (5.6%)
BNF Chapter 2 (Cardiovascular system)	15,594 (71.4%)	5,149 (70.7%)
BNF Chapter 4 (Central nervous system)	1,336 (6.1%)	431 (5.9%)

5.6 Study outcomes (death or ischaemic stroke) in the propensity score matched groups

Descriptive statistics were initially used to determine the number of deaths and ischaemic strokes during follow-up, in the propensity score matched groups. The mean duration of follow-up varied between the matched groups (66.9 months for the non-polypharmacy group versus 63.8 months for the polypharmacy group) (table 5-7).

In the propensity score matched groups, the percentage of deaths during follow-up increased from 25.5% in the non-polypharmacy group to 31.9% in the polypharmacy group. In contrast, the percentage of ischaemic strokes during follow-up decreased from 9.2% in the non-polypharmacy group to 7.4% in the polypharmacy group (table 5-7).

Table 5-7: The number of deaths and ischaemic strokes during follow-up in the propensity score matched groups (n=4,902)

	1-4 medicines (Matched non-polypharmacy) (n=2,451)	5-9 medicines (Matched polypharmacy) (n=2,451)

Total number of deaths per matched group *n* (%)	625 (25.5%)	783 (31.9%)
Total number of ischaemic strokes per matched group *n* (%)	226 (9.2 %)	181 (7.4%)
Mean follow up for the matched groups (months) (mean ± SD)	66.9 months (± 39)	63.8 months (± 39)

Logistic regression was also used to examine the associations between polypharmacy in the three months following AF diagnosis, and study outcomes (death and ischaemic stroke) during follow-up, in the propensity score matched groups. Results showed that polypharmacy was associated with an increased risk of death (HR 1.32; 95% CI 1.19 to 1.47, p<0.01) during follow-up, but not ischaemic stroke (HR 0.84; 95% CI 0.69 to 1.02, p=0.08) (table 5-8).

Table 5-8: Logistic regression to examine the associations between polypharmacy, death, and ischaemic stroke during follow-up, in the propensity score matched groups (n= 4,902)

	Hazard ratio	**95% C.I. for HR**		**Sig. level**
		Lower	**Upper**	
Polypharmacy and death	1.32	1.19	1.47	<0.01
Polypharmacy and ischaemic	0.84	0.69	1.02	0.08

The outcome data presented in this section for the propensity score matched groups, were compared to the outcome data for all study participants (Chapter 4, section 4.4). The percentage of deaths and ischaemic strokes during follow-up varied between the

polypharmacy groups, with a greater percentage of deaths and ischaemic strokes recorded for the complete polypharmacy group (table 5-9).

Table 5-9: Study outcomes (death and ischaemic stroke) during follow-up for the polypharmacy groups (complete and propensity score matched)

	Complete polypharmacy group (n= 16,271)	**Matched polypharmacy group (n= 2,451)**
Total number of deaths n (%)	6,047 (37.2%)	783 (31.9%)
Total number of ischaemic strokes *n* (%)	1447(8.9%)	181 (7.4%)

In contrast, there were similar percentages of deaths and ischaemic strokes during follow-up in the non-polypharmacy groups (complete and propensity score matched) (table 5-10).

Table 5-10: Study outcomes (death and ischaemic stroke) during follow-up for the non-polypharmacy groups (complete and propensity score matched)

	Complete non-polypharmacy group (n= 7,358)	**Matched non-polypharmacy group (n= 2,451)**
Total number of deaths n (%)	1,769 (24.0%)	625 (25.5%)
Total number of ischaemic strokes *n* (%)	659 (9.0%)	226 (9.2 %)

5.7 The associations between polypharmacy and study outcomes (death and ischaemic stroke) during follow-up: a summary

The association between polypharmacy and death during follow-up has been examined using unadjusted logistic regression (Chapter 4, section 4.4), adjusted logistic regression (Chapter 5, section 5.2). and propensity score matching (Chapter 5, section 5.6). Irrespective of the approach, a statistically significant association was found between polypharmacy in the three months following AF diagnosis, and death during follow-up (table 5-11).

Table 5-11: Summary of the association between polypharmacy and death during follow-up

	Hazard ratio	**95% C.I. for HR**		**Sig. level**
		Lower	**Upper**	
Unadjusted logistic regression (n=33,984)	1.73	1.64	1.82	<0.01
Adjusted logistic regression (n=33,984) Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	1.30	1.24	1.38	<0.01
Propensity score matched (n=4,902)	1.32	1.19	1.47	<0.01

The association between polypharmacy and ischaemic stroke during follow-up has also been examined using unadjusted logistic regression (Chapter 4, section 4.4), adjusted

logistic regression (Chapter 5, section 5.3). and propensity score matching (Chapter 5, section 5.6). The unadjusted logistic regression model showed a statistically significant association between polypharmacy in the three months following AF diagnosis, and an increased risk of ischaemic stroke during follow-up; however, this association diminished in the adjusted logistic regression models and propensity score matching analyses (table 5-12).

Table 5-12: Summary of the association between polypharmacy and ischaemic stroke during follow-up

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Unadjusted logistic regression (n=33,984)	1.10	1.00	1.20	0.05
Adjusted logistic regression (n=33,984) Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	0.91	0.83	1.01	0.07
Propensity score matched (n=4,902)	0.84	0.69	1.02	0.08

5.8 Chapter Discussion

The adjusted logistic regression showed that polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death during follow-up (HR 1.30; 95% CI 1.24 to 1.38, p<0.01), but not ischaemic stroke (HR 0.91; 95% CI 0.83 to

1.01, p=0.07). Piccini *et al.* (2016) and Eggebrecht *et al.* (2019) have reported similar findings previously.

Piccini *et al.* (2016) conducted a post-hoc analysis of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial data. After adjusting extensively for potential confounders, polypharmacy was found to be associated with an increased risk of death (HR 1.25; 95% CI 1.09 to 1.44, p<0.01), but not ischaemic stroke (HR 1.07; 95% CI 0.89 to 1.29, p=0.78). Similarly, Eggebrecht *et al.* (2019) concluded that polypharmacy, in individuals with AF, was associated with an increased risk of death (HR 1.70; 95% CI 1.17 to 2.47), but not ischaemic stroke (HR 0.43; 95% CI 0.16 to 1.16), following the analysis of data from the thromboEVAL study.

In contrast, Focks *et al.* (2016) reported that polypharmacy was associated with ischaemic stroke (HR 1.27; 95% CI 1.02 to 1.58, p<0.01) and death (HR 1.41; 95% CI 1.23 to 1.62, p<0.01) following a post-hoc analysis of data collected during the ARISTOTLE trial. One possible explanation for the differing findings could be that Focks *et al.* (2016) adjusted their logistic regression models for age, gender, and country of origin only, whereas Piccini *et al.* (2016), Eggebrecht *et al.* (2019), and the current study, adjusted the logistic regression models for a greater number of potential confounders, including diagnosed conditions.

The logistic regression models in the current study were adjusted for eleven different diagnosed conditions; whereas previous studies (Piccini *et al.*, 2016; Eggebrecht *et al.*, 2019) have adjusted for fewer diagnosed conditions, for example Piccini *et al.* (2016)

adjusted their models for seven diagnosed conditions, while Eggebrecht *et al.* (2019) adjusted their models for four diagnosed conditions. However, one limitation of the disease data analysed in the current study, and previous studies, was that the data did not provide information about the severity of the diagnosed conditions. This may need to be taken into consideration if polypharmacy is examined in relation to other adverse outcomes in the AF population.

The association between polypharmacy and mortality, in individuals with AF, has been discussed in the literature; however, further research is required to determine whether it is polypharmacy itself that is associated with mortality, or whether polypharmacy is merely a 'marker' of morbidity and it is the underlying diseases which are associated with mortality, in individuals with AF (Gomez *et al.*, 2014; Gallagher *et al.*, 2020).

To minimize the confounding effect of morbidity in the association between polypharmacy and mortality, propensity score matching was implemented in this study. By using this approach, it was possible to balance the non-polypharmacy group and polypharmacy group (1:1) based on their prognostic factors (age, gender, diagnosed conditions in the two years prior to AF diagnosis, lifestyle factors and wealth); therefore, the only measured difference between the propensity score matched groups was the number of medications they were prescribed in the three months following AF diagnosis.

The propensity score matching results showed that polypharmacy was associated with an increased risk of death during follow-up (HR 1.32; 95% CI 1.19 to 1.47, $p<0.01$), but not

ischaemic stroke (HR 0.84; 95% CI 0.69 to 1.02, p=0.08); thus, complementing the adjusted logistic regression results.

Prescribing in the three months following AF was also examined in the propensity score matched groups, and findings showed that cardiovascular medicines (BNF Chapter 2), central nervous system medicines (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1) were the most commonly prescribed types of medicines. These findings are consistent with our previous work, which examined the composition of polypharmacy among 7730 participants (≥50 years) in the English Longitudinal Study of Ageing (wave 6) (Slater *et al.*, 2020).

Cardiovascular medicines (BNF Chapter 2) accounted for over half (58.6% in the propensity score matched polypharmacy group and 59.6% in the complete polypharmacy group) of all medicines prescribed in the three months following AF diagnosis. BNF Chapter 2 (cardiovascular system) encompasses a number of different drug classes, including anticoagulants and statins; therefore, it is possible that this study found no association was found between polypharmacy and ischaemic stroke during follow-up, due to the cardioprotective nature of these medications (Davignon, 2004; Ludman *et al.*, 2009).

5.9 Chapter Summary

The adjusted logistic regression results showed that polypharmacy, in the three months following AF diagnosis, was associated with an increased risk of death, but not ischaemic

stroke during follow-up. These findings are consistent with the existing literature; however, to minimize the confounding effect of morbidity in the association between polypharmacy and mortality, propensity score matching was implemented in this study.

The propensity score matched results complemented the adjusted logistic regression results and showed that polypharmacy, in the first three months after AF diagnosis, was associated with an increased risk of death during follow-up, but not ischaemic stroke.

This chapter has examined the associations between polypharmacy and study outcomes (death and ischaemic stroke) in detail, using adjusted logistic regression and propensity score matching. In the next chapter of this thesis (Chapter 6), the associations between hyper-polypharmacy and study outcomes will be examined in detail, using the same statistical approaches.

Chapter 6: The associations between hyper-polypharmacy and study outcomes (death and ischaemic stroke): adjusted and propensity score matched analyses

6.1 Introduction

The final objective of this study was to determine whether hyper-polypharmacy, in the first three months following AF diagnosis, is associated with an increased risk of death or ischaemic stroke during follow-up, using adjusted logistic regression and propensity score matching (1:1). The adjusted logistic regression results for the association between hyper-polypharmacy and death during follow-up are presented in section 6.2, while the adjusted results for the association between hyper-polypharmacy and ischaemic stroke during follow-up are presented in section 6.3.

Following the adjusted analyses, propensity score matching (1:1) was implemented, and the results are presented in section 6.4 and section 6.5, respectively. The associations between hyper-polypharmacy and study outcomes were also examined in the propensity score matched groups, and the results are presented in section 6.6.

The association between hyper-polypharmacy in the first three months following AF diagnosis, and study outcomes (death and ischaemic stroke) has been examined using unadjusted logistic regression (Chapter 4, section 4.4), adjusted logistic regression and propensity score matching. A summary of these analyses is provided in section 6.7.

The key findings from sections 6.2 to 6.7 are discussed in section 6.8, and a chapter summary is presented in section 6.9.

6.2 Hyper-polypharmacy and death: adjusted analyses

The method for the adjusted analyses is presented in section 3.13. Logistic regression showed that hyper-polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death during follow-up (unadjusted HR 2.92; 95% CI; 2.76 to 3.08, p<0.01) (table 6-1). After adjusting for participant age, the hazard ratio (HR) reduced to 2.14 (95% CI: 2.02 to 2.26, p<0.01) (table 6-1). The HR reduced further to 1.90 (95% CI: 1.79 to 2.01, p<0.01) when the model was adjusted for diagnosed conditions, lifestyle factors and wealth, in addition to participant age and gender (table 6-1).

Table 6-1: Logistic regression to examine the association between hyper-polypharmacy and death during follow-up (n= 33,984) Duration of follow-up data is presented in table 4-6.

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Hyper-polypharmacy	2.92	2.76	3.08	<0.01
Hyper-polypharmacy Adjusted for gender	2.90	2.75	3.06	<0.01
Hyper-polypharmacy Adjusted for age	2.14	2.02	2.26	<0.01
Hyper-polypharmacy Adjusted for age, gender and diagnosed conditions	1.88	1.77	1.99	<0.01

Hyper-polypharmacy Adjusted for age, gender, diagnosed conditions and lifestyle factors	1.91	1.80	2.02	<0.01
Hyper-polypharmacy Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	1.90	1.79	2.01	<0.01

6.3 Hyper-polypharmacy and ischaemic stroke: adjusted analyses

Logistic regression was also used to examine the association between hyper-polypharmacy and ischaemic stroke. The method for the adjusted analyses is presented in section 3.13. The unadjusted results showed that hyper-polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of ischaemic stroke during follow-up (unadjusted HR 1.34, 95% CI: 1.21 to 1.49, p<0.01) (table 6-2). However, when the models were adjusted in a stepwise manner, for participant gender, age, diagnosed conditions, lifestyle factors and wealth, the HR reduced to 1.08 (95% CI; 0.97 to 1.21, p=0.16) and became statistically insignificant (table 6-2).

Table 6-2: Logistic regression to examine the association between hyper-polypharmacy and ischaemic stroke during follow-up (n= 33,984) Duration of follow-up data is presented in table 4-6.

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Hyper-polypharmacy	1.34	1.21	1.49	<0.01
Hyper-polypharmacy Adjusted for gender	1.30	1.18	1.44	<0.01
Hyper-polypharmacy Adjusted for age	1.10	0.99	1.21	0.08
Hyper-polypharmacy Adjusted for age, gender and diagnosed conditions	1.06	0.96	1.19	0.26

Hyper-polypharmacy Adjusted for age, gender, diagnosed conditions and lifestyle factors	1.08	0.97	1.20	0.19
Hyper-polypharmacy Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	1.08	0.97	1.21	0.16

6.4 Participant characteristics in the propensity score matched groups

The adjusted logistic regression results presented in sections 6.2 and 6.3 showed that hyper-polypharmacy, in the first three months following AF diagnosis, is associated with an increased risk of death during follow-up, but not ischaemic stroke. To investigate these associations further, propensity score matching (PSM) was implemented (Rosenbaum and Rubin, 1983). The purpose of PSM was to balance the non-polypharmacy group and hyper-polypharmacy group based on their prognostic factors, and thus reducing the impact of confounding in this study (Littnerová *et al.*, 2013).

Overall, 1,151 participants in the non-polypharmacy group were propensity score matched (1:1) by age, gender, diagnosed conditions in the two years prior to AF diagnosis, lifestyle factors and wealth, to 1,151 participants in the hyper-polypharmacy group. Demographic data for the propensity score matched groups are presented in table 6-3, while demographic data for all study participants has been presented previously in Chapter 4 (section 4.2).

Table 6-3: Demographic data for the propensity score matched groups (non-polypharmacy and hyper-polypharmacy) (n=2,302)

	1-4 medicines (Matched non-polypharmacy)	**≥10 medicines (Matched hyper-polypharmacy)**
Total (*n*)	**1,151**	**1,151**
Age and Gender		
Age (18-30 years) *n* (%)	0 (0.0%)	0 (0.0%)
Age (31-50 years) *n* (%)	7 (0.6%)	7 (0.6%)
Age (51-70 years) *n* (%)	268 (23.3%)	268 (23.3%)
Age (71-84 years) *n* (%)	670 (58.2%)	670 (58.2%)
Age (≥85 years) *n* (%)	206 (17.9%)	206 (17.9%)
Female Sex *n* (%)	609 (52.9%)	609 (52.9%)
Diagnosed conditions at study entry		
COPD *n* (%)	11 (1.0%)	11 (1.0%)
Diabetes *n* (%)	27 (2.3%)	27 (2.3%)
Heart failure *n* (%)	1 (0.1%)	1 (0.1%)
Hypertension *n* (%)	28 (2.4%)	28 (2.4%)
IHD or other CV conditions *n* (%)	5 (0.4%)	5 (0.4%)
Myocardial infarction *n* (%)	0 (0.0%)	0 (0.0%)
Previous stroke *n* (%)	7 (0.6%)	7 (0.6%)
Peripheral vascular disease *n* (%)	0 (0.0%)	0 (0.0%)
Sleep apnoea *n* (%)	1 (0.1%)	1 (0.1%)
Thyroid disorders *n* (%)	1 (0.1%)	1 (0.1%)
Poor renal function (EGFR ≤30ml/min/1.73m^2) *n* (%)	1 (0.1%)	1 (0.1%)
Lifestyle Factors at study entry		
Obese (BMI ≥ 30kg/m^2) *n* (%)	133 (11.6%)	133 (11.6%)
Non-obese (BMI ≤30kg/m^2) *n* (%)	434 (37.7%)	434 (37.7%)
Non-drinker (alcohol) *n* (%)	47 (4.1%)	47 (4.1%)
Drinker (alcohol) *n* (%)	355 (30.8%)	355 (30.8%)
Ex-drinker (alcohol) *n* (%)	0 (0.0%)	0 (0.0%)
Non-smoker *n* (%)	444 (38.6%)	444 (38.6%)
Smoker *n* (%)	46 (4.0%)	46 (4.0%)
Ex-smoker *n* (%)	366 (31.8%)	366 (31.8%)
Wealth at study entry		
Wealth quintile 1 (wealthiest) *n* (%)	135 (11.7%)	135 (11.7%)
Wealth quintile 2 *n* (%)	114 (9.9%)	114 (9.9%)
Wealth quintile 3 *n* (%)	104 (9.0%)	104 (9.0%)

Wealth quintile 4 *n* (%)	54 (4.7%)	54 (4.7%)
Wealth quintile 5 (poorest) *n* (%)	46 (4.0%)	46 (4.0%)

6.5 Prescribed medications in the three months following AF diagnosis, in the propensity score matched groups

Prescribed medication data for the propensity score matched groups were obtained from the Therapy file in CPRD GOLD and prescribing in the three months following AF diagnosis was examined in detail.

In contrast to the other sections in this chapter, the results presented here represent the number of all prescribed medications, rather than the number of patients. The rationale behind this approach has been discussed in section 4.3.

In the propensity score matched sample, there were 3,547 medications prescribed for the participants in the non-polypharmacy group (n= 1,151), while there were 14,340 medications prescribed for the participants in the hyper-polypharmacy group (n=1,151), in the three months following AF diagnosis. Prescribed medication data for the matched groups were stratified by British National Formulary (BNF) Chapters, and the results are presented in table 6-4 (Joint Formulary Committee, 2021).

Table 6-4: Prescribed medications in the three months following AF diagnosis stratified by British National Formulary (BNF) Chapters for the propensity score matched groups (n=17,887 medications) (Joint Formulary Committee, 2021).

	1-4 medicines (Matched non-polypharmacy) **(n= 3,547 items)**	**≥10 medicines (Matched hyper-polypharmacy)** **(n=14,340 items)**
BNF Chapter 1 (Gastrointestinal system)	183 (5.2%)	1,707 (11.9%)
BNF Chapter 2 (Cardiovascular system)	2,547 (71.8%)	5,936 (41.4%)
BNF Chapter 3 (Respiratory system)	59 (1.7%)	685 (4.8%)
BNF Chapter 4 (Central nervous system)	220 (6.2%)	1,905 (13.3%)
BNF Chapter 5 (Infections)	98 (2.8%)	809 (5.6%)
BNF Chapter 6 (Endocrine system)	90 (2.5%)	542 (3.8%)
BNF Chapter 7 (Obstetrics, gynaecology and urinary tract disorders)	29 (0.8%)	140 (1.0%)
BNF Chapter 8 (Malignant disease and immunosuppression)	7 (0.2%)	44 (0.3%)
BNF Chapter 9 (Nutrition and blood)	68 (1.9%)	622 (4.3%)
BNF Chapter 10 (Musculoskeletal and joint diseases)	56 (1.6%)	387 (2.7%)
BNF Chapter 11 (Eye)	63 (1.8%)	363 (2.5%)
BNF Chapter 12 (Ear, Nose and Oropharynx)	28 (0.8%)	170 (1.2%)
BNF Chapter 13 (Skin)	56 (1.6%)	703 (4.9%)
BNF Chapter 14 (Vaccines)	18 (0.5%)	65 (0.5%)
BNF Chapter 15 (Anaesthesia)	0 (0.0%)	21 (0.1%)
Unable to identify from codes	25 (0.7%)	241 (1.7%)

Cardiovascular medicines (BNF Chapter 2) accounted for almost half (41.4%) of all medicines prescribed for the matched hyper-polypharmacy group, in the three months following AF diagnosis (table 6-4). Other commonly prescribed medications for the

matched hyper-polypharmacy group included CNS medicines (BNF Chapter 4) (13.3%) and gastrointestinal medicines (BNF Chapter 1) (11.9%) (table 6-4).

Prescribing in the matched non-polypharmacy group was less diverse, compared to the matched hyper-polypharmacy group. Cardiovascular medicines (BNF Chapter 2) accounted for almost three-quarters (71.8%) of all medicines prescribed in the matched non-polypharmacy group, in the three months following AF diagnosis. Other commonly prescribed medicines for the matched non-polypharmacy group included CNS medicines (BNF Chapter 4) (6.2%) and gastrointestinal medicines (BNF Chapter 1) (5.2%) (table 6-4).

