Adherence to cardiovascular medication across Scotland

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Abstract

Introduction

Despite the availability of efficacious drugs, cardiovascular disease (CVD) remains a leading cause of global mortality, and prevalence of CVD is higher in Scotland than in other developed countries. Better understanding of chronic disease management is important in closing the gap between outcomes found in general practice prescribing with clinical trial findings. A key component of disease management is drug adherence, consisting of initiation, implementation, and persistence, and Scotland has valuable nation-wide administrative databases which can be used to study aspects of adherence at a population level. With these datasets, it is possible to define different CVD patient groups, to compare adherence across a range of drug classes and risk-factors, and to assess the association between drug-persistence with subsequent mortality rates.

Methods

Using the Scottish Prescribing Information System (PIS), linked to hospital admissions data (SMR) and death certificates (NRS), we have defined four patient subgroups: primary prevention (n=1,659,566), treatment for symptomatic cardiovascular disease (n = 260,516), secondary prevention (n=25,283), and secondary-prevention-with-treatment (n=23,866).

Within these patient groups, the Treatment Anniversary Model (TAM) and Proportion of Days Covered (PDC) were used to identify broad levels of persistence and implementation to ten different CVD drug-classes. Further multivariate analysis was conducted in four selected drug classes: ACE-inhibitors, antiplatelets, betablockers, and lipid-regulatory drugs. Risk factors considered include sex, age, socioeconomic status, and comorbidity.

Cox-proportional hazards models were then used to investigate the association between drug-persistence with subsequent mortality. Some additional analyses were carried out to investigate possible sources of confounding.

Results

In the unadjusted analysis, adherence tends to be associated with traditional cardiovascular risk factors (male sex, older age, higher deprivation, etc.) across the drug-classes and patient groups studied. Implementation and persistence are lowest in the primary prevention group and highest in the secondary prevention group. In the multivariate analysis, higher levels of persistence were associated with male sex (OR range 1.16 – 1.40) and increased social deprivation (OR range 1.07-1.18) across all drug-classes and patient-groups. Diabetes as a comorbidity was associated with higher persistence for the primary and treatment groups only (OR range 1.07-1.38). There was some inconsistency in the associations observed for age and for depression as a comorbidity.

The relationship observed between persistence and mortality showed a protective association across the patient-groups and drug-classes studied. Adjusting for additional confounders, such as CVD polypharmacy, did not provide additional insights to these analyses and definitions of this may need refined for future study.

Conclusion

This is a longitudinal, Scotland-wide, retrospective study of adherence to cardiovascular drugs (namely, implementation and persistence), with near-universal population coverage. This allows identification of population-level risk factors, and identification of patient groups who may require extra support. While much of these findings replicate those observed in literature review, this is the first study of its scale assessing implementation and persistence to cardiovascular medication in Scotland. It also proves as validation for Scottish administrative datasets in having the potential to assess medication adherence.

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List of Publications, Presentations, & Training

Academic Publications:

Leslie, K.H., C. McCowan, and J.P. Pell, Adherence to cardiovascular medication: a review of systematic reviews. Journal of Public Health, 2018. 41(1): p. e84-e94. https://doi.org/10.1093/pubmed/fdy088

Presentations (selected):

- Leslie K.H., McCowan C., and Pell J.P. 'Population level risk factors for nonpersistence to cardiovascular medication' European Society of Cardiology. *EuroHeartCare* 2020. Online ePoster Presentation.

- Leslie K.H., McCowan C., and Pell J.P., 'Persistence to cardiovascular medication across Scotland' Institute of Health and Wellbeing. *Research Away Day*. Glasgow; 18th Feb 2020

- Leslie K.H., McCowan C., and Pell J.P. 'Poster Presentation: Adherence to Cardiovascular Medication Across Scotland' ESPACOMP, Porto; 23rd Nov 2019

- Leslie, KH. 'Using Big Data to Mend Scotland's Heart' LUCID, *Three-minute Thesis*. Glasgow; 15th Oct 2019.

- Leslie, KH. 'Public Engagement: Communicating Your Research' The GUILD Summer School. Paris; 10th July 2019

- Leslie K.H., McCowan C., and Pell J.P. 'Adherence to Cardiovascular Medication Across Scotland' Health Data Research UK, Cambridge 12th June 2019

- Leslie, K.H., McCowan C., Robertson D., Morris A and J.P. Pell. Oral Presentation: 'Adherence to Cardiovascular Medication Across Scotland' Informatics for Health, *Pre-conference Symposium*. Manchester; 23rd April 2017

Blogs:

MRC Insight Blog

'From Max P winner to award-winning journalist' Jun 20th 2019. https://mrc.ukri.org/news/blog/from-max-p-winner-to-award-winning-journalist/

'Can big data mend a broken heart?' Oct 20th 2017 https://mrc.ukri.org/news/blog/can-big-data-mend-a-broken-heart/ [*Winner: Max Perutz Science Writing Award, 2017*]

LEADS

'The ACE link between COVID-19 and cardiovascular disease' May 5th 2020 https://www.uofgleadsforstudents.co.uk/blog/the-ace-link-between-covid-19-and-cardiovascular-disease

theGIST (selected articles)

'Bright Club: communicating research through comedy' Jan 31st 2020 https://the-gist.org/2020/01/bright-club-communicating-research-through-comedy/ [*Shortlisted Student Publications Association: Best Entertainment Piece, 2020*]

'Defining Obesity' May 8th 2019 https://the-gist.org/2019/05/defining-obesity/ [*Shortlisted Student Publications Association: Best Science/ Tech article, 2020*]

'Digital Pills: Big Data or Big Brother?' April 23rd 2018 https://the-gist.org/2018/04/digital-pills-big-data-big-brother/ [*Winner Association of British Science Writers: Student Science Journalist of the year, 2019*]

Public Outreach Activities:

- Gavinburn Primary Science-sational Evening, March 11th 2020.
- theGIST Workshop: Writing and Editing, Januray 13th 2020.
- Explorathon 2019: Design a Science Magazine with theGIST, Sept 29th 2019
- Glasgow Science Festival 2019: theGIST Junior, June 16th 2019
- Glasgow Science Festival Internship; Science Sunday June 18th 2017: Bee The Change

Training (selected):

- MRC: Research, GDPR, and confidentiality, November 15th, 2019
- Royal Society Media Skills Training Day, October 10th, 2019
- STEM Ambassador PVG Approved 5th June 2019
- Mental Health First Aid Training (two-day course). Approved 26th March 2019.
- POST training day, University of Glasgow, 16th April 2018.
- **Karolinska Institute**: *Casual Inference for Epidemiologists*. 26th Feb – March 6th 2018.
- Research Integrity Training, University of Glasgow December 2017.
- MRC: Research Data and Confidentiality e-learning course, 30th Nov 2016.
- Healthy R: Quick Start 2.5 day course, 23-25th Nov 2016 (https://healthyr.surgicalinformatics.org/) .
- DataCamp Online Training courses (throughout period of study).
- **University of Edinburgh:** *courses completed to achieve credits required in line with Precision Medicine DTP Programme*:
    - Public health informatics
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Author’s Declaration

I declare that the contents of this thesis are my own work and have not been submitted for any other degree at the University of Glasgow or any other institution. Where the work of others has been used it has been indicated and appropriately referenced

Kirstin Leslie.

Definitions/Abbreviations

ABC - Ascertaining Barriers to Compliance

ACEi – Angiotensin-Converting-Enzyme inhibitors

AMI/ MI – Acute Myocardial Infarction/ Myocardial Infarction

ARB – Angiotensin-II-Receptor Blockers

BB – Beta-blockers

BNF – British National Formulary

CCB – Calcium Chanel Blockers

CHI – Community Health Index

CMA – Continuous Measure of Medication Acquisition

CMP - Continuous Multiple Interval Measure of Oversupply

CVD – Cardiovascular Disease

DCVP - Data Capture Validation and Pricing

DDD – Defined Daily Doses

DUR - Drug Utilisation Research

eDRIS - Electronic Data Research and Innovation Service

EHR - Electronic Health Records

EMS – Electronic Monitoring System

ESPACOMP - European society for patient adherence, compliance, and persistence

EMERGE - ESPACOMP Medication Adherence Reporting Guideline

GTN – Glyceryl Trinitrate

GBTM - Group based trajectory modelling

HR – Hazard Ratio

ICD – International Classification of Diseases

MEMS - Medication Event Monitoring System

MPR – Medication Possession Ratio

NRS – National Records of Scotland

NSS – National Services Scotland

PBPP - Public Benefit and Privacy Panel

PDCa – Proportion of Days Covered (all patients)

PDCp – Proportion of Days Covered (persistent patients)

PIS – Prescribing Information System

SIGN - The Scottish Intercollegiate Guidelines Network

SIMD – Scottish Index of Multiple Deprivation

SMR – Scottish Morbidity Records

TAM – Treatment Anniversary Model

1 Introduction

This chapter provides a general background to the thesis and contextualises the basis for it. The following includes an overview of cardiovascular disease and pharmaceutical management of it, the problem of adherence to such medications and challenges in studying this, and a brief overview of pharmacoepidemiology as a means of study.

1.1 Cardiovascular Disease and Public Health

Cardiovascular disease (CVD) is a an established yet growing public health concern and is a leading cause of mortality worldwide[1], responsible for approximately 1 in 3 deaths[1, 2]. CVD is an umbrella term, covering a range of disorders such as coronary heart disease (angina, myocardial infarction (MI), heart failure), stroke, transient ischaemic attack (TIA), peripheral arterial disease, and aortic disease[3].

The burden of CVD is likely to increase as the world's population continues to age; as of 2017, the over-60 population was 962 million, and this is growing at a rate of 3% per year[4]. Other CVD risk-factors are also on the rise: rates of obesity and type-2 diabetes are increasing, and, while there has been a decline in smoking in the UK, there is an increase in smoking at a global level. The over-60 population is projected to double to 2.1 billion by the year 2050[4]. Management of CVD and associated illnesses may therefore have a significant impact on global mortality rates and should continue to be a public health priority.

In the UK, the highest prevalence of CVD is in Scotland, with the highest rate of CVD-related mortalities occurring within Scotland[5, 6]. In 2014, 15,016 deaths were caused by CVD[6], accounting for 27.7% of mortalities that year. The 2013 age-standardised mortality rate for Scotland was 327 per 100,000, compared to 268 per 100,00 in England, 304 per 100,000 in Wales, and 277 per 100,000 in Northern Ireland[6] (see **Figure 1.1**). Of the UK local authorities with the ten highest CVD mortality rates, five are located in Scotland[5]; with Glasgow City having the highest mortality rates for all ages (400 per 100,000) and for premature mortalities (i.e. under 75 years; 143 per 100,00). This indicates that,

despite a general decrease in CVD mortality in Scotland over recent decades, there is still a need to close the gap with the rest of the UK and reduce geographical health inequalities.

CVD is not just a cause of significant mortality; it is also a cause of morbidity and significant costs to the National Health Service (NHS). The gross expenditure on all CVD prescriptions in Scotland for the financial year 2017-18 was £137,175,725[7], equating to approximately 11% of all prescription costs in Scotland per year[8]. In the year 2016-17, over 7,000 incidents involving heart problems were attended by the Scottish Ambulance service, of which 6,041 resulted in conveyance to hospital[8]. Implications of CVD may have additional effects beyond this; for example, cardiometabolic disorders have been associated with a decrease in cognitive ability[9], so improvement of CVD prevention and management may have knock-on effects on rates of other diseases of ageing, such as Alzheimer's and dementia.

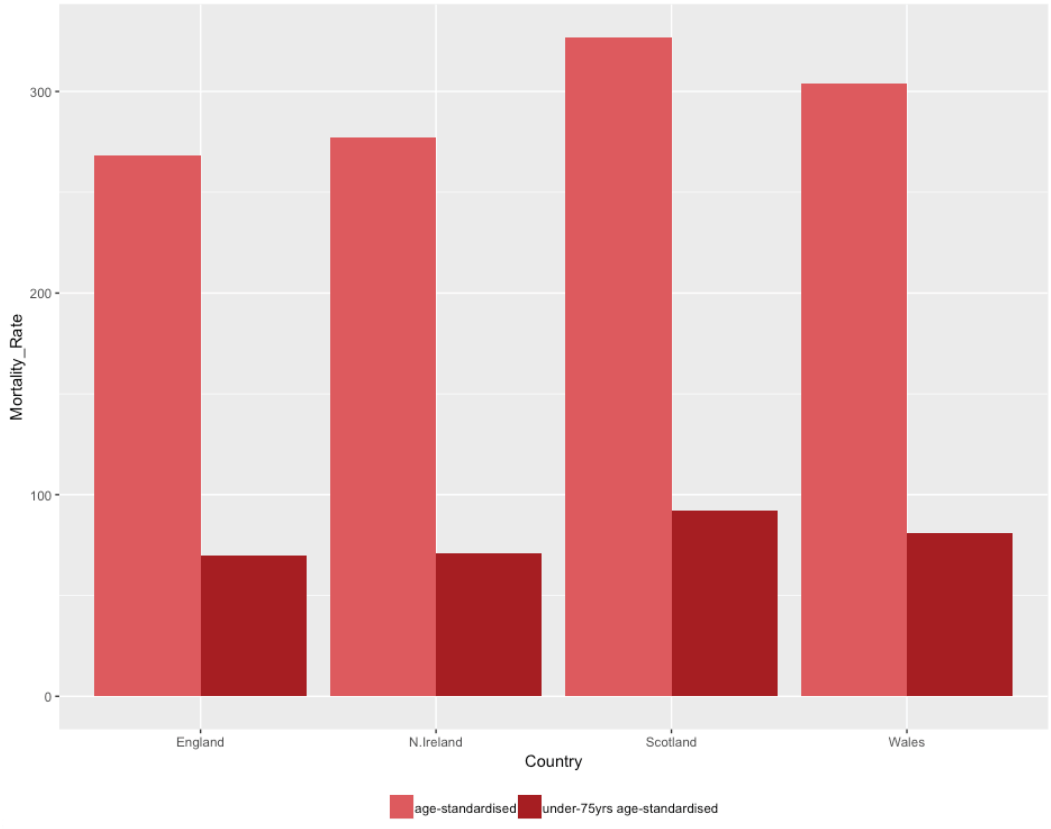

Figure 1.1: CVD age-standardised mortality rates across UK. Adapted from data in Townsend *et al*, 2015[6]. Graph designed using R package ggplot2.

Beyond the costs of routine CVD prescribing, the more significant healthcare costs come from CVD related hospitalisations. Costs of A&E admissions for CVD in the UK are approximately £47.64 million for a given year[10], while costs of hospital inpatient stays for CVD are in excess of £9,000 million[10]. A meta-analysis by Chowdhury *et al* estimated that 9% of CVD events in Europe are directly related to medication nonadherence[11], meaning that patient inability to take medications as prescribed leads to adverse outcomes in some cases. Therefore, improving adherence may reduce CVD related hospital admissions and hence costs. It is important to note that while there may be an increased cost of prescriptions when people adhere to their medication, as they will collect drugs on a more regular basis, this cost is offset by the reduced risk of costly hospitalisation events.

1.1.1 Cardiovascular Risk: Preventing and Managing Disease

CVD is complex, though there are a variety of known risk factors. Clinical factors include hypertension, hyperlipidaemia, diabetes, family history/genetic factors; while behavioural factors include smoking, alcohol consumption, physical inactivity, unhealthy diet, and obesity[1, 3, 6, 12]. Assessment of such factors can be used to predict risk and determine disease prevention and/or treatment strategies.

In Scotland, the ASSIGN score has been used to calculate CVD risk since 2007[13, 14]. It is based on the Framingham risk score, though ASSIGN includes a measure of social deprivation and family history to better fit the Scottish population[15] and to address the impact of social inequalities on health. However, at present, the tool does not account for atrial fibrillation, specific high-risk ethnic groups or women with early menopause, whose risk will be elevated above the score calculated. The Scottish Intercollegiate Guidelines Network (SIGN) recommends that all adults over the age of 40 be offered risk score assessment every five years, though individuals with previously established CVD such as MI, stroke, or TIA, or those with other comorbidities, such as chronic kidney disease, familial hypercholesterolaemia, or diabetes, may not require assessment before being classified as high risk[13]. Once risk is assessed, appropriate intervention steps can be taken.

CVD has a range of interventions available for disease prevention, including lifestyle changes (smoking cessation, physical activity, healthy diet, reduced alcohol consumption)[1, 6], and cost-effective pharmacotherapies (e.g. aspirin). For disease management, there are surgical options such as coronary artery bypass grafting to prevent disease progression, and coronary angioplasty[16]. Pharmacotherapies may also be used in CVD management, such as glyceryl trinitrate (GTN) to control symptoms.

CVD risk may be mediated at several levels of illness. An important aspect of this is disease prevention. Primary prevention of CVD is the prescription of drugs or recommendation of lifestyle changes in those with increased CVD risk (high blood pressure/ high cholesterol etc.) but with no history of CVD events or ongoing symptomatic disease. Secondary prevention of CVD is prescription of medication following a serious CVD event such as an MI in order to reduce future recurrence. The other aspect in disease management is treatment for patients with on-going symptomatic CVD, either in patients with no previous MI or for patients who are additionally undergoing secondary prevention measures.

1.1.2 Pharmaceutical Prevention & Management of Cardiovascular Disease

Drugs which mediate the cardiovascular system are listed in chapter 2 of the British national formulary (BNF)[17]. The main pharmacotherapies referenced in the SIGN guidelines are antiplatelets (e.g. aspirin, clopidogrel), lipid lowering drugs (e.g. atorvastatin, simvastatin), and antihypertensives (e.g. ace-inhibitors, angiotensin receptor blockers, calcium channel blockers)[13].

These drugs have proven efficacy in trial settings. In particular, statins have been the subject of the West of Scotland Coronary Prevention Study (WOSCOPS)[18], a trial which initially lasted 5 years and has since been followed up for 20 years using routine data records. The initial study found that pravastatin reduced cholesterol by 20% (compared to the placebo which had no effect) in men, with an associated reduced risk of MI, CVD mortalities, and all-cause mortalities of 31%, 28%, and 22% respectively[18]. Recent research from the study has found a long-standing benefit to those originally allocated to the

Drug class (BNF category)	Examples	Indications	Contra-indications	Common Side-effects	Refs
Diuretics (BNF 2.2)	Thiazides (Bendroflumethiazide), Loop diuretics (Furosemide)	Oedema; hypertension; resistant hypertension; heart failure	Addison's disease; hypocalcaemia; hyponatraemia; hypokalaemia (potassium loss); hyperuricaemia; may exacerbate gout; may exacerbate diabetes.	Electrolyte imbalance; headache; postural hypotension; dizziness; fatigue; muscle spasms; nausea	DI
Beta-blockers (BNF 2.4)	Bisoprolol fumarate, Carvedilol, Atenolol, Propranolol	Hypertension; angina; MI; arrhythmia; heart failure; thyrotoxicosis; anxiety; glaucoma (eye drops)	Asthma; diabetes; hypersensitive drug reaction; peripheral arterial disease; uncontrolled HF; anti-arrhythmics; antihypertensives; antipsychotics; clonidine; mefloquine	Dizziness; fatigue; bradycardia; diarrhoea and nausea; visual impairment; peripheral coldness; loss of libido	BB
Alpha-blockers (BNF 2.5.4)	Doxazosin Mesilate, Prazosin hydrochloride	Hypertension; benign prostatic enlargement	micturition syncope; postural hypotension; pregnant/ breastfeeding	Vertigo; urinary disorders; headache; oedema; nausea and vomiting	AB
ACE inhibitors (BNF 2.5.5.1)	Ramipril, Lisinopril, Captopril	Hypertension; Chronic HF	Combined with aliskriren: contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m^2 or patients with diabetes mellitus	Persistent dry cough; headaches; dizziness; rash	ACE
Angiotensin-2-receptor blockers (BNF 2.5.5.2)	Telmisartan, Valsartan, Losartan Potassium	Hypertension; Chronic HF second line therapy if ACEi's cause symptoms.	Combined with aliskriren: contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m^2 or patients with diabetes mellitus	Dizziness, headaches, and cold or flu-like symptoms.	ARB
Nitrates (BNF 2.6.1)	Glyceryl trinitrate, Isosorbide Mononitrate	Acute angina (used both in prophylaxis and treatment of angina attack)	Hypertrophic cardiomyopathy; Increased intracranial pressure (haemorrhage/ trauma); marked anaemia; sildenafil (Viagra)	Arrhythmias; asthenia (weakness); cerebral ischaemia; dizziness; drowsiness; flushing; headache; hypotension; nausea; vomiting	NI
Calcium Channel Blockers (BNF 2.6.2)	Amlodipine, Verapamil hydrochloride	Angina; hypertension; cluster headache; arrhythmia	Atrial fibrillation; bradycardia; history of HF; hypotension; sino-atrial block	Headaches; peripheral oedema; constipation; tachycardia; vomiting; dizziness; flushing	CCB
Antiplatelet drugs (BNF 2.9)	Aspirin, Clopidogrel, Ticagrelor	Prevention of atherothrombotic events/ TIA; secondary prevention of CVD	Active bleeding; peptic ulceration; bleeding disorders; history of intracranial haemorrhage	Diarrhoea; gastrointestinal discomfort; haemorrhage; skin reactions; bronchospasm	AP
Lipid-regulating drugs (BNF 2.12)	Atorvastatin, Simvastatin, Ezetimibe	Lower LDL/ CVD prevention	Liver disease; verapamil and diltiazem. amiodarone	Nosebleed; sore throat; headache; GI issues; muscle and joint pain; hyperglycaemia	LR

Table 1.1: CVD drugs classes and key characteristics. ***References: DI*** [19, 20], ***BB***[21-23], ***AB***[24, 25], ***ACE***[26, 27], ***ARB***[27, 28], ***NI***[29], ***CCB***[27, 30], ***AP***[31-33], ***LR***[34].

pravastatin group, with a 21% decrease in CVD mortalities over the 20 year follow-up[35]. As of yet, there is no equivalent study of this scale including women.

The range of treatments available reflects the range of different CVD risk factors which have been identified and which can be targeted therapeutically. Lipid regulatory drugs reduce cholesterol, antiplatelet drugs reduce blood clotting, while antihypertensives control water balance and hence, blood pressure. Within these broad groups, there are multiple different drug formulations, and drugs with multiple different mechanisms of action, meaning that there are alternatives that may be suited to different people. For example, PCSK-9 inhibitors would be the most suited lipid-regulatory drug for someone with familial hypercholesterolemia, while statins may be more suited for reducing circulatory LDL for those with high dietary cholesterol.

Despite the introduction of cost-effective pharmacotherapies for CVD, related mortalities have steadily increased worldwide between 2007-2017[36] and CVD rates remain high.

1.2 Adherence

One factor that may contribute to preventable CVD morbidity and mortality rates is drug adherence[37-40]. Adherence is defined by the European society for patient adherence, compliance, and persistence (ESPACOMP) as “the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation”[41-43]. Literature which pre-dates the publication of the ESPACOMP definition may use the term ‘compliance’ or ‘concordance’ to mean the same thing. The guidelines were introduced to avoid confusion, as terms have previously been used interchangeably despite not always being used to describe the same concepts. Importantly, this definition, known as ‘The ABC Taxonomy’, separates adherence into three phases: initiation, implementation, and discontinuation[41-44] and researchers should clarify which phase(s) their study focuses on.

The noted lack of consistency in studies of adherence[42, 45-48] has also led to the development of the ESPACOMP Medication Adherence Reporting Guideline (EMERGE)[41, 43], with a set of minimum reporting criteria for studies of adherence, and additional desirable items for reporting. In the interests of reproducibility and comparability, it is important for researchers to detail as many of the EMERGE criteria as is possible in their adherence reporting and consider the limitations where this is not possible.

A 2001 report by the World Health Organisation (WHO) found that overall adherence to chronic medications was only 50%[49], and concluded that: "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments"[49]. The same report found that only 25% of patients treated for hypertension reach their target BP[49]. This, along with previous studies which have identified an association between level of adherence with treatment outcomes in cardiovascular disease[11, 13, 38, 50, 51], highlights a huge gap for potential intervention.

From previous adherence research, it is hypothesised that adherence may differ across some key patient characteristics; including disease severity, drug class prescribed, comorbidities, and polypharmacy. Understanding the epidemiology of drug adherence and identifying barriers to implementing treatment regimens are essential first steps toward implementing future interventions, and thus improving levels of adherence in the future. Identifying how adherence relates to patient health outcomes may also be important to consider, as it will inform on the scope that interventions may have in improving health outcomes for patients.

1.3 Drug Utilization Research

Drug utilisation research (DUR) is a branch of pharmacoepidemiology, which helps to facilitate "safe and effective use of medicines" at a population level[52], including adherence research. This is important because, despite the obvious benefits of modern medicines to life expectancy and reduced morbidities, there are still issues in drug management, as drugs cannot work as effectively in

patients who do not adhere. Furthermore, understanding factors influencing consumption of medicines is an important step in improving management of disease.

DUR dates back to the 1960s and is useful in identifying issues with prescription drug use, such as: rare adverse drug reactions (ADR) which may not be identified in Phase Three trial; issues with prescribing, such as overprescribing of antibiotics; inappropriate polypharmacy, for example, prescribing of two drugs which contraindicate one another; and for identifying trends in drug-use habits, such as adherence and persistence[52]. Early DUR symposia helped to establish standard definitions to allow consistency between studies, such as the ATC drug classification system and the use of DDDs for comparing units[53] and, more recently, they have helped to define and standardise adherence research[42]. DUR is important in continued monitoring of drug use patterns, and can help to enhance understanding, implement policy changes around this in order to reduce morbidity and mortality, and save unnecessary expenditure[52]. Adherence research feeds into this, as one of the key founding goals of the European drug utilisation research group (EuroDURG) was "do patients take drugs correctly?"[52], and efforts to investigate this could have significant impacts for public health.

Study designs in DUR are not dissimilar from traditional epidemiology and may broadly be grouped into qualitative or quantitative. Qualitative studies utilise non-numeric data, often relating to patient experience[54] and such studies help to enhance understanding of patient and/ or prescriber perspectives on drug utilization. Data for qualitative studies may be collected through various means including interviews, focus groups, and surveys[55], and can involve many hours in designing appropriate study questions and transcribing information for further analysis. In the late 1990s and early 2000s, the value of qualitative studies in medical and public health research began to be more clearly understood, and the BMJ published a series of papers to highlight the value of qualitative methods[56], to help researchers analyse these findings[57], and to quality assess qualitative work[58].

Qualitative studies are important for understanding patient behaviours in the context of drug utilization; for example, a review of qualitative studies by

Kronish *et al*[59] identified confused perceptions of hypertension, and an assumption that high blood pressure only requires medication when accompanied by symptoms (e.g. stress, dizziness, headache), as a key barrier to cardiovascular drug adherence[60]. A more recent review by Rashidi *et al* also identified patient perception as having a key role in adherence, and further suggested that more support and guidance from healthcare professionals could facilitate this[61]. Qualitative studies are important when any policy changes are to be considered, as understanding the factors that influence healthcare providers and patients are vital to understanding how implementation may work.

The other major study design in DUR is quantitative. Quantitative studies utilise numeric data, or data that can be ranked/ grouped[55]; information may be gathered through primary data collection or secondary data collected for purposes other than research e.g. hospitalisation records). Quantitative study designs can be grouped further into descriptive and analytical. While descriptive studies present information on patterns and trends[54, 55], analytical studies go further, by looking at explanatory factors, and attempt to identify associations by using appropriate statistical tests[55]. For an adherence project, both descriptive and analytical methods can have value, as descriptive methods are useful for hypothesis generating while analytical methods can be employed for hypothesis testing.

To conduct a DUR study of adherence it is important to have a closed pharmacy system, detailing all prescriptions for the study population. This is particularly valuable for the study of chronic diseases, such as CVD, which are largely managed with prescription medications, as we expect patients to continue taking prescriptions for a prolonged time. This allows long-term follow-up using routine healthcare records.

1.4 Using Scottish Routine Healthcare Data

As health systems have moved toward digitised data storage and use of electronic health records (EHRs), the availability of large administrative and clinical datasets has increased. These can be highly valuable as a secondary data source for DUR study if there is an appropriate system in place for capturing

relevant data, linking it to other datasets, checking and maintaining the data quality, and ensuring appropriate data governance is in place.

Scotland has good resources for accessing EHRs in secondary data analysis. The NHS provides GP coverage for Scotland's 5 million residents, with less than 2% opting for additional private healthcare coverage[62], usually only for secondary care. It also has a relatively stable population[62], with low immigration and emigration, meaning longitudinal follow-up is fairly reliable. Furthermore, health records can be linked at an individual level by direct-matching methods, owing to the presence of a community health index (CHI) number automatically generated upon registering with a GP; and it has good coverage, with estimates ranging between 96.5-99.9% of the population in Scotland having a CHI number[62]. This unique CHI follows a patient through all NHS Scotland services as it is recorded on all interactions with the NHS in Scotland, even if they move between health boards, which also contributes to effective longitudinal study. Access to EHR data is managed through eDRIS, a branch of NHS Scotland's information services teams, who perform data linkage and provide extracts for research.

For adherence study, the prescribing information system (PIS) is particularly useful. It is a database of all community-dispensed prescriptions in Scotland, originally curated for the sole purpose of pharmacy reimbursement. It is CHI-linked from 2009 onwards, meaning individual follow-up is possible as it includes dosage information as free-text dosage instructions and, crucially, an algorithm has been developed to pull out important information from this (i.e. how many units of a drug to take in a given time period). With this, along with the quantity of a drug dispensed, an estimation as to how long a prescription should last can be calculated and compared to true pharmacy dispensations for an individual, to estimate drug adherence and identify gaps in treatment. This can then be linked to hospital records and death records in order to consider possible related outcomes.

1.5 Thesis Overview

1.5.1 Aims and Objectives

Aim: Utilise national prescribing data to investigate the epidemiology of adherence to cardiovascular medications in Scotland, and its subsequent association with outcomes.

Objectives:

- To conduct literature reviews to understand current research of cardiovascular adherence and the methods used in adherence study.
- To perform data cleaning and quality checks, understanding any potential issues with these data, and to develop methods for identifying adherence from the data utilised.
- To determine various levels of adherence to CVD medication in Scotland, across different classes of CVD medication, by patient subgroup (primary prevention, treatment for symptomatic CVD, secondary prevention, and secondary-prevention-with-treatment), and across key risk factors (sex, age, social deprivation, and by comorbidities).
- To describe outcomes associated with poor adherence, using linked prescription data and medical records.
- To gain an understanding of the potential strengths and limitations of using administrative data to answer these research questions.

1.5.2 Thesis Structure

Chapters 2 and 3 provide further context to this thesis in the form of reviews; Chapter 2 is a systematic review of research on adherence in cardiovascular disease, updated from a paper published in May 2018 as part of this PhD[45]. Chapter 3 is a narrative review of methods used in measuring and assessing

adherence. This is followed by Chapter 4, the first methods chapter, focusing on data sources and the cleaning and management of these, while Chapter 5 details the methods used in determining adherence and for data analysis. Chapter 6 provides descriptive baseline results, looking at the cohort across the key patient subgroups, as well as general prescribing of the CVD drugs of interest overtime. Chapter 7 shows results for adherence and persistence levels across patient subgroups and investigates different factors, while Chapter 8 considers the association between persistence with patient mortality. The thesis concludes with a discussion chapter which summarises the limitations and final conclusions.

2 Systematic Review: Adherence to Cardiovascular medication

This chapter is an update on the paper published by *Leslie et al*, "Adherence to cardiovascular medication: a review of systematic reviews"[45] (see **List of Publications**). It identifies and critiques the existing literature on adherence to cardiovascular medicine and provides context to the research area of this thesis. The literature search to identify systematic reviews on adherence to cardiovascular medication is described, along with an update to include papers published between January 2017 and February 2020. It will be split into sections, first detailing the methods and results of the search strategy used, followed by a narrative review of risk-factors for cardiovascular non-adherence, and finally a description of clinical and economic outcomes of non-adherence identified by the current literature.

2.1 Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality[63], and so management of this is a pressing area of Public Health research. Drugs are commonly prescribed for disease management, as well as in primary or secondary prevention of CVD; the latter usually following hospitalisation due to myocardial infarction (MI). However, adherence to drugs for management of chronic conditions such as CVD, and for prophylaxis of MI, can be poor, particularly if not prescribed for symptom relief[64].

Despite numerous attempts at research in this area to date, there are significant challenges in the study of adherence; many papers fail to define the term adherence and there is much methodological heterogeneity throughout the literature. A review of systematic reviews allows the existing literature to be collated and critically appraised[65] and was carried out here due to the high volume of papers in this subject area. The aim of this study was to review the existing published evidence of the factors and outcomes associated with adherence to CVD medications.

2.2 Methods

For this review, the bibliographic databases Medline (1996-present), Embase (1996-present), CINAHL (1992-present), and PsycINFO were searched. As very few systematic reviews were written before the 1990s[65], it is unlikely that many papers would be missed by limiting to the 1996 version of the databases. Search terms for each database are listed throughout to allow replication, and any adjustments used to suit individual databases noted. All papers returned were considered against inclusion and exclusion criteria and quality assessment carried out as detailed below. A 10% sample of papers were independently reviewed by a member of the PhD supervisory team. Findings were compared, and any disagreements were discussed to reach a consensus.

In February 2020, an update of this search was conducted, and papers published between the end of the previous search (Jan 2017) and the present date were added.

2.2.1 Search Strategies

The search strategy for this review was developed with assistance from a librarian. Earlier iterations of the search included MeSH terms, though these were ruled out due to a high volume of papers returned in Medline (n=40,904, limits “English language” and “humans”) and because the exact terms used covered the main scope of the MeSH terms. Limiting to systematic reviews was carried out as earlier Medline searches returned 7,042 papers, even after removal of MeSH terms and limiting to “humans” and “English language”. This also allowed an overview of systematic reviews to be performed, which can help to distil the high volume of literature into a more manageable and informative narrative.

2.2.1.1 Medline

Following earlier searches as detailed above, the final search strategy used for MEDLINE (1996 – present) was as follows:

1	(adherence or compliance or non?adherence or non?compliance or persistence or non?persistence).ti,ab.
2	(hypertens* or antihypertens*).ti,ab.
3	((cardiovascular* or CVD) and prevention).ti,ab.
4	2 or 3
5	(patient or medication* or drug or treatment).ti,ab.
6	1 and 4 and 5
7	limit 6 to (english language and humans and systematic reviews)

This returned 352 results which were added to EndNote X7 ahead of study selection. All papers returned from searches on each database were added to an EndNote library to allow removal of duplicates, before a manual search of remaining papers was carried out to remove any additional duplicates missed by the software. Following this, titles and abstracts were searched for immediate relevance, and then the remaining full-text articles were compared against inclusion and exclusion criteria as detailed below (**Section 2.2.2**). Within the 352 papers found in Medline, 3 were removed as duplicates.

The updated search in February 2020 replicated this, including a step limiting to papers published between January 2017-present. An additional 60 papers were identified in Medline, with 2 being removed as duplicates to the original search.

2.2.1.2 Embase

For Embase (1996-present), step 7 of the search strategy was edited to:

limit 6 to (human and english language and "systematic review")

This search returned 232 results. From this, 94 duplicates were removed using EndNote software, and a further 37 duplicates were removed manually as they had been missed by the software, leaving 101 titles and abstracts from Embase to be carried forward and reviewed for relevance, ahead of full-text review.