The results presented in this section for the propensity score matched groups, were compared to the results from the analysis of prescribing data for all study participants (Chapter 4, section 4.3). The most commonly prescribed medicines for participants in the hyper-polypharmacy groups (complete and matched) were cardiovascular medicines (BNF Chapter 2), CNS medicines (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1). The proportion of these medicines, in relation to overall prescribing in the three months following AF diagnosis, were similar in both hyper-polypharmacy groups (complete and matched) (table 6-5).

Table 6-5: The most commonly prescribed medications in the three months following AF diagnosis stratified by British National Formulary (BNF) Chapters, for the hyper-polypharmacy groups (complete and propensity score matched) (Joint Formulary Committee, 2021).

	Complete hyper-polypharmacy group (n=135,273 items prescribed for 10,355 participants)	**Matched hyper-polypharmacy group (n=14,340 items prescribed for 1,151 participants)**

BNF Chapter 1 (Gastrointestinal system)	14,778 (10.9%)	1,707 (11.9%)
BNF Chapter 2 (Cardiovascular system)	57,920 (42.8%)	5,936 (41.4%)
BNF Chapter 4 (Central nervous system)	16,317 (12.1%)	1,905 (13.3%)

Similarly, the most commonly prescribed medicines for participants in the non-polypharmacy groups (complete and matched) were cardiovascular medicines (BNF Chapter 2), CNS medicines (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1). The proportion of these medicines, in relation to overall prescribing in the three months following AF diagnosis, were also similar in both non-polypharmacy groups (complete and matched) (table 6-6).

Table 6-6: The most commonly prescribed medications in the three months following AF diagnosis stratified by British National Formulary (BNF) Chapters, for the non-polypharmacy groups (complete and propensity score matched) (Joint Formulary Committee, 2021).

	Complete non-polypharmacy group (n=21,846 items prescribed for 7,358 participants)	**Matched non-polypharmacy group (n=3,547 items prescribed for 1,151 participants)**
BNF Chapter 1 (Gastrointestinal system)	1,144 (5.2%)	183 (5.2%)
BNF Chapter 2 (Cardiovascular system)	15,594 (71.4%)	2,547 (71.8%)
BNF Chapter 4 (Central nervous system)	1,336 (6.1%)	220 (6.2%)

6.6 Study outcomes (death or ischaemic stroke) in the propensity score matched groups

Descriptive statistics were initially used to determine the number of deaths and ischaemic strokes during follow-up, in the propensity score matched groups. The mean duration of follow-up varied between the matched groups (64.4 months for the non-polypharmacy group versus 52.8 months for the hyper-polypharmacy group) (table 6-7).

In the propensity score matched groups, the percentage of deaths during follow-up increased from 31.5% in the non-polypharmacy group to 48.3% in the hyper-polypharmacy group. In contrast, the percentage of ischaemic strokes during follow-up were similar in the non-polypharmacy group (9.3%) and the hyper-polypharmacy group (9.1%) (table 6-7).

Table 6-7: The number of deaths and ischaemic strokes during follow-up in the propensity score matched groups (n=2,302)

	1-4 medicines (Matched non-polypharmacy) (n=1,151)	**≥10 medicines (Matched hyper-polypharmacy) (n=1,151)**
Total number of deaths per matched group *n* (%)	363 (31.5%)	556 (48.3%)
Total number of strokes per matched group *n* (%)	107 (9.3%)	105 (9.1%)
Follow up for matched groups (months) (mean ± SD)	64.4 months (± 39)	52.8 months (± 38)

Logistic regression was also used to examine the associations between hyper-polypharmacy in the three months following AF diagnosis, and study outcomes (death and ischaemic stroke) during follow-up, in the propensity score matched groups. Results showed that hyper-polypharmacy was associated with an increased risk of death (HR 1.89; 95% CI: 1.65 to 2.16, $p<0.01$) during follow-up, but not ischaemic stroke (HR 1.19; 95% CI: 0.91 to 1.57, $p=0.20$) (table 6-8).

Table 6-8: Logistic regression to examine the associations between hyper-polypharmacy, death, and ischaemic stroke during follow-up, in the propensity score matched groups (n= 2,302)

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Hyper-polypharmacy and death	1.89	1.65	2.16	<0.01
Hyper-polypharmacy and stroke	1.19	0.91	1.57	0.20

The outcome data presented in this section for the propensity score matched groups, were compared to the outcome data for all study participants (Chapter 4, section 4.4). The percentage of deaths during follow-up varied between the hyper-polypharmacy groups, with a greater percentage of deaths recorded for the complete hyper-polypharmacy group (table 6-9). However, the percentage of ischaemic strokes during follow-up was identical for the complete and propensity score matched hyper-polypharmacy groups (table 6-9).

Table 6-9: Study outcomes (death and ischaemic stroke) during follow-up for the hyper-polypharmacy groups (complete and propensity score matched)

	Complete hyper-polypharmacy group (n= 10,355)	**Matched hyper-polypharmacy group (n= 1,151)**
Total number of deaths n (%)	5,365 (51.8%)	556 (48.3%)
Total number of ischaemic strokes *n* (%)	940 (9.1%)	105 (9.1%)

In the non-polypharmacy groups (complete and propensity score matched) there was a greater percentage of deaths in the matched group, compared to the complete group. However, there was a similar percentage of ischaemic strokes in both groups (table 6-10).

Table 6-10: Study outcomes (death and ischaemic stroke) during follow-up for the non-polypharmacy groups (complete and propensity score matched)

	Complete non-polypharmacy group (n= 7,358)	**Matched non-polypharmacy group (n= 1,151)**
Total number of deaths n (%)	1,769 (24.0%)	363 (31.5%)
Total number of ischaemic strokes *n* (%)	659 (9.0%)	107 (9.3%)

6.7 The associations between hyper-polypharmacy and study outcomes (death and ischaemic stroke) during follow-up: a summary

The association between hyper-polypharmacy and the risk of death during follow-up has been examined using unadjusted logistic regression (Chapter 4, section 4.4), adjusted logistic regression (Chapter 6, section 6.2). and propensity score matching (Chapter 6, section 6.6). Irrespective of the approach, a statistically significant association was found between hyper-polypharmacy in the three months following AF diagnosis, and death during follow-up (table 6-11).

Table 6-11: Summary of the association between hyper-polypharmacy and death during follow-up

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Unadjusted logistic regression (n=33,984)	2.92	2.76	3.08	<0.01
Adjusted logistic regression (n=33,984) Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	1.90	1.79	2.01	<0.01
Propensity score matched (n=2,302)	1.89	1.65	2.16	<0.01

The association between hyper-polypharmacy and the risk of ischaemic stroke during follow-up has also been examined using unadjusted logistic regression (Chapter 4, section 4.4), adjusted logistic regression (Chapter 6, section 6.3). and propensity score matching (Chapter 6, section 6.6). The unadjusted logistic regression model showed a statistically significant association between hyper-polypharmacy in the three months following AF diagnosis, and ischaemic stroke during follow-up; however, this association diminished in the adjusted logistic regression models and propensity score matching analyses (table 6-12).

Table 6-12: Summary of the association between hyper-polypharmacy and ischaemic stroke during follow-up

	Hazard ratio	95% C.I. for HR		Sig. level
		Lower	Upper	
Unadjusted logistic regression (n=33,984)	1.34	1.21	1.48	<0.01
Adjusted logistic regression (n=33,984) Adjusted for age, gender, diagnosed conditions, lifestyle factors and wealth	1.08	0.97	1.21	0.16
Propensity score matched (n=2,302)	1.19	0.91	1.57	0.20

6.8 Chapter Discussion

The adjusted logistic regression showed that hyper-polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death during follow-up (HR 1.90; 95% CI 1.79 to 2.01, p<0.01), but not ischaemic stroke (HR 1.08; 95% CI 0.97 to 1.21, p=0.16). It is challenging to compare these findings to the literature, as few studies have examined the association between hyper-polypharmacy and adverse outcomes, in individuals with AF previously (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Eggebrecht *et al.*, 2019). Instead, most studies have examined adverse outcomes, in relation to polypharmacy (most commonly defined as ≥5 medicines) (Gasse *et al.*, 2005; Lobos-Bejarano *et al.*, 2017) .

Two studies separated hyper-polypharmacy from polypharmacy, using arbitrarily selected numeric thresholds, and examined adverse outcomes in the AF population previously (Focks *et al.*, 2016; Piccini *et al.*, 2016). The numeric thresholds varied between these studies, and differing findings were reported (Focks *et al.*, 2016; Piccini *et al.*, 2016). Similar to Piccini *et al.* (2016), the current study defined hyper-polypharmacy as '≥10 prescribed medicines', and both studies found that hyper-polypharmacy was associated with an increased risk of death during follow-up, but not ischaemic stroke, in individuals with AF. In contrast, Focks *et al.* (2016) used a lower numeric threshold to define hyper-polypharmacy ('≥9 concomitant drugs') and reported that hyper-polypharmacy was associated with ischaemic stroke and death in individuals with AF. It is possible that the numeric threshold used to define hyper-polypharmacy may have influenced the results reported; however, this requires further exploration (Focks *et al.*, 2016; Piccini *et al.*, 2016).

The current study found no association between hyper-polypharmacy, in the three months following AF diagnosis, and ischaemic stroke during follow-up. Previously, Piccini *et al.* (2016) suggested that the lack of association between hyper-polypharmacy and ischaemic stroke may be due to the inclusion criteria utilised in the 'Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)' trial. Only participants who were 'moderate to high risk of a stroke' were eligible to participate in the ROCKET AF trial. Furthermore, participants who had experienced a stroke previously, and at highest risk of a subsequent stroke, were reported to be younger and taking fewer concomitant medications, in comparison to other ROCKET AF trial participants (Piccini *et al.*, 2016). However, the

current study analysed primary care data, rather than conducting a post-hoc analysis of trial data, for all individuals with AF, irrespective of their thromboembolic risk, and still found no association between hyper-polypharmacy and ischaemic stroke during follow-up.

Focks *et al.* (2016) reported an association between hyper-polypharmacy and ischaemic stroke; however, the authors suggested that this association may have diminished if their analyses had been adjusted for 'co-morbidities at baseline'. The results from the current study support this suggestion, as no association was found between hyper-polypharmacy in the three months following AF diagnosis and ischaemic stroke during follow-up, after the logistic regression models were adjusted extensively for diagnosed conditions, in addition to participant age, gender, lifestyle factors and wealth.

This study has advanced the limited literature by using propensity score matching (PSM) to examine the associations between hyper-polypharmacy and study outcomes (death and ischaemic stroke) in detail. By using PSM, participants in the non-polypharmacy group were matched (1:1) to participants in the hyper-polypharmacy group, according to their age, gender, diagnosed conditions in the two years prior to AF diagnosis, lifestyle factors and wealth; therefore, the only measured difference between the propensity score matched groups was the number of medications they were prescribed in the three months following AF diagnosis (Rosenbaum and Rubin, 1983).

The propensity score matching results showed that hyper-polypharmacy was associated with an increased risk of death during follow-up (HR 1.89; 95% CI 1.65 to 2.16, $p<0.01$),

but not ischaemic stroke (HR 1.19; 95% CI 0.91 to 1.57, p=0.20); thus, complementing the adjusted logistic regression results.

Prescribing in the three months following AF was also examined in the propensity score matched groups, and findings showed that cardiovascular medicines (BNF Chapter 2), CNS medicines (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1) were the most commonly prescribed types of medicines. However, it is not possible to compare these findings, as no literature was found regarding the composition of hyper-polypharmacy regimens. Instead, previous studies have examined the composition of polypharmacy (defined as ‘5 or more concomitant medicines) regimens, rather than separating hyper-polypharmacy from polypharmacy, and examining the composition of these medication regimens separately (Bjerrum *et al.*, 1998; Wastesson *et al.*, 2018; Slater *et al.*, 2020). Consequently, this has identified an area for future research in hyper-polypharmacy.

6.9 Chapter Summary

The adjusted logistic regression results showed that hyper-polypharmacy, in the three months following AF diagnosis, was associated with an increased risk of death but not ischaemic stroke during follow-up. These findings are consistent with previous research which defined hyper-polypharmacy as ’10 or more concomitant medicines’ (Piccini *et al.*, 2016).

The analyses in this study were extensively adjusted for a greater number of prognostic factors, compared to previous studies; thus, reducing the likelihood of confounding.

Furthermore, propensity score matching was used to minimise the confounding effect of morbidity in the association between hyper-polypharmacy and mortality.

The propensity score matched results complemented the adjusted logistic regression results and showed that hyper-polypharmacy, in the first three months after AF diagnosis, was associated with an increased risk of death during follow-up, but not ischaemic stroke.

This thesis has three results chapters (Chapter 4, Chapter 5, and Chapter 6). The unadjusted logistic regression results for the associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke) were presented in Chapter 4. In Chapter 5, the associations between polypharmacy, in the first three months following AF diagnosis, and study outcomes were examined in detail, using adjusted logistic regression and propensity score matching. In this chapter (Chapter 6), the associations between hyper-polypharmacy, in the first three months following AF diagnosis, and study outcomes were examined using adjusted logistic regression and propensity score matching. The key findings from the three results chapters (Chapter 4, Chapter 5, and Chapter 6) will be discussed further in the subsequent chapter (Chapter 7).

Chapter 7: Discussion

7.1 Introduction

The purpose of this chapter is to discuss the key findings in this thesis. First, the key findings will be considered in the context of the thesis objectives (Chapter 3, section 3.2) and discussed in section 7.2. Following this, the key findings will be discussed in the context of the existing literature (section 7.3). The strengths and limitations of this research are discussed in section 7.4. The significance of the findings for clinical practice are discussed in section 7.5. Opportunities for future research have been identified in section 7.6, and a thesis conclusion is presented in section 7.7.

7.2 Key findings in the context of the thesis objectives

The aim of this thesis was to determine whether polypharmacy and hyper-polypharmacy, in the three months following atrial fibrillation (AF) diagnosis, were associated with an increased risk of death or ischaemic stroke during follow-up. To achieve the aim, there were five research objectives. The key findings will be discussed in the context of these objectives in the subsequent sections.

7.2.1 Polypharmacy prevalence at study entry

The first objective was to determine the prevalence of polypharmacy (5-9 prescribed medicines) and hyper-polypharmacy (≥10 prescribed medicines) in the first three months following AF diagnosis, and to stratify the prescribed medication data by polypharmacy group at baseline.

Of the 33,984 participants, 47.9% (n=16,271) were prescribed between five and nine medications concurrently (polypharmacy), 30.4% (n=10,355) were prescribed ten or more medications concurrently (hyper-polypharmacy), while 21.7% (n=7,358) were prescribed between one and four medicines concurrently (non-polypharmacy) in the three months following AF diagnosis.

Data were stratified according to participant characteristics at study entry, and the results were presented in Chapter 4. Findings showed that participants with polypharmacy and hyper-polypharmacy were older and had more diagnosed conditions in the two years prior to AF diagnosis, compared to participants with non-polypharmacy. There were also more obese participants in the polypharmacy and hyper-polypharmacy groups, compared to the non-polypharmacy group. Furthermore, polypharmacy and hyper-polypharmacy were most prevalent among participants in the poorer wealth quintiles (quintiles 4 and 5).

Analysis of prescribed medication data, according to the British National Formulary (BNF) chapters, showed that participants with polypharmacy were commonly prescribed medications which acted on the cardiovascular system (BNF Chapter 2), central nervous system (BNF Chapter 4) and gastrointestinal system (BNF Chapter 1). These types of medications were also commonly prescribed for participants with hyper-polypharmacy; however, prescribing in the latter group was more diverse. In contrast, medications which acted on the cardiovascular system (BNF Chapter 2) accounted for almost three-quarters of the prescribing in the non-polypharmacy group.

7.2.2 The unadjusted associations between polypharmacy, hyper-polypharmacy, and study outcomes

The second objective was to investigate whether polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, were associated with an increased risk of death or ischaemic stroke during follow-up, using unadjusted logistic regression.

The unadjusted results were presented and discussed in Chapter 4. Stratification of outcome data by polypharmacy group showed that the percentage of deaths during follow-up increased from 24.0% in the non-polypharmacy group to 37.2% in the polypharmacy group, and then increased further to 51.8% in the hyper-polypharmacy group, while the percentages of ischaemic strokes during follow-up were similar for all groups.

Unadjusted logistic regression showed that polypharmacy in the three months following AF diagnosis, was significantly associated with an increased risk of death (HR 1.73; 95% CI; 1.64 to 1.82, p<0.01), and ischaemic stroke (HR 1.10; 95% CI; 1.00 to 1.20, p=0.05), during follow-up. Furthermore, the risk of death (HR 2.92; 95% CI; 2.76-3.08, p<0.01) and ischaemic stroke (HR 1.34; 95% CI; 1.21-1.48, p<0.01) during follow-up, was accentuated in the hyper-polypharmacy group.

7.2.3 The associations between prognostic factors and study outcomes

The third objective was to examine the associations between each prognostic factor and study outcomes (death and ischaemic stroke). There were 17 prognostic factors included in the analyses: age, gender, eleven diagnosed conditions, obesity, alcohol consumption, smoking and wealth. The association between each prognostic factor and study outcomes were presented and discussed in Chapter 4.

Increasing age was significantly associated with an increased risk of death during follow-up, in participants aged over 50, whereas, increasing age was only significantly associated with an increased risk of ischaemic stroke during follow-up, in participants aged over 70. Furthermore, women had a greater risk of death and ischaemic stroke during follow-up, compared to men.

All diagnosed conditions, with the exception of hypertension and thyroid disorders, were significantly associated with death during follow-up. In contrast, fewer diagnosed

conditions (diabetes mellitus, peripheral vascular disease, and a history of a previous ischaemic stroke) were significantly associated with an increased risk of ischaemic stroke during follow-up. These findings highlighted the importance of adjusting the statistical analyses for diagnosed conditions, to reduce the risk of confounding, when the examining the associations between polypharmacy, hyper-polypharmacy, and study outcomes, in this thesis.

The associations between obesity, alcohol consumption and smoking, were also examined in relation to the study outcomes. Obesity was found to be inversely associated with death and ischaemic stroke during follow-up. Alcohol consumption was also inversely associated with death during follow-up; however, no association was found between alcohol consumption and ischaemic stroke during follow-up. Finally, smoking was found to be significantly associated with an increased risk of death during follow-up, but not ischaemic stroke.

Wealth was moderately associated with death during follow-up. The unadjusted hazard ratio for death increased from 1.10 (1.03 to 1.19, $p<0.01$) in wealth quintile 2, to 1.48 (1.37 to 1.60, $p<0.01$) in wealth quintile 5 (poorest). However, lower wealth was not associated with an increased risk of ischaemic stroke during follow-up. The unadjusted hazard ratio for the risk of ischaemic stroke was 0.95 (0.80 to 1.12, $p=0.53$) in wealth quintile 5.

The prognostic factors included in this study were shown to be associated with the study outcomes (death and ischaemic stroke) to varying degrees; therefore, statistical adjustments were implemented to minimise the risk of confounding when examining the association

between polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, and the risk of death or ischaemic stroke during follow-up.

7.2.4 The adjusted and propensity score matched associations between polypharmacy and study outcomes

The fourth objective was to determine whether polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death or ischaemic stroke during follow-up, using adjusted logistic regression and propensity score matching (1:1).

The adjusted and propensity score matched results for polypharmacy were presented and discussed in Chapter 5. Adjusted logistic regression showed that polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death during follow-up (HR 1.30; 95% CI 1.24 to 1.38, $p<0.01$), but not ischaemic stroke (HR 0.91; 95% CI 0.83 to 1.01, $p=0.07$). The propensity score matched results complemented the adjusted logistic regression results and showed that polypharmacy was associated with an increased risk of death during follow-up (HR 1.32; 95% CI 1.19 to 1.47, $p<0.01$), but not ischaemic stroke (HR 0.84; 95% CI 0.69 to 1.02, $p=0.08$).

7.2.5 The adjusted and propensity score matched associations between hyper-polypharmacy and study outcomes

The final objective was to determine whether hyper-polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death or ischaemic stroke during follow-up, using adjusted logistic regression and propensity score matching (1:1).

The adjusted logistic regression and propensity score matched results for hyper-polypharmacy were presented and discussed in Chapter 6. Adjusted logistic regression showed that hyper-polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death during follow-up (HR 1.90; 95% CI 1.79 to 2.01, p<0.01), but not ischaemic stroke (HR 1.08; 95% CI 0.97 to 1.21, p=0.16). Similar to the polypharmacy findings (section 7.2.4), the propensity score matched results complemented the adjusted logistic regression results and showed that hyper-polypharmacy was associated with an increased risk of death during follow-up (HR 1.89; 95% CI 1.65 to 2.16, p<0.01), but not ischaemic stroke (HR 1.19; 95% CI 0.91 to 1.57, p=0.20).