In the updated search of February 2020, a further 151 papers were identified, of which 2 were removed as duplicates to the previous search; 1 was removed as it was the original version of this very study; and 51 were removed as duplicates to the updated Embase and/or the Medline search.

2.2.1.3 CINAHL

S1	TI (adherence or compliance or non#adherence or non#compliance or persistence or non#persistence) OR AB (adherence or compliance or non#adherence or non#compliance)	Search modes - Boolean/Phrase
S2	TI (hypertens* or antihypertens*) OR AB (hypertens* or antihypertens*)	Search modes - Boolean/Phrase
S3	TI (cardiovascular* or CVD) OR AB (cardiovascular* or CVD) AND TI prevention OR AB prevention	Search modes - Boolean/Phrase
S4	S2 OR S3	Search modes - Boolean/Phrase
S5	TI (patient or medication* or drug or treatment) OR AB (patient or medication* or drug or treatment)	Search modes - Boolean/Phrase
S6	S1 AND S4 AND S5	Search modes - Boolean/Phrase
S7	S1 AND S4 AND S5	Limiters - Publication Type: Systematic Review; Language: English; Human Search modes - Boolean/Phrase

This search returned 151 papers on the CINHAL database, 24 of which were duplicates removed by software and a further 8 removed manually. The updated search found an additional 34 papers, of which 11 were removed as they had been identified in the 2017-2020 Medline or Embase search.

2.2.1.4 PsycINFO

The final stage of the search strategy was adjusted for use in PsycINFO, according to database requirements:

> Limiters - Language: English; Population Group: Human; Methodology: - Systematic Review

This search returned 50 papers, consisting of 24 duplicates; 16 picked up by EndNote software, and 8 removed manually. The updated search identified a

further 27 papers published between Jan 2017 – Feb 2020, 10 of which were removed as duplicates.

2.2.2 Eligibility criteria

Papers were included if they studied factors impacting adherence or persistence in patients taking CVD medication, such as anti-anginal drugs, or medication for primary or secondary prevention of cardiovascular events. Papers were also included if they studied outcomes related to adherence or persistence, and papers using the term "compliance" were also accepted. As this is a narrative review of systematic reviews, only systematic reviews were included. Papers were excluded if they focused on interventions to improve adherence, adherence to non-medical interventions (e.g. lifestyle changes), guidelines on management of adherence, or if they did not study relevant drugs or conditions. However, papers were included if they studied cardiovascular adherence as well

Inclusion Criteria *Systematic Reviews of:*	**Exclusion Criteria**
Factors associated with adherence to CVD medication (used for management of symptoms, primary or secondary prevention)	Focused on interventions to improve adherence
OR the association between adherence to CVD medication and health outcomes	Adherence to non-medical interventions (such as behavioural change)
Reviews that included other conditions, as well as CVD, were included	Guidelines on the management of adherence
	Not a systematic review
	Reviews that focused exclusively on non-CVD conditions
	Conference abstracts (with no paper associated that could be retrieved)
	Papers could not be accessed
	Papers that scored <=2 on quality assessment with AMSTAR tool

Table 2.1: Inclusion and exclusion criteria for literature review

as other conditions, such as diabetes or HIV. Conference abstracts were also excluded if the relevant full paper could not be accessed. The search strategy was limited to English language, as the resources were not available to translate, and this limitation may result in important papers being missed out.

2.2.3 Study Selection and Data Extraction

Following removal of duplicates, study titles and abstracts were first assessed for relevance, before full-text reviews were interrogated against eligibility criteria, with further papers being excluded at this stage. Finally, a quality assessment was carried out using the AMSTAR tool (A MeaSurement Tool to Assess systematic Reviews)[66], with those scoring below the minimum requirement being rejected.

During full-text interrogation of papers, study data were extracted, and study characteristics were compiled into an Excel spreadsheet (Office 2010). From full-text review, information on the aim and setting of each were included, as was information on the number of studies included in each review, the search strategies used, and quality assessment tools used. Adherence measurements used by the studies included in each review were also added, as was a summary of overall findings, and overall adherence if stated by the review. Papers were categorised into two tables (see **Appendix A**): studies which investigated factors impacting adherence or persistence (**supplementary table 1)**, and studies looking at outcomes related to adherence or persistence (**supplementary table 2**).

2.2.4 Quality Assessment and Publication bias

The AMSTAR tool [66] was used to assess quality of papers, and a score out of 11 given to each. The AMSTAR tool is developed especially for assessing the quality of systematic reviews; it looks at whether researchers define an ‘a priori’ design, include details of a comprehensive search strategy and specify the inclusion and exclusion criteria used for paper selection. It also examines whether more than one reviewer was involved in paper selection and extraction of information, and if a table of summary characteristics for studies is included. It is also important that papers assess publication bias, heterogeneity, and

quality, and whether or not quality of papers is considered in drawing conclusions. Finally, AMSTAR asks whether papers state any conflicts of interest in their reporting.

Based on the criteria, papers were assigned categories of either high quality (++: score of 9, 10, or 11), reasonable quality (+: score of 6, 7, or 8), poor quality (-: score of 3, 4, or 5) or rejected (score of 0, 1, or 2).

2.3 Results

2.3.1 Literature search

The initial literature search resulted in 45 eligible systematic reviews, 34 of which dealt with factors associated with non-adherence and 11 which dealt with outcomes. The updated search between January 2017 and February 2020 added 19 papers of factors and a further 3 outcomes papers, bringing this to a total of 67 papers (see **Figure 2.1**, overleaf).

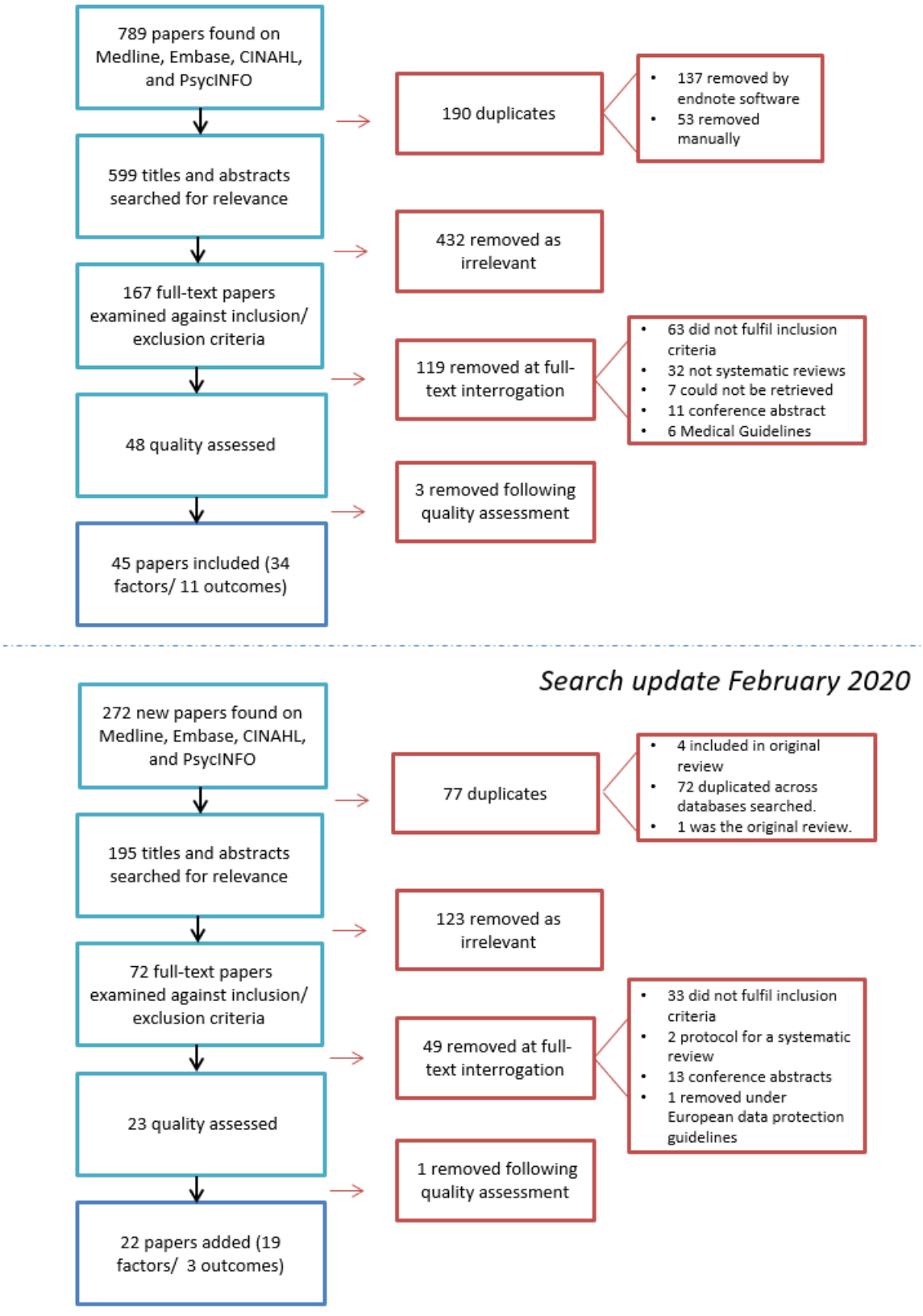

Figure 2.1: Flowchart: study selection process

2.3.2 Study characteristics

Summary tables detailing the aims, setting, methods, search strategies and findings of included reviews are listed in **Appendix A**. Overall quality assessment led to removal of four studies after the initial and updated searches, though otherwise the majority of papers scored 'very good' (n=26, 39%), or 'good' (n=28, 42%) with the AMSTAR tool. However, while quality of systematic reviews was high, many noted that the primary studies included were of a variable standard.

The vast majority of studies included in reviews focused on the USA, Europe, and generally economically developed countries, with only three systematic reviews focused on low or middle income countries (LMICS) [67-69].

Just under half (47%) of the systematic reviews identified made an attempt to derive a pooled estimate of adherence, though these estimates often had a wide range, the most extreme example ranging from 20-88% [70]. Most systematic reviews included papers using a range of methods to study adherence, with self-reporting being the most common method, followed by pharmacy claims, prescription refills, and pill counts. Electronic monitoring, such as the Medication Event Monitoring System (MEMS), were used in fewer reviews (n=15), though this may be due to the increased cost associated. Measures of adherence also varied, with many studies categorising adherence as 'good' if taken above a specified threshold (commonly 80%) and assessing the proportion of 'good' vs. 'bad' adherers. Commonly, this was measured using the Medical Possession Ratio (MPR) i.e. the 'number of days covered with medication in the refill gap, divided by the number of days in the refill gap'[71], or the Proportion of Days Covered (PDC), i.e. the 'number of days with medication supplied divided by the length of follow-up'[71]. Others considered the relative change in adherence rates between groups, or the hazard ratio for non-adherence against a reference category, though most systematic reviews failed to specify which of these metrics was used in primary studies.

2.3.3 Factors affecting cardiovascular adherence

There have been a number of factors identified as having an influence on adherence, which can be broadly categorised into disease factors, therapy factors, healthcare factors, patient factors, and social factors (**Table 2.2**). Here 53 systematic reviews identified factors which could impact on medication adherence. However, due to the heterogeneity in study design, quality, and operational definitions of adherence, it was not possible to perform meta-analysis in order to quantify the risk associated with any individual factor.

Disease factors	Therapy factors	Healthcare Factors	Patient Factors	Social factors
Disease treated **[72]**	Side-effects [67, 73-75]	Relationship/ communication with physician[76] [75, 77-79]	Sex or gender [68, 80-85]	Socioeconomic status[83] [70, 76, 79, 81, 85-89]
Primary vs Secondary disease prevention **[71, 81, 85, 88, 90, 91]**	Dosing Regimen/ frequency [67, 72, 85, 90, 92-94]	Self-monitoring [95]	Age[69, 72, 81-84, 91]	Level of education/ Health literacy [68, 96, 97]
Co-morbidity and/or disability **[70, 82, 85]**	Drug class [59, 70, 73, 74, 98]	Cost/ Co-payments [60, 67, 75, 76, 82, 85, 88, 90, 94, 99, 100]	Making time for appointments [60, 76, 101]	Ethnicity/ race [80, 83, 85]
Depression **[70, 77, 85, 102]**	Combination Pill [103] [104-110]	Routine place of care[76, 99]	Stress/ anxiety [77]	Minority status [70]
Diabetes**[70, 81, 85]**	Telemedicine [111]	Routine physician [76, 78, 99]	Forgetfulness [76, 77]	Social support [86, 112]
Duration of treatment**[85, 88, 91]**	Pill-boxes[113]	Practitioner disagreement with guidelines[77]	Lack of understanding [60, 67, 77, 78, 101]	Marital status[69]
Perception of health at baseline**[82]**		Coronary Artery Calcium (CAC) screening [114]	Alcohol consumption [115] or smoking[85]	Cultural/ religious beliefs[97]
Heart rate**[83]** or hypertension**[85]**			Patient beliefs/ Perception of drugs [67, 76-79, 89, 97, 101, 116]	

Table 2.2: Factors found to impact adherence

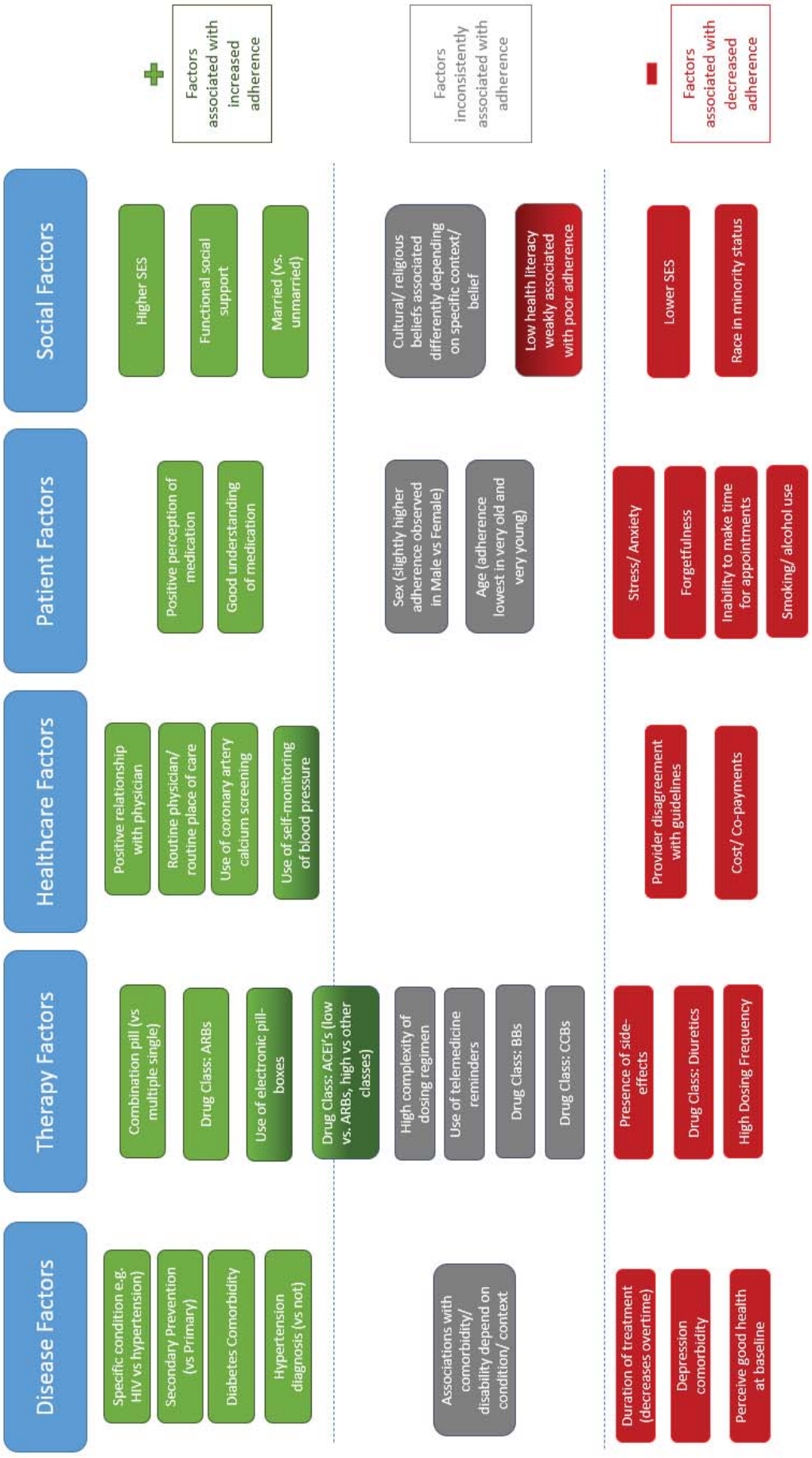

Figure 2.2 Factors and their impact on adherence

2.3.4 Outcomes of Nonadherence

14 papers were categorised as outcomes papers [11, 117-129], and all found an overall positive relationship between good adherence and clinical or economic outcomes, with the exception of the Jongstra *et al* review, which found no significant relationship between antihypertensive withdrawal and cognitive function [126] and the Murali *et al* review[128], which found an inconsistent relationship and, in some cases, a negative association between adherence and clinical outcomes. Once again, heterogeneity excluded the possibility of a meta-analysis. Overall, the quality of these systematic reviews was lower than that of reviews identifying risk factors; 71% scoring good or very good compared to 89% for factors studies.

Outcome	References
Blood Pressure Control	[122, 125]
Myocardial Infarction	[123]
Stroke risk	[129]
CVD risk	[11, 120, 127, 128]
CVD deaths	[119, 128]
All-cause mortality	[11, 127]
Healthcare costs	[118]
Cognitive function	[126]

Table 2.3: Outcomes related to non-adherence

2.4 Discussion

2.4.1 Disease Factors

While this review is focused on adherence to CVD medications, it is worthwhile putting this into context, as the specific disease or condition treated [72] [76] is a crucial factor affecting adherence. For example, Assawasuwannakit *et al* compared adherence in HIV therapy to CVD, and found that adherence to HIV medications was 5% better than to antihypertensive medications [72]. Another key disease factor was duration of treatment, as adherence also tends to decline overtime [88, 91, 130]. In contrast to this, one study found new-users of statins were 1.58 times more likely to be non-adherent[85] compared to prevalent users. This may indicate that initial uptake may be poor, but once people do initiate

treatment, implementation begins at a relatively high level, and then drops-off overtime.

Chen *et al* found that adherence to cardiovascular medication was suboptimal in secondary prevention following acute coronary syndrome [71]. However, papers which compared secondary prevention to primary prevention found that adherence was suboptimal across the board, and secondary prevention was associated with considerably greater adherence [81, 85, 88, 90, 91]. Those who had been diagnosed with hypertension or those who had a history of MI or stroke were more likely to adhere [81, 85], and this may be related to a perception of poor cardiovascular health[82] and an enhanced desire to improve their wellbeing [81]. Diabetes was another co-morbidity associated with greater CVD adherence[70, 81, 85] though this was not consistent across all studies [81].

Improved adherence with CVD drugs in diabetic patients may, again, be due to changes in patient perception and due to medication-taking behaviour being normalised into their daily routine. However, the specific nature of the co-morbid condition alters the way it influences adherence. Depression is a common comorbidity with CVD, and has notably been found to negatively impact adherence[70, 77, 85, 102]; this may be due to lack of motivation or self-efficacy commonly reported alongside depression [102].

2.4.2 Therapy factors

An important therapeutic factor which negatively influences adherence is the occurrence of side-effects. In low-middle income countries (LMIC's), ten of the fourteen studies investigating this found it to have a significant impact [67]. Patients on angiotensin converting enzyme inhibitors (ACEi's) are 68% more likely to develop a cough than those on angiotensin-II receptor blockers (ARBs) [73]. Thiazides, beta-blockers (BB's), and calcium channel blockers (CCB's) are all associated with a higher percentage of patients suffering side-effects at a standard dose compared to ACEi's [74], while ARB's were not associated with any side-effects at this dose [74]. This ties closely to healthcare related risk factors and may in-part explain associations identified between drug class and adherence.

Factors	Reviews	Findings*
Disease		
Primary vs Secondary	Mann et al 2010; Lemstra et al 2012; Xu et al 2016; Chen et al 2015	Secondary + Primary -
Comorbidity: diabetes	Mann et al 2010; Lemstra and Alsabbagh 2014; Ofori-Asenso et al (2018)a	Diabetes +
Comorbidity: depression	Khatib et al 2014; Lemstra and Alsabbagh 2014; Eze-Nliam et al 2010; Ofori-Asenso et al (2018)a	Depression -
Therapy		
Drug Class	Matchar et al 2008; Powers et al 2012; Lemstra and Alsabbagh 2014; Kronish et al 2011; Bramlage et al 2009	ARB's + ACEi's +/- CCB's +/- BB's +/- Diuretics –
Dosing frequency /Treatment Regimen	Assawasuwannakit et al 2015; Bowry et al 2011; Iskedjian et al 2002; Ingersoll et al 2008; Schneider et al. (2018)	High dosing freq. – High complexity +/-
Healthcare		
Cost	Bowry et al 2011; AlGhurair et al 2012; Lemstra et al 2012; Xu et al 2016; Marshall et al 2012; Maimaris et al 2013, Mann et al 2014; Al-Noumani, et al. (2019); Cheen et al (2019); Ofori-Asenso et al (2018)a	Higher costs -
Patient		
Gender or sex	Lewey et al 2013; Mann et al 2010; Nielsen et al 2017; Cheen et al (2019); Durand et al (2017); Ofori-Asenso et al (2018)a	Female (vs.Male) - (+)
Age	Assawasuwannakit et al 2015; Mann et al 2010; Hope, et al (2019); Ofori-Asenso, R., et al. (2018)b; Cheen et al (2019); Durand et al (2017)	Increasing age +/-
Social		
SES	AlGhurair et al 2012; Mann et al 2010; Alsabbagh et al 2014; Lemstra et al 2012; McKenzie et al 2015; Lemstra and Alsabbagh 2014; Durand et al (2017); Kristina and Wulandari (2020)	Higher SES + Lower SES -

Table 2.4 Selected risk factors and their associations with adherence. *Associated with improved adherence (+), decreased adherence (-), or inconsistent (+/-) relationship with adherence

Drug class was consistently associated with differences in adherence levels [59, 70, 73, 74, 98], despite heterogeneity in specific study settings and operational definitions of adherence [59]. Adherence and persistence were best with ARBs [59, 70, 73, 74, 98], and in pooled results, those prescribed ARBs were 30-33% more likely to be adherent overall [59, 70]. Diuretics were associated with the lowest adherence rates of any drug class [59, 70] and they also had lower persistence rates, ranging from 16-38% across studies [98]. This could have important implications in prescribing CVD drugs. Combination drugs were also found to be associated with greater adherence, ranging from 12% in one meta-analysis by Sherrill *et al*,[103] to 29% better adherence in meta-analysis by Gupta *et al* [104].

Adherence reduced as the number of doses per day increased [72, 90, 92, 93], though this effect was diminished with increased age [72]. In resource limited settings, approximately half of the studies looking at dosing complexity found a significant relationship with >1 daily dosing and nonadherence, while the other half did not find any significant association [67]. However, it is worth noting that adherence to once-daily dosing may have a greater effect on health outcomes than twice or multiple daily dosing, as missing a single pill would mean an entire days' treatment is missed [92].

2.4.3 Healthcare Factors

The cost of medication or appointments was a commonly cited healthcare factor influencing non-adherence [60, 67, 75, 76, 82, 85, 88, 90, 94, 99, 100], largely in US settings, and in one systematic review cost or co-payment was the most commonly studied aspect of adherence (29% of included studies) [90]. Patients who had to make a co-payment for their treatment were 28% less likely to be adherent to statins [88], and similar associations were found across cohort studies of adherence to antihypertensives [99], however the impact of co-payment on adherence varied from non-significant to a significant reduction of adherence, depending on the cost [100].

Continuity of care, or having a routine physician and routine place of care, is a factor found to positively influence adherence[76, 78, 99]. This could be for a number of reasons; for example, some patients received conflicting information from different physicians [78], potentially damaging trust and meaning they could be less likely to take advice seriously. Contact with one routine physician minimises the likelihood of this occurring. These factors may also tie into the relationship patients have with their physician, another important risk factor[75-79]. Short consultations and insufficient support or guidance from physicians has also been cited in self-reported studies [77], and likely contributes to a lack of patient understanding. The relationship between physician and patient is particularly important at the transition between primary and secondary care [78], as this can be a pivotal time in their treatment.

An important factor cited by practitioners was disagreement with guidelines, or the perception that guidelines may not lead to improved outcomes[77]. Personal doubts about efficacy of drugs may also make them less likely to encourage their patients to adhere[77, 79].

Some practical elements of healthcare also had an important role in adherence. Self-monitoring of blood pressure was associated with greater adherence[95], and this may due to an increased awareness of blood pressure changes by the patient, making their need for blood pressure control more palpable. Coronary artery calcium (CAC) screening was also associated with improved adherence [114] and, once again, this may be because it creates a more tangible sense of their disease state and the need for prevention of CVD events.

2.4.4 Patient factors

Sex or gender was discussed in three reviews [68, 80-85]. A majority of studies identified a link between female sex and nonadherence, with an increased risk of 7-10%. However in LMICs, the opposite was true[68], and female sex was associated with improved adherence. It has been postulated that nonadherence in women may be partly caused by perceptions that women are at lower risk of CVD [80], and that lower adherence is associated with less severe disease, or maybe because women are generally more aware of potential side-effects of treatment [81], and not adhering as a result. However, this relationship did not

exist in any study conducted in Canada[80], as male and female patients were found to be equally adherent across 11 studies [80]. It would be worthwhile identifying cultural, societal, or policy differences that may be influencing this. Sex and gender are complex factors, as it can be predictive of many other confounding factors. For example, it is more common for woman to assume a care-giving role than it is for men[80], and this has also been associated with poorer adherence[80]. Hence, better support for caregivers and social care infrastructures could potentially help contribute to better adherence in this subgroup.

Age is another demographic factor indicated in adherence research[69, 72, 81-84, 91]. Pooled results by Assawasuwannakit *et al* found that there was a 9% improvement in adherence over a 13-year increase in age (from age 40-53) in hypertensive patients [72], however these findings are not representative in the very young, as paediatric patients will receive medication from caregivers, or the very old, who may have declining cognitive function and therefore may be more likely to forget [72] . Mann *et al* found a "u-shaped" relationship between nonadherence and age [81], with middle-aged patients having better adherence than those below 50 or above 70 [81]. Age is another complex demographic factor, as it will be influenced by different perceptions about health, increased co-morbidities, and lifestyle changes.

Other patient-related barriers to adherence include stress or anxiety and difficulty in making time for appointments [60, 76, 77]. These are likely to be related to lifestyle, e.g. stress brought on by a fast-paced job and heavy workload, or perhaps difficulties with unemployment [77] and financial concern. Alcohol consumption has also been found to negatively affect adherence [77, 115] across various chronic diseases, though findings are somewhat inconsistent [115] and there is insufficient research on this in the case of hypertension [115]. Smoking is similarly associated with nonadherence[85] to statins in patients with hypertension.

In self-reported studies, forgetfulness and lack of knowledge were some of the most commonly cited barriers to adherence [76, 77]. Patient perception is an important factor which ties into many of the other disease related and healthcare related factors also. As discussed previously, patients treated for

secondary prevention of cardiovascular disease, or with certain co-morbidities, may be more likely to adhere due to an increased sense of urgency around their healthcare needs. Equally, those with asymptomatic illnesses, such as hypertension, may perceive their health to be good and may not see the need for taking medication for preventative reasons. Some also discontinue treatment following a reduction of symptoms [77], as they believe they are "better" and do not understand the chronicity of their disease. Perceptions about the medication itself can also have a great impact; some self-reported studies have cited patient fears of reliance to cardiovascular drugs [77]. Many of these perceptions' barriers come down to a lack of understanding, and so increasing patient awareness could help to reduce this.

2.4.5 Social factors

The literature on socioeconomic status (SES) is inconsistent. In the seven systematic reviews reporting SES, two found no significant link [87, 89] though did comment that the methodological heterogeneity throughout the literature may have impacted this [87]. High income status was associated with a minimum of 11% better adherence and a maximum of 26% across reviews [70, 81, 87, 88] though there was considerable variation at the individual study level. For example, in the review by Alsabbagh *et al*, 77.5% of studies found a positive association between high SES and adherence, though one study found no association, while the remaining studies found that high SES actually had a negative impact on adherence [87].

Social support is another social factor explored in two papers [76, 86]. While structural social support, i.e. married vs. unmarried/ family network etc., was found to significantly impact adherence in some studies, it appeared reliant on study design: those using pill-count methods were more likely to observe a tangible relationship than those using alternate measures [86]. However functional social support, such as informational support or operational support (e.g. help taking medications), was consistently found to be strongly associated with adherence[76, 86], with these patients being almost 4 times more likely to take their medications[76]. However when adjusted for ethnicity, the positive influence of social support was diminished [86]. This may be due to cultural

differences in family dynamics, or other social factors at play. Those of a minority ethnic group are 27% less likely to adhere compared to white patients[70] and it is worth investigating the potential causes of this as an important risk factor for health inequalities.

Loke *et al* considered the relationship between health literacy and adherence to CVD or diabetes medications, however most studies were inconclusive, with only one cardiovascular study producing a significant association between poor health literacy and poor adherence [96].

2.4.6 Outcomes associated with nonadherence

Systematic reviews investigating outcomes generally found that good adherence was associated with improved clinical and economic consequences[11, 117-129], with one noting that all studies included found a positive relationship with adherence to secondary prevention following MI [123]. Chowdhury *et al* found that CVD risk was reduced by 20% and all-cause mortality reduced by 35% with good adherence[11]. However, some reviews found no discernible difference to outcomes overall [117, 122, 126, 128], though it was highlighted that there are gaps in the literature yet to be addressed [122, 123, 128] and this could have had an impact on these findings. There was much heterogeneity across all studies with regards to how adherence rates were accessed. For example, some studies reported on the percentage of good adherers while others report on an overall average percentage. One review noted that the different methods used to study adherence altered findings[86] and Cramer *et al* identified a stronger association between adherence and outcomes in studies assessing adherence using MEMS compared with alternative methods [117].

Economic outcomes are another important consideration. Bramlage *et al* compared the cost-effect ratio across drug classes, and found newer drugs, ARB's and ACEi's, outperformed the others in spite of being more expensive per tablet [98]. This may be in part due to enhanced efficacy and also due to greater adherence to these drug classes [98], as it reduces later costs of CVD treatment and adverse events. Another study by Bitton *et al* found that in secondary prevention of coronary artery disease, patients who took less than 80% of their prescribed medication cost up to US$868 more per patient[118]. Furthermore,

Shroufi *et al* found that improving adherence may reduce healthcare costs more than earlier prescribing of statins would do [124], highlighting this as a hugely important aspect of disease management.

From these findings, it is apparent that poor adherence to CVD medications has important consequences, and it is a vital area of study in order to prevent unnecessary mortalities, adverse events, and healthcare expenses.

2.4.7 Strengths and Limitations

Performing a systematic review of reviews is a good way to collate and quality assess the numerous studies published in this field, however it is possible that important primary papers have been missed by focusing only on the reviews.

This review is limited in that it is restricted to papers written in the English language, meaning there may be a bias against research from people with different ethnic backgrounds, where English is not the first language. The high levels of heterogeneity within the systematic reviews included, and between them, made meta-analysis impossible and it is a symptom of an area of research that has been largely unstandardized in its practice. Also, as this is an overview of systematic reviews, it would be impossible to perform meta-analysis without unpicking the individual studies to ensure none are over-represented. Another issue is that the study design and method used to collect adherence data has been found to alter the rates of adherence identified, and there is no clear gold standard within the literature for analysing this. Many systematic reviews also failed to summarise the operational definitions of adherence used by primary studies, i.e. whether studies looked at adherence as a continuous variable or used a cut-off value above which individuals were considered adherent.

2.5 Chapter Summary

To-date, there are a wide range of modifiable and non-modifiable risk factors associated with cardiovascular drug adherence. Studies are of variable quality and considerable heterogeneity and there is some inconsistency across the literature for the relationships identified for the different factors. Adopting the adherence taxonomy defined by Vrijens *et al*, and appropriate care given in

defining adherence measures used, will greatly enhance this field of research. While many of the systematic reviews included consider multiple factors, many of the primary studies look at risk factors in isolation, not accounting for the interplay between them, and because of the heterogeneity there was no opportunity to study this quantitatively. This gives clear scope to perform a national study of cardiovascular adherence, to answer these questions more fully.

3 Methods Review

This chapter explores the literature describing data collection methods and analytical methods used in adherence studies, with a focus on those using pharmacy claims records such as the Prescribing Information System (PIS) database in Scotland, and some of the challenges associated with this in terms of data linkage, defining and quantifying adherence, and measuring outcomes.

3.1 Introduction

Robust methodologies are of utmost importance when carrying out any research project, and clear descriptions and definitions are necessary for reproducibility. Adherence is a complex variable to study and, as such, research to date has been largely unstandardized in its methods [131-134]. When studying adherence, whether at the initiation stage, implementation stage or discontinuation, it is important to provide an operational definition[46], and to define the metrics used to measure it, as there is no agreed consensus [48]. For example, adherence can be evaluated as either a dichotomous, categorical, or continuous variable, and can be calculated in a number of ways, such as the medication possession ratio (MPR) or the proportion of days covered (PDC). When assessing adherence as a categorical variable, many studies use 80% adherence as an arbitrary cut-off, above which adherence is considered "good" [48, 135]. However, when defining a cut-off there should be, where possible, some consideration of the underlying pharmacology, as adequate adherence depends somewhat on the half-life of the drug and the therapeutic index. It is also important to consider limitations in the methods of data collection and data linkage when it comes to analysing results and accounting for bias.

3.2 Data collection: measurements of adherence

There are a number of ways in which adherence data can be collected, however all methods have different pros and cons, and there is no gold standard [48]. Some key methods will be discussed here; administrative pharmacy records, patient self-reporting, electronic monitoring systems, and direct serum concentrations. However, it is important to note that this is not an extensive list.

3.2.1 Pharmacy records: prescription refill data

Pharmacy records are a useful tool for adherence study, as they provide practical information in a community setting, are quantifiable [136], and offer a relatively cheap resource for evidence based medicine[137] when compared to studies involving primary data collection. Additionally, they allow for much larger sample sizes and longitudinal study over many years and, because they are non-selective, provide an insight to drug effectiveness in 'real world' settings [137, 138] compared with highly selected trial participants who may be more motivated and hence more likely to adhere to medication. Furthermore, direct contact with the patient is not required [138], and in many cases informed consent is not necessary as data privacy is tightly controlled and researchers cannot access un-anonymised patient information, thus reducing the risk of patients changing their behaviour due to observation. Claims records are often very complete datasets as the data comes directly from the dispensing pharmacy and filling out these records is necessary for reimbursement. It is also often subject to strict auditing [137].

Yet, there are certain limitations with administrative pharmacy data. One important issue is the lack of data frequency [136, 139]; for example, if a drug is dispensed on an annual or six-month basis it can be difficult to gain enough insight to build a detailed picture of adherence [139]. Also, as these data are not collected for research purposes [48, 138], key information to the research question may not be routinely collected and therefore may not be available [138].

Secondary analysis of existing databases may also present issues with missing or inaccurate information [138] and coding errors could introduce bias if they occur more frequently in certain subgroups, for instance in a particular pharmacy location, or if there is confusion coding for a specific drug type. Pharmacy claims often do not take into account over-the-counter medications or drugs prescribed and dispensed within the hospital setting [140], so this information cannot be captured. While pharmacy claims do tend to have a high level of accuracy, they are often linked to medical data for study [137, 141], and these datasets are also not specifically collected for research purposes. Additionally, hospital records will only account for severe cases where an event results in hospitalization[138]; for example, if studying ischaemic heart disease as an outcome, secondary data

may only inform on those who suffer an acute myocardial infarction while missing out those with milder symptoms of angina. Even if the data were perfect, this method can only indirectly inform on adherence, as we do not know what happens to the prescription once patients take it home: they may stock-pile it, throw it away, take their medication at irregular intervals, or take "drug-holidays"[48, 138, 142, 143], and this would not necessarily be picked up from refill records. Researchers can only be sure of drug availability or lack thereof, and must make assumptions; such as, if a patient routinely picks up prescriptions around the time their previous supply runs out, it is likely that they have taken it as directed.

The Scottish Prescribing Information System (PIS) is a good example of a national prescriptions database, hosted by National Services Scotland (NSS) [140]. It can be linked to NHS data through individual community health index (CHI) numbers, at a capture rate at close to 100% [140]. CHI is a unique ID number allocated to all patients in Scotland when they first register, and it allows their health records to be linked longitudinally and across national health datasets, such as hospital admissions (SMR01, SMR04) [140], and death registrations (NRS), as well as external administrative datasets. In this way, PIS can be used to define cohorts within the population based on drug prescribing and dispensing, using pre-defined BNF (British National Formulary) codes [140], or by other patient characteristics, such as age, social factors, or disease status. Many studies using PIS to-date are drug utilization studies and health economics studies[140].

PIS shares similarities with the Nordic Prescribing databases, in that they have wide coverage due to universal, tax-funded healthcare systems [144], and unique individual patient identifiers [144], similar to CHI, allowing data linkage across medical and administrative national datasets. Furthermore, informed consent is not required from individual patients [144]. However, this level of information is only more recently available in PIS, with linkable, individual-level records dating back to 2009, and aggregate data dating back to 1993. As such, long-term follow-up studies are currently limited in comparison. **Table 3.1** summarises some of the different prescribing databases available in different countries, along with their strengths and limitations.

Country	Database(s)	Coverage	Date	Benefits	Limitations	Ref.
USA	TruvenHealth MarketScan Commercial Claims and Encounters Research Database	Commercial Database. US wide though not full population, estimate 115 million individuals included in database	First study published 1990	Records from over 100 different insurance companies covered. Individual level data linkage, Medicaid prescribing claims, health and dental records etc.	Incomplete capture rate may be subject to large amounts of missing data.	[145, 146]
Canada	Ontario Drug Benefits (ODB) claims database	Province of Ontario, Only covers patients on Ontario Health Insurance Plan (OHIP) -over 65 years old or on social assistance	April 1990 to present. Updated monthly	Complete coverage in over 65 year olds, allows study in elderly patients with linkage to other healthcare and demographic records. Audited so high coding accuracy. Information on days supplied, dosage, and strength allows for drug exposure study,	Data not representative of whole population of Ontario, only those on OHIP.	[147-149]
England	The Clinical Practice Research Datalink (CPRD)	11.3 million patients, 674 GP practices	Originates from General Practice Research Database (1993). Became CPRD in 2012.	Large database hence good statistical power for epidemiology research; long follow up (mean 9.4 years at individual level). While it does not have full population coverage, sample is representative of UK population, as it maps closely to census records. Good data quality for certain data items covered by Quality and Outcomes Framework (QOF).	Missing data 'not at random' e.g. BMI more likely to be recorded in those with related health issues. Prescribing data based on written prescription (rather than dispensed) so may not be accurate for drug exposure. Unstandardized definitions for diagnoses so individual studies may code differently and produce different results from same data source.	[150]
Scotland	Prescribing Information System (PIS) – provided by National Services Scotland (data linkage via eDRIS)	Whole Scottish population; 5.3 million people	2009 onwards provides individual-level CHI-linked data	Linkage to Scottish administrative data, medical records, and death records. High capture rate. Longitudinal study possible; individual level follow up from 2009 onwards. Data monitoring to ensure high quality.	No data capture for over-the-counter medication or drugs prescribed in hospital setting. Capture rate can vary based on prescriber and drug type. Some lags in processing of data.	[140]
Denmark	Odense University PharmacoEpidemiological Database (OPED), Aarhus University Prescription Database (AUPD), Danish National Prescription Database (DNPD)	OPED: Southern Denmark, AUPD: Central (1.2m) and Northern (0.6m) Denmark, DNPD: entire country (5.6m)	1990 OPED, 1989 AUPD, 1995 DNPD	Full population coverage, data for over 20 years allows longitudinal studies, linkage to other datasets and potentially to other Nordic countries. Based on prescriptions dispensed (rather than those written) – gives more accurate picture of usage. Also covers prescribing in nursing-home setting allowing more accurate drug-exposure studies in elderly population.	Difficulty in assessing drug exposure; lack of information about intended duration of treatment and dosage. Lack of information on over-the-counter medications.	[144, 151]

Table 3.1: Summary of selected prescribing databases

3.2.2 Self-reporting

Patient self-reporting may take the form of interviews, questionnaires, patient diaries, or focus groups [152] and it is a straightforward and inexpensive method of collecting data on adherence [48]. As such, it is a very commonly used method and, in a review by Clifford *et al.*, self-reporting was the most frequently used method of data collection in studies of adherence to diabetes medication[153]. These methods can be insightful, as diaries can give in-depth information on the drug-taking regimen [152], though it does risk two main types of error: random errors may arise from misinformation provided by patients; or systematic errors e.g. from patients consistently over-estimating their adherence. Interviews or focus groups allow patients to discuss issues or bring up barriers they feel are preventing them from adhering fully, which can be useful in developing future interventions to improve adherence. Questionnaires such as the 8-item Morisky Medication Adherence Scale (MMAS-8) are validated tools, and have been found to have high sensitivity [154]. However, all self-reported measures risk over-predicting good adherence [48] as patients may feel embarrassed or do not wish to 'let-down' their doctor. One of the most commonly cited reasons for non-adherence is forgetfulness [76, 155], and so it is likely that people can make errors in judgement when reporting on their own behaviours. Certain cognitive disorders can have a negative influence on adherence rates and may also create a barrier to the accuracy of self-reporting.

3.2.3 Electronic monitoring system (EMS)

Electronic monitoring systems, such as the Medication Event Monitoring System (MEMS) or unit dose monitor, use physical monitoring systems that record each time a pill-bottle or a blister pack is opened [136] as a measure of how often pills are removed and presumably taken. This is not a perfect system, as removal of the drug from its pack still does not ensure ingestion, and with pill-bottles there is no way to measure the number of pills removed at any one time, or indeed if any pills were removed at all. Though it does provide a more proximal picture of adherence patterns, and can add temporal measures to analysis, allowing a quantitative picture [136] of real-time drug-taking with a great level of detail. It is one of the most comprehensive measures available for adherence study, though previously, the technology has been expensive to provide on a large

scale[48] and would not be feasible for population studies. However, as the technology comes off-patent, costs will decline and make this a feasible option. Studies using EMS require patient consent and so participants who are willing to take part may not be representative of the patient population as a whole. Those who do consent may change their behaviour as they know their drug-taking is being monitored [136], potentially giving a less realistic picture compared with refill records. Once data has been collected, EMS can provide huge amounts of information which is rich in value, but which can preclude study of a large population given the volume of data produced for each individual.

3.2.4 Direct methods: serum concentration

Serological measures of adherence involve taking blood or urine samples in order to quantify the amount of medication or its metabolites present [48, 152]. Direct measures can quantitatively show the amount of medication in the body, and hence they are the only measures that concretely determine whether medications have been ingested. If serum concentrations are within the therapeutic range it is fair to assume that the patient has adhered adequately, and if it is outside of the range then it is likely that they have not. Nevertheless, this method has certain flaws attached. Similar to self-reported and EMS measures, this method requires consent and direct contact with patients, and as such, it may not always capture a representative population. Furthermore, it can be time-consuming and costly [48] and, depending on the half-life of the drug, it could be misrepresentative of the patient's medication taking behaviours due to the 'white-coat effect' [48, 152]; if in the lead-up to a visit the patient adheres better than normal, the serum levels may not reflect their true day-to-day adherence. Where possible, holding observations at random intervals [152] or organising appointments with short notice may help to reduce this. Another issue is that variations in an individual's metabolism [152] may lead some patients to appear unfairly more or less adherent than others, highlighting the complexity involved with pharmacokinetic measures.

3.2.5 Direct methods: digital pill

A more recently developed alternative is the ‘digital pill’; a pill with a tracking sensor which communicates with a patch worn by the patient once it has been ingested. Data on ingestion can then be monitored using a mobile app. This would be the most direct method of measuring adherence as it can assess drug exposure on a daily basis, and it may be more accurate than serum concentrations as it is not dependent on metabolism of the drug. It is also less affected by ‘white-coat adherence’ as, with consent, doctors can monitor usage through the app without having to physically see the patient. However, it may inflate adherence compared to general usage due to the app’s ability to track adherence and patient awareness of being monitored. The drawbacks of this method, including the invasiveness of monitoring and discomfort from continually wearing a patch on the skin[46], are not thought to merit the use of these pills over EMS systems which can still give a detailed picture of adherence and which are thought to be as reliable as direct methods[46].

Adherence Measure	Cost	Comprehensive	Accuracy	Useful for population-level study	Non-invasive
Prescription refill data	✓	–	–	✓	✓
Self-reporting	✓	✓	✗	–	✓
Electronic monitoring systems	–	✓	✓	–	✓
Serum concentration	✗	✓	–	✗	✗
Digital pill	✗	✓	–	✗	✗

Table 3.2: Comparison of adherence measures

3.3 Using data collected from electronic prescription records

3.3.1 Data linkage and handling linked data

To make use of prescription data in adherence studies, it can be valuable to link refill records to medical records, such as hospital admissions or death registries, or to other administrative datasets such as education or social care records to gain additional information about the cohort. Data linkage is the "method to bring together information contained in two or more records" [156], such as hospital records with prescribing information. Linkage to healthcare data is often carried out by a separate party from the researcher who conducts the analysis, and no one party has access to all of the records in order to protect patient privacy [157]; for example, linkage is carried out by eDRIS in Scotland and SAIL in Wales [157] for public health research using national datasets. Linkage with a unique identifier present across multiple datasets is known as deterministic linkage, and is performed by exact matching[158], i.e. linking records across datasets that share the same identifier. However, the process of data linkage can be challenging in health systems which do not have a unique identifier across datasets, and instead data-linkers must rely on information such as patient name, date of birth, sex, and patient postcode [157]. This is known as probabilistic matching[158], and it valuable for making use of datasets which do not have a common identifier. This can be imperfect and may lead to false matches, where data is spuriously linked between different individuals [141, 157, 159], or missed matches, where data which relate to one individual are not connected by the linkage algorithm. This can lead to loss of statistical power or may lead to bias if errors are over or under represented in different population subgroups [141, 157, 159].

Linkage errors mainly arise in three ways: faults in the linkage method used; challenges in complying with data protection legislation, such as the need for acquiring consent[141]; and poor-quality or missing/inaccurate information in one or more of the datasets used [141]. Bias occurs when these errors appear more commonly in certain subgroups, such as different age-groups, sexes, specific hospitals or GP practices, or socioeconomic statuses [141]. An example of this would be when using names to link data, female participants are more likely to

be missed than male participants as they are more likely to change their name following marriage [141]. This particular problem is not an issue for datasets which use unique identification numbers such as CHI for linkage, as they use exact matching which does not rely on names. However, there may still be flaws with exact methods, for instance, if a CHI number is recorded incorrectly.

Despite the benefits to patient confidentiality and research integrity by having data linkage carried out by a separate party to those conducting analysis, this can present challenges in accounting for uncertainty within the linked data during analysis [157, 159]. Errors arising from underlying data quality, such as inaccuracies with data collected by a specific hospital or GP practice [141] could be a difficult linkage error to account for, as analysts do not have access to information on the observed error-rates in different settings [141]. Access to information on the linkage methodologies used, e.g. use of probabilistic methods or deterministic methods, may also help researchers to adjust for bias [141].

3.3.2 Adherence measures

3.3.2.1 Taxonomy

Following data collection, there are a variety of methods that can be used to assess adherence, with one review identifying ten different terms describing this [42], and another review identifying eleven different calculations for comparison[143]. This lack of standardization can be problematic, as different terms can inhibit comparison of studies, while use of different criteria (e.g. different allowable gaps; different cut-off defined as an acceptable level of adherence) or calculations can result in different findings[142] from the same data source.

Since Nichol *et al.*[132] identified the poor methodological rigour and lack of consistency in this field of research in the late 1990s, numerous efforts have been made to develop a standard taxonomy and methodological approach for adherence research [42, 133, 142, 143]. The ABC taxonomy, proposed by Vrijens *et al.*[42], considers adherence as encompassing three stages; initiation, implementation, and discontinuation. Initiation involves prescription of a drug and taking the first dose[42]. Some studies are flawed in that they do not

conceptually separate initiation from implementation, though this can be difficult to capture using refill records. One method that could be used is to identify initiators from non-initiators is by calculating implementation from the start of the second dose of the specified prescription, within a pre-determined time period. Those who only ever collect their first dose may or may not have initiated with their medication – it is not clear with the level of information available from refill records - while those who do collect a second dose are more likely to have completed their initial prescription and so can be considered as having initiated treatment in follow-up analysis. To determine between new users of a drug and continuous users, a 'run-in' period, i.e. a period of monitoring prior to initiation of drug use, in which there is no exposure to the drug, should be defined[160]. 6-months is a commonly used run-in period, though this may introduce bias by including people who are not truly naïve to the medication but who had instead just had a brief break in treatment; however having a longer run-in can reduce the size of the cohort[160]. The length of run-in depends on the study requirements (how important to the research question that incident and non-incident users are differentiated) and the drug itself; for example, drugs which are common in a population are more likely to have been used previously by those who appear to be new-users than drugs which are less common[161] , and so may require longer run-in times to eliminate bias.

Implementation considers drug usage following initiation. This stage is conceptually what many previous studies would define as adherence – "the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen"[42]. Discontinuation is the end of the drug taking period – where the final prescription has been used up and no further prescriptions are collected[42]. Longer-term follow-up can help determine between "true" discontinuation and those who recommence treatment after a prolonged gap period.

3.3.2.2 Components required to calculate adherence

In adherence studies using medication records, there are clear guidelines on the minimum reporting[43, 142, 162], including operational definitions of adherence[43], and reporting of the assumptions made when preparing data[142, 163].

Generally, to calculate adherence, databases must have information on the drug name, strength e.g. milligrams per tablet, quantity e.g. the number of tablets within a packet, and dosage instructions[137] e.g. 'take one tablet daily'. Alternatively, if this level of information is not available, the World Health Organization's defined daily doses (DDD) can be used to estimate drug exposure. This is calculated by multiplying the strength of the drug by the quantity dispensed, and dividing by the DDD value [164], though there can be inaccuracies with this method as the DDD may not be reflected by the prescribing practice in the country of interest, or dosage may differ; for example, for different disease severities, for different indications[164], or due to interactions with concomitant drugs prescribed. One study by Rikala *et al* [165] found that compared to dosing instructions, DDD was subject to huge misclassification bias, leading to both under and over estimation of how long prescriptions should last. For adherence studies it is beneficial to have dosage instructions available; for instance, in the Scottish PIS dataset, dosage instructions are available for cardiovascular medications and are retrieved using a natural language processing (NLP) algorithm [166]. In this way, it is possible to work out the estimated length of time that the prescription should last and hence, when a new prescription ought to be picked up. This allows the possibility of greater accuracy in drug exposure and adherence studies.

It is also important to define a grace period, or a gap of days allowable to be without a drug supply before a patient is considered non-adherent. When defining this, it is important to note that the length of time can alter the sensitivity of analysis[142] as a smaller gap will exclude a higher number of individuals from being classed as adherent. Generally a gap of 90 days is considered acceptable[142], as above this there is less variation in the number of people excluded[142], however it is important to consider the specifics of the medication, such as the half-life of the drug or the clinical effects of withdrawal, and the condition studied when defining a grace period[142].

3.3.2.3 Common measures: medication possession ratio and proportion of days covered

There are a range of methods used to calculate the implementation phase of adherence using a closed pharmacy system (**Table 3.3**), with medication

possession ratio (MPR) and proportion of days covered (PDC) being most common. Using MPR, adherence is calculated by taking the number of days supplied with medication divided by the number of days in the refill or observation period, and multiplied by 100 to give a percentage value [131, 142, 162]. The modified MPR (MPRm) is similar, though it includes consideration of the final refill period[143]. MPR is often assessed as a binary variable, by applying a cut-off or threshold value above which adherence is considered good, and below which is described as non-adherence [135, 167]. Looking at adherence as a dichotomous variable can be a straightforward way to compare adherence within population groups, however it leads to a loss of information. For instance, someone who is classed at 50% adherent may take their medication every second day, or may have taken medication perfectly for the first half of the study period, and discontinued use for the second half[42].

Studies which utilise MPR methods commonly use ≥80% as a cut-off value, though this is an arbitrary value and the exact threshold point used can influence the sensitivity and specificity of analysis [152, 167, 168]. Karve *et al* validated 80% as a cut-off value when investigating hospitalizations as an outcome of non-adherence across five chronic disease areas; however the specific optimal value varied across diseases, from 58% in congestive heart failure to 85% in diabetes [167]. Hansen *et al* identified 80% as being a valid cut-off value in terms of sensitivity and specificity when studying hypertension and heart failure[168], though, while 80% may be acceptable as a cut-point for general study, it may be worth validating this for specific research areas[168]. Where it is not possible to study adherence as a truly continuous variable it may be preferable to group into categories, ranging from very high to very low adherence or discontinuation.

PDC is the other commonly used measure for the implementation stage of adherence study, which is a measure of the number of days a drug is available, divided by the number of days in a given time period [162, 169]. Many of the considerations required when calculating MPR, such as assessment as a dichotomous or categorical variable and grace periods, also apply to it.

3.3.2.4 Alternative methods for estimating adherence:

Usually PDC is studied as a 'time-constant' measure, meaning it is averaged over a fixed time period[170] and does not account for changes during that period. This could have clinical significance, as patients who take their medications stably over time could have different outcomes than those who take it irregularly[170]. Because of this, Bijlsma *et al* [170] proposed a time-varying method which takes into account changes in adherence overtime and is well-suited to longitudinal studies. With this model it is possible to account for drug-switching, assess exposure to polypharmacy more accurately, and to measure changes in adherence overtime [170].

Another way of utilising PDC is by developing a combined measure, using both PDC and the treatment anniversary method (TAM)[44]. TAM involves checking at an anniversary date (e.g. 6 months or 1 year after initial prescription) to identify patients who are still persistent with their medication at this point[44]. To calculate this, it is important to know the days-coverage for the prescription dispensed closest to the anniversary date [44] e.g. a drug dispensed as 28-tablets, to be taken once daily, would last 28 days. A patient prescribed this drug within 28 days of their anniversary date (plus an allowable gap) would be considered persistent; whereas a patient prescribed 56 tablets on a once-daily regimen in the prescription closest to their anniversary date would have a window of 56 days (plus allowable gap) in which they must have received a prescription in order to be considered persistent. Those classed as persistent could then have their PDC calculated to assess implementation during this period[44].

Polypharmacy is a useful aspect to consider when studying adherence [142, 171]. Many studies take the adherence estimates for each drug individually and average this[171], though this does not account for the true complexity involved with taking multiple drugs, and can lead to overestimation of adherence[171] to their overall medication regimen. Because of this, Arnet *et al* proposed the daily polypharmacy possession ratio (DPPR) which takes into account the number of medications, switching, and assesses the number of days within the observed period in which a patient had access to all prescribed medications[171].

Method	How calculated	Pros	Cons	References
Medication Possession Ratio (MPR)	Number of days supplied during refill period/ Total number of days in study period x 100 (to give a percentage) Note that some studies use term MPR but describe different calculation	Straightforward method, often data required for this is stored in administrative databases. Can access as dichotomous or continuous variable	Can overestimate adherence, subject to bias (e.g. observation period, allowable gap between refills, overlaps can all influence sensitivity and specificity of results). Caution should be used when setting cut-off for dichotomous measure and this should be validated.	[131, 162, 171]
Modified Medication Possession Ration (MPRm)	Total no. days' supply/(last claim date – first claim date + last days' supply)] × 100	Attempts to define study period based on drug dispensing, rather than by arbitrary perimeters.	Less reliable method; uses time between first and last refill as denominator which can overestimate adherence (assumes full adherence in final refill period). Does not account for premature discontinuation.	[143, 172]
Proportion of Days Covered (PDC)	Total number of days "covered" with drug supply/ number of days in observation period. Often capped at 1.0.	Less-likely to over-estimate as surplus days capped. Good predictor of hospitalization as an outcome and intuitive to read.	Requires accurate measure of days-supplied. Must be careful with grace periods/ defining point at which patient defined as 'non-persistent'.	[143, 162, 172]
Treatment Anniversary Method (TAM) with PDC	Persistence measured first with TAM – check if patient prescribed drug within a specified window around anniversary date. Those considered persistent then have PDC calculated for this period.	Straightforward calculation; Can differentiate between those who implement treatment poorly but continue to persist from those who stop taking treatment early.	Non-persistence outside TAM window may not be captured. As with PDC alone, decisions need to be made to account oversupply, switching, and polypharmacy.	[44]
Time-varying PDC	**Total days**: no. pills dispensed/ no. pills per day **Interval Length**: time between prescription date (k) and date of second prescription after this (k+2) **Adherence** = total days/ interval length (excess carried over, assumption: drug stockpiling)	Measures changes in adherence over-time; useful for time-to-event analysis.	Minimum of three refills required; cannot assess early non-adherence. Challenge in accurately estimating adherence for final interval.	[170]
Daily polypharmacy possession ratio (DPPR)	Take each day of study period separately, for each set score between 0 (no meds available) and 1 (all meds available) and compare against the number of drugs that should be taken to give a score. Find the sum scores across all days and divide by no. days in observation period to find overall proportion.	Provides standardized parameters so allows accurate comparison between studies. Accounts for polypharmacy; prevents overestimation as it reduces chance of duplication or overlapping	Cannot identify over-supply of medications. If dosing instructions are variable (for example, "take as required") then unable to calculate coverage.	[171]
Continuous measure of medication gaps (CMG)	Total number of days without a supply (gaps) divided by number of days in observation period/ time between first and last refill date.	Gives percentage of time without coverage, can highlight variability in refilling. Calculation with AdhereR.	Complex and require more data to calculate.	[143, 162]
Group based Trajectory Modelling	Using software, such as the SAS package 'Proc Traj', input monthly adherence estimates. Model runs multiple regressions and estimates groups using maximum likelihoods.	Gives a clearer picture of the dynamics of adherence and categorises people based on their medication taking behaviour. Greater accuracy than PDC.	Requires a significant amount of data cleaning prior to input to model, and computationally slow to run, especially with large amounts of data.	[173]

Table 3.3: Summary of adherence calculation methods

The ‘gap methods’, continuous measure of medication availability/gaps (CMA or CMG) and continuous multiple interval measure of oversupply (CMOS), look at the level of non-adherence rather than the level of adherence[143]. While this can be useful, it requires translation into an adherence percentage value to allow comparison with other studies[143]. An assessment of adherence measures found that methods which use a defined study period, such as 365 days, were more reliable than those which used the time period between first and last refill as the denominator in calculations[143, 172], such as the MPRm method.

The R package AdhereR can be used to calculate adherence using CMA methods[174] and this could prove a valuable tool as it could standardise adherence measurements if adopted widely. However, R can be challenging to use with large datasets due to memory restrictions[175] and alternative methods, such as using a relational database or Hadoop’s MapReduce algorithm, are required for processing[175]. This adds an extra layer of technical difficulty for an inexperienced programmer.

Group based trajectory modelling (GBTM) is another potential method for estimating adherence. It illustrates the dynamics of adherence much more clearly when compared to summary measures such as MPR and PDC[15] and in one study was shown to have greater accuracy than PDC[173]. Based on the number of groups put into the model, usually no more than 5 or 6 is enough to show marked differences without over-complicating the analysis[173], it groups a population into clusters based on their major patterns of adherence overtime[15] and applies maximum likelihood to build trajectories and to estimate group sizes[15]. The groups produced by the model can then be compared for baseline characteristics that may predict inclusion into each group[173] and subsequent outcomes may be compared. One flaw with this method in adherence study at a population level is that it can take a very long time to compute within a large cohort.

Adherence Calculation	Validity	Comparability	Ease of calculation / usability	Computability / memory usage
MPR	✗	–	✓	✓
PDC	–	✓	✓	✓
CMA	✓	✓	–	–
TAM and PDC combined measure	✓	✓	✓	✓
GBTM	✓	✓	–	✗

Table 3.4 Comparison of main adherence calculations

3.3.2.5 Persistence

Persistence is also a component of adherence; it is defined as the time between initiation and discontinuation[42], and therefore does not encompass any time following discontinuation. For studies of persistence, there are also a variety of methods available, the main basis of which is to identify the 'time to discontinuation'. In studies using pharmacy claims data, Caetano *et al* [169] identified five main methods used to measure persistence: the anniversary model, minimum refills model, refill sequence model, proportion of days covered, and the hybrid model. The anniversary model and the minimum refills

model do not take into account the amount of medication supplied or how long the prescribed drug should last[169], and in this respect are flawed, though could be used when available data are limited. As discussed previously, anniversary models can also be valuable when used as a combined measure[44]. More recent studies tend toward the use of proportion of days covered (PDC)[162] at specified time points (6 months, 12 months, 18 months etc.) and defining those as persistent if they have a PDC above a threshold value. The issue with using PDC as a persistence measure in this way is that people who implement drug use poorly may be classed as non-persistent, despite continuing to take the drug, which further confuses the conceptual difference between adherence implementation and persistence. Another possible persistence measure is the estimated level of persistence (ELPT) method, which evaluates the percentage of individuals considered persistent at any given time[162]. ELPT is useful for population level study, and can be used to create a 'persistency curve'[162], similar in principle to a Kaplan-Meier plot[162].

3.3.3 Outcomes

When carrying out an adherence study, it may be of interest to relate this to clinical outcomes in order to identify the impact of non-adherence or non-persistence[167]. This can commonly be identified through adverse events or hospitalisation, by looking for specific disease diagnosis codes for defined outcomes of interest[137]. Coding for outcomes is not always as accurate as coding in prescribing databases, especially if patient presentation is not clear cut[137]; for example, certain autoimmune conditions can present similarly or records may miss more minor events and outcomes which do not always result in hospital admissions[137]. Systems such as ICD coding work best for cases which are straightforward to diagnose, such as myocardial infarction or stroke, though it is important to also include death records in order to capture those who die without making it to hospital. The validity of such codes should be considered before use [176].

Other outcomes of interest may be the change in a certain clinical marker, such as changes in blood pressure, or low-density lipoprotein tests for identifying cholesterol levels. However, the more specific information gained from laboratory tests may not be available to large-scale study, and often in

administrative datasets it is only recorded that a test has been ordered to allow for reimbursement[137], without the results themselves being included.

3.4 Limitations in this field of study and future prospects

Research in adherence must first define the term operationally, including how the data were collected and parameters used. Also necessary is a definition of the study population, the length of the observation period, the calculation used to find the defined daily dose or direct dosing instructions, a description of how missing information was handled[142], how confounders were accounted for and a definition of outcomes. All of this is required to provide a clear data handling and analysis plan, which is vital for studies to be transparent, reproducible, and comparable to other research.

There are, as ever, issues with using secondary data. Steps in linkage, preparing, and analysing data can all be subject to selection bias or information bias and some specific information may not be captured. Using refill-records only accounts for drug availability and is not a direct measure of ingestion [48, 142, 177], however it is reasonable to assume that patients who consistently refill their prescription on time are more likely to be adherent, and that those who do not collect sufficient medication could not possibly be adherent to the prescribed regimen. Moreover, self-reporting, electronic measures, and prescription refills have all been found to have a fair level of agreement between them [168] and so despite there being no gold standard for measuring adherence, there are a range of valid methods to identify this, depending on resources available to the researcher and the study aims. Using secondary administrative data is indeed a viable way to study this, so long as the parameters, calculations used, and assumptions made are clearly stated.

A challenge to adherence research as a whole is the wide variety of methods available for calculation of adherence, and the numerous decisions and assumptions that need to be made in the preparation of data. If these are not recorded accurately then it is impossible for research to be reproducible or comparable to other adherence studies. However, this flaw can also be a strength; the wide range of methods means that adherence can be estimated in line with specific requirements of a study, even if the data available is limited.

3.5 Chapter summary

There are a breadth of methods available for collection of adherence data, though for population level study, pharmacy refill records are the most accessible. For adherence study, MPR and PDC are the most commonly used calculation methods, though it is important to justify parameters set, such as the grace period and cut-off points, and where possible it may be useful to study adherence as a continuous or categorical, rather than a dichotomous, variable. Comparison with newer methods such as the DPPR, time varying PDC, and GBTM could also be of value when conducting new research. Here, the combined TAM with PDC will be used, due to its relative ease of computability without compromising on validity. When using such data, it is important to acknowledge limitations in all stages, from data collection, linkage, analysis, and relating to outcomes.

4 Methods Chapter: Data Management

4.1 Introduction

This chapter covers the data management methods used to conduct this PhD project. It details the data sources and variables, assumptions made about the data, as well as steps in preparing and defining the cohort.

4.2 Data Approvals and Access

All data was provided by the electronic Data Research and Innovation Service (eDRIS), a division of NHS National Services Scotland (NSS). An application for data was made through the Public Benefit and Privacy Panel (PBPP) (application number 1617-0221). Once the application was approved, access to linked, anonymised records was provided through the National Safe Haven, hosted by NSS. Data exploration, cleaning and analysis was run on RStudio. The University of Glasgow MVLS Ethics Committee approved the project without the need of additional ethical review following acceptance of the PBPP (Date: 01/03/2017, See **Appendix B**).

All study data were contained within the National Safe Haven hosted by NSS and accessed remotely via VPN. Data approval was achieved through PBPP application, with data linkage and data extract provided by eDRIS. All data cleaning and analysis work was carried out by the author in accordance with the terms agreed to by signing the written National Services Scotland eDRIS user agreement[178]. Any outputs were released following disclosure control and approvals.

4.3 Linkage and Anonymization

Data linkage was performed as part of the eDRIS extraction service using CHI numbers. CHI, or community health index, is a unique, ten-digit number[179] given to all Scottish patients upon registering with a GP. Patients accessing services within Scotland cannot opt-out of the CHI system[179], giving it universal coverage, and it is used to record healthcare encounters and usage across NHS services. This also allows CHI to be used to match a patients' records across

these different services. Each individual CHI is made up of ten digits including a sex code, a 6-digit DOB, a unique code and a check digit [179] and thus includes identifying information[179]. Therefore, to protect patient anonymity, eDRIS removed the CHI following extraction of the data files and provided a unique study ID number (PatID), which has been generated for the purposes of this study. The CHI number is used for the linkage of records performed by eDRIS and is replaced by the unique PatID, which cannot be used to link to datasets outside of the extract provided for this specific study. As the researcher only has access to linked records indexed with this ID rather than original CHI numbers, this provides a higher level of data protection.

To protect patient confidentiality, and to comply with the Data Protection Act, additional steps were taken to minimise identifying information provided in the data extract provided by eDRIS: for date of birth, the month and year were provided, though no day variable. Therefore, all dates of birth were set to the first date of the month, from which ages were derived.

Other demographic information could also potentially lead to identification. Full UK postcodes pertain to an average of 15 addresses[180] and so people may be able to identify themselves or others in the data if this were provided alongside date of birth or prescription of certain medication. For example, the postcode 'G12 8RZ' pertains to very few properties, whereas the postcode sector 'G12 8' contains 288 postcodes, and hundreds of residences. Hence, provision of postcode sector rather than full postcode helps to eliminate risk of a confidentiality breach.

4.4 Data Sources

For this study, Scottish administrative and routine health data records were used. The Prescribing Information System (PIS) for the period of 2009 – 2017 inclusive was used, along with additional data on acute and psychiatric hospital admissions (Scottish Morbidity Records, SMR01/04) and deaths (NRS). These databases are detailed in **Table 4.1** and in the following sections:

Dataset	Description	Year of first available data	Years included in this study	References
SMR01	Scottish Morbidity Record 01. Scotland-wide acute hospital episode data; includes inpatient stays and day-cases; excludes obstetric and psychiatric specialties; care for the elderly long-stay data included from 2007	1981	1999 - 2017	[181, 182]
SMR04	Scottish Morbidity Record 04. Scotland-wide psychiatric facility episode data; includes inpatient stays and day case dataset; excludes community mental health care	1981	1999 - 2017	[181]
NRS deaths	National Records of Scotland Deaths. Scotland-wide death registrations	1974	2009 - 2017	[183]
PIS	Prescribing information system. Scotland-wide; medications dispensed by community pharmacies or primary care	Aggregated data from 1993; individual level data from 2009	2009 - 2017	[181]

Table 4.1: Description of datasets from which extracts were provided for this study

4.4.1 Prescribing Information System

A previous review highlighted that, in order to utilise prescribing or dispensing information to study adherence at a population level, a centralized, closed pharmacy system with consistent coding of information across all practices and pharmacies was the ideal organisational structure[184]. PIS is a closed, centralised database. It dates back to 1993, though prior to 2009 information is not linked

and can only be analysed as aggregated data on use of medications rather than at an individual level. From 2009 onwards, the community health index (CHI) identifier was appended to the information held. This is a unique ID which relates to every patient registered with a GP in Scotland, giving it universal coverage and making it possible for patient records to be linked across NHS services. The CHI number enables medications dispensed to the same individual over time to be linked and allows PIS data to be linked, at an individual level, to other health datasets.

To estimate adherence using a database it is important to have the date on when a drug was prescribed, the quantity, and dosage information. PIS contains three different date variables: prescribed date, dispensed date, and paid date. The prescribed date is the date on which the physician writes the prescription; the dispensed date is the date on which a patient fills (i.e. collects) the prescription; and the paid date is the date on which the pharmacy fills out pay claims for reimbursement of the costs, which falls on the last day of the relevant month. Ideally for an adherence study, it would be best to use the dispensed date as this is when a patient physically has access to a drug, however this often defaults to paid date, recorded at the end of month when pharmacies submit requests for bulk payments (55.23% of dispensations in our dataset fall on the end of the month, n = 102,419,655; see **Figure 4.1**) whereas with prescribed dates, this does not occur as often (11.73% prescriptions recorded as end of month, n = 21,757,669). This is still imperfect: in a year, 3.2% of days are ‘end of month’ days. However the level of systematic error is lower than with dispensing dates. This is important, as many prescriptions last for 28 days, so it would be very difficult to build an accurate picture of adherence with over half of the records skewed. The paid date variable would be the least suitable, as they are all recorded on the end of the month, when the pharmacies submit their records for reimbursement purposes.

The variables relating to quantity in the dataset are the paid quantity (PQ) and dispensed quantity (DQ). The PQ variable was used to derive the quantity of the drug supplied as it was a complete record, while DQ had substantial records missing. Dosing information came from written instructions, which were provided in a structured format (more details **Section 4.6.6**.).