7.3 Key findings in the context of the existing literature

Overall, 47.9% (n=16,271) of the participants were prescribed between five and nine medications concurrently (polypharmacy), while 30.4% (n=10,355) of the participants were prescribed ten or more medications concurrently (hyper-polypharmacy), in the three months following AF diagnosis. A meta-analysis of three post-hoc studies, which examined the adverse outcomes associated with polypharmacy in atrial fibrillation, reported a lower prevalence of polypharmacy and hyper-polypharmacy compared to this study (42.7% and 20.7% respectively) (Gallagher *et al.*, 2020). One possible explanation for the difference in prevalence data reported could be that there were different numeric thresholds and timeframes used to define polypharmacy in the studies included in the meta-analysis. For

example, Focks *et al.* (2016) defined polypharmacy as '6 to 8 concomitant drugs at baseline', and hyper-polypharmacy as '9 or more concomitant drugs at baseline', while, Piccini *et al.* (2016) defined polypharmacy as '5 to 9 medicines' and hyper-polypharmacy as '10 or more medicines'. Furthermore, all studies included in the meta-analysis determined a participant's polypharmacy status according to the number of concomitant medications taken on the day of trial enrollment, whereas the definitions of polypharmacy and hyper-polypharmacy used in this thesis considered medication usage over a broader period of time (3-month period) (section 3.6.1). The heterogeneity in polypharmacy and hyper-polypharmacy definitions makes it challenging to compare prevalence data, and thus provides support for Masnoon *et al.* (2017) suggestion to develop an "internationally agreed" definition of polypharmacy.

This thesis confirmed our previous research into the factors associated with polypharmacy, by showing that lower wealth and obesity were significantly associated with polypharmacy and hyper-polypharmacy prevalence, in addition to increasing age and morbidities (Slater *et al.*, 2018).

Fano (2014) complemented our wealth findings and concluded that individuals who resided in affluent areas were 33% less likely to experience polypharmacy, compared to individuals living in deprived areas. Increased disease burden, more severe conditions and poorer access to healthcare services, are some of the explanations offered for the association between lower wealth and polypharmacy prevalence (Department of Health, 2012; Fano, 2014; McMaughan *et al.*, 2020). Despite the significant association between lower wealth and polypharmacy prevalence, previous studies into the associations between polypharmacy

and adverse outcomes, have not adjusted their statistical models for wealth (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). To minimise confounding, statistical models were adjusted for wealth in the current study. This adjustment was important because UK wealth inequalities are continuing to broaden, and this may impact polypharmacy and hyper-polypharmacy prevalence in individuals with AF.

Lower wealth was found to be associated an increased risk of mortality, but not ischaemic stroke, in individuals with AF. While these stroke findings are supported by Avendano and Glymour, (2008), conflicting findings have been reported in other studies previously. Grimaud *et al.* (2011) concluded that individuals with a higher socio-economic status (SES) were more likely to experience an ischaemic stroke, compared to individuals with a lower SES; whereas, McFadden *et al.* (2009) reported that the incidence of ischaemic stroke was greatest among those in lower socio-economic groups. Despite the differing findings, both studies (McFadden *et al.*, 2009; Grimaud *et al.*, 2011) acknowledged that the underlying reasons for the reported associations between wealth and ischaemic stroke are not fully understood.

Obesity (defined as BMI $\geq 30 kg/m^2$) was significantly associated with polypharmacy and hyper-polypharmacy prevalence in this thesis, and thus complements the existing literature (Counterweight Project Team, 2005; Rieckert *et al.*, 2018; Assari *et al.*, 2019). Similar to the current study, Piccini *et al.* (2016) adjusted their statistical models for obesity during their post-hoc analysis of ROCKET AF trial data. However, statistical models were not adjusted for obesity in other studies, which have examined the adverse outcomes associated with polypharmacy in AF (Focks *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018).

The varying levels of adjustment, in relation to obesity, may have impacted the results reported when the associations between polypharmacy, death and ischaemic stroke, have been examined previously. Furthermore, obesity has been identified as a major public health issue (PHE, 2017). As a consequence of the current obesity epidemic, the prevalence of polypharmacy and hyper-polypharmacy, in individuals with AF, may rise too, thus highlighting the importance of including obesity as a covariate in future polypharmacy research (Slater *et al.*, 2018).

Obesity was also found to be inversely associated with death and ischaemic stroke during follow-up. Few studies support our obesity findings, in relation to mortality (Romero-Corral *et al.*, 2006; Hamer and Stamatakis, 2012; Kuk *et al.*, 2018). Instead, most studies report an association between obesity and death and attribute the association to metabolic disturbances (for example, hypertension, impaired glucose metabolism and hypercholesterolaemia), resulting in the development of cardiovascular diseases and death (Faeh *et al.*, 2011; Slater *et al.*, 2018; Tobias and Hu, 2018; Xu *et al.*, 2018). Metabolic disturbances have also been linked to the reported association between obesity and ischaemic stroke previously (Kernan *et al.*, 2013; Li *et al.*, 2016).

The association between polypharmacy prevalence and increasing age is well established (Gorard, 2006; Duerden *et al.*, 2013; Lai *et al.*, 2018; Morin *et al.*, 2018). Findings from this thesis complement the literature by showing that participants with polypharmacy and hyper-polypharmacy were older, compared to participants with non-polypharmacy.

Previous research has also shown an association between polypharmacy and morbidities (Barnett *et al.*, 2012; Payne *et al.*, 2014). This association was explored further in this thesis by analysing prescribed medication data, according to the British National Formulary (BNF) chapters. Findings showed that the prevalence of diagnosed conditions in the two years prior to AF diagnosis increased alongside the number of prescribed medications. Furthermore, participants in the non-polypharmacy group were predominantly prescribed cardiovascular medicines (BNF Chapter 2) in the three months following AF diagnosis. In contrast to the non-polypharmacy group, the proportion of cardiovascular medicines, in relation to overall prescribing, was lower in the polypharmacy and hyper-polypharmacy groups, however, there were more medicines prescribed from other BNF chapters (Joint Formulary Committee, 2021). Each BNF chapter represents a different diseased organ system; therefore, by proxy, these findings showed that polypharmacy and hyper-polypharmacy are associated with multi-morbidities, although it is not possible to determine the severity of the morbidities from the medication data analysed in this study (Duerden *et al.*, 2013; Payne *et al.*, 2014; Payne, 2016).

Cardiovascular medicines (BNF Chapter 2), CNS medicines (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1) were the most commonly prescribed types of medications in the polypharmacy and hyper-polypharmacy groups. These types of medications have been identified previously in the few studies which have examined the composition of polypharmacy regimens (Bjerrum *et al.*, 1998; Wastesson *et al.*, 2018; Slater *et al.*, 2020). CNS medicines and gastrointestinal medicines have also been shown to be associated with adverse outcomes, including an increased risk of mortality, while cardiovascular medicines have been shown to reduce the risk of mortality in individuals with pre-existing cardiovascular conditions (Tamraz *et al.*, 2019; Xie *et al.*, 2019; Ma *et al.*,

2021). However, there is currently no literature available regarding the specific combinations of medications within polypharmacy regimens, in individuals with AF, thus identifying a potential gap for future research.

The associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke) were examined using unadjusted logistic regression, adjusted logistic regression and propensity score matching (1:1), in this thesis. These study outcomes were selected based on the findings from the systematic review (Chapter 2). The systematic review showed that polypharmacy was prevalent in over half (66.8%) of the participants with AF, and the most commonly measured outcomes were mortality, the incidence of stroke and the incidence of major bleeding.

The unadjusted logistic regression models showed that polypharmacy in the three months following AF diagnosis, was associated with an increased risk of death and ischaemic stroke during follow-up. The significant association between polypharmacy and death during follow-up remained in the adjusted logistic regression models; however, the association between polypharmacy and ischaemic stroke during follow-up diminished.

Mixed findings have been reported regarding the associations between polypharmacy and study outcomes (death and ischaemic stroke) previously. Piccini *et al.* (2016) and Eggebrecht *et al.* (2019) concluded that polypharmacy, in individuals with AF, was associated with an increased risk of death, but not ischaemic stroke, following their post-hoc analyses of trial data. In contrast, Focks *et al.* (2016) reported that polypharmacy was associated with death and ischaemic stroke during follow-up. Further information about these studies are presented in the systematic review, in Chapter 2.

Despite the mixed findings reported, all of these studies examined the associations between polypharmacy and study outcomes (death and ischaemic stroke) using adjusted logistic regression, and the final model results were presented (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). This thesis has advanced the literature by showing the stepwise adjustments for prognostic factors in Chapter 5 and Chapter 6, in addition to the final model results. The stepwise adjustments enabled the confounding effects of the prognostic factors to be quantified, in relation to the association between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke).

Logistic regression showed that polypharmacy, in the first three months following AF diagnosis, was associated with an increased risk of death during follow-up (unadjusted HR 1.73; 95% CI: 1.64 to 1.82). When the model was adjusted for gender only, there was a negligible reduction in the HR (HR1.72; 95% CI:1.64 to 1.82). However, when the model was adjusted for age, in addition to gender, there was a significant reduction in the HR (1.34; 95% CI: 1.27 to 1.42). Adjustments for diagnosed conditions, lifestyle factors and wealth, further reduced the HR (HR1.30; 95% CI: 1.24 to 1.38) but did not eliminate the association. The stepwise adjustments showed that age was the greatest confounding variable included in the analyses. Similar trends were observed when the association between polypharmacy and ischaemic stroke during follow-up was examined, although the changes to the hazard ratios were smaller. In contrast, the changes to the hazard ratios were more pronounced in the hyper-polypharmacy analyses, following the stepwise adjustments.

Eleven diagnosed conditions were included as prognostic factors in the current analyses, whereas previous studies (Piccini *et al.*, 2016; Eggebrecht *et al.*, 2019) have adjusted for fewer diagnosed conditions, for example Piccini *et al.* (2016) adjusted their models for seven diagnosed conditions, while Eggebrecht *et al.* (2019) adjusted their models for four diagnosed conditions. One limitation of the disease data analysed in the current study, and the previous studies, is that the data did not provide information about the severity of the diagnosed conditions. Despite this, the stepwise adjustments demonstrated that diagnosed conditions were weak confounders in the associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke).

To advance the existing literature, and to minimise the confounding effect of morbidity in the association between polypharmacy and mortality, propensity score matching was implemented in this study. The benefits of using this statistical approach have been discussed previously in Chapter 3 (section 3.11). The propensity score matched results showed that polypharmacy and hyper-polypharmacy were associated with an increased risk of death during follow-up, but not ischaemic stroke; thus, complementing the adjusted logistic regression results.

7.4 Strengths and Limitations

This research has some key strengths. This is the first study to examine the association between polypharmacy and adverse outcomes (death and ischaemic stroke), in individuals with AF, by analysing primary care data. Few studies have examined this association previously, and most studies have been post-hoc analyses of trial data.

Data from 33,984 participants were included in the main analyses, while data from 4,902 participants, and 2,302 participants were included in the propensity score matched analyses, for polypharmacy and hyper-polypharmacy, respectively. In addition to the large sample size, the CPRD GOLD dataset analysed in this study has been shown to be representative of the UK population, in terms of age, gender and ethnicity (Herrett *et al.*, 2015). Another strength of this study is that all participants had a recorded diagnosis of AF in the CPRD GOLD dataset.

Adjusted logistic regression has been used in previous studies to examine the association between polypharmacy and adverse outcomes, in AF. (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016; Paciullo *et al.*, 2018). This study has advanced the literature in several ways. First, the stepwise adjustments for the prognostic factors were presented, in addition to the final adjusted model results. The stepwise adjustments enabled the confounding effects of the prognostic factors to be quantified, in relation to the association between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke). Age was found to be the greatest confounding variable included in the analyses, while diagnosed conditions, lifestyle factors, and wealth, were weaker confounders. Second, this is the first study to examine the associations using propensity score matching. By using propensity score matching, it was possible to balance the non-polypharmacy, polypharmacy, and hyper-polypharmacy groups, according to all prognostic factors at baseline, so the only measured difference between the groups was the number of prescribed medications in the three months following AF diagnosis, thus reducing the risk of bias due to confounding (Littnerová *et al.*, 2013). The propensity score matched results showed that

polypharmacy and hyper-polypharmacy were independently associated with an increased risk of death during follow-up, but not ischaemic stroke, in individuals with AF.

Although this research had a number of strengths, there were some limitations. Prescribed medications, recorded in the Therapy file in CPRD GOLD, were analysed in this thesis. This file does not contain details about non-prescribed medications, for example, medications which can be purchased over- the-counter (OTC) from pharmacies. Consequently, it is possible that the prevalence of polypharmacy and hyper-polypharmacy may have been underestimated in this research. Furthermore, it is not possible to determine medication adherence from the data recorded in CPRD GOLD. Instead, an assumption is made that when a prescription has been issued, it is either given to a patient or sent electronically to a community pharmacy, and that the patient collects the prescribed item and then administers the medication according to the prescriber's directions.

Participants were allocated to polypharmacy groups, according to the number of medications they were prescribed in the three months following AF diagnosis and hence it was assumed that their polypharmacy status did not change during the study period. There is limited literature available which has examined the changes in polypharmacy status over time, at an individual level (von Buedingen *et al.*, 2018). Instead, most literature has focussed on the changes in prescribing patterns and polypharmacy prevalence over time, at a general population level (Payne *et al.*, 2014; Guthrie *et al.*, 2015; Morin *et al.*, 2018). It is possible that participants may move between groups, from non-polypharmacy to polypharmacy, and then hyper-polypharmacy, as they age; however, deprescribing practices may contribute towards participants moving between groups, in the opposite direction. Therefore, further research into the changes in polypharmacy status is required.

Logistic regression models were adjusted for 17 prognostic factors, and propensity score matching was implemented to minimise the risk of bias due to confounding, in this study. However, as with all observational studies, there may be other factors which have not been accounted for in the analyses, which could explain the observed associations between polypharmacy, hyper-polypharmacy, and study outcomes (death and ischaemic stroke), in individuals with AF, for example disease severity or medication adherence. The outcomes in this study (death and ischemic stroke) were binary. From the data, it was possible to determine whether a participant had died during the study period, however, information about the cause of death was not available. It is possible that some of the deaths recorded were not cardiovascular related, for example cancer, lung disease, or road traffic accidents. To address this limitation, the dataset would have to be linked to the Death Registration Data, published by the Office for National Statistics (CPRD, 2020).

Finally, there were several procedural limitations in this study. Large data files were provided by CPRD for the analyses; however, there was insufficient IT drive space to accommodate the files and consequently modifications to the data extraction process were required to reduce the file size (section 3.12). This limitation could be addressed in future pharmacoepidemiology studies by shortening the follow-up period, restricting the participant inclusion criteria (e.g., by age), or by examining polypharmacy in a less prevalent condition.

Another procedural limitation of this research relates to time. Preparation of the ISAC application form and protocol was time consuming and required several revisions (section

3.4). Once submitted, it took several months to obtain ISAC approval and for the data to be available for extraction. This lengthy process (>1 year) would need to be taken into consideration when planning future CPRD analyses.

7.5 The significance of the findings for clinical practice

Polypharmacy and hyper-polypharmacy are modifiable factors in individuals with AF. The propensity score matched results showed that polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, were independently associated with an increased risk of death, but not ischaemic stroke.

Findings from this thesis may not directly influence clinical practice, however the data provides a baseline for future research in this area. Prescribing data were analysed at BNF chapter level in this thesis. Further analyses could be conducted at drug class or individual drug level to identify which medications, or combinations of medications, in the polypharmacy and hyper-polypharmacy regimens increase the risk of mortality in AF. By informing prescribers about these medications, the appropriateness of each 'high risk' medication within the polypharmacy or hyper-polypharmacy regimens could be reviewed, and potentially deprescribed, if considered to be clinically inappropriate, thus reducing the risk of mortality in individuals with AF. This data would also help to inform prescribers who may wish to initiate these 'high risk' medications in the three months following an AF diagnosis, by raising their awareness about the increased risk of mortality.

7.6 Future work

There were some key findings in this thesis which require further exploration. Future work could examine the changes in polypharmacy status throughout the study period (section 7.6.1); determine which medications, or combinations of medications within polypharmacy and hyper-polypharmacy regimens are associated with death during follow-up (section 7.6.2); explore the causes of death in more detail (section 7.6.3) and use propensity score matching to examine the associations between polypharmacy and other adverse outcomes (e.g., hospital admissions and falls), in AF (section 7.6.4).

7.6.1 Examine the changes in polypharmacy status throughout the study period

Previous studies examining the associations between polypharmacy, hyper-polypharmacy, and adverse outcomes, in AF, have determined a participant's polypharmacy status at a single point in time, for example, the day of trial enrolment (Focks *et al.*, 2016; Piccini *et al.*, 2016; Proietti *et al.*, 2016). This study determined a participant's polypharmacy status over a broader period of time (3-month period following AF diagnosis); however, there is limited literature available about the changes in polypharmacy status over time (von Buedingen *et al.*, 2018). Future work could examine a participant's polypharmacy status at various time points throughout the study period, for example six monthly intervals, and investigate whether the likelihood of an adverse outcomes varies because of the changes in polypharmacy status. To determine the feasibility of this research, preliminary research into the changes in polypharmacy status was conducted using the CPRD training dataset (data

from five GP surgeries) in 2019, and a similar approach could be applied when analyzing data from 500 GP surgeries, in the CPRD GOLD dataset.

7.6.2 Determine which medications, or combinations of medications, in polypharmacy and hyper-polypharmacy regimens are associated with death during follow-up.

Few studies have examined the composition of polypharmacy regimens in the general population (Bjerrum *et al.*, 1998; Wastesson *et al.*, 2018; Slater *et al.*, 2020); however, no literature was found regarding the composition of polypharmacy and hyper-polypharmacy in individuals with AF. This thesis has addressed the gap in the literature by stratifying prescribed medication data according to BNF chapters. Cardiovascular medicines (BNF Chapter 2), CNS medications (BNF Chapter 4) and gastrointestinal medicines (BNF Chapter 1) were the most commonly prescribed types of medications for participants with polypharmacy and hyper-polypharmacy. Despite this, further work is needed, preferably at drug class or individual drug level, to determine whether the presence of certain medications, or combinations of medications, within polypharmacy and hyper-polypharmacy regimens are associated with an increased risk of death during follow-up, in individual with AF. This proposed research is likely to be highly complex and may need to be conducted in several stages, based on the research team's experience of analysing CNS medicines in polypharmacy regimens previously (Slater *et al.*, 2020). The research team have previously developed several Microsoft Excel spreadsheets which contain formulae to identify combinations of medications in polypharmacy regimens, at BNF Chapter level. These formulae would need to be adapted for future work conducted at drug class or individual drug level.

7.6.3 Explore the causes of death associated with polypharmacy and hyper-polypharmacy.

A significant association was found between polypharmacy and hyper-polypharmacy in the three months following AF diagnosis, and death during follow-up. The incidence of death (defined as a death date ≥ study index date and documented in the Patient file of CPRD GOLD), was used to define death as an outcome in this study. Additional data about a participant's death could be accessed by linking the CPRD GOLD dataset to the Death Registration data (CPRD, 2020). The latter dataset is published by the Office for National Statistics and contains data regarding the cause of death, in addition to the official date of death; therefore, it may be possible to stratify the death data by cause and examine the associations with polypharmacy and hyper-polypharmacy in more detail. To conduct this research, a new application form and protocol would need to be submitted to the Independent Scientific Advisory Committee (ISAC), and this research would require a new source of funding.

7.6.4 Examine the associations between polypharmacy, hyper-polypharmacy, and other adverse outcomes, in AF, using propensity score matching.

Previous research into the adverse outcomes associated with polypharmacy, in individuals with AF, have examined the following outcomes: the incidence of major bleeding, the incidence of stroke, the incidence of mortality, the impact on quality of life, the impact on anticoagulation control, the incidence of myocardial infarctions and non-adherence.

However, other adverse outcomes, for example an increased risk of hospitalisations and falls, are reported to be associated with polypharmacy too (Maher *et al.*, 2014). The latter outcomes have not been examined within an AF population; therefore, propensity score matching could be used to examine these associations with polypharmacy and hyper-polypharmacy. Hospitalisation data could be accessed by linking the CPRD GOLD dataset to the Hospital Episode Statistics datasets (CPRD, 2020). There are several HES datasets available including HES Accident and Emergency data , HES Outpatient data and HES Admitted Patient Care data (CPRD, 2020). The latter dataset is provided by NHS Digital and contains data regarding hospital admissions and discharge dates, and the reason for admission. By linking this dataset to the CPRD GOLD dataset, it would be possible to determine the number and nature of hospital admissions, associated with polypharmacy and hyper-polypharmacy, in individuals with AF. To conduct this research, a new application form and protocol would need to be submitted to the Independent Scientific Advisory Committee (ISAC), and this research would require a new source of funding.

7.7 Conclusion

Polypharmacy and hyper-polypharmacy, in the three months following AF diagnosis, were independently associated with an increased risk of death during follow-up, but not ischaemic stroke, in individuals with AF. Furthermore, this is the first study to minimise the confounding effect of morbidity as the underlying cause of the association by using propensity score matching.

Different explanations have been offered regarding the lack of association between polypharmacy, hyper-polypharmacy, and ischaemic stroke previously, including varying levels of adjustments, differing study populations, and low statistical power. However, this study showed that participants with polypharmacy and hyper-polypharmacy were commonly prescribed cardiovascular medicines (BNF Chapter 2). BNF Chapter 2 (cardiovascular system) encompasses a number of different drug classes, including anticoagulants and statins; therefore, it is possible that this study found no association between polypharmacy and ischaemic stroke during follow-up, due to the cardioprotective nature of these medications.