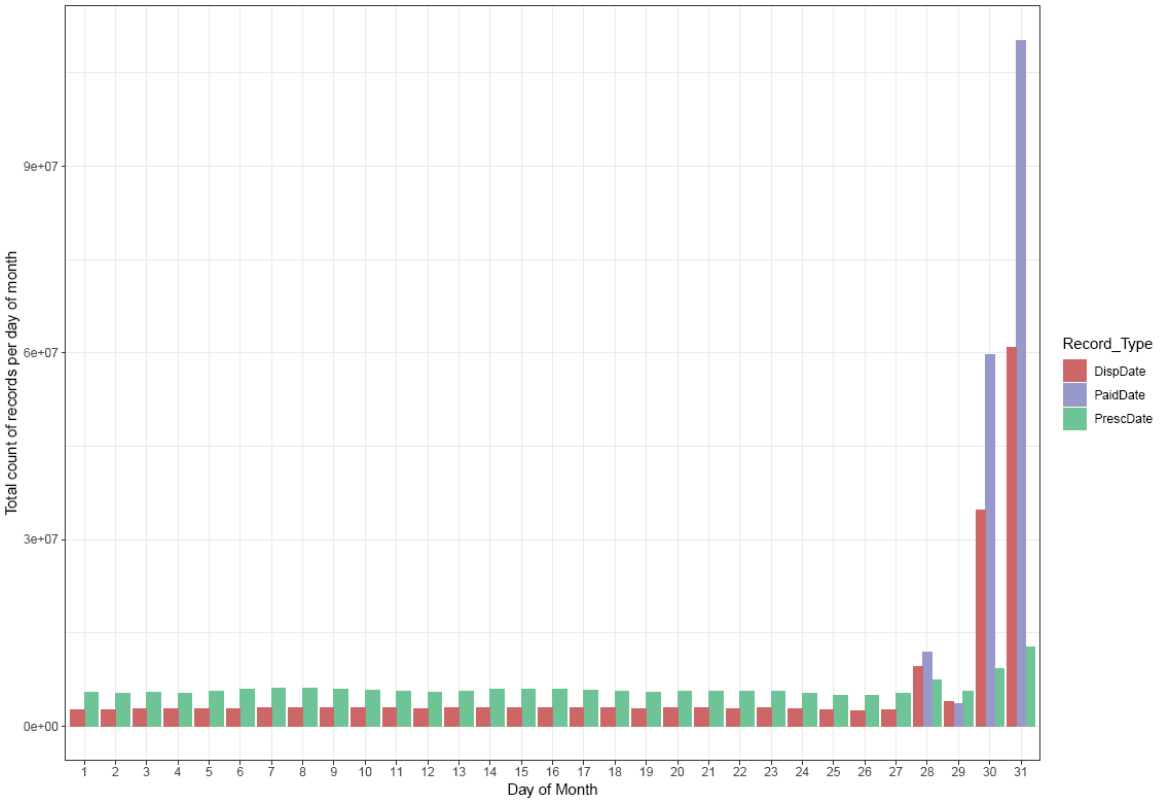

Figure 4.1: Frequency of prescribed, dispensed, and paid dates recorded on each calendar day of the month.

4.4.2 Scottish Morbidity Records

The Scottish Morbidity Record (SMR) records all inpatient and day-case hospitalisations in Scotland and is managed by the Information Services Division (ISD) of the NHS[182]. SMR01 covers all hospital specialities other than obstetric (SMR02) and psychiatric (SMR04) specialties, and the SMR is coded on completion of an episode of care due to discharge from hospital; transfer to another specialty, ward, or hospital; or death[182].

Records have a continuous inpatient stay (CIS) marker, which allows transfer of a patient between clinicians, wards or hospitals to be linked and recorded as a single episode of care, with the final discharge date relating to the patient leaving hospital, either by returning home, or by death. This is important when conducting secondary analysis, as it is important not to incorrectly list movement from one ward to another as two separate incidents and overinflating incidence measures. For an adherence study, it is also important to accurately assess the date at which a patient leaves the hospital as apparent ‘gaps’ in treatment may be identified during a hospital stay. In Scotland, patients are encouraged to take their prescription medications from home for in-patient

hospital stays[185], meaning that significant gaps in medication coverage are less likely to appear in the prescribing data due to hospitalisations.

The key variables of interest were the patient identifier (this is the study generated ID different from CHI, for reasons pertaining to patient anonymity), admission date, discharge date, CIS, main diagnosis, and the other diagnoses codes (1-5). In the SMR databases, diagnostic codes are recorded using the International Statistical Classification of Diseases and Related Health Problems (Tenth Revision) (ICD-10). Here, SMR records were used to identify the different patient subgroups based on presence of symptoms and past medical history. History of CVD was defined by presence of the following ICD10 codes:

CVD: I20, I21, I22, I23 I24 I25, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69.

MI: I21

Stroke: I63

4.4.3 National Records of Scotland Deaths

National Records of Scotland are vital statistics recorded by the Scottish Government, such as deaths, births, marriages, divorces, and adoptions. From here on in this thesis, any mention of 'NRS' refers directly to the deaths records, as this is the only NRS database which was used.

The full NRS database contains 156 variables[183], though for this study only 15 variables were requested, of which 10 were 'cause of death codes' (see **Appendix C: PBPP Application**), however, the main/ underlying cause of death is the only code of interest when differentiating CVD-mortality from all-cause mortality. Cause of death is recorded using ICD-10 codes, which are added to the NRS database by software which reads the death certificate and allocates the appropriate code, before being checked by a human coder[186].

The main variables of interest for this study were the unique patient ID ('PatID') for joining to PIS and SMR records (while the linkage had been performed by eDRIS, the datasets were provided in separate files; this study-generated PatID

was used to relate the information in each file together); the date of death ('DOD') variable was used in data cleaning stages, as well as identifying end-points for inclusion in various patient subgroups; and cause of death was of interest in differentiating CVD-specific mortality when studying outcomes.

4.5 Defining the Cohort

The cohort was identified to include all adults aged 18 to 99 in Scotland, who had been prescribed an eligible CVD drug between the years of the study period (2009 – 2017). Drugs were specified using the British National Formulary (BNF) coding system. For any patient included, their entire prescribing histories for the dates of the study period were requested to allow assessment of co-morbid conditions and polypharmacy. Previous hospital admissions (SMR01) or psychiatric hospital admissions (SMR04) were requested for the study period, with additional records dating back to 1999 in order to apply a ten year 'look-back' period, for identification of prior disease of interest. A fixed look-back period of ten-years was decided, as this was the maximum period available from the first date on which individual level, Scotland-wide PIS data were available. Those with a cohort entry date later than 2009 had their look-back period capped at 10 years, even if hospital records relating to a relevant episode of care older than this were available (e.g. those entering the cohort in 2015 would only have hospital records used from 2005 onwards) in order to avoid a bias whereby people entering the cohort later would be more likely to have had prior hospitalisations simply as a result of longer look-back.

This study used a Scotland-wide cohort of individuals. Inclusion was restricted to patients prescribed at least one of the following cardiovascular drugs during the study period. The list of appropriate drugs was produced with the assistance of a cardiologist:

- lipid-regulating drugs (BNF 2.12)
- diuretics (BNF 2.2)
- alpha-blockers (BNF 2.5.4)

- beta-blockers (BNF 2.4)
- ACE inhibitors (BNF 2.5.5.1)
- angiotensin-2-receptor blockers (BNF 2.5.5.2)
- nitrates (BNF 2.6.1)
- calcium channel blockers (BNF 2.6.2)
- other antianginal agents (2.6.3)
- antiplatelet drugs (BNF 2.9)

Subjects were excluded up until age 18 (n = 23,478 removed), as medications for paediatric patients are likely to be administered by parents or caregivers, influencing adherence for this group. Furthermore, these patients are less likely to have CVD, and congenital heart diseases were beyond the focus of this research. Subjects aged over 100 years were also excluded (n = 708). In 2015, there was an estimated 900 centenarians living in Scotland[187], accounting for just 2.3% of the over 90 population[187]. As this is a relatively small number of people, it was decided to remove those over the age of 100, in order to reduce the risk of information becoming identifiable. It is also likely that some of the birthdates provided for this group were inaccurate, as several patients had an age that exceeded records for the oldest known living person. By eliminating all centenarians from the dataset, the spurious results were removed with only a very small proportion of the "real" cohort being lost.

PIS records relating to drugs of interest were used to estimate adherence and linkage to SMR01/04 and NRS deaths records was also used to identify outcomes related to non-adherence.

4.5.1 Defining key subgroups

A major hypothesis of this PhD is that patient adherence may be affected by the presence or absence of symptoms and whether the patient has undergone an

acute, life-threatening event, such as AMI. Therefore, PIS and SMR01/04 data were used to define four patient groups within the cohort. At any given timepoint, these groups are mutually exclusive; however, patients may move from one group to another overtime e.g. a patient in the primary group who is latterly prescribed GTN could move to treatment at this point. Patients were classified into prevention and treatment groups; each of which was further classified into two sub-groups:

- prevention
    - primary prevention (drugs prescribed to prevent CVD) defined as no AMI within previous ten years and no anti-anginal glyceryl trinitrate, BNF 2.6.1
    - secondary prevention (drugs prescribed to improve prognosis following an AMI) defined as drugs commenced within 42 days of hospital discharge following an AMI, and no anti-anginal glyceryl trinitrate, BNF 2.6.1
- treatment
    - treatment / no previous AMI (drugs prescribed to manage disease and control symptoms) defined as taking glyceryl trinitrate, BNF 2.6.1 and no AMI within previous ten years
    - treatment / secondary prevention (drugs prescribed to manage disease and control symptoms) defined as fulfilling the criteria for secondary prevention group, plus prescribing of glyceryl trinitrate, BNF 2.6.1.

More details of the inclusion and exclusion criteria for these groups and how they were determined can be found in **Section 4.6.5.**

4.6 Data Cleaning

4.6.1 Data Quality Checks

Checks were carried out to assess the quality of the data. In data quality checks, it is important to assess completeness (number of missing or incomplete records), correctness (extreme or implausible outliers, for example death records preceding hospitalisations or prescription records, or multiple deaths recorded for one individual), and consistency (does information that should remain the same over time stay that way? For example, date of birth and sex should not change for any given person).

The initial cohort, derived from the listed drugs of interest during the period of 2009-2017, resulted in almost 2 million subjects (n=1,948,198) (**Figure 4.2**). Following application of the age range inclusion criterion this fell to 1,906,110. These were then linked to death data and checked to determine if data errors were present: potential subjects were checked for multiple dates of death recorded, although none existed, or if their death was listed as having occurred prior to admission to hospital or drug prescription. Those who are recorded as having a hospital admission following their death date must either have an inaccuracy in their death records or in their SMR records, or an inaccuracy in the data linkage. Those who die before their first prescription could not feasibly be followed up, and some error in the date of death or an error in the date of prescription is likely for this issue to arise. Any subject with a prescription recorded more than 30 days before their death date were also excluded, with a window to allow for delays in processing by the pharmacy. This left a remaining 1,901,693 subjects who were eligible to be checked for inclusion into the different patient sub-groups.

4.6.2 Reformatting Data and Variable Selection

All data were imported into R as a .csv file with the argument ‘stringsAsFactors = FALSE’. Variables were therefore imported as strings/character variables and had to be reformatted in order to be used in later analysis (i.e. factors, character, string, numeric).

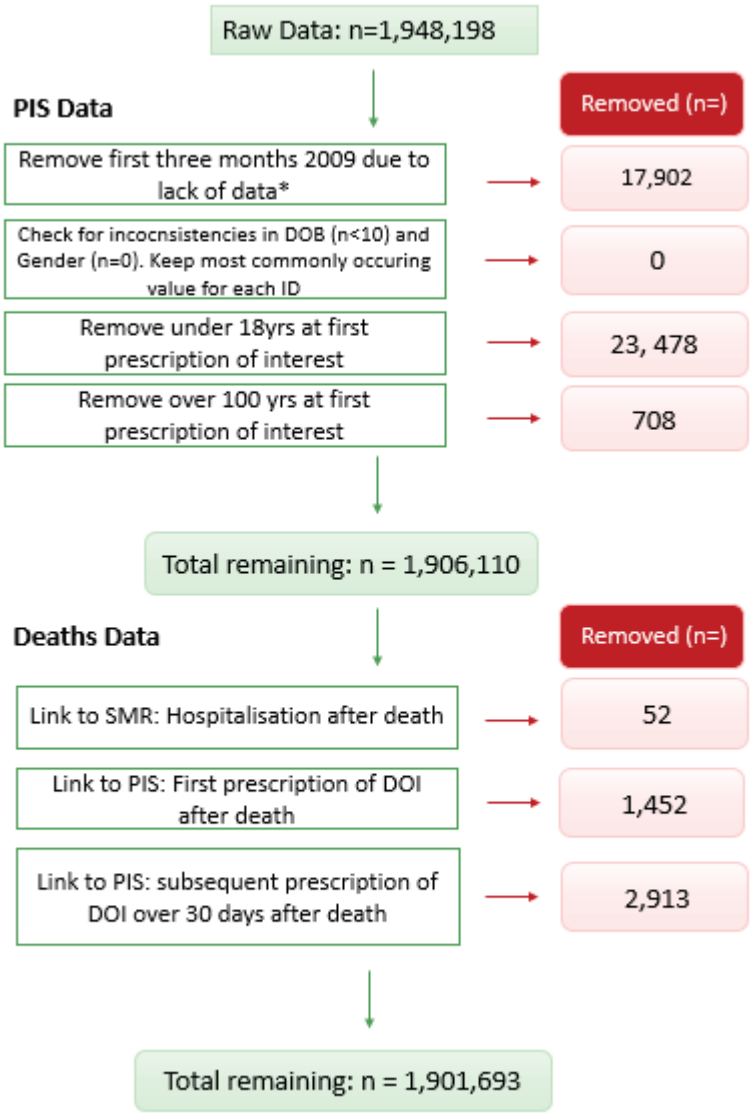

Figure 4.2: Initial data quality checks: reasons for data removal and number of records removed. First set of checks carried out on PIS data, while second set of checks included information from NRS deaths data and SMR data.

The default for missing data in R is not applicable (NA). Once a character variable is converted into dates, factors, or numerics, any missing records default to NA. This was used throughout for ease.

4.6.3 Demographic Data

No demographic description was included in the data output, beyond the information contained in the PIS data capture validation and pricing (DCVP) files. Therefore, a demographic dataset was constructed by extracting this information from the datasets available. The PIS DCVP dataset was used to derive a single demographic record for each individual ID, with additional information from linked SMR and death records included where applicable. The resultant dataset included summary information pertaining to sex, DOB, postcode sector, date of entry to study, variables to indicate inclusion into sub-groups (primary prevention, secondary prevention, treatment/no AMI, treatment/secondary prevention), and dates of entry and exit to each group (full list of headings and how these were derived in **Appendix D: Demographic Dataset Assumptions Table**). For variables such as DOB and sex, which would be expected to remain constant overtime, counts were added for the number of times details appeared together. The number of cases where DOB changed for an individual was (n<10) and no individuals were recorded as having changed sex (**Figure 4.2**). In the former cases, the most commonly occurring DOB was selected for inclusion in the demographic file, likely eliminating spurious data entries (for example, a mis-typed DOB). There were no ties, i.e. no one individual recorded as having two different DOBs with the same frequency.

4.6.3.1 Entry Dates

Cohort entry dates for each subject were defined as the first prescription date recorded for an eligible drug. This was used to check against inclusion and exclusion criteria for each of the main patient groups; for example, in defining the primary group, the 10-year look-back period to check for previous history of CVD would range from the entry date to 10 years previously.

Demographic Date Variable	Definition
Entry Date	First date in study period (between April 2009 – March 2017) where drug of interest (as listed section **4.5 Defining the Cohort**) was prescribed for individual patient.
Primary Start Date	Date of first prescription for all primary subjects. Same as entry date, as inclusion criteria for this group does not allow inclusion in any other group beforehand.
Treatment Start Date	Date of first GTN prescription within the study period. May be the same as the entry date if GTN happens to be the first drug of interest prescribed.
Secondary Start Date	Date of first prescription following MI during study period. Must be within 6 weeks of hospital discharge.
Secondary with Treatment start date	Date of first GTN prescription following inclusion in secondary group.

Table 4.2: Describing the different start date variables.

Records from January, February, and March 2009 were excluded (**Figure 4.2**) as all records in this timeframe had a prescribed date listed as the end of the month. This does not give a great enough level of granularity for estimating adherence, as it creates a four-week window of potential error.

4.6.3.2 Age at First Prescription

From PIS, age at first prescription was evaluated by adding a dummy day column of '01' to the DOB variable (given in the format mm/YYYY) and transforming into the format YYYY/mm/dd using the lubridate package. The interval between this date and the date at which each individual was first prescribed an eligible drug was then calculated to give an age variable and added as a column to the data frame. Ages were also recalculated in a similar way when subjects entered a different sub-group (primary, secondary, etc.).

4.6.3.3 Socioeconomic Status

The measure of area-based socioeconomic status was provided by eDRIS. The full patient postcode held within PIS was used to derive the Scottish Index of Multiple Deprivation (SIMD) 2012, a metric derived from 38 indicators across seven distinct domains[188]: employment, income, health, education and skills training, crime, geographic access to services, and housing[188]. Each of the ten domains are given a standardized weighting and combined, which can be used to rank each postcode area in the country in terms of relative deprivation[188]. The advantage of using an index such as SIMD is that it is calculated using routinely collected administrative data, and hence can be updated more regularly than Townsend or Carstairs measures, which rely on census information[189]. However, as it is an area based measure, there is a possibility of misclassification at an individual level[190], particularly in rural or remote areas where data-zones may cover a larger and more variable population group[190]. 18% of Scotland's population were classed as living in accessible rural or remote rural areas in 2013, accounting for 97% of land, and so this may have an effect on SIMDs recorded[191].

The information provided for this study grouped overall SIMD-2012 scores into deciles and quintiles, categorising each postcode sector between 1-10 or 1–5 respectively, with 1 being most deprived and 10 or 5 being least deprived. SIMD information is based on weightings across the general population within Scotland and not limited solely to the study population.

SIMD information was taken from the details correct at the date of index prescription. Although SIMD may be subject to change, for example, if an individual moves to a new home which is in a different postcode sector, and hence a different data-zone which may be associated with a different SIMD-2012 value, to study this as a factor we want to take the measure of socioeconomic status from a fixed point in time to allow comparability. Best practice is to use the index closest to time when the data is extracted[189]; although some within our cohort will have a cohort entry date closest to the SIMD-2009, and others will be closer to SIMD-2016, SIMD-2012 is more representative of the cohort as a whole. It is also important to take socioeconomic information from earliest possible time-point to prevent identifying cases of reverse causation[192], for example, if a patient becomes ill and is unable to work, this may impact their ability to pay rent, leading to reduced social mobility, which could in turn prompt a move to an area which is less affluent[192].

4.6.4 Prescribing Information System Data

The PIS data provided were given as two separate file types: data capture validation and pricing (DCVP) files, which contains prescribing, dispensing and paid dates, drug ID, BNF codes, drug formulations, drug strengths, and the quantity prescribed, dispensed, and paid. The other file type included dosage instruction information, which had been extracted from written messages provided on all ePrescribed items using a natural language processing (NLP) algorithm[166]. This was linkable to DCVP files through a dosage information key and a lookup-file.

4.6.5 Primary, Treatment, Secondary, Secondary-with-Treatment:

The key patient subgroups in this study were created as it was hypothesised that adherence differs by disease severity, and that the consequences of non-adherence may also differ according to this. Conceptually, the primary prevention group are people with no history of myocardial infarction and no angina (defined by no concurrent prescription of GTN); the treatment group had symptomatic CVD (as evidenced by GTN prescription); the secondary prevention group had suffered an AMI and were recieveing follow-up prohylaxis to prevent future CVD events; and the secondary-with-treatment group included those who

had suffered an AMI and receieved prohylactic medication, but also had additional evidence of symptomatic CVD (as evidenced by GTN prescription).

Patients could move group over time based on changes to their medical circumstances. Patients who fulfil criteria for the primary prevention group and who later receive a GTN prescription could move into the treatment group at this point. Similarly, those who suffer a subsequent MI could then be moved into the secondary group providing they receive a relevant prescription; and so on.

Information from SMR01 was required prior to defining subgroups in order to identify previous CVD hospitalisations which affect inclusion within the different patient groups, and subsequent hospitalisation events that rule individuals out of each group. The following section describes how these groups were derived from the data. **Figure 4.3** shows potential pathways through the different subgroups**, while Figures 4.4, 4.5 and 4.6** depict the selection process into each of the subgroups.

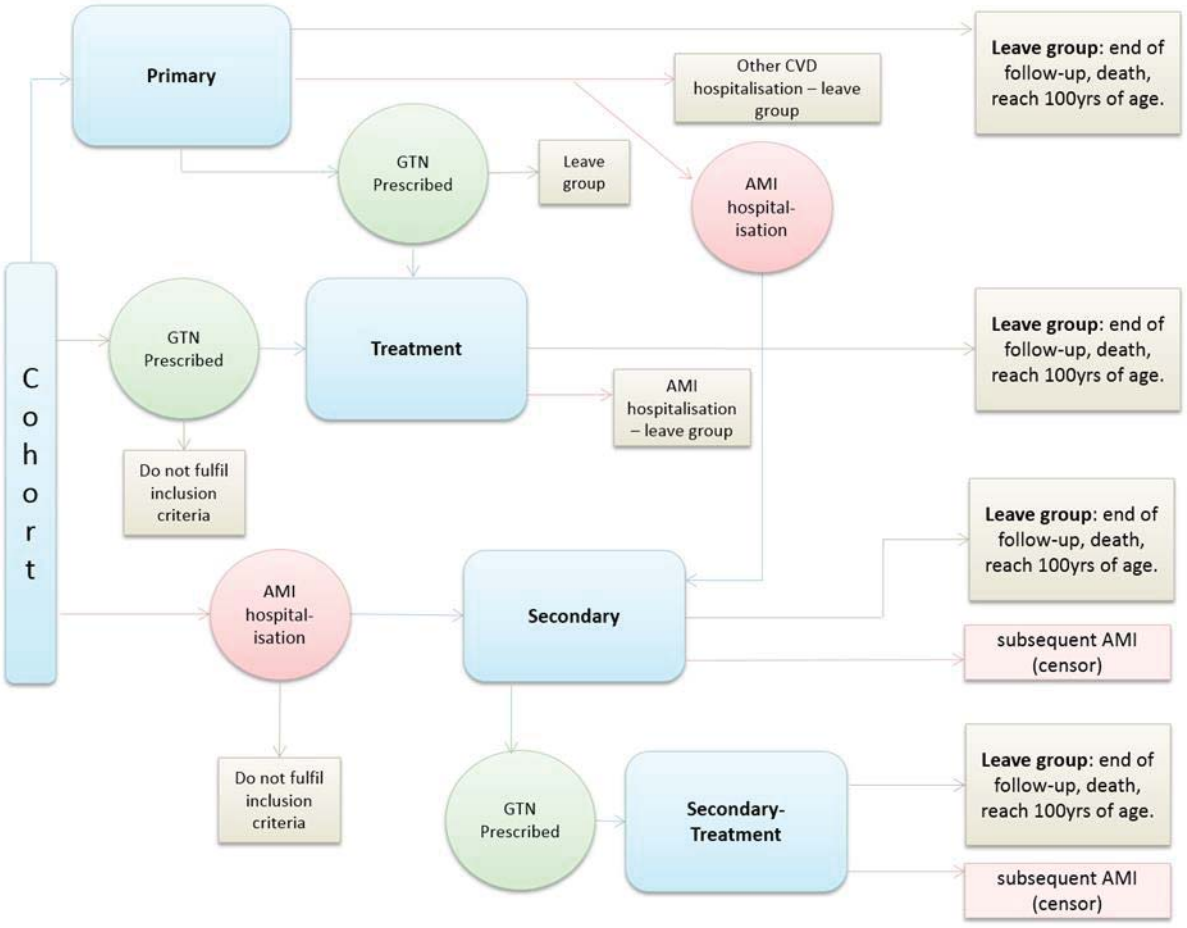

Figure 4.3: Possible pathways for an individual through the four main patient subgroups

4.6.5.1 Primary prevention

Subjects were defined as being in the primary prevention group if they had been prescribed any of the drugs (listed) other than GTN during the study period and had no hospital record with a CVD disease code (listed) recorded in the main or any position, in the ten years preceding their index date. Subjects were excluded from the primary prevention group if they had a concurrent prescription of gylceryl trinitrate (GTN) with the BNF code starting with '0206010FO' as this indication is exclusively for management of angina and would be classed as a symptomatic disease (treatment group). The primary index date was the date of a subject's first relevant CVD drug prescription within the study period. The primary end date was the date at which subjects left the group, either due to a change in status to secondary or treatment group, or exclusion from group due to hospitalisation with a CVD disease code (listed), death, reaching 100 years of age, or end of follow up.

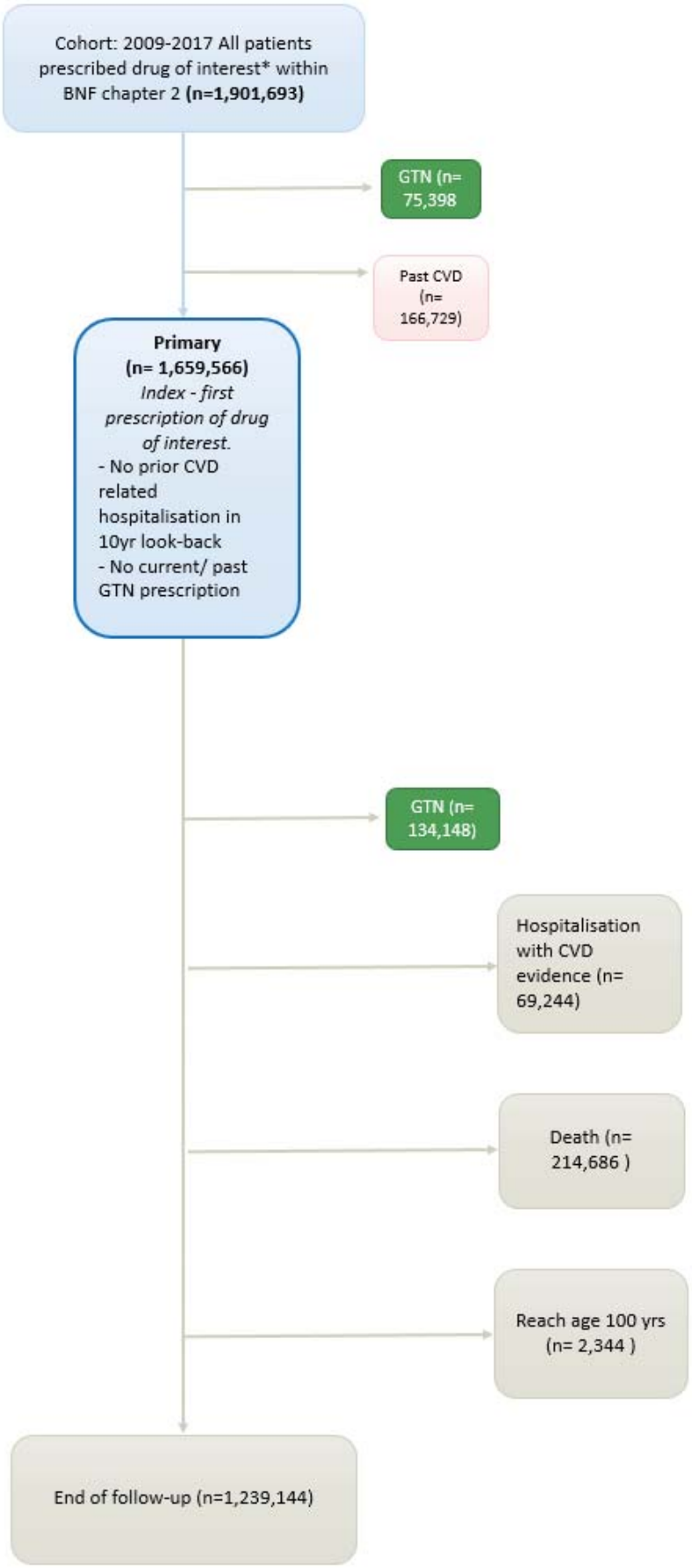

Figure 4.4: Flowchart of Inclusion and Exclusion for Primary Group

4.6.5.2 Treatment

Subjects were included in the treatment group if they had a prescription of GTN during the study period. Those who had suffered an AMI in the 10 years prior to their first GTN prescription (listed under main condition in their associated SMR record) were excluded.

Date of entry to the treatment group was classified as the date of first GTN prescription with the BNF code starting with '0206010FO'. As GTN is for management of an ongoing episode of angina, or prevention of an imminent attack, adherence to this drug could not be calculated, so subjects would also need to have a prescription of another drug of interest in order for adherence to be modelled.

End points for inclusion in the treatment group are; hospitalisation with AMI, death, turning 100, or end of follow up (**Figure 4.5**).

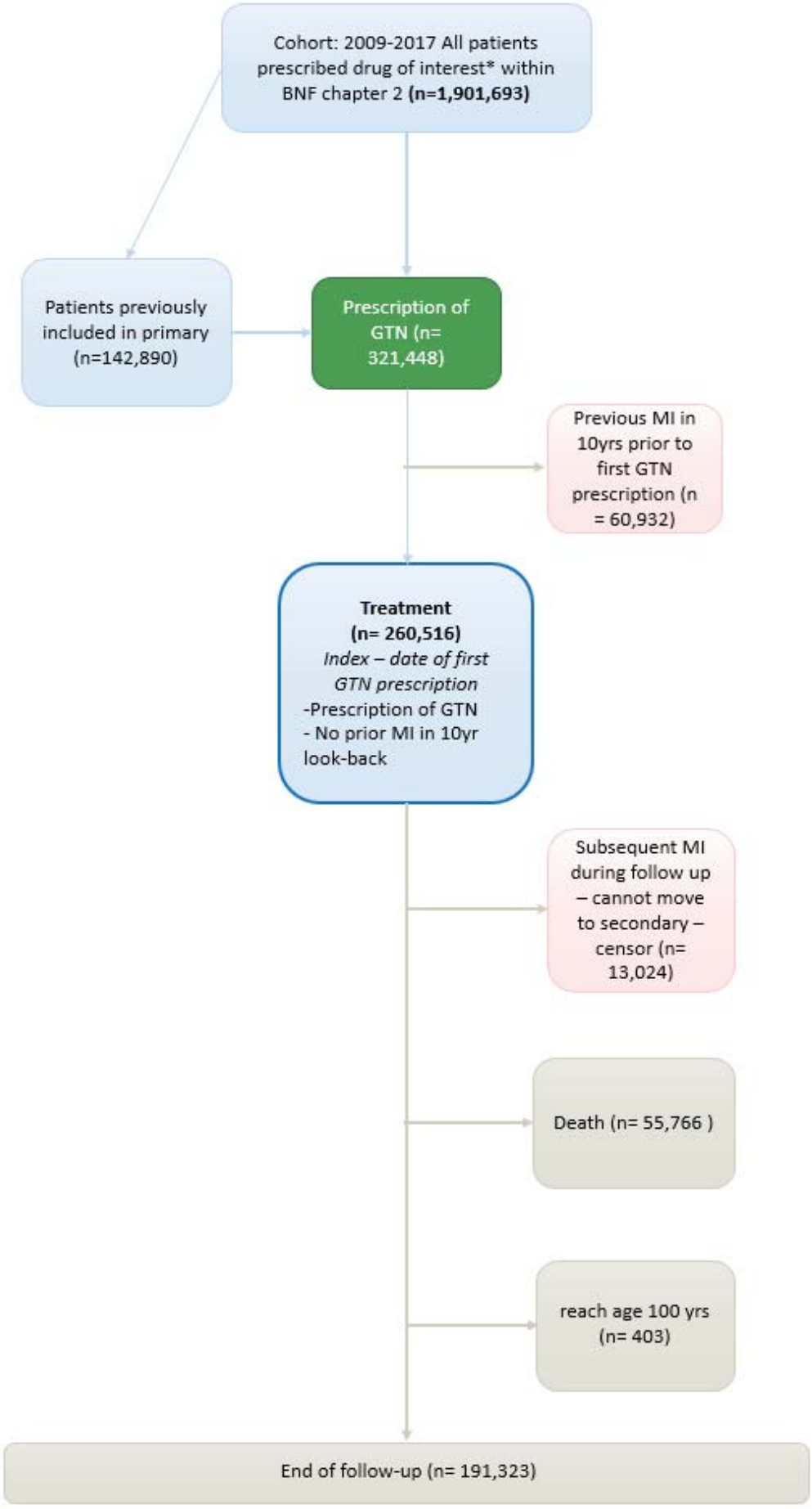

Figure 4.5: Flowchart of Inclusion and Exclusion for Treatment Group

4.6.5.3 Secondary

Subjects were included in the secondary group if they suffered an AMI during the study period and had a subsequent prescription of a relevant CVD drug (other than GTN) within a specified timeframe. Of the group identified, those who had a concurrent prescription of GTN and those who had had a prior MI in the 10 years preceding this (listed under main condition in their associated SMR record) were excluded.

Secondary start date was calculated by identifying all MIs that occurred during the study period (2009-2017). For each subject, their first MI in this time frame was identified, and this was linked to PIS to identify those who received a prescription of a relevant drug within 6weeks (42 days) of discharge.

End points for inclusion in the secondary group are; prescribed GTN, death, reach age 100, or end of follow up. Those prescribed GTN move into the **'Secondary-Treatment group' (Figure 4.5)**.

4.6.5.4 Secondary-Treatment

The secondary-treatment group was conceptually separate from the secondary group, as it was hypothesised that patients who are high risk (following AMI) and have current symptomatic CHD may have different adherence behaviours to those who are simply high risk but with no symptomatic CHD. Therefore, all patients who had previously been sorted into the secondary group and then received a prescription of GTN moved to 'secondary-treatment'.

The start date for this group was the date of first GTN prescription following inclusion into the secondary group. End points for inclusion are; death, reach age 100, or final record relating to that individual (**Figure 4.5**).