Future research conducted at drug class or individual drug level, could identify which medications, or combinations of medications, within polypharmacy and hyper-polypharmacy regimens are associated with an increased risk of death. Identifying these medications could help to inform prescribing decisions and deprescribing practices in AF. Furthermore, this research may develop our understanding regarding the lack of association between polypharmacy, hyper-polypharmacy, and ischemic stroke in AF.

Chapter 8: Bibliography

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Appendices

Appendix 1: List of PICO search terms

Table A1-1: ***List of search terms for polypharmacy, atrial fibrillation, and outcomes.***

Polypharmacy	**Atrial Fibrillation**	**Outcomes**
Drug combination	AF	Consequence
Drug combinations	Fibrillation	Conclusion
Drug therapy, combinations	Arrythmia (s)	Event
Polymedication	Cardiac arrythmia	Reaction
Multiple medication(s)	Persistent atrial fibrillation	Impact
Multiple medicine(s)	Paroxysmal atrial fibrillation	Result
Multiple drug (s)	Familial atrial fibrillation	Aftereffect
Many medication (s)	Auricular fibrillation	Aftermath
Many medicine (s)	Non-rheumatic atrial fibrillation	Effect
Many drug (s)	Permanent atrial fibrillation	End result
Minor polypharmacy	Chronic atrial fibrillation	
Moderate polypharmacy		
Major polypharmacy		
Hyper polypharmacy		
Excessive polypharmacy		
Severe polypharmacy		
Persistent polypharmacy		
Chronic polypharmacy		
Appropriate polypharmacy		
Inappropriate polypharmacy		

Appendix 2: RoBANS (Risk-of-bias assessment tool for non-randomised studies) for the studies eligible for inclusion in the systematic review (Chapter 2)(Kim *et al.*, 2013)

Table A2-1: RoBANS for the included studies

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting	Overall risk-of-bias
Gasse *et al.* (2005)	Low	Low	Low	Low	Low	Low	**Low**
Focks *et al.* (2016)	Low	High	Low	Low	Unclear	Low	**Unclear**
Piccini *et al.* *(*2016)	Low	Low	Low	Low	Low	Low	**Low**
Proietti *et al.* *(*2016)	Low	Low	Low	Low	Low	Low	**Low**
Roalfe *et al.* (2012)	High	Unclear	Low	Unclear	Low	Unclear	**Unclear**
Mohammed *et al.* (2017)	Low	High	Low	Low	Unclear	Low	**Unclear**
Wang *et al*. (2016)	Low	High	Unclear	Unclear	Unclear	Low	**Unclear**
Lobos-Bejarano *et al.* (2017)	Low	Low	Low	Low	Unclear	Low	**Low**
Rodriguez-Bernal *et al.* (2018)	Low	Low	Low	Low	Low	Low	**Low**
Márquez-Contreras *et al.* (2017)	Low	Unclear	Low	Unclear	Low	Low	**Unclear**
Paciullo *et al.* (2018)	Low	Low	Low	Low	High	Low	**Low**

Appendix 3: Independent Scientific Advisory Committee (ISAC) application form

ISAC APPLICATION FORM

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

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

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title[§] (*Please state the study title below)*

Is polypharmacy associated with death or ischaemic stroke in individuals newly diagnosed with atrial fibrillation? A prognostic cohort study using data from The Clinical Practice Research Datalink (CPRD)

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

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

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

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

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix 1 to this protocol :*

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

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☒	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐

Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☒	Other*	☐

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

5. Health Outcomes to be Measured§

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

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

Primary outcomes:

- **Incidence of death during follow up period**
- **Incidence of ischaemic stroke during follow up period**

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

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

If Other, please provide further information:* **Findings from this research will be included in a PhD thesis

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator§

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

Dr Martin Frisher, Reader in Health Services Research, School of Pharmacy, Keele University, m.frisher@keele.ac.uk

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

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

An updated CV is being submitted with this protocol ☐

8. Affiliation of Chief Investigator (full address)

School of Pharmacy,

Hornbeam Building,

Keele University,

ST5 5BG

9. Corresponding Applicant§

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

Natasha Slater, School of Pharmacy, Keele University, n.slater@keele.ac.uk

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

Same as chief investigator ☐

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☒

An updated CV is being submitted with this protocol ☐

10. List of all investigators/collaborators§

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

Dr Simon White, School of Pharmacy, Keele University, s.j.white@keele.ac.uk

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

Other investigator: **Dr Simon White**

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☒

An updated CV is being submitted with this protocol ☐

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

11. Conflict of interest statement*

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

All authors have completed the ICMJE form for disclosure of potential conflicts of interest available from www.icmje.org/coi_disclosure.pdf and declare that there is nothing to disclose.

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

12. Experience/expertise available

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

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

Experience/Expertise available	**Yes**	**No**
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* **Dr Martin Frisher**	☒	☐
Is experience of handling large data sets (≥1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* **Dr Martin Frisher**	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* **Natasha Slater and Dr Simon White**	☒	☐

13. References relating to your study

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

1. Proietti M, Raparelli V, Olshansky B, Lip GYH. Polypharmacy and major adverse events in atrial fibrillation: observations from the AFFIRM trial. Clin Res Cardiol2016;105:412-20.
2. Piccini JP, Hellkamp AS, Washam JB, Becker RC, Breithardt G, Berkowitz SD, Halperin JL, Hankey GJ, Hacke W, Mahaffey KW, Nessel CC. Polypharmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of ischaemic stroke in patients with nonvalvular atrial fibrillation. Circulation. 2015 Dec 16.
3. Focks JJ, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB, Lanas F, Xavier D, Husted S, Wallentin L, Alexander JH. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. bmj. 2016 Jun 15;353:i2868.

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

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

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☐	*Please specify name and country:*
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☒	

15. Type of Institution conducting the research

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

16. Data access arrangements

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

If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*

***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*

[¥]*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of ≥300,000 patients is required.*

[€]*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

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

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.

Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

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

18. Site Location of Data

a) Processing location(s):

Location area - UK / EEA / Worldwide: UK

Organisation address:

School of Pharmacy,

Hornbeam Building,

Keele University,

ST5 5BG

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

b) Storage Location(s)

Location area - UK / EEA / Worldwide: UK

Organisation address:

School of Pharmacy,

Hornbeam Building,

Keele University,

ST5 5BG

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

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

Organisation address:

School of Pharmacy,

Hornbeam Building,

Keele University,

ST5 5BG

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

SECTION D: INFORMATION ON DATA LINKAGES

19. Does this protocol seek access to linked data

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

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

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

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

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

20. Please select the source(s) of linked data being requested§
§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☐ ONS Death Registration Data

☐ HES Admitted Patient Care

☐ NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data *

☐ HES Outpatient

☐ NCRAS Cancer Patient Experience Survey (CPES) data*

☐ HES Accident and Emergency

☐ HES Diagnostic Imaging Dataset

☐ HES PROMS (Patient Reported Outcomes Measure)**

☐ CPRD Mother Baby Link

☐ Pregnancy Register

☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*

☐ Mental Health Services Data Set (MHDS)

☒ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☒ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

**Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an Appendix 1 to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*

***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only available for non-commercial purposes, such as academic research, or in connection with delivering services to the NHS.*

**** 'Patient level IMD and Townsend scores will not be supplied for the same study*

*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

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

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

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count)* 0

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

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

Yes* ☐ No ☒

**If yes, please provide further details:*

¥ *Data from defined geographical areas i.e. non-national datasets.*

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

Yes* ☐ No ☒

** If yes, please provide further details:*

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

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

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

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

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

Yes* ☐ No ☒

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

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

Is the questionnaire a validated instrument? Yes ☐ No ☐

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

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

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

Yes* ☐ No ☒

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

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

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

29. Signature from the Chief Investigator

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

Name: **Martin** **Frisher** Date: **17/5/2018** e-Signature (type name): **M.Frisher**

Appendix 4: Independent Scientific Advisory Committee (ISAC) protocol

ISAC PROTOCOL

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

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

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

Is polypharmacy associated with death or ischaemic stroke in individuals newly diagnosed with atrial fibrillation? A prognostic cohort study using data from The Clinical Practice Research Datalink (CPRD)

B. Lay Summary (Max. 200 words)[§]

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

The term polypharmacy describes the practice of prescribing multiple medicines for one individual. This practice has been increasing over the past decade and is most likely attributable to a growing ageing population who have an increased number of long-term conditions. There is some evidence to suggest that polypharmacy may be beneficial; however, other researchers report that this practice is associated with harmful consequences, including falls, hospitalisations and death.

Several studies have been conducted to determine whether polypharmacy is associated with certain medications or specific long-term conditions. Findings showed that medications which act on the heart are most commonly prescribed in polypharmacy regimens, in addition to establishing an association between polypharmacy and heart conditions.

This study will focus on one heart condition, atrial fibrillation (AF). The condition currently affects 1.4 million adults living in England and like polypharmacy, the incidence of AF increases with age. If left untreated or managed inappropriately, AF can cause strokes, heart failure and death. The aim of this study is to determine whether polypharmacy is associated with death or strokes in patients who have been newly diagnosed with AF.

C. Technical Summary (Max. 200 words)[§]

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

This prognostic cohort study has been designed to determine whether polypharmacy is associated with death or ischaemic stroke among individuals who have been newly diagnosed with atrial fibrillation. Only data labelled as 'acceptable' by CPRD will be used in this study. All patients

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

with a recorded diagnosis of AF will be identified. The earliest record of AF will be defined as the index date. Details of prescribed medications, issued within the first three months of the index date, will be obtained for each patient. Using this data, patients will be allocated into one of the following three groups: unexposed at study entry (1-4 different prescribed medicines), exposed to polypharmacy at study entry (5-9 different prescribed medicines) or exposed to hyper-polypharmacy at study entry (≥10 different prescribed medicines). Patients will be followed until the occurrence of a study outcome (i.e. death or ischaemic stroke) or until the end of follow-up (10 years maximum). Comparisons will be made between the incidence of death and ischaemic stroke in the exposed, compared to the unexposed groups. All models will be adjusted for known prognostic factors, which will be measured in the two years prior to index date.

D. Objectives, Specific Aims and Rationale

Objective

To determine whether polypharmacy is associated with death and ischaemic stroke among individuals who have been newly diagnosed with AF.

Specific Aims and Hypotheses

1. To establish the prevalence of polypharmacy (5-9 different prescribed medications) and hyper-polypharmacy (≥10 different prescribed medications) among individuals who have been newly diagnosed with AF.
2. To test the null hypothesis that individuals with AF, who are exposed to polypharmacy and hyper-polypharmacy at diagnosis, are not at an increased risk of experiencing ischaemic strokes or death during follow-up, compared to the unexposed.

Rationale

To date, few studies have examined polypharmacy in individuals with AF, even though polypharmacy and atrial fibrillation are both associated with potentially-life threatening outcomes. This study aims to address the existing gap in the literature by investigating whether polypharmacy is associated with death and ischaemic stroke in individuals who have been newly diagnosed with AF, after controlling for known prognostic factors.

E. Study Background

Polypharmacy describes the practice of prescribing multiple different medicines for one individual. This practice has been increasing over the past decade, and previous studies have shown that polypharmacy is being driven by a growing, ageing population who have an increased number of chronic conditions. [1,2] There is evidence to suggest that polypharmacy is associated with adverse drug reactions and subsequent hospitalisations, particularly among older people. [3] Findings from a population-based prospective study revealed that polypharmacy is also associated with an increased risk of mortality. [4]

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

Polypharmacy and Cardiovascular Medicines

Previous research has examined the types of medications and conditions commonly associated with polypharmacy. Guthrie et al [1] report that polypharmacy prevalence in Scotland increased between 1995 and 2010. Stratification of their data, according to the British National Formulary (BNF) chapters, showed that 16.8% (n=50,593) of the general population were receiving BNF Chapter 2 (cardiovascular system) drugs in 1995, which increased to 27.3% (n=85,140) in 2010. Drugs in other BNF chapters, for example Chapter 4 (central nervous system) drugs and Chapter 1 (gastrointestinal system) drugs had also experienced large increases in prescribing; however, the most substantial increase was seen among BNF Chapter 2 drugs. Walckiers et al [5] also examined polypharmacy prescribing patterns and reported that that 92.2% (n=748/811) of the polypharmacy group (5-9 different prescribed medicines) and 95.3% (n=243/255) of the hyper-polypharmacy group (≥10 different prescribed medicines) were prescribed at least one cardiovascular medicine respectively. [5] The association between cardiovascular medicines and polypharmacy regimens is supported by Linjakumpu et al [6] too.

Polypharmacy and Cardiovascular Conditions

Other studies have been conducted to determine whether polypharmacy is associated with specific chronic conditions. Aubert et al [7] analysed primary care prescribing data and calculated adjusted odds ratios, with 95% confidence intervals. Strong associations were detected between polypharmacy and hypertension (OR 8.49, 5.25-13.73), diabetes mellitus (OR 4.47, 3.23-6.20) and cardiovascular diseases, including angina, coronary artery disease and myocardial infarctions (OR 3.74, 2.76-5.08). Payne et al [8] conducted similar research and concluded that cardiovascular conditions are most frequently associated with polypharmacy. However, the aforementioned studies [7,8] are cross-sectional, therefore it is not possible to determine the direction of the association. While findings from the REPOSI study [9] show that hypertension ($p<0.0001$), ischaemic heart disease ($p=0.003$), atrial fibrillation ($p=0.009$) and heart failure ($p<0.001$) are strong predictors of polypharmacy at hospital discharge.

The existing evidence suggests that polypharmacy is associated with cardiovascular conditions. However, the term "cardiovascular conditions" is broad and is often used by authors to encompass a wide range of conditions, for example Aubert et al [7] calculated adjusted odds ratios for cardiovascular conditions, excluding hypertension; whereas, another study included hypertension in their definition of cardiovascular conditions. [9] To address the heterogeneity issue associated with the previous studies [7-9], this research will focus on one cardiovascular condition, atrial fibrillation (AF).

Atrial Fibrillation and Polypharmacy

Atrial fibrillation was selected because it is the most common sustained cardiac arrhythmia, affecting approximately 1.4 million adults living in England. [10,11] By 2025, the prevalence of the condition is expected to have doubled. [12] The condition is most prevalent among males and like polypharmacy, the prevalence of AF rises with increasing age (3.7%-4.2% prevalence in

individuals aged 60-70 years versus 10.0% to 17.0% prevalence in individuals aged above 80 years old). [13] If left untreated or managed inappropriately, Wang et al [14] report that AF can increase an individual's risk of ischaemic stroke, heart failure and dementia; whilst a post-hoc analysis of the Framingham Heart Study cohort data revealed that AF is associated with a 1.5-fold to 1.9-fold increase in mortality, after adjusting for covariates (age, hypertension, smoking, diabetes mellitus and cardiovascular diseases). [15]. Although polypharmacy and atrial fibrillation are independently associated with adverse outcomes, few studies have examined whether polypharmacy is associated with adverse outcomes in individuals with AF.

Gasse et al [16] used the UK General Practice Research Database (GPRD) to determine whether the concomitant administration of multiple medications, in addition to warfarin, would increase an individual's risk of bleeding. Results showed that an individual with AF, who were prescribed warfarin in addition to their other medications, was 3 to 4.5 times more likely to bleed compared to the unexposed. Similarly, Abdelhafiz and Wheeldon [17] analysed a secondary care database and concluded that polypharmacy was a significant risk factor for major bleeding, particularly among older people with AF (OR 3.0;95% CI, 1.2-7.88, p=0.002). The findings from the previous studies [16,17] were generated by analysing databases; however, findings from several post-hoc analyses, involving AF trial data, have also been published.

The post-hoc analysis of the ARISTOTLE (apixaban for reduction in ischaemic stroke and other thromboembolic events in atrial fibrillation) trial dataset aimed to determine whether polypharmacy was associated with mortality or ischaemic strokes, in individuals with AF. [18] The adjusted hazard ratios for ischaemic stroke, all-cause mortality and major bleeding, in individuals who were regularly prescribed 6-8 medicines, were 1.48 (1.14-1.92), 1.41 (1.23-1.61) and 1.24 (1.04-1.49) respectively. [18] The adjusted hazard ratios for ischaemic stroke, all-cause mortality and major bleeding were more pronounced (1.74 (1.28-2.37), 2.03(1.74-2.38) and 1.72 (1.41-2.10) respectively) in individuals prescribed 9 or more regular medications. [18]

Another post-hoc analysis, using the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial dataset was conducted by Proietti et al [19], to determine whether polypharmacy was associated with ischaemic stroke and mortality, among individuals with AF. The analysis revealed a statistically significant association between polypharmacy and death (HR 1.47, 95% CI; 1.18-1.82, p<0.001) but no association between polypharmacy and the incidence of ischaemic stroke (HR 1.17, 95%CI; 0.85-1.60, p=0.340) was detected. However, all findings regarding polypharmacy may have been underestimated in this study because only drugs which acted on the cardiovascular system were documented for each participant during the data collection phase of the AFFIRM trial. [19]

Similar findings were generated from a post-hoc analysis of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Ischaemic stroke and Embolism Trial in Atrial Fibrillation) trial dataset. Piccini et al [20] report

that polypharmacy was associated with major bleeding (HR 1.46, 95%CI; 1.22-1.76, p<0.0001) and mortality (HR 1.25, 95%CI; 1.09-1.44, p=0.0005). However, no association between polypharmacy and the incidence of ischaemic stroke (HR 1.07, 95%CI; 0.89-1.29, p=0.78) was established, after adjusting for covariates including age, gender, geographical location and co-morbidities. [20] Piccini et al [20] suggest that the latter finding may have been influenced by the ROCKET AF inclusion criteria because these criteria provided an opportunity for selection bias and consequently, their findings may not be generalizable to all individuals with AF.

Although the post-hoc analyses of the ARISTOTLE [18], AFFIRM [19] and ROCKET AF [20] trial datasets have suggested that polypharmacy is associated with mortality, differing results have been generated when the association between polypharmacy and ischaemic stroke was examined. Piccini et al [20] suggest the differing results may be attributable to the trials varying inclusion criteria; whereas, Frocks et al [18] anticipate that the association they detected between polypharmacy and ischaemic stroke would diminish if further adjustments, for co-morbidity and frailty at baseline, were made to their multivariate model. Another possible explanation for the inconsistent findings is that polypharmacy was only determined at a single point in time (study entry). During the studies [18-20], changes in polypharmacy prevalence were not examined, and this may have contributed towards the differing results. Rather than conducting analyses on previous trial data, this research will use anonymised primary care data, from the Clinical Practice Research Datalink (CPRD) to determine whether polypharmacy is associated with adverse outcomes among individuals with AF. [21]

This primary care database was selected because it contains over 20 million patient records; therefore, enhancing the statistical power of any analyses and improving the reliability of any association detected between study variables. [22,23] The size of the database means that any study findings will be generalisable to the wider population. Since the introduction of The Quality and Outcomes Framework (QOF) in 2004, CPRD has become a rich source of information about patients with AF. The framework specifies that practices must meet performance indicators to receive financial rewards. For AF, GPs must "establish and maintain a register of all AF patients". They must also determine an individuals' risk of ischaemic stroke by using the CHA_2DS_2-VASc scoring system. [24] Therefore, it is essential for practices to keep accurate and up-to-date records so that they can report good quality data about AF, to receive their QOF payments. [25]

F. Study Type

Hypothesis testing

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

G. Study Design

This is a prospective cohort study which will determine whether polypharmacy is associated with death and ischaemic stroke, in individuals newly diagnosed with atrial fibrillation

H. Feasibility counts

Based upon the figures generated during our feasibility counts, it is anticipated that there will be 291,600 patients within 500 CPRD practices who have acceptable data and have received an AF diagnosis. Of these patients, there will be 209,100 who have been prescribed a minimum of one medication in the first three months following their AF diagnosis which equates to ~128,800 control patients, 66,200 polypharmacy patients and 14,100 hyper-polypharmacy patients, using the percentages calculated from the training set. Further information about our feasibility counts can be found in Appendix 2.

I. Sample size considerations

Polypharmacy in the first three months following AF diagnosis and death during follow-up.

To examine this association, 8021 participants with polypharmacy and 8021 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference between the two aforementioned groups, at a 95% confidence level [26]

Polypharmacy in the first three months following AF diagnosis and ischaemic stroke during follow-up

To examine this association, 502 participants with polypharmacy and 502 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference between the two aforementioned groups, at a 95% confidence level. [26]

Hyper-polypharmacy in the first three months following AF diagnosis and death during follow-up

To examine this association, 2842 participants with hyper-polypharmacy and 2842 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference between the two aforementioned groups, at a 95% confidence level. [26]

Hyper-polypharmacy in the first three months following AF diagnosis and ischaemic stroke during follow-up

To examine this association, 896 participants with hyper-polypharmacy and 896 participants with non-polypharmacy were required, to achieve a power of 80% for detecting a difference between the two aforementioned groups, at a 95% confidence level. [26]

Further information about our sample size considerations can be found in Appendix 3.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

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

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

Our previous research showed an association between polypharmacy and lower wealth; therefore, we have requested access to Patient Level Index of Multiple Deprivation data as this will be a key covariate in our analysis. We recognise that IMD data is not available for all patients; therefore, our main analyses will include all patients, irrespective of their IMD status, and a secondary analysis will be conducted which will be restricted to those with patient-level IMD.