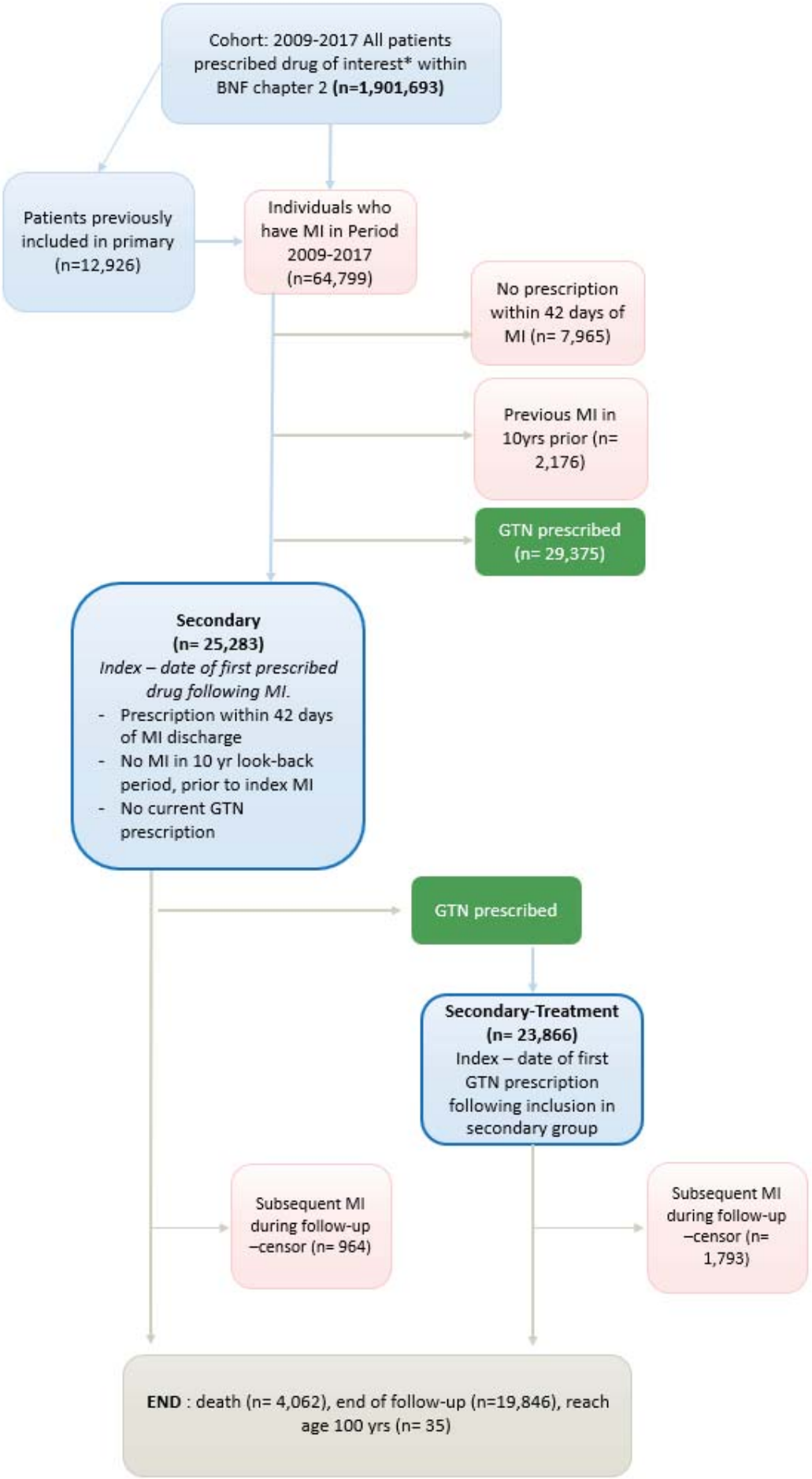

Figure 4.6: Flowchart of Inclusion and Exclusion for Secondary and Secondary-Treatment Groups.

4.6.6 Dosage instructions

Information on dosage instructions was provided by eDRIS for the cardiovascular drugs specified, derived from free-text dosage instructions using a natural language processing (NLP) algorithm[193]. Dosage instruction data were held in a separate file from other PIS records, which could be linked via a barcode key. The NLP algorithm has a reported accuracy of 94.2%[193] and gives a structured output for 96.8% of cardiovascular drugs[193], giving it a very high capture rate for this therapeutic area. Here, only 90.4% of CVD records had a link to dosage instruction data, with a complete link (after cleaning) in only 88.8% of records. This discrepancy will be partly due to the fact that this dataset only has information on the specified CVD drugs of interest, and these may have a lower capture rate than the average across all CVD drugs. Also, due to the greater level of information required for this project, the dosage instruction information had to be of a high standard and so some which had a link to dosage information had to be rejected for other reasons, as detailed below.

Due to the scale of the data (185,427,312 CVD prescription records), processing of dosage instruction data was split into drug categories: Diuretics (BNF 2.2), Beta-blockers (BNF 2.4), Alpha-blockers (BNF 2.5.4), ACE-inhibitors (BNF 2.5.5.1), Angiotensin-2-receptor blockers (BNF 2.5.5.2), Nitrates (BNF 2.6.1), Calcium Channel Blockers (BNF 2.6.2), Other Anti-anginal agents (BNF 2.6.3), Antiplatelet drugs (BNF2.9), and Lipid-regulating drugs (BNF 2.12). Quality checks were carried out to ensure that the dosage units (e.g. mg, ml, spray, inject), were appropriate given the specific drug to which they related; for example ‘spray’ is an appropriate dosage unit for Glyceryl Trinitrate (GTN) as this drug is available in a spray formulation for common use, though it would not be appropriate for Amlodipine or Simvastatin as these are commonly prescribed as a capsule or tablet and do not come in a spray formulation. Equally, a dosage unit of “ml” would not make sense for a drug that is not available in a liquid formulation. Some such errors could arise from incorrect linkage to the dosage instructions or errors with the NLP algorithm identifying information from the free-text instructions. However, these errors were rare, accounting for 0.02% of all records (n = 44,793; of which, 25,957 are diuretics) (**Table 4.3**). A validity flag was created to highlight these erroneous records, as well as to highlight records which did not have any link to dosage instruction data, which made up

Data quality issue	Drug Class (BNF)									
Imputed – count (% of all records for class)	Lipid Regs (0212)	Anti-platelets (0209)	Nitrates (020601)	CCBs (020602)	Anti-Anginal (020603)	Alpha-Blockers (020504)	ACEi's (02050501)	ARB's (02050502)	Beta-Blockers (0204)	Diuretics (0202)
Implausible days coverage (convert to NA)	13,106	15,200	4,058	6,391	1,419	1,390	12,069	2,460	19,265	22,866
No link to doasge instructions	3,708,998	2,646,229	592,199	1,964,173	211,990	315,021	2,590,573	964,053	2,208,556	2,601,969
Incomplete dosage instructions - no amt_min or max:	402,011	412,355	214,116	161,466	47,990	49,862	292,236	93,943	356,239	453,749
Incomplete dosage instructions - no timing or interval given:	53,428	70,233	10,563	40,444	2,189	6,060	39,791	12,888	127,414	96,511
Formulation does not viably match amt_unit	2,327	2,590	1,055 (note: 723 are invalid formulation*)	2,062	193	114	1,805	391	8,299	25,957
Other/ did not fulfill criteria for any multiplier function (A-G)	792	727	5,614	871	63	103	355	197	7,233	1,102
Use = as required; cannot determine days coverage	2,535	1,966	221,762	3,453	223	113	1,438	279	50,046	18,488
Total missing days coverage before imputation	4,180,662	3,147,334	3,069,602	2,175,407	263,844	372,550	2,936,829	1,073,932	2,727,006	3,202,154

2,241,997 classed as prn at outset (GTN in any formulation other than patch)
*ointment - should not be listed under BNF020601

Table 4.3: Data cleaning for dosage instruction data – reasons for days coverage variable requiring imputation and counts across drug classes

9.6% of records (n = 17,803,761) (**Table 4.3**). Other data quality issues included incomplete dosage instructions, either due to missing dosage amount or having no timing or dosage interval given, respectively accounting for 1.34% and 0.25% of all records (**Table 4.3**).

All records considered 'valid' at this stage were then processed to calculate a 'days-coverage' (DC) variable (as detailed in **Section 4.7.1**). Records that had not been highlighted by previous quality checks but that also did not fulfil the criteria of any of the functions used to calculate DC accounted for 0.01% of records (n=17,057).

Once the DC variable was calculated, further quality issues could be assessed as some records appeared to have either exceptionally high or low days coverage. This was often due to improbable paid-quantity values, for example, a drug which is usually dispensed in packets of 56 tabs having a paid quantity of 5,656. While a 56-tablet packet would last 2 months given a prescription of 1 tab per day, a packet of 5,656 would last 101 months, or 8.4 years. On the other extreme, paid quantities were sometimes given as 0.28 – an unlikely value given the challenge in providing this proportion of a tablet to a patient. These errors are likely to be mis-typed values. Furthermore, even if these values were accurate, they would be challenging to work with when estimating adherence overtime. Therefore, a cap of 168 days (6 months) was set as an upper limit for days covered, and 7 days (1 week) as a lower limit and any days-coverage values outside of this range were set as 'NA'. These accounted for 0.05% of records (n = 98,224).

For the records identified as having an implausible days-coverage, and the remaining records which did not have a days-coverage value, either due to missing linkage to dosage instructions or data quality issues, imputations were carried out, as detailed in **Section 4.8.1**.

4.7 Drug utilization data

4.7.1 Derivation of Days Coverage

A vital piece of information for measuring adherence is the length of time that the prescription would be expected to last, or the day's coverage (DC) value. The dataset provided included a defined daily dosage (DDD) variable which has previously been used in similar studies to calculate the drugs coverage; however, this is not always a reliable measure as the DDD is derived from the most common indication of a drug at a global level and therefore, may not be applicable in every instance. A robust method for calculating coverage is to use dosage instructions provided to the patient, along with the quantity of the drug prescribed (paid quantity, PQ). **Table 4.4** details the variables provided by eDRIS which relate to dosage information.

Variable(s)	Definition
di_key	Diagnosis key - numeric key, used along with barcode-key to link dosage instructions to PIS DCVP records.
Native Dose Instructions	Free-text written instructions as directed by doctor, included in original prescription, e.g. "1 tab per day". NLP algorithm based on these instructions.
amount min, amount max, amount unit	Derived by NLP algorithm: relates to quantity e.g. "1 tab", "5ml" etc.
timing frequency min, timing frequency max, timing frequency unit	Derived by NLP algorithm: relates to frequency e.g. 1-2 times/ day
timing interval min, timing interval max, timing interval unit	Derived by NLP algorithm: relates to frequency. Interval of time between doses e.g. every 6 hours
as required	Derived by NLP algorithm: can not accurately calculate days coverage for records where direction is 'as required', as dose is not fixed.
as directed	Derived by NLP algorithm: highlights records where "as directed" is included in instructions.

Table 4.4: Dose information variables provided in dataset

To estimate a DC value, the dosage instructions data was used, along with other variables from the PIS DCVP files: Patient ID (PatID), quantity (paid_quantity), and details about the specific drug (bnf_item_desc, bnf_item_code, and drug class – derived from BNF item code). Multiple functions were developed to extract a DC value for each record (**Table 4.5**), with variations in the code to allow for differences in the data available – most notably, calculating DC using a timing frequency differs from using an interval. For a simplified example, a prescription where a patient is prescribed 56 tablets with bi-daily dosing may have the instructions "take 1 tab twice a day" (timing frequency = 2; amount = 1) or this could be written as "take 1 tab every 12 hrs" (interval = 12; amount =1). To derive DC, calculations would differ as so:

Days coverage = paid quantity/(amount * timing frequency) = 56/(1*2) = 28	Days coverage = paid quantity/(amount * 24/interval) = 56/(1 * 24/12) = 28

Most records fulfilled the requirements for Method A (87.37%, n = 162,008,395), which included all records that did not have a specified amount unit (e.g. 1 per day), used timing frequency with either a non-specified timing unit or given as "day", and which had passed initial data cleaning checks (as detailed in **Section 4.6.4**). All other methods accounted for far fewer records, ranging from 0.001% (Method E) to 0.064% (Method D).

Method	Description	Lipid-Regs (0212)	Anti-platelets (0209)	Nitrates (020601)	CCB's (020602)	Anti-Anginal (020603)	Alpha-Blockers (020504)	ACEi's (02050501)	ARB's (02050502)	Beta-blockers (0204)	Diuretics (0202)
A	'valid' records with blank amount unit, using timing frequency	35,154,116 (89.27)	23,693,698 (88.19)	3,201,594 (51.05)	18,477,698 (89.35)	2,139,875 (88.99)	2,923,759 (88.63)	23,829,884 (88.98)	9,108,853 (89.41)	21,220,198 (88.41)	22,263,717 (87.10)
B	'valid' records with blank amount unit, using timing interval	10,909 (0.03)	5,223 (0.02)	32 (0.00)	1,845 (0.01)	2 (0.00)	155 (0.00)	856 (0.00)	540 (0.00)	4,312 (0.02)	58,299 (0.23)
C	'valid' records with 'ml' amount unit, using timing frequency	14,905 (0.04)	9,203 (0.03)	0 (0.00)	3,566 (0.02)	0 (0.00)	0 (0.00)	4,500 (0.02)	746 (0.01)	45,979 (0.19)	34,327 (0.13)
D	'valid' records with 'mg' amount unit, using timing frequency. Strength in MG	18,654 (0.05)	15,750 (0.06)	3,005 (0.05)	24,857 (0.12)	2,163 (0.09)	3,217 (0.10)	15,334 (0.057)	5,223 (0.05)	16,949 (0.07)	14,402 (0.56)
E	'valid' records with 'mg amount unit, using timing frequency. Strengths in mg/ml; divide by 5	243 (0.00)	189 (0.00)	0 (0.00)	171 (0.00)	0 (0.00)	0 (0.00)	280 (0.00)	37 (0.00)	1,153 (0.00)	929 (0.00)
F	Same as 'A' but with 'week' timing unit	4,675 (0.01)	1,011 (0.00)	44 (0.00)	169 (0.00)	22 (0.00)	5 (0.00)	206 (0.00)	30 (0.00)	268 (0.00)	4,262 (0.02)
G	Same as 'A', but timing freq corrected from week, month, or fortnight	9,514 (0.02)	7,706 (0.03)	514 (0.00)	3,094 (0.01)	137 (0.01)	398 (0.01)	3,811 (0.01)	1,296 (0.013)	3,002 (0.01)	4,695 (0.02)
NA	Did not meet criteria for any method	4,167,556 (10.58)	3,132,144 (11.66)	3,065,544 (48.89)	2,169,016 (10.49)	262,425 (10.91)	371,160 (11.25)	2,924,760 (10.92)	1,071,472 (10.52)	2,707,741 (11.28)	3,179,288 (12.44)
	Total	39,380,572	26,864,924	6,270,733	20,680,416	2,404,624	3,298,694	26,779,631	10,188,197	23,999,602	25,559,919

Table 4.5: Methods used to derive days-coverage and counts of records for which these applied, across drug groups.

After all 7 methods had been sequentially run, any remaining records without a DC, or those with a DC below 7 days or above 6 months, had to be imputed. Imputations were carried out sequentially (**Table 4.6**). First, by last-observation carried forward (LOCF) and then last-observation carried back (LOCB), Mean (for specific drug and paid-quantity for that patient), Mean (for specific drug and paid-quantity but across patients), Mean (for that specific drug for that patient but with any paid-quantity – thus accounting for records with suspicious paid-quantities as detailed previously). The majority of imputed records (55.07%) were imputed by the method whereby the mean days-coverage was taken across records for a specified drug, strength, formulation, and paid-quantity.

Imputation Method	Lipid Regs (0212)	Anti-platelets (0209)	Nitrates (020601)	CCBs (020602)	Anti-Anginal (020603)	Alpha-Blockers (020504)	ACEI's (02050501)	ARB's (02050502)	Beta-Blockers (0204)	Diuretics (0202)
LOCF *	1,287,896	931,524	124,338	671,546	72,738	115,148	881,590	328,566	794,207	907,509
LOCB ǂ	623,231	454,653	60,720	335,640	41,159	58,480	451,159	166,526	395,774	458,020
Mean (for specific Pat, Drug, and PQ)	20,861	20,635	3,613	10,790	1,319	2,357	15,803	4,969	14,536	19,501
Mean (for specific Drug, Strength, Formulation and PQ, any Pat)	2,232,325	1,725,038	415,067	1,145,998	147,675	194,810	1,565,843	569,376	1,457,704	1,789,679
Mean (for specific Drug, Strength, and Formulation, any PQ	13,800	13,518	2,105	7,978	730	1,640	20,996	4,196	14,734	8,957
Missed/ not imputed	14	0	0	2	0	2	0	0	2	0
Total records imputed	**4,178,127**	**3,145,368**	**605,843**	**2,171,954**	**263,261**	**372,437**	**2,935,391**	**1,073,653**	**2,676,957**	**3,183,666**
Total full records (after imputed and removing prn records)	39,375,186	26,962,249	3,806,641	20,671,173	2,404,230	3,298,387	26,777,712	10,187,667	23,770,302	25,469,398

* Arrange by: *PatID, Drug, Prescription Date, Formulation, Strength*. Group By: *Drug, PQ*. Max gap = 1
ǂ Arrange by: *PatID, Drug, Prescription Date, Formulation, Strength*. Group By: *Drug, PQ*. Max gap = 2

Table 4.6: Imputations for days coverage value

4.7.2 Repeat Prescriptions

Repeat prescriptions are commonly used, particularly for chronic conditions. To account for repeat prescriptions, records with the same patient ID, prescription date, dispensed date, drug approved name, drug formulation, drug strength, and paid quantity were grouped together and counted to create a new variable indicating the number of repeats ('n_repeat'). For example, if there was only one record where the patient ID, prescription date, dispensed date, etc., were identical, then n_repeat would be equal to 1; if there were two records where all of these variables were identical, then n_repeat would be equal to 2; and so on.

Using the n-repeat variable, it was possible to cap the maximum number of identical repeat prescriptions that seemed likely to be correct. There are reasons that multiple prescriptions may be collected on the same date; if a patient is going on holiday, they may need to collect additional supplies to cover their time away, or they may collect extra to pre-emptively avoid repeat visits to the pharmacist. However, in some cases these identical records appeared to be spurious – e.g. 6 identical records, which would provide 6 months coverage, however, prescriptions still being routinely collected in each of the 6 months following. This could be a case where a 6 month repeat prescription is made but has erroneously been replicated as multiple records. For this reason, repeat prescriptions were capped at 2 when the initial adherence estimates were calculated, comparing across the different disease severity, drug class, and demographic groups.

4.8 Chapter Summary

Data cleaning is a long and arduous process, though it is important to record the details of this meticulously, particularly when using secondary data sources to ensure that work can be reproduced and held up to scrutiny. Here, the data sources and access has been described, along with a through explanation of the different patient sub-groups, as well as the steps taken to derive a key variable to adherence study, days-coverage, from the dosage instruction information. Further details on how adherence was defined and derived are included in the **Chapter 5**.

5 Methods Chapter: Analysis Methods

This chapter will detail the different analysis methods used for this thesis, including methods of measuring adherence and persistence and the underlying assumptions made, and detail of data preparation and tools used for univariate and multivariate modelling.

5.1 Defining variables for univariate analysis

Sex: Sex was derived from the chi-number, as previously described in this thesis. In the dataset provided, 1 indicated male gender, while 2 indicated female gender. Reporting throughout will indicate male as 'M' and female as 'F'.

Age: Age was divided into three broad groups: below 55-years old, between 55 and 65 years, and above 65 years. As prior exclusion criteria ruled out those below the age of 18 and above the age of 100, these ages form the lower and upper bounds of the below-55 and above-65 groups respectively. These narrow age groups were defined for ease of analyses, allowing comparison across categorical risk-factors. The specific age bands selected were based around expected relevance to CVD adherence following literature review, and the 'n' shaped relationship between age and adherence.

SIMD: SIMD was derived from the SIMD-2012 deciles and divided into three broad groups: low (SIMD 1-3), mid (SIMD 4-7), and high (SIMD 8-10).

Comorbidity status: Following on from the systematic review of cardiovascular adherence studies (**Chapter 2**), there were two main comorbidities associated with cardiovascular adherence: diabetes has been noted to have a positive association with adherence, while depression tends to be associated with a reduction in adherence. It was for this reason that these two specific comorbidities were chosen for further interrogation. Therefore, the specific groups compared in the analysis were: neither comorbidity, diabetes only, depression only, both (diabetes and depression).

To define each of these comorbidities within the dataset, PIS data was used to identify relevant prescriptions for each. Some prescriptions led to exclusion from

the analysis, as patients with these could not confidently be classed as having or not having the relevant comorbidity. This criterion was defined with help from a clinician and built on definitions used in prior research involving PIS data[194]. **Tables 5.1 and 5.2** show the inclusion and exclusion criteria for these.

Include if prescription of any drug from **BNF Chapter 6.1 'Drugs Used in Diabetes'** code: filter(grepl("^0601", PIBNFItemCode))	
Include if	Drug received within one year of start date/ date of inclusion into patient group.
Exclude if	Any of the 'unknown' drugs for depression are prescribed (see Table 5.2) without eligible antidepressant medications also prescribed; cannot differentiate people with diabetes only from people with diabetes and depression on basis of these drugs alone.

Table 5.1 Defining patients with diabetes using PIS data

Include if prescription of any drug from **BNF Chapter 4.3 'Antidepressant Drugs'** code: filter(grepl("^0403", PIBNFItemCode))		
Include if	Drug received within one year of start date/ date of inclusion into patient group.	
Exclude if	Any of the 'unknown' drugs for depression are prescribed, without eligible antidepressant medications prescribed. These drugs have other indications as well, so prescription of this alone cannot indicate depression.	*'Unknown' drugs:* Amitriptyline (if less than 75mg), duloxetine, flupentixol, moclobemide, reboxetine, agomelatine, phenelzine, tranylcypromine, tryptophan.

Table 5.2 Defining patients with depression using PIS data

5.2 Adherence measures: treatment anniversary model, proportion of days covered, and combined measure.

5.2.1 Justification of adherence measures and assumptions used

Chapter 3 details methods commonly used in adherence research and justifies the use of methods chosen for this study. A basic and technical definition of these is provided in **Table 5.3**.

Adherence measure name, (acronym)	Basic definition	Technical definition and parameters set for study
Treatment anniversary model (TAM)	Is patient still taking any drug in class X at 12-month anniversary time point?	Patients persistent at 12-month anniversary for any drug within class, defined by a relevant drug prescription within 56 days before or after the treatment anniversary date.
Combined measure: Proportion of days Covered for persistent patients (PDCp)	Of patients who are still taking a drug in class X, is their drug supply/ coverage at least 80%?	Of patients who were considered persistent at 12-months with TAM: Patients classed as adherent if supply for drug class covers ≥80% of the time in the 12-months since first prescribed.
Proportion of days Covered for all patients (PDCa)	Of any patient initially prescribed a drug of class X, is their drug supply/ coverage at least 80%? i.e. includes patients who are not persistent as defined by TAM, as well as those who are.	For all patients who are included; those classed as adherent if supply for drug class covers ≥80% of the time in the 12-months since first prescribed.

Table 5.3 Adherence measures used; their basic and technical definitions

As has previously been highlighted in this thesis, adherence research has been plagued by a lack of standardisation. For this reason, it is important to select methods that closely fit the guidelines for adherence research, as laid out by Vrijens *et al*, while allowing for any limitations in the data available.

When selecting a tool for adherence measurement, it is important to consider its computability, usability, validity, and comparability. The TAM and PDCp combined measure was used, as this method is considered valid, and it is described as such in 'Drug Utilization Research Textbook' – written in part by key adherence researchers. The combined measure is also used in some previous studies[195, 196]. This is also relatively straightforward computationally, which is important when using a large dataset.

In estimating persistence with TAM, the gap used here is generous: 56 days either side of treatment anniversary date i.e. a four-month gap. This gap-length was chosen as 56 days is a common drug supply length in our dataset, so a shorter gap may have missed out lots of prescriptions. Also, some gap is permissible, as we do not want to erroneously classify people as nonpersistent if they have just taken a gap in treatment. Other studies use a similar method where they look to see if a prescription was filled in the last 90-days of a 365-day period[197]. TAM is a good way of comparing adherence across a fixed time-frame but may not take into account the fact that adherence declines over time. This is why adherence at one year is compared between groups, as the comparatively longer the follow-up times in the primary and treatment groups could otherwise bias results.

For patients who were found to be persistent with TAM, implementation was estimated using the PDC method with an 80% cut-off. The number of days covered with a drug supply for the first year of treatment was summated, divided by 365 and multiplied by 100 to give a percentage of days across the year where a patient had access to the drug. Patients were classed as adherent if their drug supply was ≥80% for the year from their first prescription of any drug in a particular class. This measure was labelled PDCp, as it is a straightforward PDC calculation for the persistent group.

A standard PDC measure, PDCa, with no consideration of persistence, was also included for comparability to other studies. This was calculated in the same way as PDCp, though also included patients who had not been classed as persistent, and it is a commonly used metric. For all three measures of adherence, a number of underlying assumptions about the data needed to be made and maintained, as detailed in **Table 5.4**.

Decision	Assumption made and limitation
How to define start and end dates	Start: first prescription of any drug in specific class, following inclusion in patient group (primary, secondary etc). Note an individual patient may have multiple start dates/ one for each group they meet the inclusion criteria for and one for each drug-class prescribed. End: Treatment anniversary date (1 calendar year from start date).
How to determine treatment initiated (note: 10% of all prescribed never filled)	All records provided in the data output have been dispensed by the pharmacy, therefore assume patient has at least collected prescription/ has possession of drug. Assume initiation in all cases.
How to handle people who fulfil an exclusion criterion before end of adherence measurement period	Censor those who die/ turn 100/ have a subsequent CVD event that would lead to exclusion from the group. This is to reduce underestimation of adherence e.g. those who are dead cannot be expected to adhere to treatment
How to handle stock-piling/ carry-over	Cap 1-year PDC at 100%. Preferable to specify an allowed carry-forward of drug coverage for each individual prescription, rather than averaging across the whole year.
How to handle switching	Patients must adhere/ persist to any drug within that same class (of the ten classes defined for this study). May underestimate adherence where people switch between classes for the same indication or may overestimate adherence if two drugs of one class are prescribed concomitantly.
How to consider regimens with multiple drugs	Looking at adherence/ persistence on a class-by-class basis. May overestimate adherence, especially in secondary group where SIGN guidelines indicate patients should be taking drugs of multiple classes in the year following an MI. Therefore, to be truly adherent to their regimen, adherence to multiple drug-classes may be important.

Table 5.4 Assumptions made in defining adherence

5.3 Initiators vs non-initiators

As the TAM and PDC were calculated within each of the patient groups for the first year that an individual patient used a particular class of drug, it was important to identify new/ incident users of a drug. For the primary and treatment groups, it is possible that patients would have been prescribed these drugs and would have been eligible for inclusion within this group prior to 2009, before data for this study was available. Therefore, a minimum drug-free period (a minimum amount of time without any prescription of a given drug-class prior to initiation) had to be set to determine new-users of a drug-class vs continuing users. This is important as adherence declines overtime (see **Chapter 2** - systematic review) and so including continuing users in the year-one analysis could introduce bias. When deciding a minimum drug-free period, there must be a balance between using a shorter period, as many will be counted incident users even when it is not truly their first-use; and using a longer period, which may be more accurate, but which could reduce the size of the cohort and lead to loss of information. Here, any patient in the primary or treatment groups who had their first prescription in 2009 was excluded from the analysis.

In the secondary and secondary-treatment group, all patients were classed as incident users due to their change of status, leading to inclusion into the group. People who could have been eligible for inclusion in secondary group prior to PIS data availability were removed by dint of the exclusion criteria, stating that those with history of an MI hospitalisation in the ten-years prior would be excluded, and so all in this group can be classed as new secondary-users (refer back to Chapter 4 for more information on inclusion and exclusion criteria for the four patient groups). The same is true of the secondary-treatment group, as patients must have had an MI during the study period and move through the secondary group in order to be included.

5.4 Univariate analyses

Initial analyses was carried out to identify levels of adherence across different patient groups (primary, treatment, secondary, and secondary-with-treatment) and for the different factors (age, sex, SIMD, and comorbidity), giving rise to 16

univariate tables (see **Chapter 7**), plus one last table comparing overall adherence levels between each of the patient groups.

Within each group, patients were subdivided into the different factor levels (e.g. for sex, patients were divided into M and F) and into the 10 different drug-classes of interest (alpha-blockers, ACEi's, anti-anginals, etc). During the time in which a patient was eligible for inclusion in any given group, the date they were first prescribed a drug of any particular class was identified, and the treatment anniversary was calculated from this date plus 365 days. Therefore, any one individual patient could be represented numerous times within the data, depending on the number of different drug classes they were treated with while included in any one patient group, and depending on the number of groups they are included in over time; patients would have a different start date and anniversary date for each instance.

Adherence was expressed as the percentage of patients in the group who started treatment with a given class of drug and who did not leave the group before the end of the treatment anniversary period. P-values were calculated using chi-squared tests, or for groups where n<5, Fischer's exact test was used instead.

5.5 Multivariate analyses

At the annual ESPACOMP 2020 meeting round table discussion, a room of experts in adherence research agreed that 'persistence' is the preferred metric of adherence to study[198], over and above the two other metrics of initiation and implementation. It is for this reason, and because sensitivity analysis found little difference in outputs between the measures, that the TAM was used in the subsequent multivariate analysis and survival analysis.

For the multi-variate analysis, we also chose to refine focus to four key drug-classes for clarity of information: ACE-inhibitors, antiplatelets, beta-blocker and lipid-regulatory drugs. These are the most commonly used drug-classes across the data.

To perform multivariate analysis the R-package finalfit was used. The function glmmulti() was used to perform a multivariate analysis, namely a logistic binomial regression, for each risk-factor(sex, age etc.) within each patient group and drug-class. The models from this were then run through the function fit2df(), along with the R-Markdown function kable(), to visualise outputs as a table. Here, a logistic binomial regression was chosen as the outcome variable was binary (persistence yes or no), while the predictors were the risk factors of interest. Logistic regression is common statistical technique used to identify relationships between variables and is particularly useful as it allows inclusion of multiple variables in one model. Addition of each predictor variable was considered incrementally, meaning that first the analysis was performed including sex and age only as predictors, then sex, age, and SIMD-group, then sex age, and comorbidity status; and finally, sex, age, SIMD-group, and comorbidity status. Only the final models are shown in **Chapter 7**, presented as forest-plots, with additional models presented in **Appendix E**. For each model, the 'goodness-of-fit' was assessed by calculating the C-stat.

5.6 Outcomes of Non-persistence

To investigate the association between CVD drug adherence and clinical outcomes, Cox-proportional hazards models were performed for each patient subgroup (primary, treatment, secondary, secondary-treatment) and for each of the drug-classes (ACEi, antiplatelet, beta-blockers, lipid-regulatory) for all-cause mortality 5-years after the study-period (i.e. the first year of medication for which patient was determined persistent or nonpersistent). The function finalfit() from R-package finalfit was used to calculate Cox-proportional hazards. Results are presented to include univariate and multivariate hazard ratios for each of the risk factors included in the model.

Survival plots were constructed using the function surv_plot(), also from the finalfit package, in order to test an underlying assumption of Cox-proportional hazards, that the hazards remain proportional overtime (i.e. that survival curves do not cross). Schoenfeld residuals were also performed (included in **Appendix**).

5.7 Investigating Potential Confounding

Initial investigations of Cox-proportional hazards modelling produced some results that warranted further investigation (Results presented in **Chapter 8**). Inclusion of a 'drug-count' variable to account for cardiovascular polypharmacy was added to the analysis. All-cause mortality at 1-year after the study periods/ -year on from when patients were defined as persistent or non-persistent was also included to investigate the shorter-term association between adherence and outcomes, and to acknowledge that adherence levels may have changed over the time of follow-up. In two drug-classes, beta-blockers and antiplatelets, a comparison of persistence to individual drugs was performed. Additionally, to account for the potential that some patients were prescribed beta-blockers for anxiety rather than CVD, we repeated analysis in the primary prevention group excluding those who we could not confirm as having CVD. Using guidance from a clinician, we only included patients who had been prescribed a beta-blocker alongside CCBs or ACEi's into the new analysis.

5.8 Chapter Summary

This chapter has provided an overview of the measures used to define adherence and persistence, as well as the statistical analyses performed, and the further investigations conducted to identify possible sources of confounding.

6 Results: Summary Statistics

This chapter details descriptive statistics about the study data, including summaries of the four main patient subgroups, CVD drug prescribing during the study period, common causes of death, and common causes of hospitalisation.

6.1 Summary Statistics: Patient Cohort

Characteristic	Overall cohort (n = 1,901,693)
Sex, n (%)	
male	859,199 (45.2)
female	1,042,494 (54.8)
Age of first CVD prescription	
Mean (SD)	59.2 (16.7)
Median (IQR)	61 (24)
SIMD 2012 quintile, n (%)	
1 (most deprived)	426,487 (22.4)
2	408,350 (21.5)
3	379,976 (20.0)
4	355,432 (18.7)
5 (most affluent)	325,474 (17.1)
NA	5,974 (0.3)

Table 6.1a: Demographic summary statistics for full cohort

Table 6.1a shows demographic information for the full patient cohort, including those who were excluded due to failure to fit criteria for any one patient group. This provides contextual background information, and somewhat suprisingly indicates a greater representation of female compared to male patients (54.8% vs 45.2%). The average age is ~60years, and there is a slightly lower represntation of people from SIMD 5 (affluent), incrementally increasing with each lower SIMD grouping.

Characteristic	Primary Prevention (n= 1,659,566)	Treatment (n=260,516)	Secondary Prevention (n=25,283)	Secondary-Treatment (n=23,866)
Gender, n (%)				
male	717,082 (43.2)	132,484 (50.9)	16,224 (64.2)	15,383 (64.5)
female	942,484 (56.8)	128,032 (49.1)	9,059 (35.8)	8,483 (35.5)
Age on entry to sub-group				
Mean (SD)	58.7 (17)	67.9 (12.4)	66.9 (13.1)	67.4 (13)
Median (IQR)	60 (24)	69 (18)	67 (20)	68 (19)
SIMD 2012 quintile, n (%)				
1 (most deprived)	364,818 (22.0)	66,993 (25.7)	6,141 (24.3)	5,780 (24.2)
2	353,362 (21.3)	59,118 (22.7)	5,613 (22.2)	5,295 (22.2)
3	333,094 (20.1)	50,910 (19.5)	5,115 (20.2)	4,841 (20.3)
4	313,661 (18.9)	44,895 (17.2)	4,630 (18.3)	4,384 (18.4)
5 (most affluent)	289,161 (17.4)	38,015 (14.6)	3,755 (14.9)	3,540 (14.8)
NA	5,470 (0.3)	585 (0.2)	29 (0.1)	26 (0.1)

Table 6.1b: Demographic summary statistics for primary prevention, secondary prevention, treatment, and secondary-treatment sub-groups

There were differences in key characteristics across the four patient groups (**Table 6.1b**). The primary prevention group was over 6 times larger at 1,659,566 patients, compared to the next largest group, the treatment-group, at 260,526. The secondary prevention group and secondary-with-treatment group were much smaller at 25,283 and 23,866 patients respectively.

There were differences by sex between groups: in the primary group, 57% of patients are female, whereas in the other three groups, less than half of the patients are. In the treatment group there is a roughly 50:50 split, with 51%

male vs. 49% female, while in the secondary and secondary-treatment groups, ~64% are male vs just ~36% female.

Mean age of entry to each of the patient groups also differs substantially between the primary group and the three other patient groups. On average, age of entry to treatment, secondary, and secondary-treatment group is ~8 years older than that of the primary.

Across the four groups the distribution of SIMD is largely similar, with the most affluent quintile (SIMD 5) being least represented, making up 14.6-17.4% of each of the groups. The most deprived quintile (SIMD 1) is also the most represented SIMD across the four patient groups, making up between 22.0-25.7%.

6.2 Summary Statistics: Prescribing within patient groups

The larger number of patients in the primary prevention group compared with the other three patient groups likely contributes to the total combined patient years being much larger (**Table 6.2**), 6.5x more than the total patient years of the next largest group, the treatment group. However, when patient follow-up is considered as a median per patient (i.e. how long people tended to stay in the group) this gap narrows somewhat, with patients being in the primary group for 5 years and 5 months vs. 4 years and 10 months in the treatment group. In the secondary group, mean follow-up time is very limited, at just over 3 months. The main reason for patients leaving this group is prescription of GTN, so it is likely that this is due to patients moving to the secondary-treatment group. As well as this, patients who have suffered an MI are at a greater risk of subsequent MI, stroke, or death compared to the primary and treatment groups, possibly contributing to this also.