K. Study population

Source population:

We will identify all patients who have received an AF diagnosis (Read codes available in Appendix 1). The diagnosis must have been recorded as a med code (located in the clinical file) in CPRD. If multiple diagnosis dates are recorded, the earliest date will be considered as the index date. Eligible participants must have also been prescribed a minimum of one medication in the first three months following their first AF diagnosis. Details about prescribed medications will be obtained from the therapy file in CPRD. Patients prescribed no medications in the three months after their AF diagnosis will be excluded from this study. All patients eligible for inclusion must have 'acceptable' data. Acceptable CPRD data is defined as a coded value of 1 in the patient file. In addition, all patients must be registered with an 'up to standard' GP practice, for a minimum of 2 years prior to their AF diagnosis/index date.

L. Selection of comparison group(s) or controls

In this study, patients eligible for inclusion in the unexposed group (1-4 different prescribed medicines) will be selected from the source population and individually matched (1:1) at random, by age (+/- 2 years for exposed), gender, practice, total number of co-morbidities and type of co-morbidity, to patients in the exposed groups. [32] Kripke et al [32] describe the process of matching by number and type of co-morbidity. Controls must have registered with an 'up to standard' GP practice for a minimum of 2 years prior to index date. By matching the exposed to unexposed, variability caused by patient and practice factors will be minimised, thus reducing the influence of these factors on the primary outcomes. Other confounding factors will be controlled for during the analyses.

M. Exposures, Health Outcomes[§] and Covariates

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

Exposure

The number of different prescribed medications will be the exposure in this study. Details about prescribed medications will be obtained from the Therapy file in CPRD. This information will be

linked to the Product file in CPRD to provide further information about drug substance, strength, formulation, route of administration, BNF code and BNF chapter. The total number of different prescribed medications issued in the three months after AF diagnosis (index date), will be defined as the total number of different British National Formulary (BNF) codes. A 3-month time frame was selected because it is the maximum duration of repeat prescriptions (i.e. a prescriber should not prescribe more than 84 days' worth of medication on an NHS prescription). The unexposed group will comprise of patients prescribed between 1 and 4 different medicines at study entry. The polypharmacy group will comprise of patients prescribed between 5 and 9 different medicines at study entry [1]. The hyper-polypharmacy group will comprise of patients prescribed 10 or more different medicines at study entry [1]. Polypharmacy and hyper-polypharmacy prevalence will be determined throughout this study, at six monthly intervals. The number of patients switching between groups will also be reported. This time frame has been used previously in other studies. [30,31]

Outcomes

The incidence of death (defined as a date ≥ index date and documented in the patient record) and ischaemic stroke (defined as a record of a Read code for ischaemic stroke, as listed in Appendix 1, and documented in the patient's clinical record) are the two primary outcomes in this study. Follow-up will commence at 3 months after the index date. Patients who experience an outcome of interest or leave CPRD in the three months after index date will be excluded from follow-up. The maximum follow-up period for this study is 10 years. However, the follow up period will terminate with the occurrence of any of the following events, whichever occurs first: outcome of interest (death), outcome of interest (ischaemic stroke) or patient transferred out of the practice. The incidence of death and ischaemic stroke for the exposed versus unexposed will be compared.

Covariates

Prognostic factor data will be collected in the two years prior to index date. All prognostic factors have been previously identified in other studies. [19,28,29] The following factors will be considered as prognostic factors:

- Pre-existing medical conditions (hypertension, diabetes mellitus, heart failure, ischaemic heart disease, thyroid disorders, peripheral valvular disease, chronic obstructive pulmonary disease, obstructive sleep apnoea). Read codes for pre-existing medical conditions are available in Appendix 1.
- Ischaemic stroke prior to index date (defined as a record of a Read code for ischaemic stroke, as listed in Appendix 1, and documented in the patient's clinical record,
- Myocardial infarction prior to index date (defined as a record of a Read code for myocardial infarction, as listed in Appendix 1, and documented in the patient's clinical record)
- Renal insufficiency (defined as a record a creatinine clearance ≤30 ml/minutes in the patient's test record) This will be the latest (i.e. most recent) creatinine clearance value recorded in the two years prior to index date

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
• Obesity (defined as a BMI ≥30kg/m^2 and documented in the patient's clinical record. This will be the latest (i.e. most recent) BMI value recorded in the two years prior to index date. • Smoking (defined as Read code for smoking and documented in the patient's clinical record. Additional information will be obtained from additional file entity=4) This will be the most recent smoking data recorded in the two years prior to index date. • Alcohol consumption (defined as Read code for alcohol consumption and documented in the patient's clinical record. Additional information will be obtained from additional file entity=5) This will be the most recent alcohol data recorded in the two years prior to index date. • Wealth (based on the English Index of Multiple Deprivation) This data will not be available for all patients; therefore, a secondary analysis will be conducted using IMD data. • Number of cardiovascular medications prescribed (defined as the total number of different British National Formulary (BNF) codes, listed within BNF Chapter 2: Cardiovascular System. Information will be obtained from the patient's therapy file) Please refer to Appendix 1 for further information about prognostic factors.
N. Data/ Statistical Analysis Descriptive statistics will be used to profile the exposed and unexposed groups at study entry, using data collected in the two years prior to index date. Polypharmacy prevalence at study entry will be reported. Cox proportional hazard regression models will use the baseline polypharmacy data to generate hazard ratios, after adjustments for confounders have been made. Hazard ratios with 95% confidence intervals will be presented for the exposed and unexposed groups, as well as for the potential confounders. Data from the models will be considered statistically significant if $p<0.05$. Comparisons will be made between the exposed and unexposed groups to determine whether polypharmacy or hyper-polypharmacy are associated with death and ischaemic stroke in patients who have been newly diagnosed with atrial fibrillation. For each comparison in this study, survival curves will be plotted. All statistical analyses will be undertaken using SPSS (version 24.0). Secondary analyses will be conducted to determine polypharmacy prevalence at six monthly intervals throughout the study, and descriptive statistics will be used to report any changes in prevalence. Descriptive statistics will also be used to report the number of patients moving between groups.
O. Plan for addressing confounding This study will use all data available in CPRD to control for potential confounders, as described in the "Exposures, Health Outcomes§ and Covariates" section. However, as with all observational studies, there may be additional factors that are not measurable in this study and that could explain any observed association between polypharmacy and the incidence of ischaemic stroke or death in individuals with atrial fibrillation.
P. Plans for addressing missing data

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
For each stage of the study, missing data figures for smoking, BMI, socio-economic status and alcohol consumption will be reported. The missing data will be coded as "missing" and will appear as a separate category in the multivariate analysis.
Q. Patient or user group involvement (if applicable) No patients will be involved in this study.
R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication Findings will be presented in a PhD thesis, in addition to being disseminated in peer-reviewed scientific journals and at conferences. We anticipate that our findings will be attract the attention of top-impact scientific journals, particularly to those with an interest in polypharmacy. The findings may also be of interest to policy makers, including the National Institute for Health and Care Excellence (NICE).
S. Limitations of the study design, data sources, and analytic methods This study investigates polypharmacy in respect to prescribed medicines; however, polypharmacy prevalence may be underestimated because information about patient's over the counter (OTC) medicine usage is not recorded in CPRD. There is also no information about medication compliance within CPRD. In this study, it is assumed that all prescribed medications are dispensed by pharmacies and taken by patients, according to their prescriber's directions. There is potential for misclassification of patients, particularly in terms of diagnosis, within this study. Differing codes may be used by GPs to code a diagnosis and it is assumed that the absence of a code indicates the absence of a disease. However, there will be some patients who are suffering from a disease but have failed to visit their GP to receive a diagnosis. [22] Data entry by GPs may also result in the misclassification of patients. If a GP enters information about a patient as text, rather than codes, there is a risk that this information will be missed during the data extraction stage of this study. Matching patients by the number and type of co-morbidity may be influenced by this limitation. To minimise the impact of confounders, Cox proportional hazard regression models will be implemented throughout this study. This will allow adjustments for known prognostic factors to be made. However, there may be additional factors that are not measurable in this study and that could explain any observed association between polypharmacy and the incidence of ischaemic stroke or death in individuals with atrial fibrillation. Also, data for several prognostic factors, for example smoking habits and alcohol consumption has been collected through self-reporting. This method of data collection relies on all patients accurately and truthfully recalling information to prevent bias.

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
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Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
List of Appendices *(Submit all appendices as separate documents to this application)* 1. Appendix 1: Read Codes for Atrial Fibrillation, Ischaemic Stroke and Prognostic Factors 2. Appendix 2: Feasibility Counts (using 5 CPRD practices) 3. Appendix 3: Sample Size Considerations (using 5 CPRD practices)

Appendix 5: Read code lists for atrial fibrillation, ischaemic stroke, and all prognostic factors.

Table A5-1: Read code list for atrial fibrillation.

Pegasus Dictionary Code	Read Code	Description
1268	G573200	Paroxysmal AF
1664	G573000	Atrial fibrillation (AF)
2212	G573.00	AF with flutter
3757	3272.00	ECG: Atrial fibrillation
23437	G573z00	AF and flutter NOS (no other symptoms)
35127	G573300	Non-rheumatic AF
96076	G573500	Persistent AF
96277	G573400	Permanent AF

Table A5-2: Read code list for ischaemic stroke.

Pegasus Dictionary Code	Read Code	Description
504	G65..00	Transient cerebral ischaemia
569	G64..12	Infarction - cerebral
1298	G66..11	Cerebrovascular accident (CVA) -not specified
1433	G65..12	Transient ischaemic attack
1469	G66..00	Stroke and CVA
1895	G65z.00	Transient cerebral ischaemia NOS
2417	G65..13	Vertebro-basilar insufficiency
3149	G64z.00	Cerebral infarction NOS
3979	G672.00	Hypertensive encephalopathy
4152	G631.12	Thrombosis, carotid artery
4240	G631.00	Carotid artery occlusion
5184	G670.11	Precerebral atherosclerosis
5185	G64z111	Lateral medullary syndrome
5268	G650.11	Insufficiency - basilar artery
5363	G64..11	CVA – cerebral artery occlusion
5602	G64z.12	Cerebellar infarction
6116	G66..13	CVA- cerebrovascular accident – not specified
6155	G64..13	Stroke due to cerebral arterial occlusion
6228	G68x.00	Sequelae of stroke – not specified as haemorrhagic or ischaemic
6253	G66..12	Stroke – not specified
6489	G655.00	Transient global amnesia
7780	G667.00	Left-sided CVA
8443	G663.00	Brain stem stroke syndrome
8837	G64..00	Cerebral arterial occlusion
9985	G642200	Left-sided cerebral infarction
10062	G6z..00	Cerebrovascular disease NOS

10504	G64z300	Right-sided cerebral infarction
11171	G670.00	Cerebral atherosclerosis
12555	G671z00	Generalised ischaemic cerebrovascular disease NOS
12833	G668.00	Right-sided CVA
13577	G67..00	Other cerebrovascular disease
15019	G641.00	Cerebral embolism
15252	G64z.11	Brainstem infarction NOS
15788	G65zz00	Transient cerebral ischaemia NOS
16507	G65z100	Intermittent cerebral ischaemia
16517	G640.00	Cerebral thrombosis
17322	G664.00	Cerebellar stroke
18689	G660.00	Middle cerebral artery syndrome
19260	G662.00	Posterior cerebral artery syndrome
19280	G661.00	Anterior cerebral artery syndrome
19348	ZV12511	[V]Personal history of stroke
19354	G65y.00	Other transient cerebral ischaemia
21118	G651000	Vertebro-basilar artery syndrome
23465	G652.00	Subclavian steal syndrome
23671	G63y000	Cerebral infarction due to thrombosis of the pre-cerebral arteries
23942	G650.00	Basilar artery syndrome
24385	G671100	Chronic cerebral ischaemia
24446	G63y100	Cerebral infarction due to embolism in the pre-cerebral arteries
25615	G64z000	Brainstem infarction
27975	G641000	Cerebral infarction due to embolism in the cerebral arteries
32447	G630.00	Basilar artery occlusion
33377	G651.00	Vertebral artery syndrome
33499	G665.00	Pure motor lacunar syndrome
33543	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
34117	G67y.00	Other cerebrovascular disease OS
34758	G641.11	Cerebral embolus
36717	G640000	Cerebral infarction due to thrombosis of the cerebral arteries
37493	G67z.00	Other cerebrovascular disease NOS
39344	G676000	Cerebral infarction due to cerebral venous thrombosis
39403	G683.00	Sequelae of cerebral infarction
40053	G671.00	Generalised ischaemic cerebrovascular disease NOS
40758	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
40847	G632.00	Vertebral artery occlusion
44765	G653.00	Carotid artery syndrome hemispheric
45781	G63..00	Precerebral arterial occlusion
47642	G64z100	Wallenberg syndrome
50594	G654.00	Multiple and bilateral precerebral artery syndromes
51311	G6y..00	Other specified cerebrovascular disease
51326	G63y.00	Other precerebral artery occlusion
51767	G666.00	Pure sensory lacunar syndrome
53475	Gyu6400	Cerebral infarction (other)
55247	G65z000	Impending cerebral ischaemia
57495	G63..11	Infarction - precerebral

70536	G671000	Acute cerebrovascular insufficiency NOS
71585	G63z.00	Precerebral artery occlusion NOS
73901	Gyu6.00	[X]Cerebrovascular diseases
91627	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
94482	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
98642	G633.00	Multiple and bilateral precerebral arterial occlusion

Table A5-3: Read code list for Body Mass Index (BMI)

Pegasus Dictionary Code	**Read Code**	**Description**
9015	22K4.00	BMI 25-29 (overweight)
13278	22K5.00	BMI 30+ (obese)
22556	22K7.00	BMI >40 (severely obese)
24498	22K6.00	BMI <20
28937	22K2.00	BMI high
28946	22K1.00	BMI normal
44291	22K8.00	BMI 20-24

Note: Actual BMI values will be obtained from additional file in patient records via enttype 13 = weight and data 3 =BMI

Table A5-4: Read code list for hypertension

Pegasus Dictionary Code	**Read Code**	**Description**
204	G2...00	Hypertensive disease
351	G20..11	High blood pressure
799	G20..00	Essential hypertension
1894	G201.00	Benign essential hypertension
3425	662O.00	On treatment for hypertension
3712	G20z.11	Hypertension NOS
4372	G202.00	Systolic hypertension
4668	G22..00	Hypertensive renal disease
7057	G2z..00	Hypertensive disease NOS
7329	G24..00	Secondary hypertension
8732	G2...11	BP - hypertensive disease
8857	G21z011	Cardiomegaly - hypertensive
10818	G20z.00	Essential hypertension NOS
13188	662G.00	Hypertensive treatm.changed
15106	G22z.00	Hypertensive renal disease NOS
15377	G200.00	Malignant essential hypertension
16059	G24z.00	Secondary hypertension NOS
16173	G21zz00	Hypertensive heart disease NOS
16292	G21..00	Hypertensive heart disease
18765	G2y..00	Other specified hypertensive disease
21826	662F.00	Hypertension treatm. started
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure

25371	G241000	Secondary benign renovascular hypertension
27511	6628	Poor hypertension control
28684	G233.00	Hypertensive heart and renal disease with renal failure
29310	G22z.11	Renal hypertension
31341	G24z100	Hypertension secondary to drug
31387	G24z000	Secondary renovascular hypertension NOS
31464	G21z.00	Hypertensive heart disease NOS
31755	G240.00	Secondary malignant hypertension
31816	G672.11	Hypertensive crisis
32423	G222.00	Hypertensive renal disease with renal failure
34744	G244.00	Hypertension secondary to endocrine disorders
39649	G220.00	Malignant hypertensive renal disease
42229	G24zz00	Secondary hypertension NOS
43935	G221.00	Benign hypertensive renal disease
50157	G210.00	Malignant hypertensive heart disease
51635	G241z00	Secondary benign hypertension NOS
52127	G211100	Benign hypertensive heart disease with CCF
52427	G211.00	Benign hypertensive heart disease
57288	G241.00	Secondary benign hypertension
57987	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
59383	G240000	Secondary malignant renovascular hypertension
61166	G21z000	Hypertensive heart disease NOS without CCF
61660	G211000	Benign hypertensive heart disease without CCF
62718	G21z100	Hypertensive heart disease NOS with CCF
63000	G231.00	Benign hypertensive heart and renal disease
63466	G23..00	Hypertensive heart and renal disease
67232	G230.00	Malignant hypertensive heart and renal disease
68659	G23z.00	Hypertensive heart and renal disease NOS
69753	Gyu2.00	[X]Hypertensive diseases
72668	G210100	Malignant hypertensive heart disease with CCF
73293	G240z00	Secondary malignant hypertension NOS
95334	G210000	Malignant hypertensive heart disease without CCF
97533	Gyu2100	[X]Hypertension secondary to other renal disorders
102458	Gyu2000	[X]Other secondary hypertension

Table A5-5: Read code list for diabetes mellitus

Pegasus Dictionary Code	**Read Code**	**Description**
506	C100112	Non-insulin dependent diabetes mellitus
711	C10..00	Diabetes mellitus
758	C10F.00	Type 2 diabetes mellitus
1038	C100011	Insulin dependent diabetes mellitus
1045	C135.00	Diabetes insipidus
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
1549	C10E.00	Type 1 diabetes mellitus

1647	C108.00	Insulin dependent diabetes mellitus
1682	C101.00	Diabetes mellitus with ketoacidosis
2378	66AJ.00	Diabetic - poor control
2471	K01x100	Nephrotic syndrome in diabetes mellitus
2478	66AJ100	Brittle diabetes
4513	C109.00	Non-insulin dependent diabetes mellitus
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
6430	9NM0.00	Attending diabetes clinic
6509	C108700	Insulin dependent diabetes mellitus with retinopathy
6791	C108800	Insulin dependent diabetes mellitus - poor control
6813	1434	H/O: diabetes mellitus
7045	14F4.00	H/O: Admission in last year for diabetes foot problem
7563	66A3.00	Diabetic on diet only
7795	C106.12	Diabetes mellitus with neuropathy
8306	8H7f.00	Referral to diabetes nurse
8403	C109700	Diabetes mellitus with neuropathy
8836	66AR.00	Diabetes management plan given
8842	66A5.00	Diabetic on insulin
9013	66AJ.11	Unstable diabetes
9897	9OL..00	Diabetes monitoring admin.
10098	C10yy00	Other specified diabetes mellitus with other spec comps
10418	C10ED00	Type 1 diabetes mellitus with nephropathy
10642	ZC2C800	Dietary advice for diabetes mellitus
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis
11359	L180.00	Diabetes mellitus during pregnancy/childbirth/puerperium
11471	8B3l.00	Diabetes medication review
11551	C10B.00	Diabetes mellitus induced by steroids
11599	7276	Pan retinal photocoagulation for diabetes
11848	C314.11	Renal diabetes
11930	9NN9.00	Under care of diabetes specialist nurse
11977	ZL62500	Referral to diabetes nurse
12030	9OL6.00	Diabetes monitoring 3rd letter
12213	8BL2.00	Patient on maximal tolerated therapy for diabetes
12307	66AU.00	Diabetes care by hospital only
12455	C10E.11	Type I diabetes mellitus
12506	66AP.00	Diabetes: practice programme
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
12675	66AQ.00	Diabetes: shared care programme
12682	679R.00	Patient offered diabetes structured education programme
12703	3881	Education score - diabetes
12736	C10F500	Type 2 diabetes mellitus with gangrene
13057	679L.00	Health education - diabetes
13069	66A8.00	Has seen dietician - diabetes
13191	9OL..11	Diabetes clinic administration
13192	9OLA.00	Diabetes monitor. check done
13194	9OL4.00	Diabetes monitoring 1st letter
13195	9OL5.00	Diabetes monitoring 2nd letter
13197	9OL1.00	Attends diabetes monitoring

13279	C104y00	Other specified diabetes mellitus with renal complications
13071	66AI.00	Diabetic - good control
14889	C100111	Maturity onset diabetes
14803	C100100	Diabetes mellitus, adult onset, no mention of complication
15690	C103.00	Diabetes mellitus with ketoacidotic coma
16230	C106.00	Diabetes mellitus with neurological manifestation
16491	C106.13	Diabetes mellitus with polyneuropathy
16502	C104.00	Diabetes mellitus with renal manifestation
16881	ZV65312	[V]Dietary counselling in diabetes mellitus
17067	F171100	Autonomic neuropathy due to diabetes
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
17545	C108F11	Type I diabetes mellitus with diabetic cataract
17858	C108.12	Type 1 diabetes mellitus
17859	C109.12	Type 2 diabetes mellitus
17869	66AL.00	Diabetic-uncooperative patient
18056	2G5C.00	Foot abnormality - diabetes related
18143	C109G11	Type II diabetes mellitus with arthropathy
18209	C109012	Type 2 diabetes mellitus with renal complications
18219	C109.13	Type II diabetes mellitus
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
18264	C109J12	Insulin treated Type II diabetes mellitus
18278	C109J00	Insulin treated Type 2 diabetes mellitus
18387	B906800	Type 1 diabetes mellitus with retinopathy
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
18496	C10F600	Type 2 diabetes mellitus with retinopathy
18505	C108.11	IDDM-Insulin dependent diabetes mellitus
18642	C10EH00	Type 1 diabetes mellitus with arthropathy
18683	C10E500	Type 1 diabetes mellitus with ulcer
18766	212H.00	Diabetes resolved
18777	C10F000	Type 2 diabetes mellitus with renal complications
20900	9OLA.11	Diabetes monitored
21482	C102.00	Diabetes mellitus with hyperosmolar coma
21983	C108012	Type 1 diabetes mellitus with renal complications
22487	C10N.00	Secondary diabetes mellitus
22023	66AJz00	Diabetic - poor control NOS
22573	C106z00	Diabetes mellitus NOS with neurological manifestation
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
22884	C10F.11	Type II diabetes mellitus
22967	2BBF.00	Retinal abnormality - diabetes related
23479	C350011	Bronzed diabetes
24423	C108.13	Type I diabetes mellitus
24458	C109711	Type II diabetes mellitus - poor control
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy

24836	C109C12	Type 2 diabetes mellitus with nephropathy
25041	ZC2CA00	Dietary advice for type II diabetes
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
25627	C10F700	Type 2 diabetes mellitus - poor control
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
26108	C10B000	Steroid induced diabetes mellitus without complication
26605	9OLB.00	Attended diabetes structured education programme
26855	C108400	Unstable insulin dependent diabetes mellitus
27921	2G51000	Foot abnormality - diabetes related
28622	2126300	Diabetes resolved
28856	8CP2.00	Transition of diabetes care options discussed
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
30970	Q44B.00	Syndrome of infant of mother with gestational diabetes
31141	9OL8.00	Diabetes monitor.phone invite
31240	9OL7.00	Diabetes monitor.verbal invite
31241	9OLZ.00	Diabetes monitoring admin.NOS
31310	C108900	Insulin dependent diabetes maturity onset
31790	F372.00	Polyneuropathy in diabetes
32193	C11y000	Steroid induced diabetes
32359	ZRbH.00	Perceived control of insulin-dependent diabetes
32403	C107.11	Diabetes mellitus with gangrene
32556	C107.12	Diabetes with gangrene
32619	66Af.00	Patient diabetes education review
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
32739	9N0n.00	Seen in community diabetes specialist clinic
33254	C105.00	Diabetes mellitus with ophthalmic manifestation
33343	C10y.00	Diabetes mellitus with other specified manifestation
33807	C107200	Diabetes mellitus, adult with gangrene
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
34268	C10F200	Type 2 diabetes mellitus with neurological complications
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation
35107	C104z00	Diabetes mellitus with nephropathy NOS
35288	C10E800	Type 1 diabetes mellitus - poor control
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
36695	C10D.00	Diabetes mellitus autosomal dominant type 2
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
38078	66A9.00	Understands diet - diabetes
38161	C108711	Type I diabetes mellitus with retinopathy
38617	C101y00	Other specified diabetes mellitus with ketoacidosis
38986	C100.00	Diabetes mellitus with no mention of complication

39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
40682	C10E900	Type 1 diabetes mellitus maturity onset
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
41049	C108712	Type 1 diabetes mellitus with retinopathy
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
41686	Cyu2000	[X]Other specified diabetes mellitus
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
42505	C101z00	Diabetes mellitus NOS with ketoacidosis
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma
42762	C109612	Type 2 diabetes mellitus with retinopathy
42831	C10E200	Type 1 diabetes mellitus with neurological complications
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
43453	C10C.00	Diabetes mellitus autosomal dominant
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
43857	C10M.00	Lipoatrophic diabetes mellitus
43921	C10E400	Unstable type 1 diabetes mellitus
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
44312	9M10.00	Informed dissent for diabetes national audit
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
44443	C108500	Insulin dependent diabetes mellitus with ulcer
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
45491	C10z.00	Diabetes mellitus with unspecified complication
45913	C109712	Type 2 diabetes mellitus - poor control
45914	C108812	Type 1 diabetes mellitus - poor control
45919	C109212	Type 2 diabetes mellitus with neurological complications
46150	C109512	Type 2 diabetes mellitus with gangrene
46290	C108y00	Other specified diabetes mellitus with multiple comps
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
46577	66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
46624	C10C.11	Maturity onset diabetes in youth
46850	C108811	Type I diabetes mellitus - poor control
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
46963	C108000	Insulin-dependent diabetes mellitus with renal complications
47011	8Hj0.00	Referral to diabetes structured education programme
47032	8CS0.00	Diabetes care plan agreed
47058	8Hg4.00	Discharged from care of diabetes specialist nurse
47315	C10F711	Type II diabetes mellitus - poor control
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
47409	C109B11	Type II diabetes mellitus with polyneuropathy
47582	C10E000	Type 1 diabetes mellitus with renal complications

47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications
47650	C10E300	Type 1 diabetes mellitus with multiple complications
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
47954	C10F900	Type 2 diabetes mellitus without complication
48192	C109E11	Type II diabetes mellitus with diabetic cataract
49074	C10F400	Type 2 diabetes mellitus with ulcer
49146	C108211	Type I diabetes mellitus with neurological complications
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
49869	C109G12	Type 2 diabetes mellitus with arthropathy
49949	C10E411	Unstable type I diabetes mellitus
50225	C109011	Type II diabetes mellitus with renal complications
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
50813	C109A11	Type II diabetes mellitus with mononeuropathy
50937	8HTe.00	Referral to diabetes preconception counselling clinic
50960	L180500	Pre-existing diabetes mellitus, insulin-dependent
50972	C100z00	Diabetes mellitus NOS with no mention of complication
51261	C10E.12	Insulin dependent diabetes mellitus
51697	C10G.00	Secondary pancreatic diabetes mellitus
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
51957	C108511	Type I diabetes mellitus with ulcer
52104	C108300	Insulin dependent diabetes mellitus with multiple complication
52212	Cyu2.00	[X]Diabetes mellitus
52236	C10A.00	Malnutrition-related diabetes mellitus
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
54419	918T.00	Diabetes key contact
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
55075	C109411	Type II diabetes mellitus with ulcer
55329	C10EQ00	Type 1 diabetes mellitus with gastroparesis
55431	L180X00	Pre-existing diabetes mellitus, unspecified
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
56448	C108A00	Insulin-dependent diabetes without complication
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy
58604	C109611	Type II diabetes mellitus with retinopathy
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
59288	C103y00	Other specified diabetes mellitus with coma
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
59725	C109111	Type II diabetes mellitus with ophthalmic complications
59991	C10D.11	Maturity onset diabetes in youth type 2
60107	C108411	Unstable type I diabetes mellitus
60499	C108600	Insulin dependent diabetes mellitus with gangrene
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy

60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
61344	C108011	Type I diabetes mellitus with renal complications
61461	9M00.00	Informed consent for diabetes national audit
61523	C106y00	Other specified diabetes mellitus with neurological comps
61829	C108212	Type 1 diabetes mellitus with neurological complications
62107	C109511	Type II diabetes mellitus with gangrene
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
62209	C10EM11	Type I diabetes mellitus with ketoacidosis
62352	C108H11	Type I diabetes mellitus with arthropathy
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
63017	C108911	Type I diabetes mellitus maturity onset
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
63412	8CR2.00	Diabetes clinical management plan
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
64283	C10zy00	Other specified diabetes mellitus with unspecified comps
64357	C10zz00	Diabetes mellitus NOS with unspecified complication
64384	L180z00	Diabetes mellitus in pregnancy/childbirth/puerperium NOS
64449	C108z00	Unspecified diabetes mellitus with multiple complications
64571	C109C11	Type II diabetes mellitus with nephropathy
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma
65267	C10F300	Type 2 diabetes mellitus with multiple complications
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
65704	C109412	Type 2 diabetes mellitus with ulcer
66675	C10A000	Malnutrition-related diabetes mellitus with coma
66872	C108D11	Type I diabetes mellitus with nephropathy
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
67635	L180000	Diabetes mellitus - unspec whether in pregnancy/puerperium
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation
67905	C109211	Type II diabetes mellitus with neurological complications
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
68390	C108512	Type 1 diabetes mellitus with ulcer
68546	ZRB4.00	Diabetes clinic satisfaction questionnaire
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
68818	ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
69043	ZC2C900	Dietary advice for type I diabetes
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
69676	C10EA00	Type 1 diabetes mellitus without complication
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
69993	C10E600	Type 1 diabetes mellitus with gangrene
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma

70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
91646	C10F411	Type II diabetes mellitus with ulcer
93727	C10FE11	Type II diabetes mellitus with diabetic cataract
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
95343	C10E711	Type I diabetes mellitus with retinopathy
95994	66Aq.00	Diabetic foot screen
96010	66Ap.00	Insulin treatment initiated
97474	C108412	Unstable type 1 diabetes mellitus
97849	C10E912	Insulin dependent diabetes maturity onset
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
98954	3883	Diabetes treatment satisfaction questionnaire
99231	C108B11	Type I diabetes mellitus with mononeuropathy
99311	C10E111	Type I diabetes mellitus with ophthalmic complications
99628	Kyu0300	[X]Glomerular disorders in diabetes mellitus
100292	Cyu2300	[X]Unspecified diabetes mellitus with renal complications
100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
100791	66Ar.00	Insulin treatment stopped
100964	C10F111	Type II diabetes mellitus with ophthalmic complications
102201	C10FC11	Type II diabetes mellitus with nephropathy
102434	66Au.00	Diabetic erectile dysfunction review
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications
103798	9b92000	Diabetic medicine
106528	C10FN11	Type II diabetes mellitus with ketoacidosis
108007	C108311	Type I diabetes mellitus with multiple complications

Table A5-6: Read code list for heart failure

Pegasus Dictionary Code	**Read Code**	**Description**
398	G580.00	Congestive heart failure
884	G581.00	Left ventricular failure
1223	G58..11	Cardiac failure
2062	G58..00	Heart failure
2906	G580.11	Congestive cardiac failure
4024	G58z.00	Heart failure NOS
5255	G581000	Acute left ventricular failure
5942	G581.13	Impaired left ventricular function
10079	G580.12	Right heart failure
10154	G580.13	Right ventricular failure
11424	G580300	Compensated cardiac failure
13189	662g.00	New York Heart Association classification - class II
15058	14A6.00	H/O: heart failure
17278	G58z.12	Cardiac failure NOS

18853	662f.00	New York Heart Association classification - class I
23707	G580000	Acute congestive heart failure
27884	G580200	Decompensated cardiac failure
27964	G582.00	Acute heart failure
32671	G580100	Chronic congestive heart failure

Table A5-7: Read code list for ischaemic heart disease and other cardiac ischaemic conditions.

Pegasus Dictionary Code	**Read Code**	**Description**
240	G3...00	Ischaemic heart disease
509	G5y3.00	Cardiomegaly
562	G5y3411	Left ventricular hypertrophy
1318	G700.00	Aortic atherosclerosis
1344	G340.12	Coronary artery disease
1414	G33z300	Angina on effort
1430	G33..00	Angina pectoris
1431	G311.13	Unstable angina
1655	G340.11	Triple vessel disease of the heart
1676	G3z..00	Ischaemic heart disease NOS
1735	G71..00	Aortic aneurysm
1792	G3...13	IHD - Ischaemic heart disease
1876	G714.00	Abdominal aortic aneurysm without mention of rupture
2155	G341000	Ventricular cardiac aneurysm
2491	G30..12	Coronary thrombosis
3729	G5y3100	Ventricular dilatation
3999	G340000	Single coronary vessel disease
2724	G5y3400	Ventricular hypertrophy
4656	G311.11	Crescendo angina
5254	G340100	Double coronary vessel disease
5413	G340.00	Coronary atherosclerosis
6331	G341.00	Aneurysm of heart
6336	14A5.00	H/O: angina pectoris
6872	G71z.00	Aortic aneurysm NOS
7320	G343.00	Ischaemic cardiomyopathy
8568	G37..00	Cardiac syndrome X
9276	G31y000	Acute coronary insufficiency
9413	G31y.00	Other acute and subacute ischaemic heart disease
11048	G331.11	Variant angina pectoris
13571	G30..16	Thrombosis - coronary
13578	G5y3.11	Dilatation - cardiac
14904	G5y3z00	Cardiomegaly NOS
15304	G715.00	Ruptured aortic aneurysm NOS
15754	G34z.00	Other chronic ischaemic heart disease NOS
16034	G716.00	Aortic aneurysm without mention of rupture NOS
16521	G710.00	Dissecting aortic aneurysm
16993	14AE.00	H/O: aortic aneurysm
18125	G330000	Nocturnal angina

19655	G311.14	Angina at rest
20416	G3...12	Atherosclerotic heart disease
22383	G3y..00	Other specified ischaemic heart disease
23078	G34y100	Chronic myocardial ischaemia
24540	G34y000	Chronic coronary insufficiency
24783	G3...11	Arteriosclerotic heart disease
25842	G33z.00	Angina pectoris NOS
27484	G341.11	Cardiac aneurysm
27951	G31..00	Other acute and subacute ischaemic heart disease
27977	G31yz00	Other acute and subacute ischaemic heart disease NOS
28004	G74..13	Arterial embolic and thrombotic occlusion
28062	G743.00	Embolism and thrombosis of other and unspec parts aorta
28138	G34..00	Other chronic ischaemic heart disease
28554	G33zz00	Angina pectoris NOS
31900	G740.11	Aortic bifurcation syndrome
34633	G34y.00	Other specified chronic ischaemic heart disease
35713	G34yz00	Other specified chronic ischaemic heart disease NOS
36609	G342.00	Atherosclerotic cardiovascular disease
39449	G312.00	Coronary thrombosis not resulting in myocardial infarction
39546	Gyu3000	[X]Other forms of angina pectoris
41677	G341z00	Aneurysm of heart NOS
42014	G5y3200	Cardiac dilatation NOS
47637	Gyu3300	[X]Other forms of chronic ischaemic heart disease
52517	Gyu3.00	[X]Ischaemic heart diseases
56621	G5y2.00	Cardiovascular arteriosclerosis unspecified
57062	14AJ.00	H/O: Angina in last year
61124	G5y3500	Cardiac hypertrophy NOS
68401	Gyu3200	[X]Other forms of acute ischaemic heart disease
70260	G717.00	Aortic aneurysm - syphilitic
102719	Gyu7200	[X]Aortic aneurysm of unspecified site, nonruptured
102725	Gyu7100	[X]Aortic aneurysm of unspecified site, ruptured

Table A5-8: Read code list for myocardial infarction

Pegasus Dictionary Code	**Read Code**	**Description**
241	G30..00	Acute myocardial infarction
1204	G30..14	Heart attack
1677	G30..15	MI - acute myocardial infarction
1678	G308.00	Inferior myocardial infarction NOS
2099	G575.00	Cardiac arrest
3704	G307.00	Acute subendocardial infarction
5387	G301.00	Other specified anterior myocardial infarction
7783	323..00	ECG: myocardial infarction
8935	G302.00	Acute inferolateral infarction
12139	G300.00	Acute anterolateral infarction
13566	G30..11	Attack – heart
14658	G30z.00	Acute myocardial infarction NOS

14897	G301z00	Anterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
16408	G32..11	Healed myocardial infarction
17464	G32..12	Personal history of myocardial infarction
17689	G30..17	Silent myocardial infarction
17872	G301100	Acute anteroseptal infarction
18842	G35..00	Subsequent myocardial infarction
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
23892	G304.00	Posterior myocardial infarction NOS
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct
26972	3234	ECG:posterior/inferior infarct
26975	3233	ECG: antero-septal infarct.
28736	G30y000	Acute atrial infarction
29421	G344.00	Silent myocardial ischaemia
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
29643	G303.00	Acute inferoposterior infarction
29758	G30X.00	Acute transmural myocardial infarction of unspecif site
30421	G30..13	Cardiac rupture following myocardial infarction (MI)
33402	G575.12	Asystole
33899	G575000	Cardiac arrest with successful resuscitation
34803	G30y.00	Other acute myocardial infarction
35119	G501.00	Post infarction pericarditis
35674	14A3.00	H/O: myocardial infarct <60
36423	G36..00	Certain current complication follow acute myocardial infarct
36523	G311.00	Preinfarction syndrome
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
38609	G351.00	Subsequent myocardial infarction of inferior wall
39655	G311.12	Impending infarction
3990	323	ECG: old myocardial infarction
40399	14A4.00	H/O: myocardial infarct >60
40429	G301000	Acute anteroapical infarction
41221	G30y200	Acute septal infarction
45809	G350.00	Subsequent myocardial infarction of anterior wall
46017	G30yz00	Other acute myocardial infarction NOS
46166	G35X.00	Subsequent myocardial infarction of unspecified site
50372	14AH.00	H/O: Myocardial infarction in last year
52705	3236	ECG: lateral infarction
54251	G311z00	Preinfarction syndrome NOS
55401	3235	ECG: subendocardial infarct
59032	323Z.00	ECG: myocardial infarct NOS
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
63467	G306.00	True posterior myocardial infarction
68357	G31y100	Microinfarction of heart
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
72562	G353.00	Subsequent myocardial infarction of other sites
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site

99991	Gyu3600	[X]Subsequent myocardial infarction of unspecified site

Table A5-9: Read code list for peripheral valvular disease

Pegasus Dictionary Code	Read Code	Description
996	G70..11	Arteriosclerosis
1517	G73z000	Intermittent claudication
2065	G742400	Embolism and thrombosis of the femoral artery
2760	G73zz00	Peripheral vascular disease NOS
3588	G72z.00	Aneurysm NOS
3714	G74z.00	Arterial embolism and thrombosis NOS
3995	G70z.00	Arteriosclerotic vascular disease NOS
4289	G74..00	Arterial embolism and thrombosis
4539	G742500	Embolism and thrombosis of the popliteal artery
5168	G70y.00	Other specified artery atheroma
5640	G70..00	Atherosclerosis
5650	G740.12	Aortoiliac obstruction
5702	G73..11	Peripheral ischaemic vascular disease
5943	G73..00	Other peripheral vascular disease
6684	G723000	Aneurysm of femoral artery
6827	G73..13	Peripheral ischaemia
6853	G73z011	Claudication
6900	G74y500	Embolism and thrombosis of the subclavian artery
8998	G74..11	Arterial embolus and thrombosis
9364	G74..12	Thrombosis – arterial
9454	G72..00	Other aneurysm
9759	G718.00	Leaking abdominal aortic aneurysm
11430	G715000	Thoracoabdominal aortic aneurysm, ruptured
13572	G713.11	Ruptured abdominal aortic aneurysm
14797	G702.00	Extremity artery atheroma
15253	G740.00	Embolism and thrombosis of the abdominal aorta
15302	G742z00	Peripheral arterial embolism and thrombosis NOS
16068	G72yz00	Other aneurysm NOS
16284	G701.00	Renal artery atherosclerosis
16366	G723100	Aneurysm of popliteal artery
16395	G722000	Aneurysm of common iliac artery
16800	G711.11	Ruptured thoracic aortic aneurysm
17345	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
17560	G722.00	Aneurysm of iliac artery
17767	G713.00	Abdominal aortic aneurysm which has ruptured
18478	G721.00	Aneurysm of renal artery
19155	G700.11	Aorto-iliac disease
23532	G712.00	Thoracic aortic aneurysm without mention of rupture
25438	G720100	Aneurysm of radial artery
27389	G72yA00	Aneurysm of hepatic artery
27494	G74y300	Embolism and thrombosis of the iliac artery unspecified
27563	G711.00	Thoracic aortic aneurysm which has ruptured

29372	G742100	Embolism and thrombosis of the radial artery
30248	G720200	Aneurysm of ulnar artery
30495	G742300	Embolism and thrombosis of an arm artery NOS
31460	G74y700	Embolism and thrombosis of the axillary artery
31876	G72y000	Aneurysm of common carotid art
32235	G74y.00	Embolism and thrombosis of other specified artery
32634	G74y100	Embolism and/or thrombosis of the internal iliac artery
33613	G720000	Aneurysm of brachial artery
34159	G742000	Embolism and thrombosis of the brachial artery
35529	G72y400	Aneurysm of subclavian artery
36390	G72y200	Aneurysm of internal carotid artery
38732	G72y500	Aneurysm of splenic artery
40787	G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
41171	G72y.00	Aneurysm of other artery
41597	G74yz00	Embolism and thrombosis of other arteries NOS
44085	G742.00	Embolism and thrombosis of an arm or leg artery
44835	G742900	Embolism and thrombosis of a leg artery NOS
45000	G723.00	Aneurysm of leg artery
45645	G741.00	Embolism and thrombosis of the thoracic aorta
47655	G74y800	Embolism and thrombosis of the coeliac artery
49490	G74y900	Embolism and thrombosis of the hepatic artery
50678	G72y100	Aneurysm of external carotid artery
52549	G72y600	Aneurysm of axillary artery
54865	G74y000	Embolism and/or thrombosis of the common iliac artery
56919	G74y200	Embolism and/or thrombosis of the external iliac artery
57135	G72y900	Aneurysm of inferior mesenteric artery
58698	G72y300	Aneurysm of neck artery NOS
58794	G722200	Aneurysm of internal iliac artery
59193	G341200	Aneurysm of coronary vessels
59492	G720.00	Aneurysm of artery of arm
59536	G72yB00	Aneurysm of other visceral artery
59538	G72y800	Aneurysm of superior mesenteric artery
59671	G722z00	Aneurysm of iliac artery NOS
60879	G722100	Aneurysm of external iliac artery
62368	G742200	Embolism and thrombosis of the ulnar artery
63059	G723z00	Aneurysm of leg artery NOS
66823	G72y700	Aneurysm of coeliac artery
66981	G74y600	Embolism and thrombosis of the splenic artery
67026	G723200	Aneurysm of anterior tibial artery
67087	G341100	Other cardiac wall aneurysm
69232	G742600	Embolism and thrombosis of the anterior tibial artery
69847	G723300	Aneurysm of dorsalis pedis artery
71860	G742700	Embolism and thrombosis of the dorsalis pedis artery
72062	G723400	Aneurysm of posterior tibial artery
94408	G720z00	Aneurysm of arm artery NOS
95381	Gyu7300	[X]Aneurysm of other specified arteries
99532	G742800	Embolism and thrombosis of the posterior tibial artery

100579	Gyu7000	[X]Atherosclerosis of other arteries

Table A5-10: Read code list for thyroid diseases

Pegasus Dictionary Code	Read Code	Description
273	C04..13	Hypothyroidism
1472	C02..11	Hyperthyroidism
1658	R145.00	[D]Thyroid function test abnormal
1882	C0...00	Disorders of thyroid gland
3611	1432.00	H/O: hypothyroidism
3941	C04z.00	Hypothyroidism NOS
4937	143..11	H/O: thyroid disorder
6245	1431.00	H/O: hyperthyroidism
10097	C03..00	Congenital hypothyroidism
11146	C134300	TSH - thyroid-stimulating hormone deficiency
14704	C04..12	Thyroid deficiency
18282	C04z.13	Hypothyroid goitre, acquired
18598	442I.00	Thyroid function tests abnormal
20970	442G.00	Thyroid hormone tests abnormal
23014	C04z.12	Thyroid insufficiency
27278	4422.00	Thyroid hormone tests high
31612	C03y000	Congenital hypothyroidism with diffuse goitre
33292	4423.00	Thyroid hormone tests low
34221	C042.00	Iodine hypothyroidism
35608	1433.00	H/O: thyroid disorder NOS
35957	C06z.00	Thyroid disorder NOS
38976	C043z00	Iatrogenic hypothyroidism NOS
48045	R145z00	[D]Thyroid function tests abnormal NOS
51481	C03z.00	Congenital hypothyroidism NOS
65175	Cyu1.00	[X]Disorders of thyroid gland
69290	C03y.00	Other specified congenital hypothyroidism
93159	C03y100	Congenital hypothyroidism without goitre
93323	C03z.11	Congenital thyroid insufficiency
95830	C047.00	Subclinical hypothyroidism
102442	1JM..00	Suspected hypothyroidism
106640	C025.00	Subclinical hyperthyroidism
108482	1JM0.00	Suspected congenital hypothyroidism

Table A5-11: Read code list for chronic obstructive pulmonary disease

Pegasus Dictionary Code	Read Code	Description
148	H30..00	Bronchitis unspecified
152	H302.00	Wheezy bronchitis

794	H32..00	Emphysema
998	H3...11	Chronic obstructive airways disease
1001	H3...00	Chronic obstructive pulmonary disease
1446	H312200	Acute exacerbation of chronic obstructive airways disease
3243	H31..00	Chronic bronchitis
3480	H30z.00	Bronchitis NOS
5710	H3z..00	Chronic obstructive airways disease NOS
5909	H312011	Chronic wheezy bronchitis
7092	H30..12	Recurrent wheezy bronchitis
7884	H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec
9520	66YB.00	Chronic obstructive pulmonary disease monitoring
9876	H38..00	Severe chronic obstructive pulmonary disease
10802	H37..00	Moderate chronic obstructive pulmonary disease
10863	H36..00	Mild chronic obstructive pulmonary disease
10980	H322.00	Centrilobular emphysema
11019	8H2R.00	Admit COPD emergency
11150	H311.00	Mucopurulent chronic bronchitis
11287	66YM.00	Chronic obstructive pulmonary disease annual review
12166	H3y..00	Other specified chronic obstructive airways disease
14798	H312100	Emphysematous bronchitis
15157	H31z.00	Chronic bronchitis NOS
15626	H310000	Chronic catarrhal bronchitis
16410	H32yz00	Other emphysema NOS
17359	H30..11	Chest infection - unspecified bronchitis
18207	H33zz13	Allergic bronchitis NEC
18476	66YL.11	COPD follow-up
18501	66YI.00	COPD self-management plan given
18621	66YL.00	Chronic obstructive pulmonary disease follow-up
18792	9Oi..00	Chronic obstructive pulmonary disease monitoring
19003	66Ye.00	Emergency COPD admission since last appointment
19106	66Yd.00	COPD accident and emergency attendance since last visit
19428	1I70.00	Chronic obstructive pulmonary disease excluded by spirometry
19434	1J71.00	Suspected chronic obstructive pulmonary disease
21061	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn
23492	H320z00	Chronic bullous emphysema NOS
24248	H313.00	Mixed simple and mucopurulent chronic bronchitis
25603	H310.00	Simple chronic bronchitis
26018	66YS.00	Chronic obstructive pulmonary disease monitoring by nurse
26306	H320.00	Chronic bullous emphysema
27819	H312.00	Obstructive chronic bronchitis
28743	66Yf.00	Number of COPD exacerbations in past year
28755	9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter
33450	H32z.00	Emphysema NOS
34202	9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter
34215	9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter

37247	H3z..11	Chronic obstructive pulmonary disease NOS
37247	H3z..11	Chronic obstructive pulmonary disease NOS
37371	66YD.00	Chronic obstructive pulmonary disease monitoring due
37959	H311100	Fetid chronic bronchitis
38074	9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite
40159	H311000	Purulent chronic bronchitis
40788	H32y.00	Other emphysema
42258	9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite
42313	679V.00	Health education - chronic obstructive pulmonary disease
44525	H312z00	Obstructive chronic bronchitis NOS
45770	66Yg.00	Chronic obstructive pulmonary disease disturbs sleep
45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
45777	8CR1.00	Chronic obstructive pulmonary disease clini management plan
45998	66YT.00	Chronic obstructive pulmonary disease monitoring by doctor
46036	66Yi.00	Multiple COPD emergency hospital admissions
46578	H321.00	Panlobular emphysema
46977	H35z.00	Allergic alveolitis and pneumonitis NOS
56860	H320000	Segmental bullous emphysema
59263	H32y111	Acute interstitial emphysema
60188	H320200	Giant bullous emphysema
61118	H310z00	Simple chronic bronchitis NOS
61513	H311z00	Mucopurulent chronic bronchitis NOS
63479	H32y200	MacLeod's unilateral emphysema
65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease
66043	H31y.00	Other chronic bronchitis
67040	H3y..11	Other specified chronic obstructive pulmonary disease
67040	H3y..11	Other specified chronic obstructive pulmonary disease
68066	H31yz00	Other chronic bronchitis NOS
68662	H320100	Zonal bullous emphysema
70787	H32y100	Atrophic (senile) emphysema
92955	H32y000	Acute vesicular emphysema
93568	H39..00	Very severe chronic obstructive pulmonary disease
97800	9kf..00	COPD - enhanced services administration
98284	9kf1.00	Refer COPD structured smoking assessment - enhanc serv admin
99536	H320300	Bullous emphysema with collapse
99948	9kf0.00	COPD patient unsuitable for pulmonary rehab - enh serv admin
101042	8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack
102685	66YB000	Chronic obstructive pulmonary disease 3 monthly review
103558	8CeD.00	Preferred place of care for next exacerbation of COPD
103864	9kf0.11	COPD patient unsuitable for pulmonary rehabilitation
103494	14B3.12	History of chronic obstructive pulmonary disease
104481	8CMV.00	Has chronic obstructive pulmonary disease care plan
104710	9NgP.11	On COPD (chr obstruc pulmonary disease) supportv cre pathway

104985	9NgP.00	On chronic obstructive pulmonary disease supprtv cre pathway
104117	661M300	COPD self-management plan agreed
105457	8CMW500	Chronic obstructive pulmonary disease care pathway
106637	9Nk7000	Seen in chronic obstructive pulmonary disease clinic

Table A5-12: Read code list for obstructive sleep apnoea

Pegasus Dictionary Code	**Read Code**	**Description**
1244	R005000	[D]Sleep disturbance, unspecified
2506	R005311	[D]Sleep apnoea syndrome
7603	Fy03.00	Sleep apnoea
8084	R005.00	[D]Sleep disturbances
8148	Fy03.11	Obstructive sleep apnoea
20438	R005312	[D]Syndrome sleep apnoea
20748	H5B0.00	Obstructive sleep apnoea
23779	H5B..00	Sleep apnoea
36301	R005300	[D]Hypersomnia with sleep apnoea
48539	R005100	[D]Insomnia with sleep apnoea
93615	9Nk0.00	Seen in sleep clinic
95887	8HTn.00	Referral to sleep clinic
100177	38Da.00	Berlin questionnaire for sleep apnoea

Appendix 6: Feasibility counts for the Independent Scientific Advisory Committee (ISAC) application

Using data from 5 CPRD practices, feasibility counts were conducted. Overall, 2916 patients had received an AF diagnosis and their data was considered acceptable, according to the quality markers in CPRD. Patients were allocated into one of three groups. Numbers for the individuals in each group are presented in table A6-1.

Table A6-1: Feasibility Counts (5 CPRD Practices)

All patients with an AF diagnosis	n=5893
All patients with an AF diagnosis + acceptable data	n=2916
Earliest diagnosis date calculated	n=2916
Number of patients prescribed medications in the first three months following their AF diagnosis	n=2091
Unexposed group at study entry (1-4 different prescribed medicines)	n=1288
Exposed to polypharmacy at study entry (5-9 different prescribed medicines)	n=662
Exposed to hyper-polypharmacy at study entry (10 or more different prescribed medicines)	n=141

The values in table A6-1 are for 5 CPRD practices; therefore, numbers need to be multiplied by 100 to determine the number of patients in 500 CPRD practices.

Appendix 7: Sample size calculations for the Independent Scientific Advisory Committee (ISAC) application

Using data from 5 CPRD practices (accessed from the Keele University training data set), the incidence of death and ischaemic stroke was determined for each group. Findings are presented in the table A7-1 (mortality) and table A7-2 (ischaemic stroke) respectively.

Table A7-1: Incidence of mortality (5 CPRD Practices)

Mortality after AF diagnosis	n=949 (45.3%)
Unexposed group at study entry (1-4 different prescribed medicines)	n= 592 (46.0%)
Exposed to polypharmacy at study entry (5-9 different prescribed medicines)	n=290 (43.8%)
Exposed to hyper-polypharmacy at study entry (10 or more different prescribed medicines)	n= 67 (47.5%)

Table A7-2: Incidence of ischaemic stroke (5 CPRD Practices)

Ischaemic stroke after AF diagnosis	n=254 (12.2%)
Unexposed group at study entry (1-4 different prescribed medicines)	n=183 (14.2%)
Exposed to polypharmacy at study entry (5-9 different prescribed medicines)	n=57 (8.6%)
Exposed to hyper-polypharmacy at study entry (10 or more different prescribed medicines)	n=14 (9.9%)

Note: The values in table A7-1 and table A7-2 are for 5 CPRD practices; therefore, numbers need to be multiplied by 100 to determine the number of patients in 500 CPRD practices.

Appendix 8: Independent Scientific Advisory Committee (ISAC) approval for ISAC Protocol_18_151

FEEDBACK TO APPLICANTS

CONFIDENTIAL	*by e-mail*
PROTOCOL NO:	18_151
PROTOCOL TITLE:	Is polypharmacy associated with death or ischaemic stroke in individuals newly diagnosed with atrial fibrillation? A prognostic cohort study using data from The Clinical Practice Research Datalink (CPRD)
APPLICANT:	Dr Martin Frisher, Reader in Health Services Research, School of Pharmacy, Keele University, m.frisher@keele.ac.uk

APPROVED ☐	**APPROVED WITH COMMENTS** **(resubmission not required)** ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:

Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.

REVIEWER COMMENTS:

Overall comments

(A) Applicants need to address the following points

1. Appendices are missing and could therefore not be evaluated (Read Codes, Feasibility Counts, and Sample Size Considerations).

(B) Discretionary advice for the applicants

1. Whilst follow-up should indeed terminate at death when examining stroke, the reverse is not true. i.e. An incidence of stroke should not terminate follow-up when examining death, as this would bias results.
2. The applicants could consider polypharmacy as a continuous variable, i.e. total number of BNF codes in 3-month period, rather than as a categorical variable.
3. Both patient-level and practice-level IMD data have been requested but only justification for patient-level IMD has been provided in Section J – in future it would be helpful to specify why both version of IMD are being requested

General comment:

It is essential that consideration is given to preserving confidentiality at the reporting stage. The possibility of unintentional (deductive) disclosure arises when cells with small numbers of patients are quoted. Please note that, when reporting the data, CPRD policy is that no cell should contain <5 events and where necessary 'protect' these counts with secondary suppression. Please contact CPRD for further information if you encounter this issue during publication.

Reviewer 2

Study Design

A big potential problem with this study is that more unwell people are likely to be prescribed more drugs. Therefore, there is a question as to if all confounding can be measured and controlled for in the analysis.

Also, there is potential for recording bias in relation to QOF payments for recording AF and CHADS-VAS scores for patients. In addition, researchers should note that QOF payments stopped in Scotland at end of (?2016_17)

Study Population

It is unclear why excluding those with AF not prescribed any medications

Plan for addressing missing data

Measurement of confounding factors is very important (more unwell patients may be prescribed more drugs). If missing data are associated with polypharmacy, it would raise concerns regarding the ability to control for confounding

Is patient group involvement proposed and acceptable?

Some indication of compliance with polypharmacy might help interpretation of results

Overall comments

Important public health problem, which this study attempts to provide information for. However, there is a relatively high risk that confounding won't be controlled for adequately and so the results difficult to interpret

APPLICANT FEEDBACK:

DATE OF ISAC FEEDBACK:	09/08/18
DATE OF APPLICANT FEEDBACK:	

Appendix 9: Independent Scientific Advisory Committee (ISAC) Extension Request for Data Use application form

Date .12.../11..../2020….

Extension Request for Data Use – please return completed form to enquiries@cprd.com

Project Information	
ISAC Protocol Number: (if applicable)	18_151
Study title:	Is polypharmacy associated with death or ischaemic stroke in individuals newly diagnosed with atrial
Chief Investigator: (if applicable)	Martin Frisher

Licensee Details	
Licensee:	Keele University

Type of Data that Extension is Required	
List all data involved in protocol and the data that you are requesting extension for eg HES APC, HES DID, ONS etc CPRD GOLD Patient Level IMD	
CPRD Data Release Reference: (if applicable)	

Reason for Extension Request
Enter the reason for the extension request, specifying the objectives/aims of your approved ISAC protocol that are still being analysed and/or are yet to be published The reason for requesting an extension is so that we have still have access to the data if the reviewers of the paper that we are about to submit require further analysis. Therefore, the request relates to the same objectives as listed in the approved ISAC protocol (listed below). Objective To determine whether polypharmacy is associated with death and ischaemic stroke among individuals who have been newly diagnosed with AF. Specific Aims and Hypotheses To establish the prevalence of polypharmacy (5-9 different prescribed medications) and hyper-polypharmacy (≥10 different prescribed medications) among individuals who have been newly diagnosed with AF. To test the null hypothesis that individuals with AF, who are exposed to polypharmacy and hyper-polypharmacy at diagnosis, are not at an increased risk of experiencing ischaemic strokes or death during follow-up, compared to the unexposed.

Date Extension is requested to 31st January 2022
Enter the date that you wish to extend the data until – please note that the maximum length of time for a request is 12 months from the initial date of data delivery OR 12 months from the last extension granted date. If an extension may have been previously granted this does not mean that a second request will be granted.

Data Storage Location School of Pharmacy, Keele University
Enter the location that the RAW data is stored (City & Country)

Data Processing Location School of Pharmacy, Keele University
Enter the location that the RAW data is processed (City & Country)

Territory of Analysis. UK
Enter the location that the data analysis is carried out (UK, EEA, Worldwide)

Requestor Name and Title
Dr Martin Frisher

CPRD Decision APPROVE

CPRD Date extension approved to: 31st January 2022

Appendix 10: Microsoft Access queries

Table A10-1: All Microsoft Access queries conducted during this study

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
1	Make Table	Identify all patients with AF	None	Patient	All AF pats	124,969	
2	Make Table	Create Look Up table for AF diagnosis codes	None	Medical	Lookup AF	8	
3	Make Table	All diagnosis dates of AF	None	Clinical Lookup AF	All AF diags	187,562	
4	Make Table	Earliest AF diagnosis date	MinAF	All AF diags	All AF with index date	122,262	
5	Make Table	Earliest diagnosis date between 1/6/06 and 31/12/2009	None	All AF with index date	AF group 1	37,311	Allows for 10-year follow-up
6	Make Table	Add 3 months onto index date	minaf3	AF group 1	AF group 1 plus 3	37,311	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
7	Make Table	Identify all products issued within 3 months following index date	None	AF group 1 plus 3 Therapy	Drugs in 3 months after index	339,914	Eventdate2 (correct format) Product code only
8	Make Table	Identify all drug substances issued in 3 months following index date	None	Drugs in 3 months after index Product	Drugs in 3 months unique drug substances	293,877	Devices have blank for drug substance but are allocated a product code; therefore, by using drug substance for the count, we are making sure devices are excluded from polypharmacy count
9	Make Table	Count number of drug substances in 3 months following index date	Ndrugs	Drugs in 3 months unique drug substances	Count of 3m drugs	36,107	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
10	Make Table	Identify patients with no drugs in 3 months after index date	None	Count of 3m drugs	AF_0 drugs	33	
11	Make Table	Identify patients with 1-4 drugs in 3 months after index date	None	Count of 3m drugs	AF_1to4drugs	7,853	
12	Make Table	Identify patients with 5-9 drugs in 3 months after index date	None	Count of 3m drugs	AF_5to9drugs	17,156	
13	Make Table	Identify patients with ≥10 drugs in 3 months after index date	None	Count of 3m drugs	AF_10plusdrugs	11,065	
14	Make Table	Year of index date	Yearindex	AF group 1 plus 3	Year of index date	37,311	
15	Make Table	Age at index	AgeIndex	Year of index date	Age at index date	37,311	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
16	Make Table	Calculate end date for all AF patients	Indexdate (replaces minAF)	AF group 1 plus 3	All AF with end date	37,311	
17	Make Table	Add patient details	None	All AF with end date Patient Age at index date	AF patient with age, gender, tod, reason etc	37,311	
18	Update table	Give polygroup variable a value (1)	Polygroup	AF_1to4drugs	AF_1to4drugs	7,853	
19	Update table	Give polygroup variable a value (2)	Polygroup	AF_5to9drugs	AF_5to9drugs	17,156	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
20	Update table	Give polygroup variable a value (3)	Polygroup	AF_10plusdrugs	AF_10plusdrugs	11,065	To append the polygroups into one table, make a copy of one of these tables and append into copy.
21	Append tables	Join all polygroups from separate tables together	None	Copy of AF_10plusdrugs AF_5to9drugs AF_1to4drugs	AF polygroups	36,074	Number of patients with AF who are taking one or more drugs
22	Make table	Add polygroup column to demographics table	None	AF patient with age, gender, tod, reason etc AF polygroups	AF patients with age, gender etc and polygroups	36,074	
23	Make table	Calculate the difference between index and tod dates (ie. details about follow-up)	Daystotod, monthstotod, yearstotod	AF patients with age, gender etc and polygroups	Difference between index date and tod dates	36,074	Table also contains all polygroup and demographic information

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
24	Make table	Calculate the difference between index and death dates (ie. details about follow-up)	Daystodeath, monthstodeath, yearstodeath	Difference between index date and tod dates	Difference between index date and death dates	36,074	As above
25	Make table	Identify stroke data for AF patients	None	Clincal AF group 1 plus 3	Stroke diags	13,777	
26	Make table	Identify people who had stroke after AF diagnosis	Strokediff (difference between stroke date and index date in days)	Stroke diags AF patients with age, gender etc and polygroups	Stroke diags after index date	5,035	Criteria for Strokediff >0
27	Make table	Earliest stroke date, after index date	Strokenmindate Group =1 (ie. all patients who had stroke after index date)	Stroke diags after index date	Stroke diags after index date min	3,648	Update query to add 1 to group column

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
28	Make Table (unmatched query using wizard)	Identify all patients who haven't had a stroke	Group = 0 (ie. no stroke)	Stroke diags after index date min AF patients with age, gender etc and polygroups	Patients with no stroke	32,426	Update query to add 0 to group column
29	Make table	Add demographic information for all who had a stroke	None	Stroke diags after index date min AF patients with age, gender etc and polygroups	Demographics Stroke	3,648	
30	Make table	Add demographic information for all who had not had stroke	None	No stroke	Demographics no stroke	32,426	Just removed date difference columns from no stroke table
31	Make table	Append stroke data	None	Demographics stroke Demographics no stroke	Demographics stroke and no stroke	36,074	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
32	Make table	To find earliest end date	Final date Group changed to stroke group	NG queries to find min date Demographics stroke and no stroke	Demographics stroke and no stroke inc. final date	36,074	NG used several queries to identify end date for all participants. If there is a stroke date, then final date=stroke date. If no stroke date the final date = earliest of tod or death date or last collection date (practice table)
33	Make table	Identify all patients with death date	None	Demographics stroke and no stroke inc. final date	All patients with death date	14,643	
34	Update table	Put into 2 groups (alive=0, dead=1)	Deathgroup	All patients with death date	All patients with death date	14,643	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
35	Make Table (unmatched query using wizard)	Identify all patients who haven't died	Deathgroup = 0 (ie. alive)	Demographics stroke and no stroke inc. final date All patients with death date	No death date	21,431	Update query to add 0 to deathgroup column
36	Make table	Append deathgroups into one table	None	Copy of all patients with death date No death date	Copy of all patients with death date	36,074	