Polypharmacy is much higher in the treatment, secondary, and secondary-with-treatment groups compared to the primary, with over half of the patients in this group receiving more than five different drugs during their first year upon entering the study group, compared to just 19% of the primary group. Less than 1% of patients in the more severe CVD groups receive just one drug, compared to 18% of the primary group.

	Primary	Treatment	Secondary	Secondary-treatment
N prescriptions	122,634,677	37,237,317	792,976	2,916,797
N drugs	114	111	83	90
Total patient years	7,310,230	1,122,838	18,181	70,151
Median years per patient	5.38 (5.59)	4.86 (4.71)	0.28 (0.84)	2.64 (3.27)
Median no. of prescriptions per pat/ year	9.29	23.87	50	36.36
percentage of patients prescribed n different drugs during time in group				
n= 1	7.85	0.03	0.28	0.01
2	13.88	0.49	0.52	0.05
3	18.12	1.87	1.83	0.4
4	18.87	5.87	9.14	2.78
5+	41.27	91.73	88.22	96.76
percentage of patients prescribed n different drugs during first year in group				
n= 1	18.05	0.17	0.41	0.02
2	21.93	1.35	0.73	0.12
3	22.36	4.63	2.36	0.82
4	18.54	12.48	10.86	4.68
5+	19.11	81.37	85.63	94.36
Top 5 most common drugs (% of patients in group prescribed drug)	SIMVASTATIN (38.98%)	GLYCERYL TRINITRATE (100%)	ASPIRIN (82.07%)	GLYCERYL TRINITRATE (100%)
	ASPIRIN (31.40%)	ASPIRIN (74.37%)	BISOPROLOL FUMARATE (66.35%)	ASPIRIN (89.01%)
	AMLODIPINE (26.68%)	SIMVASTATIN (52.36%)	CLOPIDOGREL (63.10%)	BISOPROLOL FUMARATE (73.06%)
	BENDROFLUMETHIAZIDE (25.48%)	BISOPROLOL FUMARATE (37.63%)	RAMIPRIL (58.10%)	RAMIPRIL (58.48%)
	RAMIPRIL (18.34%)	ATORVASTATIN (36.21%)	SIMVASTATIN (43.27%)	ATORVASTATIN (52.07%)

Table 6.2: Summary statistics for primary prevention, secondary prevention, treatment, and secondary-treatment sub-groups

The drugs most commonly prescribed also differ between groups. As GTN is an inclusion criterion for the treatment and secondary-treatment groups, 100% of these patients have a prescription for it, though as an exclusion criterion from the primary and secondary prevention groups, it does not feature for these patients. Aspirin is also one of the most common drugs prescribed in all patient groups and is prescribed in over two-thirds of patients in the treatment, secondary, and secondary-treatment groups. Statins are also common (Table 6.2), with simvastatin and/or atorvastatin being in the five most common drugs for each of these groups. Ramipril is the most common ACEi drug represented across the four patient groups; amlodipine is the most common CCB; bendroflumethiazide is the most common diuretic drug; bisoprolol fumarate is the most common beta-blocker; and clopidogrel is the most common antiplatelet other than aspirin.

6.3 CVD Drug Prescribing

Overall, the most commonly prescribed CVD drug-class in the cohort was lipid-regulating drugs (BNF 2.12), while the least commonly prescribed was the anti-anginal drugs (BNF 2.6.3) – See **Figure 6.1**. Of the lipid-regulatory drugs, the most commonly prescribed therapeutic was simvastatin. During the years of the study period, prescribing of antiplatelets and diuretics showed a general decline (n= 3,015,090 patients prescribed with antiplatelets in 2010 vs. n= 2,649,786 in 2016; n= 2,980,971 patients prescribed with diuretics in 2010 vs. n= 2,421,416 in 2016), while prescribing of nitrates, alpha-blockers, and anti-anginal drugs showed a much more modest decline, remaining largely steady. Decline of use in these drug-classes, particularly for antiplatelets, may be due to the introduction of novel anticoagulant drugs; direct oral anticoagulants (DOACs). These drugs have an improved safety profile compared to older anticoagulants (e.g. warfarin). While adherence to these drugs has been studied previously with PIS data[199] it is a noted flaw of this study that this class has not been included.

Prescribing of lipid-regulating drugs, ACE-inhibitors, BBs, CCBs, and ARBs increased during the study period.

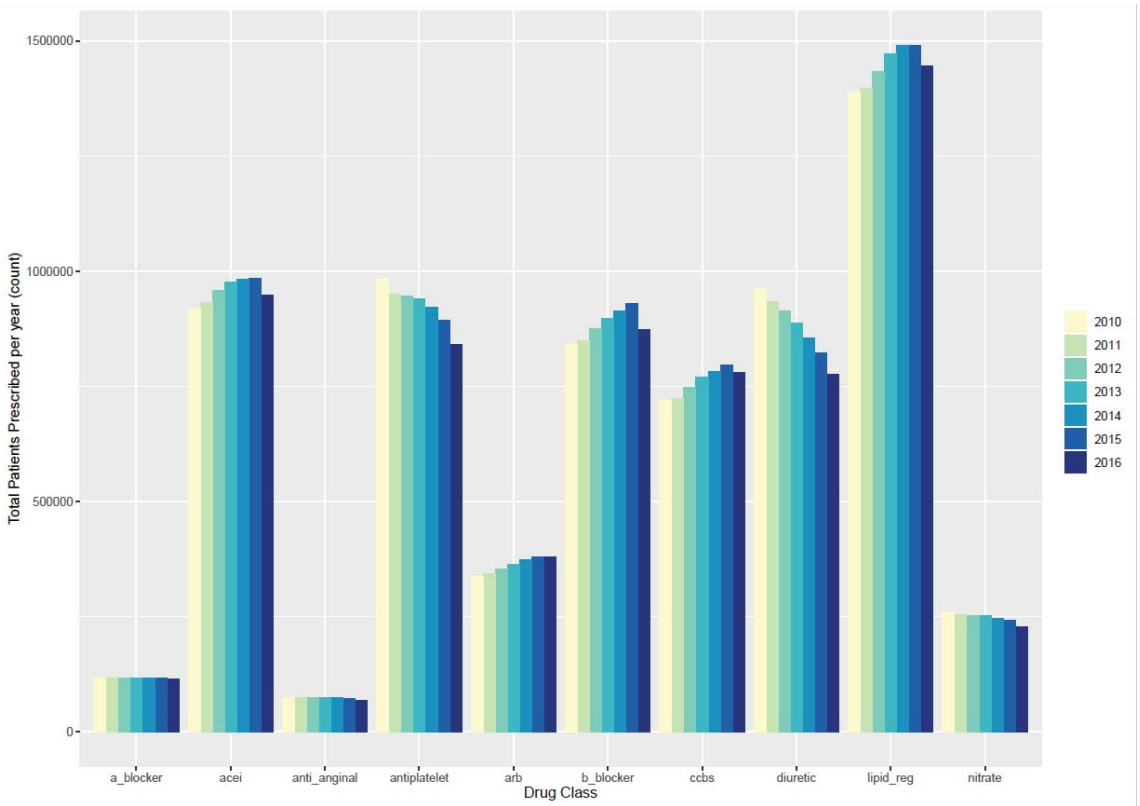

Figure 6.1: Frequency counts of CVD prescribing by drug-class between 2010-2016.

6.4 Deaths Data

All-cause mortality across the study period (**Figure 6.1**) showed a seasonal trend, with peaks during the Winter months and dips in the Summer. There was a slight increase in average mortality over the period from 2009 to 2017.

There were 338,140 deaths within the entire cohort during the years of the study (**Table 6.3**). The majority of these (63%) occurred within the largest primary group, while 19% occurred out-with inclusion within the patient groups. Deaths that occurred out-with inclusion in these groups could still be captured in follow-up (Cox analyses, Chapter 8), as inclusion in these groups was only essential for defining adherence (Chapter 7).

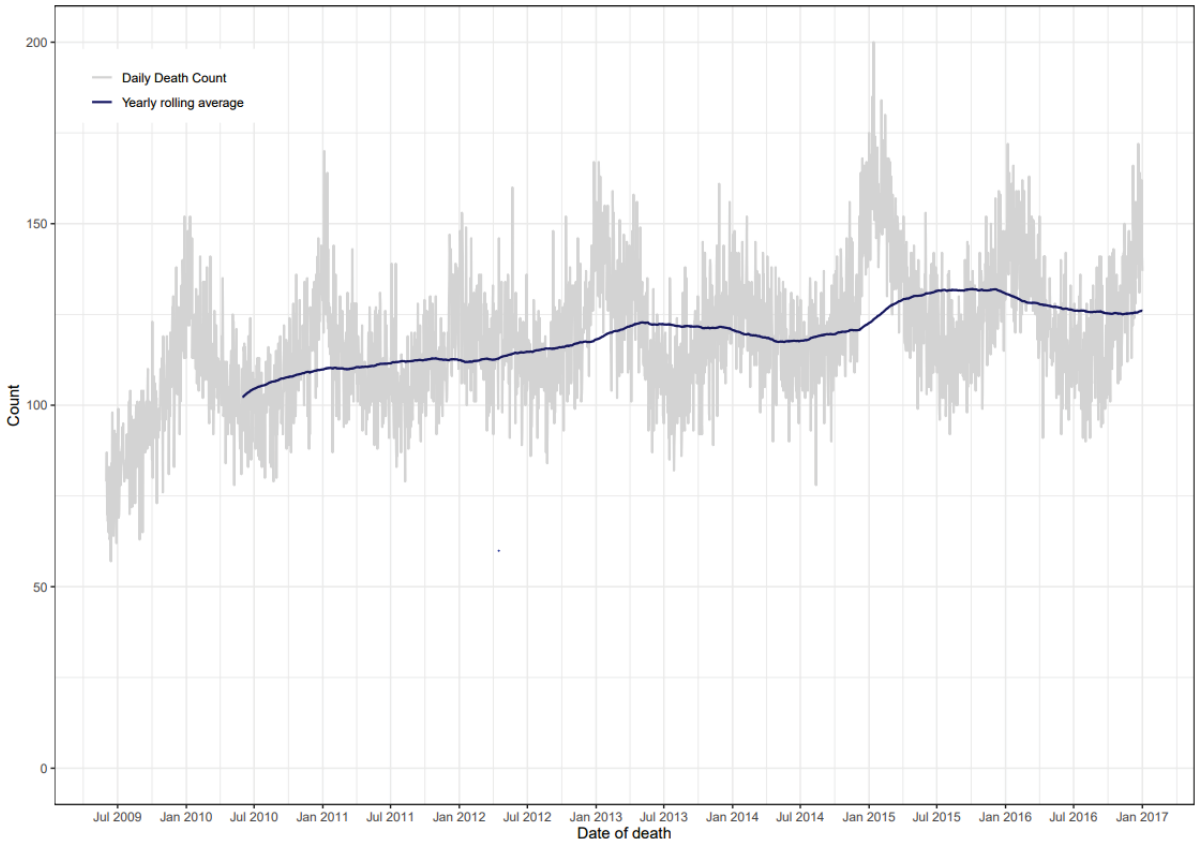

Figure 6.2.1: All-cause mortality across the full patient cohort, July 2009 – Jan 2017

All cause mortality	
Primary	214,686
Treatment	55,766
Secondary/ Secondary-treatment	4,062
Died outwith* inclusion in patient groups	63,626
Total	338,140

* Note may sill be included in cox analysis of 1- and 5-years follow-up (did not need to remain in group)

Table 6.3: All-cause mortalities during inclusion in each patient group

In order, the five most common causes of death in the cohort are AMI (ICD-10 code I219), lung cancer (C349), ischemic heart disease (I259), dementia (F03), and stroke (I64). It is notable that three of these causes are directly related to CVD. Dementia has also been associated with CVD in previous studies[9]. This is comparable with findings reported by ISD for the years of 2017 and 2018, which lists ischaemic heart diseases (ICD I20-I25) as the main cause of death reported in Scotland across all ages; followed by dementia and Alzheimer diseases (F01, F02, G30); trachea, bronchus and lung cancer (C33-C34); cerebrovascular disease (I60-I69); and chronic lower respiratory diseases (J40-J47)[200, 201].

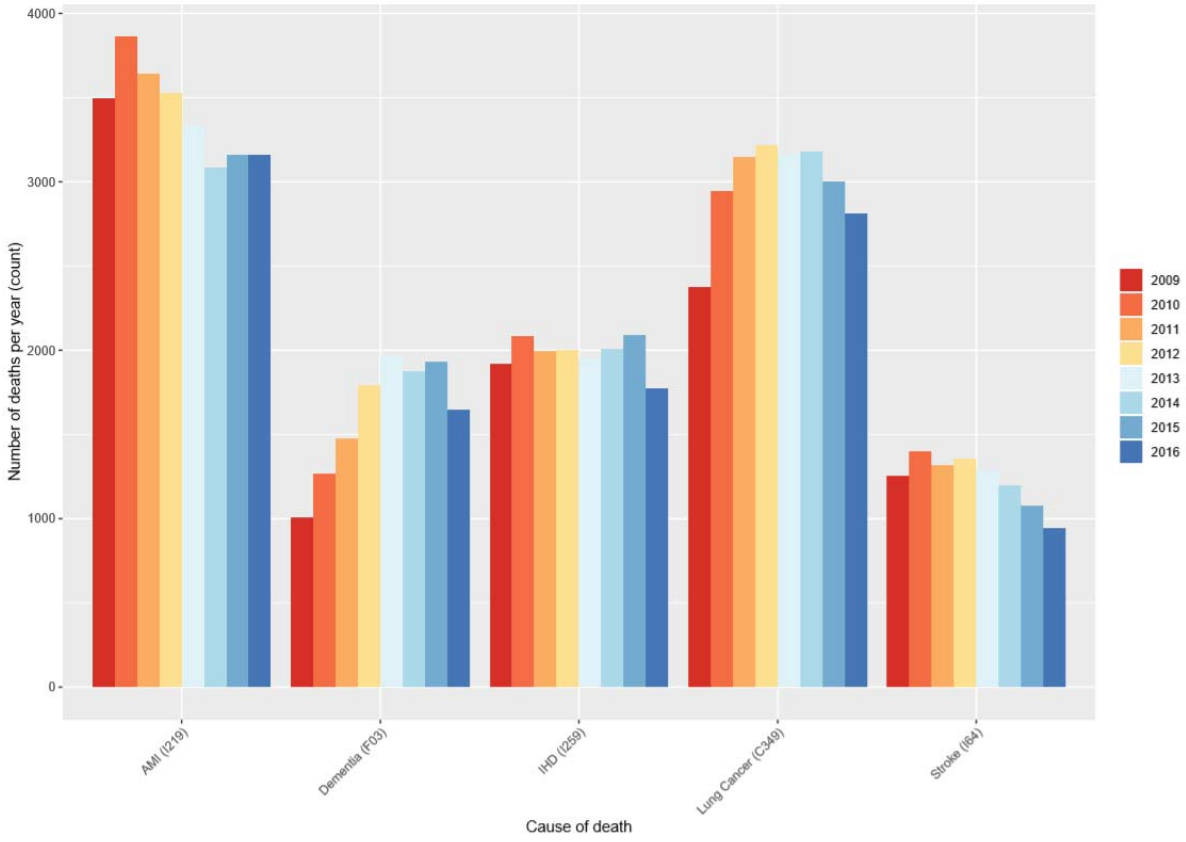

Figure 6.2.2: Main causes of death in patients prescribed any drug of interest between the years of 2009-2016

6.5 Common Causes of Hospitalisation

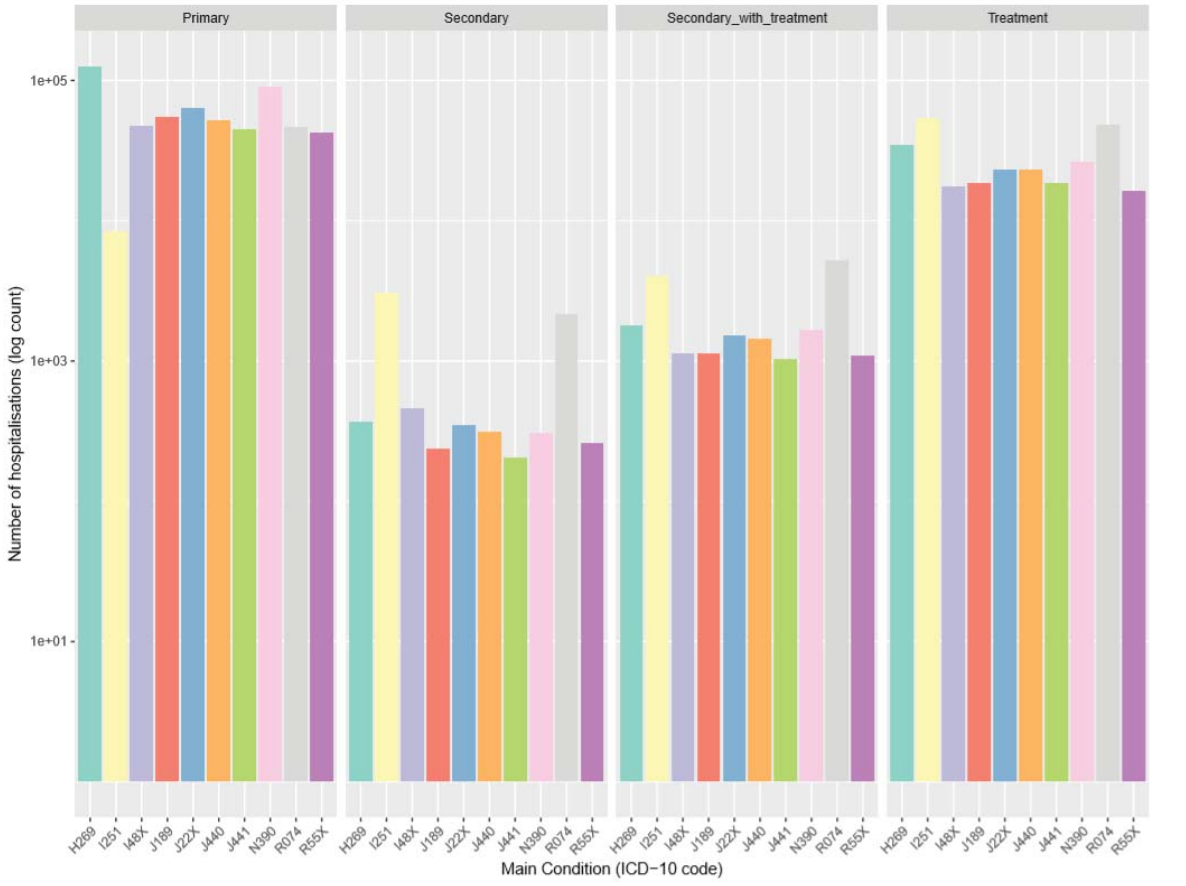

Figure 6.3: Counts of common hospitalisations by four main patient groups – legend (right) details relevant ICD-10 codes and indicates if CVD ♥ or related to CVD ♡.

Figure 6.3 shows the ten most common causes of hospitalisation, sorted by patient group. Notably, there are more hospitalisations overall in the primary and treatment groups, though these groups are far larger in comparison. Notably, the most common cause of hospitalisation differs in the primary group to the three groups with more severe CVD. The most common main diagnosis codes for hospitalisation in the primary groups are cataracts (unspecified, H269) and urinary tract infection (N390). In the other three patient groups, the most common ICD-10 codes relate to atherosclerotic heart disease (I251) and unspecified chest pain (R074). While unspecified chest pain cannot be directly attributed to CVD, it may be worth consideration in sensitivity analyses for studies using hospitalisation codes.

Other common causes of hospitalisation included atrial fibrillation and flutter (I48X), influenza and acute lower respiratory infections (J189, J22), chronic obstructive pulmonary disease (J440, J441), and syncope and collapse (R55x).

6.6 Discussion

Lipid-regulatory drugs are the most commonly prescribed class of CVD drug in our dataset, and simvastatin and atorvastatin both feature in the most commonly prescribed drugs across multiple patient groups (**Figure 6.1**).

The primary group is a much larger group than the other three, as would be expected in a country where prophylactic CVD prescribing is recommended. The ASSIGN guidelines for assessing risk of CVD suggest that the majority of adults aged 65 or over are likely to be above the threshold for intervention, and that anyone over the age of 40 could be considered for risk-assessment[13]. For this reason, along with the increase in CVD risk and disease severity with older age, it is also in line with our expectations to see the primary group having a considerably younger mean age overall.

On first glance, it may be unexpected that there is a slightly higher representation of female to male patients in the primary group, as male patients are known to be at higher risk of CVD[202, 203], and as the imbalance observed in this group exceeds the 51:49, female: male gender split observed across the background population, i.e. across the full population of Scotland[204]. However, as CVD disease severity increases in the treatment, secondary, and secondary-treatment groups, this is reversed. This indicates that, as expected, male patients do suffer from more severe CVD. The higher representation in the primary group may be due to different health-seeking behaviours in women compared to men, or perhaps could be related to menopause: hormone replacement therapy (HRT) is not appropriate for women with uncontrolled high blood pressure. Therefore, a higher proportion of women compared to men will have their blood pressure checked by a doctor in this period of their lives as there is a direct clinical need. In turn, a higher proportion of women with hypertension may be identified and prescribed CVD prophylaxis in this way.

While there are not large differences in SIMD across the groups, it is notable that the highest representation of affluent patients is in the primary group (17%) compared to the other three groups (14%). This may be due to increased access to healthcare and these patients therefore having greater opportunity to access preventative CVD care.

Increased CVD polypharmacy in the treatment, secondary, and secondary-with-treatment groups compared to the primary is in line with our expectations: standard care following an MI involves multiple different drugs, including dual-antiplatelet therapy, statins, beta-blockers, ACEi's [205]. As the inclusion criteria for the treatment group requires a prescription of GTN, these patients are likely to be on additional CVD prophylaxis to manage angina. For example, in the SIGN guidelines for acute coronary syndrome, patients with unstable angina are recommended ACEi therapy[205]. Comparatively, it is quite likely for primary prevention patients to be prescribed just one drug in the first instance, such as statins in response to having clinically high cholesterol levels.

6.7 Chapter Summary

This chapter presented basic baseline information about the patient groups, alongside other information about prescribing, hospitalisations, and deaths. Understanding the data and differences between patient groups is important to consider before deeper analysis and comparisons of adherence and outcomes, as these may relate to confounders that must be considered.

7 Results: Epidemiology of Adherence

This chapter concerns the epidemiology of adherence across the main patient subgroups of primary prevention, treatment, secondary prevention, and secondary prevention with treatment. Within these groups, levels of adherence are compared between men and women; age groups of below-55, 55-65, and above-65 years; socioeconomic groups derived from SIMD, of low (SIMD deciles 1-3), mid (SIMD deciles 4-7), and high (SIMD deciles 8-10), with low deciles being the most-deprived and high being the most affluent; and between those with comorbid diabetes, comorbid depression, both or neither. In each instance, adherence measures are derived separately for the ten drug classes: *diuretics (BNF 2.2), beta-blockers (BNF 2.4), alpha-blockers (BNF 2.5.4), ACE-inhibitors (BNF 2.5.5.1), angiotensin-2-receptor blockers (BNF 2.5.5.2), nitrates (BNF 2.6.1), calcium channel blockers (BNF 2.6.2), other anti-anginal agents (BNF 2.6.3), antiplatelet drugs (BNF2.9), and lipid-regulating drugs (BNF 2.12)*.

Adherence is measured in a combined method: the treatment anniversary model (**TAM**) indicates the percentage of patients found to be persistent at 12 months; the proportion of day's covered (**PDCp**) indicates the percentage of persistent patients (as identified with TAM) who received over 80% of their drug coverage in the first 12 months of treatment; and the proportion of days covered for the 'intention to treat' group (**PDCa**) is the proportion of all patients within the group who started treatment of a particular drug class, and received over 80% of their drug coverage in the first 12 months of treatment (i.e. includes patients who were persistent with TAM, as well as those who were not).

These three measures allow investigation of two key stages of adherence: implementation and persistence. PDCa is more comparable with the majority of adherence studies, which fail to use a mixed method of measuring adherence, while TAM and PDCp together give more insight, as it informs us whether people who are persistent are also adhering to their drugs.

7.1 Primary Prevention

7.1.1 Sex

		Male			Female			
Drug Class	Adherence measure	n start	n adhere	% adherent	n start	n adhere	% adherent	p-value
a-blockers	TAM	22,892	13,189	57.61	23,378	11,418	48.84	>0.0001
	PDCp	13,189	11,841	89.78	11,418	10,275	89.99	0.6004
	PDCa	22,892	12,875	56.24	23,378	11,222	48.00	>0.0001
ACEi	TAM	121,059	83,063	68.61	121,281	72,540	59.81	0
	PDCp	83,063	74,267	89.41	72,540	65,830	90.75	>0.0001
	PDCa	121,059	78,684	65.00	121,281	70,705	58.30	>0.0001
anti_anginal	TAM	1,188	646	54.38	1,584	749	47.29	0.0003
	PDCp	646	561	86.84	749	660	88.12	0.5237
	PDCa	1,188	592	49.83	1,584	722	45.58	0.0293
antiplatelets	TAM	70,493	43,990	62.40	84,404	42,467	50.31	0
	PDCp	43,990	34,944	79.44	42,467	34,595	81.46	>0.0001
	PDCa	70,493	36,817	52.23	84,404	36,661	43.44	>0.0001
ARB	TAM	40,144	29,277	72.93	50,565	35,872	70.94	>0.0001
	PDCp	29,277	26,594	90.84	35,872	32,969	91.91	>0.0001
	PDCa	40,144	28,192	70.23	50,565	34,967	69.15	0.00049
BBs	TAM	100,560	46,351	46.09	172,120	64,079	37.23	0
	PDCp	46,351	36,240	78.19	64,079	44,807	69.92	>0.0001
	PDCa	100,560	38,709	38.49	172,120	48,193	28.00	0
CCBs	TAM	114,002	76,497	67.10	135,334	74,477	55.03	0
	PDCp	76,497	67,185	87.83	74,477	64,874	87.11	>0.0001
	PDCa	114,002	71,148	62.41	135,334	69,480	51.34	0
diuretics	TAM	83,220	48,193	57.91	120,080	62,161	51.77	>0.0001
	PDCp	48,193	40,262	83.54	62,161	49,967	80.38	>0.0001
	PDCa	83,220	43,040	51.72	120,080	53,146	44.26	>0.0001
lipid-regs	TAM	134,042	96,405	71.92	129,719	88,561	68.27	>0.0001
	PDCp	96,405	76,544	79.40	88,561	72,217	81.54	>0.0001
	PDCa	134,042	79,774	59.51	129,719	75,697	58.35	>0.0001
nitrates	TAM	1,827	914	50.03	2,285	1,008	44.11	0.0002
	PDCp	914	797	87.20	1,008	882	87.50	0.8970
	PDCa	1,827	851	46.58	2,285	940	41.14	0.0005
Range across all classes		***Min***		38.49			28.00	
		Max		90.84			91.91	

Table 7.1.1 Adherence by sex in the primary prevention group at one year

Overall, male patients have a higher level of adherence compared with female patients in the primary prevention group (**Table 7.1.1**). Across the ten drug-

classes and three different measures of adherence used, adherence ranged from 38-91% for men and 28-92% for women. Looking at all combinations of drug and adherence indicator, adherence was only higher for women in 23% of cases, all of which were measured by PDCp. This indicates that while women may be less likely to persist with medication-taking, those who do persist display implementation to a higher level compared to male patients. It is also notable that for both male and female patients, PDCp is generally much higher than the other two measures. The median PDCp across all ten drug-classes is 87.02 for men while it is 87.30 for women. This compares to a median TAM of 60.16 for males and 51.04 for females; and a PDCa of 54.24 for males and 46.79 for females. This suggests that in persistent patients, implementation of CVD drug regimens is generally good, and there is little sex difference in implementation. However, when persistence is considered, stark differences between male and female sex emerge.

Persistence (TAM) is highest for ARBs, lipid-regulatory drugs, and ACEi's in both male and female patients. Implementation across all (i.e. including persistent and non-persistent) patients (PDCa) is highest in these same drug-classes for females, though differs for male patients: ARBs, ACEi's, and CCBs. Compared with other drug classes, adherence to BBs is considerably lower – with only 37% of all female patients and 46% of all male patients persisting at 1-year. Nitrates and antianginals were the two drug-classes with the next-lowest persistence rates in both male and female patients: TAM of 50% and 54% respectively for males, and 44% and 47% respectively for females.

7.1.2 Age

		Below 55			55 - 65				Above 65			
Drug Class	Adherence measure	n start	n adhere	% adherent	n start	n adhere	% adherent	p-value	n start	n adhere	% adherent	p-value
a-blockers	TAM	11,850	6,238	52.64	13,636	7,597	55.71	> 0.0001	20,784	10,772	51.83	0.1608
	PDCp	6,238	5,306	85.06	7,597	6,963	91.65	> 0.0001	10,772	9,847	91.41	> 0.0001
	PDCa	11,850	5,837	49.26	13,636	7,599	55.73	> 0.0001	20,784	10,661	51.29	0.0004
ACEi	TAM	97,417	64,063	65.76	71,105	46,317	65.14	0.0080	73,818	45,223	61.26	> 0.0001
	PDCp	64,063	55,492	86.62	46,317	42,514	91.79	> 0.0001	45,223	42,091	93.07	> 0.0001
	PDCa	97,417	58,990	60.55	71,105	45,330	63.75	> 0.0001	73,818	45,069	61.05	0.0363
anti_anginal	TAM	850	385	45.29	701	342	48.79	0.1865	1,221	668	54.71	> 0.0001
	PDCp	385	325	84.42	342	301	88.01	0.1964	668	595	89.07	0.0362
	PDCa	850	351	41.29	701	321	45.79	0.0841	1,221	642	52.58	> 0.0001
antiplatelets	TAM	43,707	16,648	38.09	42,931	25,753	59.99	> 0.0001	68,259	44,056	64.54	0
	PDCp	16,648	12,224	73.43	25,753	20,244	78.61	> 0.0001	44,056	37,071	84.15	> 0.0001
	PDCa	43,707	13,096	29.96	42,931	21,410	49.87	> 0.0001	68,259	38,972	57.09	0
ARB	TAM	31,259	22,205	71.04	28,612	20,960	73.26	> 0.0001	30,838	21,984	71.29	0.4919
	PDCp	22,205	19,495	87.80	20,960	19,480	92.94	> 0.0001	21,984	20,588	93.65	> 0.0001
	PDCa	31,259	20,734	66.33	28,612	20,658	72.20	> 0.0001	30,838	21,767	70.58	> 0.0001
BBs	TAM	170,852	53,282	31.19	47,350	23,709	50.07	0	54,478	33,439	61.38	0
	PDCp	53,282	31,220	58.59	23,709	19,591	82.63	0	33,439	30,236	90.42	0
	PDCa	170,852	33,814	19.79	47,350	20,958	44.26	0	54,478	32,130	58.98	0
CCBs	TAM	75,619	43,971	58.15	81,077	51,839	63.94	> 0.0001	92,640	55,164	59.55	> 0.0001
	PDCp	43,971	36,191	82.31	51,839	46,352	89.42	> 0.0001	55,164	49,516	89.76	> 0.0001
	PDCa	75,619	38,804	51.32	81,077	49,245	60.74	0	92,640	52,579	56.76	> 0.0001
diuretics	TAM	57,033	28,181	49.41	55,897	31,671	56.66	> 0.0001	90,370	50,502	55.88	> 0.0001
	PDCp	28,181	21,805	77.37	31,671	26,547	83.82	> 0.0001	50,502	41,877	82.92	> 0.0001
	PDCa	57,033	23,417	41.06	55,897	28,276	50.59	> 0.0001	90,370	44,493	49.23	> 0.0001
lipid-regs	TAM	80,340	53,369	66.43	92,044	66,232	71.96	> 0.0001	91,377	65,365	71.53	> 0.0001
	PDCp	53,369	39,591	74.18	66,232	53,781	81.20	> 0.0001	65,365	55,389	84.74	0
	PDCa	80,340	41,559	51.73	92,044	56,138	60.99	0	91,377	57,774	63.23	0
nitrates	TAM	540	166	30.74	935	365	39.04	0.0017	2,637	1,391	52.75	> 0.0001
	PDCp	166	131	78.92	365	297	81.37	0.5860	1,391	1,251	89.94	> 0.0001
	PDCa	540	143	26.48	935	326	34.87	0.0011	2,637	1,322	50.13	> 0.0001
Range across all classes		***Min***		19.79			34.87				49.23	
		Max		87.80			92.94				93.65	

Table 7.1.2 Adherence by age in the primary prevention group at one year

Adherence tends to be highest in the older age group (above 65-years) and lowest in the youngest age group (below 55-years) in the first year of CVD primary prevention (**Table 7.1.2**). Across the ten drug-classes and three adherence measures, adherence tends to increase with age: ranging from 20-88% in the below-55-year group, to 35-93% in the mid-group, to 49-94% in the oldest group. This is fairly consistent, as, when compared across the individual drug-classes and adherence measures, all but two of the lowest adherence scores are

found in the youngest age group, and the highest adherence scores are found most often in the oldest age group. There are two drug-classes where adherence is highest in the middle (55-65-year) group, consistent across TAM, PDCp, and PDCa: alpha-blockers and diuretics; and four drug-classes where adherence is highest in the over 65-year group, consistent across all three measures: antianginals, antiplatelets, BBs, and nitrates.

The drug-classes found to have highest or lowest persistence levels vary by age-group; however, across all age-groups, persistence was high for ARBs, lipid-regulatory drugs, and ACEi's. Persistence to BBs varied by age: in the youngest age group, this is the class to which patients were least persistent, whereas in the over-65's, this is one the drug-classes to which people were most persistent. This indicates that age may be associated with adherence in different ways, depending on the drug-class studied.

Age may also partially explain the low adherence levels observed for BBs, as there is a higher proportion of BB prescriptions in younger patients. 30% of the prescriptions in the below-55-year group are for BBs (170,852 out of a total of 569,467 prescriptions across all drug-classes), compared to approximately 10% representation in the 55-65 and over-65 years age groups.