NAME:

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
37	Make table	Add deathgroup to demographics table	None	Copy of all patients with death date Demographics stroke and no stroke inc. final date	Demographics inc stroke death and final date	36,074	
38	Make table	Calculate difference in days, months and years between index date and final date	Daysdiff, monthsdiff, yearsdiff	Demographics inc stroke death and final date	Difference between index and final date	36,074	Incorrect date diff, should be between start date and final date, not index date and final date
39	Make Table	Add 3 months onto index date to get study start date	startdate	Demographics inc stroke death and final date	Start and end dates for study	36,074	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
40	Make table	Calculate difference in days, months and years between index date and final date	Daysdiff, monthsdiff, yearsdiff	Start and end dates for study	Difference between START and FINAL date	36,074	This file transferred to Excel
41	Make table	Calculate the date 2 years prior to index date	Progdate	Difference between START and FINAL date	Prognostic date	36,074	This date is needed to work out pre-existing conditions in 2 years prior to AF diagnosis
42	Make Table	Identify all with hypertension in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags hypertension	5,880	
43a	Make Table	Identify all with DM in 2 years prior to AF diagnosis (part 1)		Clinical Prognostic date	Diabetes Part 1	16,286	
43b	Make Table	Identify all with DM in 2 years prior to AF diagnosis (part 2)		Clinical Prognostic date	Diabetes Part 2	352	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
43c	Make Table	Identify all with DM in 2 years prior to AF diagnosis (part 3)		Clinical Prognostic date	Diabetes Part 3	97	
43d	Make Table	Identify all with DM in 2 years prior to AF diagnosis (part 4)		Clinical Prognostic date	Diabetes Part 4	75	
43e	Make table	Append all diabetes results into one table		Diag diabetes part 1, diag diabetes part 2, diag diabetes part 3, diag diabetes part 4	Diags diabetes 1-4	16,810	
44	Make Table	Identify all with heart failure in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Heart failure	3,127	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
45	Make Table	Identify all with IHD or other ischaemic heart conditions in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags cardiac	3,469	
46	Make Table	Identify all with myocardial infarction in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags MI	893	
47	Make Table	Identify all with peripheral valvular disease (PVD) in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags peripheral valvular	710	
48	Make Table	Identify all with thyroid diseases in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags thyroid disease	866	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
49	Make Table	Identify all with COPD in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags COPD	8,947	
50	Make Table	Identify all with sleep apnoea in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags sleep apnoea	580	
51	Make Table	Identify all with BMI record in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diag BMI (not value)	1,847	Not BMI value, just category
52	Make Table	Identify all with ischaemic stroke in 2 years prior to AF diagnosis (index date)		Clinical Prognostic date	Diags ischaemic stroke	3,172	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
53	Update tables	Give all diagnoses a number	Diseasecode (1-10)	Output from 42-52	Diags ALL	44,454	1. Previous ischaemic stroke 2. HTN 3. DM 4. HF 5. IHD/Cardiac 6. MI 7. PVD 8. Thyroid 9. COPD 10. Apnoea

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
54	Make Table	Earliest date for each disease code (within 2 years of index)		Diags ALL	Min of Disease codes all	20,656	1.2,400 2. 3,653 3. 4,388 4. 2,462 5. 2,470 6. 760 7.539 8.648 9.2902 10.434 (Values are number of pts with each condition)
55	Make Table	COPD by patients	COPD	Diags COPD	Diags COPD by PATIENTS	2,902	Add column COPD for update query
56	Make Table	MI by patients	MI	Diags MI	Diags MI by PATIENTS	760	Pat id needs to be changed to number

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
57	Make table	PVD by patients	PVD	Diags peripheral valvular disease	Diags PVD by PATIENTS	539	
58	Make table	Sleep Ap by patients	SLEEP	Diags Sleep Aponea	Diags SLEEP by PATIENTS	434	
59	Make table	Thyroid by patients	THYROID	Diags Thyroid	Diags Thyroid by PATIENTS	648	
60	Make table	HTN by patients	HTN	Diags hypertensio n	Diags HTN by PATIENTS	3653	
61	Make table	HF by patients	HF	Diags heart failure	Diags HF by PATIENTS	2462	
62	Make table	DM by patients	DM	Diags diabetes 1-4	Diags DM by PATIENTS	4388	
63	Make table	Cardiac by patients	CARDIAC	Diags cardiac	Diags cardiac by PATIENTS	2470	
64	Make table	Previous ischaemic stroke by patients	PREVIOUSS TROKE	Diags previous ischaemic stroke	Diags previous ischaemic stroke by PATIENTS	2400	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
65	Make table	Create a table for all diagnoses in 2 years prior to index for all pts		Tables 55-64	Diags ALL in 2 years prior to index	36,074	
New database created (Additional Info) for covariates (MF)							
BMI							
66	Make table	Get BMI values for All AF patients from 1st Additional File	BMI BMIval	AF_V3_14052019_Extract_Additional_001 And AllAF with index date	bmi add1	1,082,835	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
67	Make table	Get BMI values for All AF pats from 2nd additional info	BMI BMIval	AF_V3_14052019_Extract_Additional_002 And AllAF with index date	bmi add2	349,937	
68	Append	Append bmi add2 to bmi add1		bmi add1 bmi add 2	bmi all	1,432,272	
69	Make table	To get eventdate and adid from clinical 1		AF_V3_14052019_Extract_Clinical_001	bmi from clin1 with date and adid	159,880	Don't group-exceeds memory
70	Make table	To get eventdate and adid from clinical 2		AF_V3_14052019_Extract_Clinical_002	bmi from clin2 with date and adid	162,608	
71	Make table	To get eventdate and adid from clinical 3		AF_V3_14052019_Extract_Clinical_003	bmi from clin3 with date and adid	171,062	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
72	Make table	To get eventdate and adid from clinical 4		AF_V3_14052019_Extract_Clinical_004	bmi from clin4 with date and adid	167,657	
73	Make table	To get eventdate and adid from clinical 5		AF_V3_14052019_Extract_Clinical_005	bmi from clin5 with date and adid	165,740	
74	Make table	To get eventdate and adid from clinical 6		AF_V3_14052019_Extract_Clinical_006	bmi from clin6 with date and adid	160,392	
75	Make table	To get eventdate and adid from clinical 7		AF_V3_14052019_Extract_Clinical_007	bmi from clin7 with date and adid	172,702	
76	Make table	To get eventdate and adid from clinical 8		AF_V3_14052019_Extract_Clinical_008	bmi from clin8 with date and adid	160,174	
77	Make table	To get eventdate and adid from clinical 9		AF_V3_14052019_Extract_Clinical_009	bmi from clin9 with date and adid	141,327	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
78	Append	Append bmi from clin 2-9 to bmi from clin1 with data and adid		Tables 69-77	bmi from clin1 to clin9 with date and adid	1,461,542	
79	Make table	To get all bmi values for AF patients with dates from clinical tables 1-9		bmi from clin1to clin 9 with date and adid and bmi all	bmi all values with clin1 to clin9 dates	1,432,272	Double join patid and adid Numbers checked
Smoking							
80	Make table	Get smoking values for All AF patients from 1st Additional File	Smokeval	AF_V3_14052019_Extract_Additional_001 And All AF with index date	smoking add1	1,078,629	Lookup YND **YND** **Field1** / **Field2** Smoke/Drink S 0 Data Not Ente 1 Yes 2 No 3 Ex

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
81	Make table	Get smoking values for All AF patients from 2nd Additional File	Smokeval	AF_V3_140 52019_Extr act_Addition al_002 And All AF with index date	smoking add2	378,541	
82	Append	Join tables 80-81 together		smoking add1 smoking add2	Smoking all	1,457,17 0	
83	Make table	To get smoking values with dates from clinical 1		AF_V3_140 52019_Extr act_Clinical_ 001	smoking from clin1 with date and adid	160,599	
84	Make table	To get smoking values with dates from clinical 2		AF_V3_140 52019_Extr act_Clinical_ 002	smoking from clin2 with date and adid	159,733	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
85	Make table	To get smoking values with dates from clinical 3		AF_V3_140 52019_Extr act_Clinical_ 003	smoking from clin3 with date and adid	170,205	
86	Make table	To get smoking values with dates from clinical 4		AF_V3_140 52019_Extr act_Clinical_ 004	smoking from clin4 with date and adid	160,504	
87	Make table	To get smoking values with dates from clinical 5		AF_V3_140 52019_Extr act_Clinical_ 005	smoking from clin5 with date and adid	161,776	
88	Make table	To get smoking values with dates from clinical 6		AF_V3_140 52019_Extr act_Clinical_ 006	smoking from clin6 with date and adid	166,874	
89	Make table	To get smoking values with dates from clinical 7		AF_V3_140 52019_Extr act_Clinical_ 007	smoking from clin7 with date and adid	183,731	
90	Make table	To get smoking values with dates from clinical 8		AF_V3_140 52019_Extr act_Clinical_ 008	smoking from clin8 with date and adid	174,109	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
100	Make table	To get smoking values with dates from clinical 9		AF_V3_14052019_Extract_Clinical_009	smoking from clin9 with date and adid	148,739	
101	Append	Append smoking from clin 2-9 to smoking from clin1 with data and adid		Tables 83-100	smoking from clin1to clin 9 with date and adid	1,486,310	
102	Make table	To get all smoking values for AF patients with dates from clinical tables 1-9		smoking from clin1to clin 9 with date and adid and Smoking all	smoking all values with clin1 to clin 9 dates	1,457,170	Double join patid and adid Numbers checked
Alcohol							

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
103	Make table	Get alcohol values for All AF patients from 1st additional info file	Alcohol Alcohol val	AF_V3_14052019_Extract_Additional_001 And All AF with index date	alcohol add1	550,189	Lookup YND **YND** **Field1** / **Field2** Smoke/Drink S 0 Data Not Ente 1 Yes 2 No 3 Ex

Query name	Type	Purpose	Variables Created	Input	Output	N records in output	Comment
104	Make table	Get alcohol values for All AF patients from 2nd additional info file	Alcohol Alcohol val	AF_V3_14052019_Extract_Additional_002 And All AF with index date	alcohol add2	189,643	Lookup YND YND Field1 | Field2 Smoke/Drink S 0 Data Not Ente 1 Yes 2 No 3 Ex
105	Append	Join together tables 103 and 104		alcohol add1 alcohol add2	Alcohol all from add	740,462	
106	Make table	To get alcohol values with dates from clinical 1		AF_V3_14052019_Extract_Clinical_001	alcohol from clin1 with date and adid	82,272	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
107	Make table	To get alcohol values with dates from clinical 2		AF_V3_140 52019_Extr act_Clinical_ 002	alcohol from clin2 with date and adid	79,188	
108	Make table	To get alcohol values with dates from clinical 3		AF_V3_140 52019_Extr act_Clinical_ 003	alcohol from clin3 with date and adid	87,725	
109	Make table	To get alcohol values with dates from clinical 4		AF_V3_140 52019_Extr act_Clinical_ 004	alcohol from clin4 with date and adid	83,875	
110	Make table	To get alcohol values with dates from clinical 5		AF_V3_140 52019_Extr act_Clinical_ 005	alcohol from clin5 with date and adid	85,468	
111	Make table	To get alcohol values with dates from clinical 6		AF_V3_140 52019_Extr act_Clinical_ 006	alcohol from clin6 with date and adid	82,766	
112	Make table	To get alcohol values with dates from clinical 7		AF_V3_140 52019_Extr act_Clinical_ 007	alcohol from clin7 with date and adid	89,596	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
113	Make table	To get alcohol values with dates from clinical 8		AF_V3_14052019_Extract_Clinical_008	alcohol from clin8 with date and adid	84,522	
114	Make table	To get alcohol values with dates from clinical 9		AF_V3_14052019_Extract_Clinical_009	alcohol from clin9 with date and adid	79,374	
115	Append	Append alcohol from clin 2-9 to alcohol from clin1 with data and adid		Tables 106-115	alcohol from clin1to clin 9 with date and adid	754,786	
116	Make table	To get all alcohol values for AF patients with dates from clinical tables 1-9		Alcohol from clin1to clin 9 with date and adid and Alcohol all from add	Alcohol all values with clin1 to clin 9 dates	740,462	Numbers checked
EGFR							

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
117	Make table	To get EGFR values with dates from test 1	Gf Gfdate Gfvalue Operator	AF_V3_140 52019_Extr act_Test_00 1	gf from test1 with date and adid	126,499	From the 12 test files (not the additional files as above) Value in data 2 Entyype:466 (from Entity Table)
118	Make table	To get EGFR values with dates from test 2	Gf Gfdate Gfvalue Operator	AF_V3_140 52019_Extr act_Test_00 2	gf from test2 with date and adid	133,131	
119	Make table	To get EGFR values with dates from test 3	Gf Gfdate Gfvalue Operator	AF_V3_140 52019_Extr act_Test_00 3	gf from test3 with date and adid	116,841	
120	Make table	To get EGFR values with dates from test 4	Gf Gfdate Gfvalue Operator	AF_V3_140 52019_Extr act_Test_00 4	gf from test4 with date and adid	121,260	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
121	Make table	To get EGFR values with dates from test 5	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_005	gf from test5 with date and adid	121,857	
122	Make table	To get EGFR values with dates from test 6	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_006	gf from test6 with date and adid	143,315	
123	Make table	To get EGFR values with dates from test 7	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_007	gf from test7 with date and adid	125,756	
124	Make table	To get EGFR values with dates from test 8	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_008	gf from test8 with date and adid	143,878	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
125	Make table	To get EGFR values with dates from test 9	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_009	gf from test9 with date and adid	148,766	
126	Make table	To get EGFR values with dates from test 10	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_0010	gf from test10 with date and adid	126,078	
127	Make table	To get EGFR values with dates from test 11	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_0011	gf from test11 with date and adid	158,274	
128	Make table	To get EGFR values with dates from test 12	Gf Gfdate Gfvalue Operator	AF_V3_14052019_Extract_Test_0012	gf from test12 with date and adid	149,857	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
129	Append	To get all EGFR values for AF patients with dates from test tables 1-12		Tables 117-128	GF all values with date and adid	1,615,462	Numbers checked
Finding the most recent results							
130	Make table	To get most recent BMI result before AF diagnosis		bmi all values with clin1 to clin9 dates Prognostic date	BMI in 2 years before AF	56,211	Between [] and[]
131	Make table	Maximum event date in 2 years		BMI in 2 years before AF	BMI max date in 2 years before AF	23,168	
132	Make table	Find BMI value for maximum event date	Bmidate (i.e. latest BMI date)	BMI in 2 years before AF BMI max date in 2 years before AF	BMI most recent	22,820	Criteria >0

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
133	Make table	To get most recent EGFR result before AF diagnosis		gf all with date and adid Prognostic date	EGFR in 2 years before AF	53,808	
134	Make table	Maximum event date in 2 years		EGFR in 2 years before AF	EGFR max date in 2 years before AF	17,329	
135	Make table	Find EGFR value for maximum event date		EGFR in 2 years before AF EGFR max date in 2 years before AF	EGFR most recent	16,604	Criteria >0
136	Make table	To get most recent alcohol record before AF diagnosis	alcoholdate	Alcohol all values with clin1 to clin9 dates	Alcohol in 2 years before AF	27,522	
137	Make Table	Maximum event date in the 2 yrs		Alcohol in 2 years before AF	Alcohol max date in 2 years before AF	16,295	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
138	Make table	Find Alcohol value for maximum event date		Alcohol in 2 years before AF Alcohol max date in 2 years before AF	Alcohol most recent	16,377	
139	Make table	To get most recent smoking record before AF diagnosis	smokedate	Smoking all values with clin1 to clin9 dates	Smoking in 2 years before AF	68,744	
140	Make Table	Maximum event date in the 2 yrs		Smoking in 2 years before AF	Smoking max date in 2 years before AF	30,007	
141	Make table	Find smoking value for maximum event date		Smoking in 2 years before AF Smoking max date in 2 years before AF	Smoking most recent	30,065	
142	Make table	Identifying all pts with BMI ≥30.0	Obese =2	BMI most recent	BMI Obese	7,933	Obese column added to this table.

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
143	Make table	Identifying all pts with BMI <30.0	Obese =1	BMI most recent	BMI NON obese	14,887	**Obese = 2** **Non obese =1** **Missing =0**
144	Make Table	Put non obese, obese and missing results together	Obese =0	BMI missing BMI Obese BMI non obese	BMI ALL	36,074	
145	Make table	Identifying all EGFR ≤30	EGFR=2	EGFR most recent	EGFR POOR	533	
146	Make table	Identifying all EGFR <30	EGFR=1	EGFR most recent	EGFR >30	16,071	
147	Make table	Put all EGFR results together	EGFR =0	EGFR Poor EGFR >30 EGFR Missing	EGFR ALL	36,074	**Poor =2** **>30 =1** **Missing =0**
148	Make table	Identifying all pts with missing smoking values	Smokeval missing =0	Smoking most recent	Smoking missing	6,067	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
149	Make table	Put all smoking results together		Smoking most recent Smoking missing	Smoking ALL	36,074	**Ex smoker =3** **Non smoker = 2** **Smoker =1** **Missing = 0**
150	Make table	Identifying all pts with missing alcohol values	Alcoholval =0	Alcohol most recent	Alcohol missing	19,779	
151	Make table	Put all alcohol results together		Alcohol most recent Alcohol missing	Alcohol ALL	36,074	**Ex drinker =3** **Non drinker = 2** **drinker =1** **Missing = 0**
152	Make table	Put obese, EGFR, smoking and alcohol values in 1 table		Alcohol ALL Smoking ALL EGFR ALL BMI ALL	Lifestyle covariates	36,074	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
153	Make table	Identifying all pts with missing IMD values	Imd2015_5	Sheet 2 Prognostic	IMD missing	15,869	**Imd2015_5 = 0** **1-5 are quintile values.** IMD 2015 quintile (**1=LEAST deprived,…, 5=MOST deprived**) – from O:\CPRD Data\Natasha\Results_Keele_18_151 IMD\Results\Documentation\Set 17
154	Make table	Identify all AF pts with IMD	Imd2015_5	Sheet 2 Prognostic	IMD	20,205	
155	Make table	Put all IMD results for study participants together	Imd2015_5	IMD IMD missing	IMD data for AF including missing	36,074	
156	Make table	Lookup CV drugs		Product	Lookup CV drugs	4,748	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
157	Make table	CV drugs for each patient		Lookup CV drugs Drugs in 3 months after index	CV drugs for each participant	177,135	
158	Make table	Count of different CV drugs	CVDRUGCOUNT	CV drugs for each participant	CV drugs COUNT	35,250	
159	Make table	No CV drugs	CVDRUGCOUNT=0	CV drugs COUNT Prognostic	CV drugs NONE	824	158+159 combined to CV COUNT ALL
160	Make table	Add CV drug count to covariate table		CV count ALL Lifestyle covariates +IMD	**Lifestyle covariates+IMD+CVcount**	36,074	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
161	Make table	Practice codes for each participant	Lookup Practice Region	Lifestyle covariates+ IMD+ CV count Patid practid link Practice Lookup Practice region	AF patients PRACTICE	36,074	
162	Make table	Get all drugs in 3m with bnf codes and chapters		All drugs bnf chapter codes for 3m after index	All drugs BNF codes and chapter V2	287,249	'is not null' to filter blank cells for drug substance (e.g. appliances)
163	Make table	Identify all patients with positive datediff value		Prognostic date	Patient ID with positive date diff	33,984	

Query name	*Type*	*Purpose*	*Variables Created*	*Input*	*Output*	*N records in output*	*Comment*
164	Make table	Identify all patients with positive datediff value and add polygroup		Patient ID with positive date diff Prognostic date	All pts with positive date diff and polygroup	33,984	**KEY TABLE**
165	Make table	Drugs (3m from index) for all pts with positive date diff and polygroup		All pts with positive date diff and polygroup All drugs BNF codes and chapter V2	All drugs positive date diff and polygroup_export to SPSS	270,018	can only export if you don't tick formatting box.
166	Make table	Q165 file too large for Excel so split information into each group		All drugs positive date diff and polygroup_ export to SPSS	Drugs_3m_positive cases only 1-4 group	21,846	

Query name	***Type***	***Purpose***	***Variables Created***	***Input***	***Output***	***N records in output***	***Comment***
167	Make table	Q165 file too large for Excel so split information into each group		All drugs positive date diff and polygroup_ export to SPSS	Drugs_3m_positive cases only 5-9 group	112,899	
168	Make table	Q165 file too large for Excel so split information into each group		All drugs positive date diff and polygroup_ export to SPSS	Drugs_3m_positive cases only 10 plus group	135,273	