7.1.3 Deprivation

		High (SIMD 8-10)			Mid (SIMD 4-7)				Low (SIMD 1-3)			
Drug Class	Adherence measure	n start	n adhere	% adherent	n start	n adhere	% adherent	p-value	n start	n adhere	% adherent	p-value
a-blockers	TAM	13,026	6,702	51.45	19,557	10,407	53.21	0.0019	13,635	7,477	54.84	> 0.0001
	PDCp	6,702	6,127	91.42	10,407	9,376	90.09	0.0040	7,477	6,595	88.20	> 0.0001
	PDCa	13,026	6,740	51.74	19,557	10,215	52.23	0.3927	13,635	7,122	52.23	0.4300
ACEi	TAM	67,630	42,723	63.17	99,371	63,781	64.18	> 0.0001	74,838	48,821	65.24	> 0.0001
	PDCp	42,723	39,343	92.09	63,781	57,493	90.14	> 0.0001	48,821	43,019	88.12	> 0.0001
	PDCa	67,630	42,145	62.32	99,371	61,321	61.71	0.0122	74,838	45,665	61.02	> 0.0001
anti_anginal	TAM	682	315	46.19	1,144	590	51.57	0.0294	942	488	51.80	0.0289
	PDCp	315	274	86.98	590	521	88.31	0.6365	488	424	86.89	1
	PDCa	682	302	44.28	1,144	557	48.69	0.0756	942	453	48.09	0.1421
antiplatelets	TAM	41,247	23,020	55.81	62,623	35,181	56.18	0.2437	50,596	28,068	55.47	0.3121
	PDCp	23,020	18,721	81.32	35,181	28,315	80.48	0.0121	28,068	22,354	79.64	> 0.0001
	PDCa	41,247	19,792	47.98	62,623	29,948	47.82	0.6148	50,596	23,580	46.60	> 0.0001
ARB	TAM	28,109	20,324	72.30	38,339	27,600	71.99	0.3759	24,040	17,098	71.12	0.0029
	PDCp	20,324	18,819	92.59	27,600	25,190	91.27	> 0.0001	17,098	15,440	90.30	> 0.0001
	PDCa	28,109	20,016	71.21	38,339	26,700	69.64	> 0.0001	24,040	16,317	67.87	> 0.0001
BBs	TAM	68,582	28,278	41.23	107,069	44,307	41.38	0.5385	96,120	37,619	39.14	> 0.0001
	PDCp	28,278	21,865	77.32	44,307	33,386	75.35	> 0.0001	37,619	25,642	68.16	> 0.0001
	PDCa	68,582	23,602	34.41	107,069	35,812	33.45	> 0.0001	96,120	27,321	28.42	> 0.0001
CCBs	TAM	72,424	43,571	60.16	102,398	61,629	60.19	0.9210	73,975	45,505	61.51	> 0.0001
	PDCp	43,571	38,987	89.48	61,629	53,974	87.58	> 0.0001	45,505	38,871	85.42	> 0.0001
	PDCa	72,424	41,624	57.47	102,398	57,403	56.06	> 0.0001	73,975	41,359	55.91	> 0.0001
diuretics	TAM	53,530	29,535	55.17	84,297	46,307	54.93	0.3827	65,029	34,308	52.76	> 0.0001
	PDCp	29,535	25,082	84.92	46,307	37,822	81.68	> 0.0001	34,308	27,174	79.21	> 0.0001
	PDCa	53,530	26,795	50.06	84,297	40,255	47.75	> 0.0001	65,029	28,975	44.56	> 0.0001
lipid-regs	TAM	69,177	48,880	70.66	105,818	73,878	69.82	0.0002	88,154	61,836	70.15	0.0271
	PDCp	48,880	40,435	82.72	73,878	59,625	80.71	> 0.0001	61,836	48,402	78.27	> 0.0001
	PDCa	69,177	42,325	61.18	105,818	62,324	58.90	> 0.0001	88,154	50,510	57.30	> 0.0001
nitrates	TAM	995	448	45.03	1,880	891	47.39	0.2413	1,226	580	47.31	0.3028
	PDCp	448	403	89.96	891	784	87.99	0.3281	580	490	84.48	0.0130
	PDCa	995	427	42.91	1,880	844	44.89	0.3286	1,226	518	42.25	0.7862
Range across all classes	***Min***			34.41			33.45				28.42	
	Max			92.59			91.27				90.30	

Table 7.1.3 Adherence by SIMD in the primary prevention group at one year

Across the three SIMD categories, adherence is lowest in the most-deprived SIMD groups, as it is found to be lowest in this group in 23 out of the 30 measures studied. This is consistent for TAM, PDCp, and PDCa in four drug-classes: antiplatelets, ARBs, BBs, and diuretics. The reverse also holds true, in that the highest adherence levels tend to be observed in the more affluent (high) SIMD

groups, in 19 of the 30 measures. This was consistent in three drug-classes: ARBs, diuretics, and lipid-regulating drugs.

Across all ten drug-classes and all 3 adherence measures, adherence for the low-SIMD group was 28-90%, rising to 33-91% for the mid-SIMD group, and again to 44-93% in the most affluent high-SIMD group.

The drug-classes with the highest and lowest persistence rates are identical across the three different SIMD groups. The highest levels of persistence are observed in ARBs (72, 72, and 71% respectively across high, mid, and low-SIMD), lipid-regulatory drugs (71, 70, 70%), and ACEi's (63, 64, 65%), while the lowest persistence rates are consistently observed across BBs (41, 41, 39%), nitrates (45, 47, 47%), and antianginals (46, 51, 51%). This suggests that, unlike age, deprivation does not appear to have different associations with adherence, dependent on the drug-class studied.

7.1.4 Comorbidity

Drug Class	Adherence measure	Neither comorbidty			Diabetes			Depression			Both		
		n Patients	% adherent		n Patients	% adherent	p-value	n Patients	% adherent	p-value	n Patients	% adherent	p-value
a-blockers	TAM	30,688	52.21		6,309	60.94	> 0.0001	5,206	49.15	> 0.0001	1,067	58.95	> 0.0001
	PDCp	16,021	90.30		3,845	90.35	0.9478	2,559	86.44	> 0.0001	629	90.62	0.84361
	PDCa	30,688	51.48		6,309	59.11	> 0.0001	5,206	46.41	> 0.0001	1,067	57.36	0.00018
ACEi	TAM	170,480	64.14		22,427	68.49	> 0.0001	30,486	61.52	> 0.0001	4,795	66.51	0.0008
	PDCp	109,351	90.54		15,360	87.47	> 0.0001	18,755	89.34	> 0.0001	3,189	86.48	> 0.0001
	PDCa	170,480	61.87		22,427	63.41	> 0.0001	30,486	59.21	> 0.0001	4,795	61.29	0.42884
anti_anginal	TAM	1,632	48.96		295	57.29	0.0102	510	50.39	0.6068	88	47.73	0.90799
	PDCp	799	85.61		169	89.35	0.2457	257	91.05	0.0319	42	85-90	1
	PDCa	1,632	45.28		295	52.54	0.0252	510	48.43	0.2322	88	48.86	0.5841
antiplatelets	TAM	107,493	55.73		11,603	55.85	0.8193	23,064	55.06	0.0633	2,663	57.15	0.15005
	PDCp	59,908	80.38		6,480	78.64	0.0009	12,699	81.49	0.0045	1,522	79.11	0.22743
	PDCa	107,493	47.27		11,603	46.59	0.1677	23,064	47.67	0.2697	2,663	47.92	0.5217
ARB	TAM	64,450	72.22		8,673	72.89	0.1922	10,433	69.63	> 0.0001	1,695	74.28	0.06558
	PDCp	46,545	91.78		6,322	90.51	0.0007	7,264	89.81	> 0.0001	1,259	91.18	0.47909
	PDCa	64,450	70.27		8,673	69.76	0.3357	10,433	66.57	> 0.0001	1,695	70.97	0.5476
BBs	TAM	156,675	42.64		10,358	56.88	> 0.0001	85,931	34.14	0.0000	3,442	47.56	> 0.0001
	PDCp	66,806	77.96		5,892	87.54	> 0.0001	29,333	59.02	0.0000	1,637	78.74	0.47188
	PDCa	156,675	35.50		10,358	53.56	> 0.0001	85,931	21.82	0.0000	3,442	40.15	> 0.0001
CCBs	TAM	181,376	60.57		18,184	66.20	> 0.0001	31,114	58.61	> 0.0001	3,371	63.42	0.00083
	PDCp	109,856	87.72		12,038	89.18	> 0.0001	18,235	85.65	> 0.0001	2,138	86.95	0.29814
	PDCa	181,376	56.49		18,184	62.69	> 0.0001	31,114	53.73	> 0.0001	3,371	59.03	0.00331
diuretics	TAM	137,943	55.72		15,817	57.27	0.0002	31,485	48.49	> 0.0001	3,627	52.69	0.00031
	PDCp	76,857	82.88		9,059	82.17	0.0949	15,267	77.61	> 0.0001	1,911	77.29	> 0.0001
	PDCa	137,943	49.16		15,817	50.18	0.0157	31,485	40.36	> 0.0001	3,627	43.26	> 0.0001
lipid-regs	TAM	175,192	69.57		26,572	74.83	> 0.0001	39,102	68.62	0.0002	6,266	76.46	> 0.0001
	PDCp	121,876	81.04		19,884	76.57	> 0.0001	26,831	80.29	0.0049	4,791	76.98	> 0.0001
	PDCa	175,192	58.94		26,572	59.45	0.1179	39,102	57.82	> 0.0001	6,266	61.30	0.0002
nitrates	TAM	2,474	44.10		551	55.72	> 0.0001	620	46.29	0.3489	140	56.43	0.00566
	PDCp	1,091	86.89		307	88.27	0.5871	287	87.11	1.0000	79	87.34	1
	PDCa	2,474	40.95		551	52.45	> 0.0001	620	43.23	0.3246	140	52.14	0.01149
Range across all classes		***Min***	***35.50***			***46.59***			***21.82***			***40.15***	
		Max	***91.78***			***90.51***			***91.05***			***91.18***	

Table 7.1.4 Adherence by comorbidity in the primary prevention group at one year
percentages are rounded where the number of nonadherent people is < 10 to protect anonymity (while the number of nonadherent patients is not provided, it could otherwise be inferred from percentages)

When considering adherence rates by comorbidity status in the primary prevention group, the trend toward increased adherence in diabetic patients and reduced adherence in patients with depression (as observed in literature

review), tends to hold (**Table 7.1.4**). Across all ten drug-classes and all three measures, adherence ranged from 47-90% for patients with diabetes. Patients with depression as a comorbidity ranged from a minimum of 22-91%, though the minimum end of this range relates to beta-blockers and is somewhat of an outlier.

Adherence to CVD medication is found to be highest in patients with diabetes for over half (57%) of the individual measures. This is consistent across TAM, PDCp, and PDCa in two different drug-classes: BBs and CCBs.

Conversely, CVD adherence is found to be lowest in primary prevention patients who are concurrently being treated with anti-depressant drugs, compared to those with diabetes, diabetes and depression, or those with neither comorbidity. This was found to be the case across 18 of the 30 measures presented, and was consistent for TAM, PDCp, and PDCa for four drug classes: alpha-blockers, ARBs, BBs, and CCBs.

The group of patients who were medicated for both diabetes and depression were found to be slightly more adherent overall when compared to those who had no evidence of either condition (found to be the most adherent of the four groups in 23% of instances vs 13%). Neither of these groups were associated with poorer adherence, with the exception of adherence to nitrates: this was lowest across all three adherence measures in the patients who had neither comorbidity.

Whether diabetes comorbidity has a positive effect on medication taking behaviour (e.g. patients are ‘used-to’ daily medication taking behaviour) or if there is a skew toward older aged patients in this group, particularly those with type-2 diabetes, cannot be discerned from this table alone. Similarly, lower adherence in the group of patients with depression as a comorbidity could to due symptoms of this condition (low mood, hopelessness, little motivation), or due to younger average age. The potential confounding effect of age will be an important consideration in the multivariate analyses.

7.2 Treatment

7.2.1 Sex

	Male				Female			
Drug Class	Adherence measure	n start	n adhere	% adherent	n start	n adhere	% adherent	p-value
a-blockers	TAM	6,333	3,927	62.01	5,973	3,345	56.00	> 0.0001
	PDCp	3,927	3,561	90.68	3,345	2,966	88.67	0.0055
	PDCa	6,333	3,824	60.38	5,973	3,225	53.99	> 0.0001
ACEi	TAM	41,482	32,002	77.15	31,554	22,429	71.08	> 0.0001
	PDCp	32,002	29,475	92.10	22,429	20,622	91.94	0.5072
	PDCa	41,482	30,957	74.63	31,554	21,898	69.40	> 0.0001
anti_anginal	TAM	15,080	9,481	62.87	12,875	7,997	62.11	0.1957
	PDCp	9,481	8,501	89.66	7,997	7,084	88.58	0.0235
	PDCa	15,080	9,174	60.84	12,875	7,592	58.97	0.0015
antiplatelets	TAM	63,328	48,320	76.30	56,533	39,586	70.02	> 0.0001
	PDCp	48,320	41,965	86.85	39,586	33,428	84.44	> 0.0001
	PDCa	63,328	43,899	69.32	56,533	35,103	62.09	> 0.0001
ARB	TAM	14,268	10,953	76.77	15,951	12,216	76.58	0.7195
	PDCp	10,953	10,211	93.23	12,216	11,353	92.94	0.3996
	PDCa	14,268	10,747	75.32	15,951	11,986	75.14	0.7278
BBs	TAM	52,609	40,105	76.23	45,519	32,109	70.54	> 0.0001
	PDCp	40,105	36,586	91.23	32,109	29,179	90.87	0.1033
	PDCa	52,609	38,181	72.58	45,519	30,575	67.17	> 0.0001
CCBs	TAM	35,719	25,163	70.45	36,285	23,431	64.57	> 0.0001
	PDCp	25,163	22,748	90.40	23,431	20,759	88.60	> 0.0001
	PDCa	35,719	23,990	67.16	36,285	22,043	60.75	> 0.0001
diuretics	TAM	32,984	21,742	65.92	41,489	27,898	67.24	0.0001
	PDCp	21,742	18,848	86.69	27,898	23,621	84.67	> 0.0001
	PDCa	32,984	19,996	60.62	41,489	24,933	60.10	0.1456
lipid-regs	TAM	64,888	53,428	82.34	56,204	43,404	77.23	> 0.0001
	PDCp	53,428	46,264	86.59	43,404	36,904	85.02	> 0.0001
	PDCa	64,888	47,886	73.80	56,204	38,461	68.43	> 0.0001
nitrates	TAM	24,088	14,117	58.61	23,057	13,884	60.22	0.0004
	PDCp	14,117	12,285	87.02	13,884	12,103	87.17	0.7223
	PDCa	24,088	13,033	54.11	23,057	12,781	55.43	0.0039
Range across all classes		***Min***		54.11			53.99	
		Max		93.23			92.94	

Table 7.2.1 Adherence by sex in the treatment group at one year

Like the primary prevention patients, adherence to CVD medications is consistently greater in male patients compared to female patients for the treatment group (**Table 7.2.1**). On a drug-by-drug basis, males generally tend to

be more adherent, though across the ten drug-classes and three different measures of adherence used, both range from 54-93%. Adherence levels in the treatment group are notably higher than adherence for both sexes in the primary prevention group. There is an exception, as adherence to nitrates is higher for females compared to males, across TAM, PDCp, and PDCa.

Persistence is greatest for lipid-regulatory drugs, at 82% for male and 77% for female patients. For male patients, there is a marked difference between this and the drug to which persistence is next-highest: 77% of male patients persist with ACEi's. For female patients, there is less than a 1% gap to the next drug-class, as 76.58% adhere to ARBs. Male patients are least persistent to nitrates (59%), α-blockers (62%) and antianginals (63%), while female patients are least persistent to the same three classes of drug: alpha-blockers (56%), nitrates (60%), and antianginals (62%).

Unlike the primary group, adherence to BBs is generally good.

Again, PDCp is the adherence measure which scores highest, and shows the least variation between drug-classes. It ranges from 86 to 93% for males and from 84 to 93% for females. TAM ranges from 58 to 82% for males and 56 to 77% for females, while PDCa ranges from 54 to 75% and 53 to 75% respectively. This indicates that, for either sex, patients who are persistent tend to have good implementation, whereas persistence is more variable.

7.2.2 Age

		Below 55			55 - 65				Above 65			
Drug Class	Adherence measure	n start	n adhere	% adherent	n start	n adhere	% adherent	p-value	n start	n adhere	% adherent	p-value
a-blockers	TAM	1,171	696	59.44	2,888	1,718	59.49	1.0000	8,247	4,858	58.91	0.7540
	PDCp	696	552	79.31	1,718	1,511	87.95	> 0.0001	4,858	4,464	91.89	> 0.0001
	PDCa	1,171	597	50.98	2,888	1,625	56.27	0.0024	8,247	4,827	58.53	> 0.0001
ACEi	TAM	10,329	7,558	73.17	19,833	14,895	75.10	0.0003	42,874	31,978	74.59	0.0033
	PDCp	7,558	6,512	86.16	14,895	13,645	91.61	> 0.0001	31,978	29,940	93.63	> 0.0001
	PDCa	10,329	6,877	66.58	19,833	14,351	72.36	> 0.0001	42,874	31,627	73.77	> 0.0001
anti_anginal	TAM	3,318	1,818	54.79	7,631	4,481	58.72	0.0001	17,006	11,179	65.74	> 0.0001
	PDCp	1,818	1,492	82.07	4,481	3,924	87.57	> 0.0001	11,179	10,169	90.97	> 0.0001
	PDCa	3,318	1,615	48.67	7,631	4,245	55.63	> 0.0001	17,006	10,906	64.13	> 0.0001
antiplatelets	TAM	17,198	10,116	58.82	32,670	23,106	70.73	> 0.0001	69,993	54,684	78.13	> 0.0001
	PDCp	10,116	8,080	79.87	23,106	19,454	84.19	> 0.0001	54,684	47,859	87.52	> 0.0001
	PDCa	17,198	8,567	49.81	32,670	20,430	62.53	> 0.0001	69,993	50,005	71.44	> 0.0001
ARB	TAM	3,024	2,195	72.59	7,699	5,861	76.13	0.0001	19,496	15,113	77.52	> 0.0001
	PDCp	2,195	1,883	85.79	5,861	5,380	91.79	> 0.0001	15,113	14,301	94.63	> 0.0001
	PDCa	3,024	2,004	66.27	7,699	5,685	73.84	> 0.0001	19,496	15,044	77.16	> 0.0001
BBs	TAM	14,737	9,005	61.10	26,583	19,131	71.97	> 0.0001	56,808	44,078	77.59	> 0.0001
	PDCp	9,005	7,406	82.24	19,131	17,183	89.82	> 0.0001	44,078	41,176	93.42	> 0.0001
	PDCa	14,737	7,825	53.10	26,583	17,978	67.63	> 0.0001	56,808	42,953	75.61	> 0.0001
CCBs	TAM	8,719	5,539	63.53	19,117	12,784	66.87	> 0.0001	44,168	30,271	68.54	> 0.0001
	PDCp	5,539	4,531	81.80	12,784	11,313	88.49	> 0.0001	30,271	27,663	91.38	> 0.0001
	PDCa	8,719	4,838	55.49	19,117	11,970	62.61	> 0.0001	44,168	29,225	66.17	> 0.0001
diuretics	TAM	6,262	3,658	58.42	15,930	10,241	64.29	> 0.0001	52,281	35,741	68.36	> 0.0001
	PDCp	3,658	2,881	78.76	10,241	8,702	84.97	> 0.0001	35,741	30,886	86.42	> 0.0001
	PDCa	6,262	3,102	49.54	15,930	9,213	57.83	> 0.0001	52,281	32,614	62.38	> 0.0001
lipid-regs	TAM	16,811	12,122	72.11	33,779	26,751	79.19	> 0.0001	70,502	57,959	82.21	> 0.0001
	PDCp	12,122	9,418	77.69	26,751	22,584	84.42	> 0.0001	57,959	51,166	88.28	> 0.0001
	PDCa	16,811	9,870	58.71	33,779	23,418	69.33	> 0.0001	70,502	53,059	75.26	> 0.0001
nitrates	TAM	5,963	2,479	41.57	11,630	6,087	52.34	> 0.0001	29,552	19,435	65.77	> 0.0001
	PDCp	2,479	1,920	77.45	6,087	5,095	83.70	> 0.0001	19,435	17,373	89.39	> 0.0001
	PDCa	5,963	2,082	34.92	11,630	5,433	46.72	> 0.0001	29,552	18,299	61.92	> 0.0001
Range across all classes		***Min***		34.92			46.72				58.53	
		Max		86.16			91.79				94.63	

Table 7.2.2 Adherence by age in the treatment group at one year

In the treatment group, there is a clear association between age and level of adherence (**Table 7.2.2**). Across the ten drug classes, adherence ranges from 35-

86% in the below-55 age group, rising to 47-92% for the 55-65-year group, and to 59-95% for the over 65-year group. Comparing at the drug-class level, adherence is consistently highest for TAM, PDCp, and PDCa, in the over-65 age group for antianginals, antiplatelets, ARBs, BBs, CCBs, diuretics, lipid-regulatory drugs, and nitrates. Adherence is lowest in the below-55 age group, consistently for the three adherence measures for all of the same drug-classes, with the addition of ACEi's. In fact, the only instance where adherence is not lowest for the youngest age group is persistence (TAM) for alpha-blockers.

Similar to the primary prevention group, the drug-classes to which patients are most or least persistent after 1-year varies by age-group. For the under-55's, more patients were persistent to ACEi's (73%), ARBs (73%), and lipid-regs (72%), and least persistent to nitrates (41%), antianginals (55%), and diuretics (58%). The 55-65-year age group have greater levels of persistence observed in the same three drug-classes, though with the highest share of patients persisting to lipid-regulatory drugs (79%), followed by ARBs (76%) and ACEi's (75%). The drug-classes which showed lower persistence levels also included nitrates (52%) and antianginals (59%) but, unlike their younger counterparts, the drug-class with the next lowest persistence was alpha-blockers (59%). The oldest patient group, those aged over 65-years, also showed the highest level of persistence for lipid-regulatory drugs (82%). Adherence was also high to antiplatelets (78%) and BBs (78%). Their lowest persistence levels were observed in alpha-blockers (59%), antianginals (66%) and nitrates (66%).

7.2.3 Deprivation

		High (SIMD 8-10)			Mid (SIMD 4-7)				Low (SIMD 1-3)			
Drug Class	Adherence measure	n start	n adhere	% adherent	n start	n adhere	% adherent	p-value	n start	n adhere	% adherent	p-value
a-blockers	TAM	2,958	1,686	57.00	5,028	2,942	58.51	0.1935	4,299	2,630	61.18	0.0004
	PDCp	1,686	1,557	92.35	2,942	2,660	90.41	0.0298	2,630	2,300	87.45	> 0.0001
	PDCa	2,958	1,701	57.51	5,028	2,871	57.10	0.7416	4,299	2,466	57.36	0.9229
ACEi	TAM	17,326	12,803	73.89	29,270	21,774	74.39	0.2418	26,326	19,780	75.13	0.0037
	PDCp	12,803	12,009	93.80	21,774	20,113	92.37	> 0.0001	19,780	17,909	90.54	> 0.0001
	PDCa	17,326	12,700	73.30	29,270	21,212	72.47	0.0530	26,326	18,870	71.68	0.0002
anti_anginal	TAM	6,257	3,669	58.64	11,001	6,776	61.59	0.0001	10,654	7,009	65.79	> 0.0001
	PDCp	3,669	3,317	90.41	6,776	6,052	89.32	0.0860	7,009	6,196	88.40	0.0018
	PDCa	6,257	3,601	57.55	11,001	6,558	59.61	0.0086	10,654	6,586	61.82	> 0.0001
antiplatelets	TAM	29,631	21,619	72.96	47,605	34,918	73.35	0.2390	42,411	31,240	73.66	0.0374
	PDCp	21,619	18,835	87.12	34,918	30,068	86.11	0.0007	31,240	26,385	84.46	> 0.0001
	PDCa	29,631	19,786	66.77	47,605	31,538	66.25	0.1347	42,411	27,566	65.00	> 0.0001
ARB	TAM	8,030	6,199	77.20	12,533	9,623	76.78	0.4996	9,612	7,317	76.12	0.0967
	PDCp	6,199	5,808	93.69	9,623	9,008	93.61	0.8598	7,317	6,720	91.84	> 0.0001
	PDCa	8,030	6,125	76.28	12,533	9,490	75.72	0.3714	9,612	7,086	73.72	0.0001
BBs	TAM	25,013	18,358	73.39	39,313	28,880	73.46	0.8565	33,639	24,868	73.93	0.1503
	PDCp	18,358	17,029	92.76	28,880	26,452	91.59	> 0.0001	24,868	22,184	89.21	> 0.0001
	PDCa	25,013	17,893	71.53	39,313	27,636	70.30	0.0008	33,639	23,119	68.73	> 0.0001
CCBs	TAM	17,523	11,552	65.92	28,810	19,242	66.79	0.0573	25,564	17,734	69.37	> 0.0001
	PDCp	11,552	10,565	91.46	19,242	17,319	90.01	> 0.0001	17,734	15,567	87.78	> 0.0001
	PDCa	17,523	11,248	64.19	28,810	18,339	63.65	0.2492	25,564	16,388	64.11	0.8660
diuretics	TAM	17,091	11,368	66.51	30,216	20,117	66.58	0.8975	27,070	18,092	66.83	0.4941
	PDCp	11,368	10,010	88.05	20,117	17,288	85.94	> 0.0001	18,092	15,115	83.55	> 0.0001
	PDCa	17,091	10,646	62.29	30,216	18,289	60.53	0.0002	27,070	15,935	58.87	> 0.0001
lipid-regs	TAM	29,985	24,040	80.17	48,020	38,340	79.84	0.2641	42,891	34,316	80.01	0.5875
	PDCp	24,040	21,188	88.14	38,340	33,131	86.41	> 0.0001	34,316	28,739	83.75	> 0.0001
	PDCa	29,985	22,005	73.39	48,020	34,401	71.64	> 0.0001	42,891	29,825	69.54	> 0.0001
nitrates	TAM	11,013	6,091	55.31	19,366	11,512	59.44	> 0.0001	16,677	10,352	62.07	> 0.0001
	PDCp	6,091	5,400	88.66	11,512	10,110	87.82	0.1092	10,352	8,839	85.38	> 0.0001
	PDCa	11,013	5,780	52.48	19,366	10,667	55.08	> 0.0001	16,677	9,328	55.93	> 0.0001
Range across all classes	***Min***			52.48			55.08				55.93	
	Max			93.80			93.61				91.84	

Table 7.2.3: Adherence by SIMD in the treatment group at one year

In the treatment group, differences between SIMD categories are even more subtle than those observed in the primary prevention group (**Table 7.2.3**). Across the ten drug-classes, adherence ranges little between SIMD levels, with all groups having minimum level of adherence of 52-56% and a maximum of 92-94%.

The drug-classes which represent those that patients are most or least persistent to is consistent across the different SIMD levels. A higher proportion of patients are persistent to lipid-regulatory drugs (rounds to 80% across high, mid, and low SIMD-groups), ARBs (77% for high and mid SIMD, 76% for low SIMD group), and ACEi's (74% for high and mid SIMD groups, 75% for the low SIMD group). The lowest levels of persistence were observed across nitrates (55%), alpha-blockers (57%) and antianginals (59%) in the high-SIMD group. The mid- and low-SIMD groups were also least persistent to the same three drug-classes: alpha-blockers (58% for mid-SIMD, 61% for low-SIMD), nitrates (59% and 62%), and antianginals (62% and 66%).

7.2.4 Comorbidity

	Neither comorbidty			Diabetes			Depression			Both		
Drug Class	Adherence measure	n Patients	% adherent	n Patients	% adherent	p-value	n Patients	% adherent	p-value	n Patients	% adherent	p-value
a-blockers	TAM	6,763	56.85	2,375	63.66	> 0.0001	1,402	58.42	0.2953	653	64.62	0.0001
	PDCp	3,845	90.33	1,512	89.68	0.5097	819	87.91	0.0437	422	88.15	0.1823
	PDCa	6,763	55.63	2,375	60.97	> 0.0001	1,402	55.71	0.9798	653	61.10	0.0080
ACEi	TAM	44,723	74.12	9,691	77.96	> 0.0001	10,072	72.61	0.0018	2,984	76.11	0.0175
	PDCp	33,150	92.61	7,555	91.79	0.0160	7,313	90.29	> 0.0001	2,271	90.80	0.0017
	PDCa	44,723	72.37	9,691	75.49	> 0.0001	10,072	69.27	> 0.0001	2,984	72.65	0.7507
anti_angi nal	TAM	16,502	60.27	3,337	67.61	> 0.0001	4,662	63.73	> 0.0001	1,171	69.60	> 0.0001
	PDCp	9,945	88.51	2,256	92.46	> 0.0001	2,971	88.59	0.9270	815	89.33	0.5166
	PDCa	16,502	57.59	3,337	67.16	> 0.0001	4,662	60.21	0.0014	1,171	66.78	> 0.0001
antiplatel ets	TAM	74,661	73.27	12,550	78.13	> 0.0001	19,289	69.70	> 0.0001	4,155	77.26	> 0.0001
	PDCp	54,704	85.88	9,805	87.51	> 0.0001	13,444	84.19	> 0.0001	3,210	85.98	0.8983
	PDCa	74,661	65.84	12,550	71.75	> 0.0001	19,289	61.70	> 0.0001	4,155	69.75	> 0.0001
ARB	TAM	17,978	76.63	4,392	78.46	0.0104	4,047	74.72	0.0104	1,307	78.12	0.2328
	PDCp	13,777	93.51	3,446	93.15	0.4692	3,024	91.50	> 0.0001	1,021	91.28	0.0071
	PDCa	17,978	75.45	4,392	77.09	0.0236	4,047	72.47	> 0.0001	1,307	75.29	0.9226
BBs	TAM	61,690	74.01	10,592	79.22	> 0.0001	15,294	68.03	> 0.0001	3,202	75.05	0.1977
	PDCp	45,655	91.68	8,391	92.34	0.0460	10,405	87.77	> 0.0001	2,403	90.14	0.0088
	PDCa	61,690	70.82	10,592	76.20	> 0.0001	15,294	62.99	> 0.0001	3,202	70.74	0.9401
CCBs	TAM	44,150	66.53	8,190	72.14	> 0.0001	11,067	66.31	0.6558	2,681	73.48	> 0.0001
	PDCp	29,375	89.81	5,908	90.67	0.0459	7,338	87.69	> 0.0001	1,970	90.51	0.3383
	PDCa	44,150	63.24	8,190	68.68	> 0.0001	11,067	61.84	0.0067	2,681	69.90	> 0.0001
diuretics	TAM	43,784	66.23	9,252	70.78	> 0.0001	11,763	64.46	> 0.0001	3,064	69.03	0.0016
	PDCp	28,999	85.59	6,549	86.93	0.0052	7,582	84.38	0.0089	2,115	86.90	0.1015
	PDCa	43,784	59.93	9,252	64.92	> 0.0001	11,763	57.86	> 0.0001	3,064	63.67	> 0.0001
lipid-regs	TAM	74,253	79.33	13,622	84.25	> 0.0001	19,132	78.26	0.0012	4,634	84.29	> 0.0001
	PDCp	58,906	85.79	11,476	87.84	> 0.0001	14,973	84.29	> 0.0001	3,906	85.94	0.8126
	PDCa	74,253	70.64	13,622	76.49	> 0.0001	19,132	68.62	> 0.0001	4,634	75.23	> 0.0001
nitrates	TAM	28,185	57.86	5,278	65.04	> 0.0001	7,798	58.66	0.2104	1,904	68.22	> 0.0001
	PDCp	16,307	87.38	3,433	88.73	0.0316	4,574	85.57	0.0014	1,299	85.76	0.1003
	PDCa	28,185	53.45	5,278	61.18	> 0.0001	7,798	53.35	0.8770	1,904	62.08	> 0.0001
Range across all classes	***Min***	53.45		60.97			53.35			61.10		
	Max	93.51		93.15			91.50			91.28		

Table 7.2.4: Adherence by comorbidity in the treatment group at one year

There is a similar association between adherence and comorbidity in the treatment group (**Table 7.2.4**) as was observed in the primary prevention group.

Adherence tended to be highest for those with diabetes as a comorbidity (61-93%) and lowest in those with depression or neither comorbidity (53-91% and 53-94% respectively).

At a class-by-class level, adherence is lowest in patients with depression as a comorbidity, consistent across TAM, PDCp, and PDCa for six classes of drugs: ACEi's, antiplatelets, BBs, CCBs, diuretics, and lipid-regulatory drugs. Antianginals notably differ, as they are consistently found to have the lowest adherence level in the group of patients who neither have diabetes nor depression as a comorbidity. Adherence is highest across TAM, PDCp, and PDCa in patients with diabetes as a comorbidity in three different drug-classes: antiplatelets, BBs, and CCBs. Patients with both diabetes and depression are associated with higher adherence when compared with those who have no evidence of either.

Looking across the drug-classes, the class to which most patients are persistent (TAM) is lipid-regulatory drugs, regardless of comorbidity status (neither: 79%, diabetes: 84%, depression: 78%, diabetes and depression: 84%), followed by ARBs (neither: 77%, depression: 75%, diabetes and depression: 78%). For patients with diabetes, the drug-class to which persistence is second-highest is BBs (79%). The drug-classes to which a lower proportion of patients persist are alpha-blockers (neither: 57%, diabetes: 64%, depression: 58%, diabetes and depression: 65%), and nitrates (neither: 58%, diabetes: 65%, depression: 59%, diabetes and depression: 68%), consistent across the different comorbidity statuses.

7.3 Secondary Prevention

7.3.1 Sex

		Male			Female			
Drug Class	Adherence measure	n start	n adhere	% adherent	n start	n adhere	% adherent	p-value
a-blockers	TAM	104	70	67.31	73	51	69.86	0.8449
	PDCp	70	67	95.71	51	48	94.12	1.3919
	PDCa	104	65	62.50	73	46	63.01	1.0000
ACEi	TAM	3,182	2,612	82.09	1,616	1,181	73.08	> 0.0001
	PDCp	2,612	2,539	97.21	1,181	1,153	97.63	0.5209
	PDCa	3,182	2,552	80.20	1,616	1,175	72.71	> 0.0001
anti_anginal	TAM	398	264	66.33	278	192	69.06	0.5074
	PDCp	264	244	92.42	192	188	97.92	0.0173
	PDCa	398	252	63.32	278	193	69.42	0.1175
antiplatelets	TAM	3,842	3,411	88.78	2,180	1,875	86.01	0.0018
	PDCp	3,411	3,363	98.59	1,875	1,846	98.45	0.7757
	PDCa	3,842	3,474	90.42	2,180	1,926	88.35	0.0126
ARB	TAM	576	490	85.07	477	395	82.81	0.3615
	PDCp	490	481	98.16	395	382	96.71	0.2443
	PDCa	576	479	83.16	477	377	79.04	0.1033
BBs	TAM	3,355	2,916	86.92	1,819	1,556	85.54	0.1819
	PDCp	2,916	2,849	97.70	1,556	1,526	98.07	0.4836
	PDCa	3,355	2,866	85.42	1,819	1,540	84.66	0.4865
CCBs	TAM	739	549	74.29	492	350	71.14	0.2482
	PDCp	549	527	95.99	350	336	96.00	1.0000
	PDCa	739	514	69.55	492	335	68.09	0.6305
diuretics	TAM	1,045	779	74.55	897	692	77.15	0.2006
	PDCp	779	743	95.38	692	659	95.23	0.9920
	PDCa	1,045	733	70.14	897	647	72.13	0.3618
lipid-regs	TAM	3,769	3,399	90.18	2,077	1,786	85.99	> 0.0001
	PDCp	3,399	3,239	95.29	1,786	1,700	95.18	0.9163
	PDCa	3,769	3,179	84.35	2,077	1,671	80.45	0.0002
nitrates	TAM	467	304	65.10	369	266	72.09	0.0375
	PDCp	304	285	93.75	266	261	98.12	0.0172
	PDCa	467	283	60.60	369	253	68.56	0.0208
Range across all classes		***Min***		60.60			63.01	
		Max		98.59			98.45	

Table 7.3.1 Adherence by sex in the secondary prevention group at one year

p-values derived from Fisher's exact test where n < 5; In all other instances, p derived from chi-squared test.

In the secondary prevention group, adherence is higher for male patients compared to female patients, though with a smaller sex difference compared

with that observed for the primary prevention or treatment groups (average 83.02% adherent for men across all ten drugs classes, vs average 82.89% for women) (**Table 7.3.1**). Generally, patients who are found to be persistent at the end of year 1 tend also to have very high levels of adherence, with the PDCp ranging from approximately 92-98% across male and female patients for any drug class.

For antiplatelets, ARBs, and lipid-regulating drugs, male patients have higher implementation and persistence compared with female patients; for nitrates and antianginals the reverse is true, with women having higher levels of adherence across all measures. Alpha-blockers, ACEi's, CCBs, BBs, and diuretics show a mix of male and female patients displaying higher rates of adherence, depending on the measure used. In all cases, the adherence in patients who were persistent (PDCp) is the value which contradicts the other two. For patients who do persist with treatment, there are very little differences in levels of implementation between the sexes.

The drug-classes to which male patients are most persistent are lipid-regs (90%), antiplatelets (89%), and BBs (87%), while female patients are most adherent to antiplatelets (86%), closely followed by lipid-regulators and BBs (both of which round-up to 86%). The drugs to which males are least persistent are nitrates (65%), followed by antianginals (66%) and alpha-blockers (67%). For female patients, adherence to nitrates is comparatively higher, at 72%, while the drugs to which they are least persistent are antianginals (69%), alpha-blockers (70%), and CCBs (71%).

In the secondary prevention group, we might expect people to be very adherent initially following their heart attack and for this to drop-off later; however it is difficult to study this accurately as very few people stay in this group for a long time, with a median follow-up time of just less than 4 months (see previous chapter, showing summary statistics for each of the patient groups). Comparing adherence over the first year of secondary prevention can only give us limited insight.

7.3.2 Age

Drug Class	Adherence measure	Below 55			55 - 65				Above 65			
		n start	n adhere	% adherent	n start	n adhere	% adherent	p-value	n start	n adhere	% adherent	p-value
a-blockers	TAM	16	10	62.50	41	29	70.73	0.7766	120	82	68.33	0.8540
	PDCp	10	8	80.00	29	29	100.00	NA	82	78	95.12	4.7400
	PDCa	16	7	43.75	41	27	65.85	0.2194	120	77	64.17	0.1920
ACEi	TAM	948	793	83.65	1,394	1,138	81.64	0.2292	2,456	1,862	75.81	> 0.0001
	PDCp	793	752	94.83	1,138	1,110	97.54	0.0024	1,862	1,830	98.28	> 0.0001
	PDCa	948	757	79.85	1,394	1,116	80.06	0.9449	2,456	1,854	75.49	0.0079
anti_anginal	TAM	59	38	64.41	136	85	62.50	0.9267	481	333	69.23	0.5449
	PDCp	38	34	89.47	85	81	95.29	2.3637	333	317	95.20	2.3238
	PDCa	59	36	61.02	136	78	57.35	0.7499	481	331	68.81	0.2875
antiplatelets	TAM	1,083	978	90.30	1,616	1,482	91.71	0.2346	3,323	2,826	85.04	> 0.0001
	PDCp	978	959	98.06	1,482	1,463	98.72	0.2571	2,826	2,787	98.62	0.2773
	PDCa	1,083	998	92.15	1,616	1,499	92.76	0.6071	3,323	2,903	87.36	> 0.0001
ARB	TAM	104	87	83.65	268	232	86.57	0.5781	681	566	83.11	1.0000
	PDCp	87	80	91.95	232	230	99.14	9.9764	566	553	97.70	0.0104
	PDCa	104	76	73.08	268	226	84.33	0.0191	681	554	81.35	0.0655
BBs	TAM	976	847	86.78	1,417	1,263	89.13	0.0921	2,781	2,362	84.93	0.1752
	PDCp	847	816	96.34	1,263	1,235	97.78	0.0663	2,362	2,324	98.39	0.0007
	PDCa	976	809	82.89	1,417	1,238	87.37	0.0027	2,781	2,359	84.83	0.1675
CCBs	TAM	134	84	62.69	297	230	77.44	0.0021	800	585	73.13	0.0174
	PDCp	84	77	91.67	230	223	96.96	0.0888	585	563	96.24	0.1014
	PDCa	134	77	57.46	297	218	73.40	0.0015	800	554	69.25	0.0094
diuretics	TAM	135	102	75.56	364	272	74.73	0.9411	1,443	1,097	76.02	0.9872
	PDCp	102	94	92.16	272	257	94.49	0.5531	1,097	1,051	95.81	0.1469
	PDCa	135	92	68.15	364	253	69.51	0.8552	1,443	1,035	71.73	0.4353
lipid-regs	TAM	1,066	964	90.43	1,593	1,462	91.78	0.2576	3,187	2,759	86.57	0.0012
	PDCp	964	896	92.95	1,462	1,394	95.35	0.0152	2,759	2,649	96.01	0.0002
	PDCa	1,066	872	81.80	1,593	1,350	84.75	0.0506	3,187	2,628	82.46	0.6588
nitrates	TAM	65	32	49.23	129	81	62.79	0.0982	642	457	71.18	0.0004
	PDCp	32	30	93.75	81	75	92.59	0.8346	457	441	96.50	1.8345
	PDCa	65	29	44.62	129	69	53.49	0.3103	642	438	68.22	0.0002
Range across all classes		***Min***		43.75			53.49				64.17	
		Max		98.06			100.00				98.62	

Table 7.3.2 Adherence by age in the secondary prevention group at one year

p-values derived from Fisher's exact test where n < 5; In all other instances, p derived from chi-squared test.

For the secondary prevention group, average TAM across all drugs classes is lowest in the below-55 group (75%), highest in 55-65-year olds (79%), and slightly lower again in the over 65-year group (77%) (**Table 7.3.2**). This is consistent with

the ‘U-shaped’ association between age and nonadherence, as described by Mann *et al* (Chapter 2, literature review). However, this is not quite reflected in PDCp or PDCa measures, as adherence is lower in the below-55 age group (PDCp 92%/ PDCa 68%) but remains constant between the 55-65 and above-65 age categories (PDCp 96%/PDCa 75%). This differs from primary prevention and treatment groups, where increased age seemed to have a clear positive trend with adherence.

There is only one instance where the below-55 group have the highest adherence, and this is the TAM for ACEi’s. Adherence is consistently highest across TAM, PDCp, and PDCa in the 55-65 age group for five different drug-classes: alpha-blockers, antiplatelets, ARBs, CCBs, and lipid-regs, while it is highest in the older (plus-65) group for diuretics, and nitrates. Lowest adherence levels were observed in the younger age-group in almost two-thirds of cases (19 out of 30 measures), and this is consistent for the three adherence measures in alpha-blockers and CCBs.

The drug-classes to which patients are most persistent differ slightly by age. Lipid-regulatory drugs were the class to which persistence was highest: at 90% for the below-55 group, 92% for the 55-65 group, and 87% for the above-65 group. This is followed by antiplatelets (90%, 92%, 85% respectively), and then ARBs tied with ACEi for the younger age-group (both 84%) and BBs for the mid- and older groups (89 and 85%). Patients were least persistent to alpha-blockers, antianginals, and nitrates in all age-groups, though to varying degrees. For the below-55 group, persistence was lowest for nitrates (49%), alpha-blockers (62%), and then antianginals (64%); for the 55-65-year group, the lowest persistence level was to antianginals (62%), followed by nitrates (63%), and alpha-blockers (71%); in the above-65 group, persistence was lowest for alpha-blockers (68%), antianginals (69%), and nitrates (71%).

7.3.3 Deprivation

Drug Class	Adherence measure	High (SIMD 8-10)			Mid (SIMD 4-7)				Low (SIMD 1-3)			
		n start	n adhere	% adherent	n start	n adhere	% adherent	p-value	n start	n adhere	% adherent	p-value
a-blockers	TAM	52	32	61.54	75	56	74.67	0.1671	49	33	67.35	0.6882
	PDCp	32	31	96.88	56	53	94.64	1.7445	33	31	93.94	1.9795
	PDCa	52	33	63.46	75	50	66.67	0.8543	49	28	57.14	0.6560
ACEi	TAM	1,324	1,041	78.63	1,985	1,567	78.94	0.8611	1,480	1,179	79.66	0.5298
	PDCp	1,041	1,018	97.79	1,567	1,530	97.64	0.9046	1,179	1,138	96.52	0.0979
	PDCa	1,324	1,023	77.27	1,985	1,556	78.39	0.4716	1,480	1,142	77.16	0.9838
anti_anginal	TAM	176	109	61.93	251	165	65.74	0.4810	249	182	73.09	0.0196
	PDCp	109	105	96.33	165	155	93.94	1.6905	182	172	94.51	1.5241
	PDCa	176	113	64.20	251	158	62.95	0.8703	249	174	69.88	0.2604
antiplatelets	TAM	1,664	1,456	87.50	2,512	2,219	88.34	0.4441	1,837	1,604	87.32	0.9103
	PDCp	1,456	1,430	98.21	2,219	2,191	98.74	0.2498	1,604	1,581	98.57	0.5286
	PDCa	1,664	1,498	90.02	2,512	2,266	90.21	0.8878	1,837	1,629	88.68	0.2174
ARB	TAM	325	270	83.08	446	378	84.75	0.5974	282	237	84.04	0.8335
	PDCp	270	263	97.41	378	370	97.88	0.8946	237	230	97.05	1.0000
	PDCa	325	259	79.69	446	370	82.96	0.2884	282	227	80.50	0.8843
BBs	TAM	1,418	1,229	86.67	2,170	1,885	86.87	0.9059	1,579	1,353	85.69	0.4679
	PDCp	1,229	1,206	98.13	1,885	1,846	97.93	0.7991	1,353	1,318	97.41	0.2747
	PDCa	1,418	1,216	85.75	2,170	1,852	85.35	0.7705	1,579	1,333	84.42	0.3314
CCBs	TAM	331	239	72.21	518	381	73.55	0.7249	381	278	72.97	0.8865
	PDCp	239	228	95.40	381	369	96.85	0.4756	278	265	95.32	1.0000
	PDCa	331	226	68.28	518	363	70.08	0.6324	381	259	67.98	0.9962
diuretics	TAM	517	390	75.44	787	585	74.33	0.7016	633	492	77.73	0.3989
	PDCp	390	373	95.64	585	563	96.24	0.7640	492	462	93.90	0.3218
	PDCa	517	372	71.95	787	561	71.28	0.8417	633	444	70.14	0.5433
lipid-regs	TAM	1,605	1,438	89.60	2,436	2,162	88.75	0.4299	1,795	1,577	87.86	0.1226
	PDCp	1,438	1,376	95.69	2,162	2,057	95.14	0.4961	1,577	1,498	94.99	0.4121
	PDCa	1,605	1,366	85.11	2,436	2,019	82.88	0.0665	1,795	1,458	81.23	0.0030
nitrates	TAM	200	131	65.50	359	251	69.92	0.3265	276	187	67.75	0.6769
	PDCp	131	125	95.42	251	241	96.02	0.9944	187	179	95.72	1.0000
	PDCa	200	131	65.50	359	233	64.90	0.9605	276	171	61.96	0.4865
Range across all classes		***Min***		61.54			62.95				57.14	
		Max		98.21			98.74				98.57	

Table 7.3.3 Adherence by SIMD in the secondary prevention group at one year

p-values derived from Fisher's exact test where n < 5; In all other instances, p derived from chi-squared test.

Across all drug-classes, there is very little difference in adherence between the SIMD-groups for secondary prevention patients (**Table 7.3.3**).

Adherence to antiplatelets, ARBs, and CCBs, is highest in the middle SIMD groups, consistent across all measures of adherence, while adherence to lipid-regulatory drugs is greatest in the high SIMD groups across all measures. All other drug classes vary depending on which adherence measure is used.

The drug-classes to which patients were most persistent was consistent across the SIMD-groups: it was highest for lipid-regulatory drugs (90%, 89%, 88% respectively for high-, mid-, and low-SIMD), followed by antiplatelets (87%, 88%, 87%), and BBs (87% for high- and mid-SIMD, 86% for low-SIMD).

Persistence was lowest overall to alpha-blockers, antianginals, and nitrates, though this did vary by SIMD group. For example, in both the high- and low-SIMD groups, adherence was lowest to alpha-blockers (62 and 67% respectively), however for the mid-SIMD group, persistence was 75% - roughly middle of the range of TAM values for this group, and 10 percentage points higher than the drug-class to which they were least adherent, antianginals. For the high-SIMD group, persistence was also lower for this drug class (62%), while the low-SIMD group was the outlier this time, with a much higher persistence of 73%. Instead, the class to which they were next associated with lower persistence levels was nitrates (68%), which was also poorly persisted to in the high- and mid- groups also (65% and 67% respectively). While there is some consistency here, there is not a clear pattern to the differences that can be observed.

7.3.4 Comorbidity

		Neither comorbidty		Diabetes			Depression			Both		
Drug Class	Adherence measure	n Patients	% adherent	n Patients	% adherent	p-value	n Patients	% adherent	p-value	n Patients	% adherent	p-value
a-blockers	TAM	88	62.50	48	75.00	0.1971	23	70-75	0.4380	>10	70-75	1.7899
	PDCp	55	100.00	36	90-95	0.1149	16-18	85-80	NA	>10	100.00	NA
	PDCa	88	60.23	48	66.67	0.5782	23	65-70	0.8438	>10	60-65	1.0996
ACEi	TAM	3,321	79.58	529	79.58	1.0000	591	75.13	0.0167	125	80.00	0.9999
	PDCp	2,643	97.81	421	95.49	0.0079	444	97.07	0.4337	100	90-95	0.1340
	PDCa	3,321	78.86	529	77.13	0.3970	591	72.25	0.0004	125	74.40	0.2780
anti_anginal	TAM	383	62.92	109	76.15	0.0141	92	71.74	0.1425	48	70.83	0.3599
	PDCp	241	95-100	83	95-100	0.9158	66	85-90	0.0348	34	90-95	0.5508
	PDCa	383	63.71	109	73.39	0.0772	92	66.30	0.7298	48	68.75	0.5979
antiplatelets	TAM	4,068	88.08	698	85.53	0.0671	769	88.04	1.0000	172	88.95	0.8201
	PDCp	3,583	98.69	597	97.82	0.1441	677	95-100	0.6853	153	95-100	0.0201
	PDCa	4,068	90.22	698	88.68	0.2381	769	88.95	0.3118	172	86.63	0.1582
ARB	TAM	670	85.37	142	82.39	0.4410	150	82.67	0.4775	38	73.68	0.0859
	PDCp	572	98.08	117	95-100	0.2297	124	95-100	1.1958	28	85-90	0.1187
	PDCa	670	83.88	142	78.17	0.1288	150	78.67	0.1574	38	60.53	0.0005
BBs	TAM	3,534	86.56	609	84.89	0.2979	632	85.44	0.4898	137	90.51	0.2268
	PDCp	3,059	97.78	517	95-100	0.4121	540	97.59	0.9131	124	95-100	0.9170
	PDCa	3,534	85.57	609	84.73	0.6309	632	82.75	0.0764	137	84.67	0.8657
CCBs	TAM	711	75.81	215	68.37	0.0365	160	71.25	0.2706	67	67.16	0.1568
	PDCp	539	96.66	147	93.20	0.0998	114	95-100	1.2779	45	90-95	0.4845
	PDCa	711	71.87	215	65.12	0.0697	160	66.88	0.2456	67	58.21	0.0272
diuretics	TAM	1,108	74.55	361	78.39	0.1602	254	77.95	0.2927	97	75.26	0.9743
	PDCp	826	96.00	283	94.70	0.4461	198	93.94	0.2799	73	95-100	0.9710
	PDCa	1,108	70.31	361	74.24	0.1717	254	72.44	0.5501	97	67.01	0.5727
lipid-regs	TAM	3,963	89.43	667	87.26	0.1100	740	87.84	0.2251	172	88.95	0.9433
	PDCp	3,544	95.20	582	96.05	0.4302	650	94.92	0.8364	153	92.81	0.2495
	PDCa	3,963	83.67	667	82.46	0.4679	740	82.16	0.3362	172	75.00	0.0039
nitrates	TAM	464	67.67	142	74.65	0.1407	134	61.19	0.1960	45	77.78	0.2202
	PDCp	314	95.54	106	95-100	1.6007	82	90-95	0.7427	35	100.00	NA
	PDCa	464	64.01	142	71.13	0.1437	134	57.46	0.2013	45	73.33	0.2769
			Min		60.23		65.12		57.46		58.21	
	Range across all classes		***Max***		100.00		97.82		97.59		100.00	

Table 7.3.4 Adherence by comorbidity in the secondary prevention group at one year

*p-values derived from Fisher's exact test where n < 5; In all other instances, p derived from chi-squared test. Percentages are rounded where the number of nonadherent people is < 10 to protect anonymity (while the number of nonadherent patients is not provided, it could otherwise be inferred from percentages). Note that **N patients** for PDCp is equivalent to the number of patients found to be persistent with TAM (PDCp = proportion of **persistent** patients who are adherent). Where percentages are rounded for TAM, the N patients for PDCp is expressed as the values equivalent to the range of percentages given for TAM, as the true value could otherwise be inferred.*

Comparing adherence in the secondary prevention group is hindered by small group numbers, and reporting was subject to disclosure control. If these ranges are crudely rounded to the higher value (i.e. if the range is 95-100, take 100% as the value) in order to allow an overall average to be calculated, the pattern follows that observed in the primary prevention and treatment groups, in that adherence tends to be highest in those with diabetes.

It is worth noting that most of the instances where rounding was necessary were in PDCp, as implementation rates were generally high, never dipping below 90%. This suggests that patients who do persist with a CVD treatment in the first year of secondary prevention therapy tend to implement this to a very high level.

Comparing persistence across the groups, the drug-classes to which patients are most persistent are lipid-regulatory drugs for patients with neither comorbidity or with diabetes only (89% and 87% respectively), antiplatelets for those with depression only as a comorbidity (88%) and BBs for those with both diabetes and depression (90%). Persistence is also high to antiplatelets for those with neither comorbidity or those with diabetes only (88% and 86% respectively). For those with depression only, persistence was high to lipid-regulatory drugs (88%).

The drugs to which patients were least persistent included alpha-blockers, antianginals, CCBs, and nitrates, though this varied across the groups.

7.4 Secondary Prevention with Treatment

7.4.1 Sex

		Male			Female			
Drug Class	Adherence Measure	n patients	n adhere	% adherent	n patients	n adhere	% adherent	p-value
a-blockers	TAM	488	298	61.07	340	183	53.82	0.0448
	PDCp	298	282	94.63	183	175	95.63	0.7855
	PDCa	488	296	60.66	340	187	55.00	0.1206
ACEi	TAM	10,886	8,572	78.74	5,012	3,718	74.18	> 0.0001
	PDCp	8,572	8,329	97.17	3,718	3,624	97.47	0.3703
	PDCa	10,886	8,497	78.05	5,012	3,765	75.12	> 0.0001
anti_anginal	TAM	2,187	1,434	65.57	1,460	987	67.60	0.2157
	PDCp	1,434	1,379	96.16	987	955	96.76	0.5095
	PDCa	2,187	1,448	66.21	1,460	983	67.33	0.5050
antiplatelets	TAM	13,544	11,146	82.29	7,133	5,731	80.34	0.0006
	PDCp	11,146	10,898	97.77	5,731	5,593	97.59	0.4849
	PDCa	13,544	11,547	85.26	7,133	5,890	82.57	> 0.0001
ARB	TAM	2,601	1,920	73.82	1,808	1,351	74.72	0.5216
	PDCp	1,920	1,877	97.76	1,351	1,310	96.97	0.1924
	PDCa	2,601	1,957	75.24	1,808	1,354	74.89	0.8184
BBs	TAM	11,966	9,690	80.98	6,126	4,871	79.51	0.0196
	PDCp	9,690	9,460	97.63	4,871	4,761	97.74	0.7065
	PDCa	11,966	9,612	80.33	6,126	4,850	79.17	0.0689
CCBs	TAM	3,397	2,274	66.94	2,213	1,381	62.40	0.0005
	PDCp	2,274	2,197	96.61	1,381	1,321	95.66	0.1647
	PDCa	3,397	2,267	66.74	2,213	1,367	61.77	0.0002
diuretics	TAM	4,361	2,941	67.44	3,537	2,411	68.17	0.5075
	PDCp	2,941	2,809	95.51	2,411	2,272	94.23	0.0397
	PDCa	4,361	2,903	66.57	3,537	2,296	64.91	0.1293
lipid-regs	TAM	13,552	11,138	82.19	6,914	5,548	80.24	0.0007
	PDCp	11,138	10,639	95.52	5,548	5,311	95.73	0.5636
	PDCa	13,552	10,595	78.18	6,914	5,316	76.89	0.0370
nitrates	TAM	2,951	1,808	61.27	2,105	1,395	66.27	0.0003
	PDCp	1,808	1,733	95.85	1,395	1,344	96.34	0.5359
	PDCa	2,951	1,763	59.74	2,105	1,344	63.85	0.0034
Range across all classes		***Min***		59.74			53.82	
		Max		97.77			97.74	

Table 7.4.1 Adherence by sex in the secondary prevention with treatment group at one year

As with the previous patient groups examined, for patients undergoing secondary prevention along with treatment for symptomatic CVD, male patients tend to be more adherent than female patients after 1 year (**Table 7.4.1**). Half of the instances in which females were found to be more adherent were measured by PDCp, suggesting that women tend to be less persistent, but where they are persistent, their implementation is to a high level. However, it is worth noting

that the PDCp measure is rarely statistically significant. Antianginals and nitrates were the only drug classes where women were found to be more adherent across all three adherence measures. The drug-classes to which patients in the secondary-treatment group were most persistent are antiplatelets (82.29% for males and 80.34% for females), closely followed by lipid-regulating drugs (M: 82.19%, F: 80.24%) and BBs (M: 80.98%, F: 79.51%). Patients in this group were least persistent to alpha-blockers (M: 61.07%, F: 53.82%).

7.4.2 Age

		Age below 55			Age 55-65				Age above 65			
Drug Class	Adherence Measure	n patients	n adhere	% adherent	n patients	n adhere	% adherent	p-value	n patients	n adhere	% adherent	p-value
a-blockers	TAM	77	48	62.34	175	100	57.14	0.5269	576	333	57.81	0.5265
	PDCp	48	40	83.33	100	96	96.00	0.0203	333	321	96.40	0.0006
	PDCa	77	41	53.25	175	97	55.43	0.8547	576	345	59.90	0.3216
ACEi	TAM	3,623	2,978	82.20	4,659	3,718	79.80	0.0065	7,616	5,594	73.45	> 0.0001
	PDCp	2,978	2,839	95.33	3,718	3,608	97.04	0.0003	5,594	5,506	98.43	> 0.0001
	PDCa	3,623	2,834	78.22	4,659	3,659	78.54	0.7511	7,616	5,769	75.75	0.0041
anti_anginal	TAM	559	339	60.64	855	547	63.98	0.2261	2,233	1,535	68.74	0.0003
	PDCp	339	321	94.69	547	526	96.16	0.3850	1,535	1,487	96.87	0.0702
	PDCa	559	324	57.96	855	545	63.74	0.0333	2,233	1,562	69.95	> 0.0001
antiplatelets	TAM	4,226	3,661	86.63	5,673	4,771	84.10	0.0005	10,778	8,445	78.35	> 0.0001
	PDCp	3,661	3,566	97.41	4,771	4,653	97.53	0.7773	8,445	8,272	97.95	0.0704
	PDCa	4,226	3,693	87.39	5,673	4,875	85.93	0.0386	10,778	8,869	82.29	> 0.0001
ARB	TAM	578	439	75.95	1,121	825	73.60	0.3194	2,710	2,007	74.06	0.3714
	PDCp	439	420	95.67	825	807	97.82	0.0477	2,007	1,960	97.66	0.0305
	PDCa	578	431	74.57	1,121	827	73.77	0.7678	2,710	2,053	75.76	0.5820
BBs	TAM	3,756	3,162	84.19	5,017	4,141	82.54	0.0440	9,319	7,258	77.88	> 0.0001
	PDCp	3,162	3,027	95.73	4,141	4,045	97.68	> 0.0001	7,258	7,149	98.50	> 0.0001
	PDCa	3,756	3,018	80.35	5,017	4,090	81.52	0.1748	9,319	7,354	78.91	0.0699
CCBs	TAM	798	555	69.55	1,401	948	67.67	0.3870	3,411	2,152	63.09	0.0007
	PDCp	555	520	93.69	948	907	95.68	0.1164	2,152	2,091	97.17	0.0001
	PDCa	798	511	64.04	1,401	923	65.88	0.4079	3,411	2,200	64.50	0.8380
diuretics	TAM	774	479	61.89	1,512	994	65.74	0.0758	5,612	3,879	69.12	> 0.0001
	PDCp	479	444	92.69	994	938	94.37	0.2568	3,879	3,699	95.36	0.0151
	PDCa	774	457	59.04	1,512	960	63.49	0.0426	5,612	3,782	67.39	> 0.0001
lipid-regs	TAM	4,193	3,584	85.48	5,651	4,704	83.24	0.0029	10,622	8,398	79.06	> 0.0001
	PDCp	3,584	3,360	93.75	4,704	4,490	95.45	0.0007	8,398	8,100	96.45	> 0.0001
	PDCa	4,193	3,275	78.11	5,651	4,470	79.10	0.2434	10,622	8,166	76.88	0.1132
nitrates	TAM	716	367	51.26	1,076	641	59.57	0.0006	3,264	2,195	67.25	> 0.0001
	PDCp	367	346	94.28	641	597	93.14	0.5638	2,195	2,134	97.22	0.0050
	PDCa	716	341	47.63	1,076	599	55.67	0.0010	3,264	2,167	66.39	> 0.0001
Range across all classes		***Min***		47.63			55.43				57.81	
		Max		97.41			97.82				98.50	

Table 7.4.2 Adherence by age in the secondary prevention with treatment group at one year

For the patients who are in secondary prevention with treatment group, adherence tends to be highest in the over-65's group overall (**Table 7.4.2**), ranking highest across 16 of the 30 measures. This was consistent across TAM, PDCp, and PDCa for antianginals, diuretics, and nitrates.

Adherence is lowest in the below-55 age group in 50% of instances, and this was consistent across all three measures for antianginals and diuretics. However, overall differences in adherence between the groups were subtle; across the ten drug classes and three adherence measures, average adherence was 78% for the below-55 age group, 79% for the 55-65 age group, and 80% for the above 65's. Looking at persistence only (TAM) this flips, with the youngest group being the most persistent (72%) and the over-65 group being the least persistent (71%). This may indicate that older patients who do persist are comparatively better at implementing regimens. Across the ten drug-classes, the range from maximum to minimum persistence level is wider in the younger patient group (ranges from 51-87%; i.e. 36% difference), compared with the group aged over 65 (ranges from 58 – 79%, i.e. 21% difference).

The drugs classes to which patients in the below-55 and 55-65 groups are most persistent are antiplatelets (87 and 84%), followed by lipid regulatory drugs (85% and 83%), and then BBs (84% and 83%). The over 65's are most persistent to the same three drug-classes, but they are most persistent to lipid regulatory drugs (79%) followed by antiplatelets (78%) and BBs (78%). The classes to which persistence is lowest varies by age group: for the under-55's, it is lowest for nitrates (51%), antianginals (61%), and diuretics (62%); for the 55-65-year group, persistence is lowest to alpha-blockers (57%), nitrates (60%), and antianginals (64%); and for the over-65's, adherence is again lowest to alpha-blockers (58%), followed by CCBs (63%) and then nitrates (67%).

7.4.3 Deprivation

		High SIMD (8-10)			Mid SIMD (4-7)			Low SIMD (1-3)			
Drug Class	Adherence Measure	n patients	n adhere	% adherent	n patients	n adhere	% adherent	p-value	n patients	n adhere	% adherent	p-value
a-blockers	TAM	204	132	64.71	345	198	57.39	0.4612	279	151	54.12	0.0252
	PDCp	132	125	94.70	198	187	94.44	0.6677	151	145	96.03	0.8038
	PDCa	204	135	66.18	345	190	55.07	0.7576	279	158	56.63	0.0427
ACEi	TAM	3,663	2,793	76.25	6,390	4,945	77.39	0.5553	5,828	4,537	77.85	0.0745
	PDCp	2,793	2,747	98.35	4,945	4,809	97.25	0.0689	4,537	4,382	96.58	> 0.0001
	PDCa	3,663	2,853	77.89	6,390	4,923	77.04	0.6848	5,828	4,471	76.72	0.1943
anti_anginal	TAM	758	496	65.44	1,452	967	66.60	1.0000	1,434	955	66.60	0.6175
	PDCp	496	480	96.77	967	926	95.76	0.2478	955	925	96.86	1.0000
	PDCa	758	503	66.36	1,452	961	66.18	0.5801	1,434	964	67.22	0.7173
antiplatelets	TAM	4,902	3,951	80.60	8,445	6,888	81.56	0.1919	7,309	6,021	82.38	0.0137
	PDCp	3,951	3,865	97.82	6,888	6,746	97.94	0.0396	6,021	5,863	97.38	0.1775
	PDCa	4,902	4,143	84.52	8,445	7,128	84.40	0.5850	7,309	6,145	84.07	0.5273
ARB	TAM	1,262	950	75.28	1,833	1,344	73.32	0.5368	1,311	975	74.37	0.6282
	PDCp	950	931	98.00	1,344	1,309	97.40	0.5800	975	945	96.92	0.1754
	PDCa	1,262	979	77.58	1,833	1,362	74.30	0.7627	1,311	967	73.76	0.0273
BBs	TAM	4,277	3,420	79.96	7,391	5,934	80.29	0.2499	6,405	5,193	81.08	0.1605
	PDCp	3,420	3,366	98.42	5,934	5,796	97.67	0.0922	5,193	5,045	97.15	0.0002
	PDCa	4,277	3,453	80.73	7,391	5,890	79.69	0.9763	6,405	5,102	79.66	0.1796
CCBs	TAM	1,330	832	62.56	2,302	1,488	64.64	0.0564	1,973	1,331	67.46	0.0041
	PDCp	832	811	97.48	1,488	1,431	96.17	0.4786	1,331	1,272	95.57	0.0299
	PDCa	1,330	853	64.14	2,302	1,491	64.77	0.8041	1,973	1,286	65.18	0.5625
diuretics	TAM	1,797	1,237	68.84	3,259	2,174	66.71	0.2079	2,829	1,931	68.26	0.7031
	PDCp	1,237	1,174	94.91	2,174	2,072	95.31	0.2750	1,931	1,825	94.51	0.6867
	PDCa	1,797	1,209	67.28	3,259	2,128	65.30	0.9116	2,829	1,852	65.46	0.2153
lipid-regs	TAM	4,872	3,925	80.56	8,350	6,799	81.43	0.1666	7,224	5,945	82.30	0.0169
	PDCp	3,925	3,781	96.33	6,799	6,505	95.68	0.0719	5,945	5,647	94.99	0.0019
	PDCa	4,872	3,848	78.98	8,350	6,477	77.57	0.4887	7,224	5,569	77.09	0.0149
nitrates	TAM	1,076	671	62.36	2,126	1,335	62.79	0.2633	1,848	1,193	64.56	0.2497
	PDCp	671	645	96.13	1,335	1,285	96.25	0.6370	1,193	1,143	95.81	0.8341
	PDCa	1,076	651	60.50	2,126	1,302	61.24	0.5444	1,848	1,150	62.23	0.3752
Range across all classes		***Min***		60.50			55.07				54.12	
		Max		98.42			97.94				97.38	

Table 7.4.3 Adherence by SIMD in the secondary prevention with treatment group at one year

Across SIMD groups, adherence tends to be highest in the more affluent groups and lowest in the most deprived groups (**Table 7.4.3**). However, this is not so clear cut, as there is much variation by drug-class and measure used. 7 of the 14

instances where adherence is lowest in the most deprived patients, PDCp is the measure used. PDCp is possibly less informative when compared with TAM and PDCa, as there is very little difference between the maximum and minimum values (ranges from 94.44 – 98.42%) and it only reaches a significant p-value for one out of the ten drug-classes when comparing the low to mid-SIMD groups, and in five of the ten drug-classes when comparing the low to high-SIMD groups. This could also indicate that differences are only significant when comparing extremes.

For both age and SIMD, the middle groups (age 55-65 years; SIMD 4-7) are least likely to have the highest or lowest adherence levels. This is to be expected if there is a linear correlation i.e. as age increases, adherence increases; as affluence increases, adherence increase – at the univariate level.

Regardless of SIMD status, persistence is highest for antiplatelets, followed by lipid-regulatory drugs, and BBs. Persistence to all three classes is very high, reaching 80-82% in each SIMD group. However, the classes to which patients are least persistent does vary slightly by SIMD status. The affluent, high-SIMD, group are least adherent to nitrates (62%), CCBs (63%), and alpha-blockers (65%). The mid-SIMD group are least persistent to alpha-blockers (57%), nitrates (63%) and CCBs (65%), while the most deprived group are least persistent to alpha-blockers (54%), nitrates (65%), and antianginals (67%).

7.4.4 Comorbidity

Drug Class	Adherence measure	Neither comorbidty n Patients	Neither comorbidty % adherent	Diabetes n Patients	Diabetes % adherent	Diabetes p-value	Depression n Patients	Depression % adherent	Depression p-value	Both n Patients	Both % adherent	Both p-value
a-blockers	TAM	413	58.84	222	55.86	0.5214	85	58.82	1.0000	57	54.39	0.6201
	PDCp	243	95.88	124	93.55	0.4686	50	95-100	1.0299	31	90-95	0.6236
	PDCa	413	60.05	222	54.50	0.2056	85	57.65	0.7722	57	54.39	0.5015
ACEi	TAM	10,421	78.01	1,809	74.96	0.0046	2,285	76.67	0.1742	467	74.95	0.1333
	PDCp	8,129	97.45	1,356	97.12	0.5387	1,752	96.80	0.1468	350	95-100	0.8964
	PDCa	10,421	78.02	1,809	74.90	0.0038	2,285	76.02	0.0405	467	74.52	0.0847
anti_anginal	TAM	2,011	65.84	540	69.07	0.1727	629	66.14	0.9284	215	64.65	0.7849
	PDCp	1,324	96.07	373	98.12	0.0802	416	95.43	0.6648	139	100.00	0.0325
	PDCa	2,011	65.39	540	71.67	0.0070	629	66.30	0.7121	215	68.37	0.4239
antiplatelets	TAM	13,355	82.20	2,395	78.50	> 0.0001	3,035	81.88	0.6939	659	78.45	0.0166
	PDCp	10,978	97.74	1,880	98.19	0.2513	2,485	97.71	0.9758	517	97.10	0.4214
	PDCa	13,355	84.60	2,395	83.84	0.3625	3,035	84.45	0.8588	659	81.03	0.0160
ARB	TAM	2,779	74.96	636	71.07	0.0487	569	71.88	0.1392	146	79.45	0.2594
	PDCp	2,083	97.89	452	96.46	0.1012	409	97.07	0.3995	116	95-100	0.0670
	PDCa	2,779	75.78	636	71.70	0.0361	569	73.81	0.3468	146	78.77	0.4697
BBs	TAM	11,705	81.38	2,213	78.31	0.0008	2,548	79.75	0.0598	560	77.68	0.0325
	PDCp	9,526	97.84	1,733	97.69	0.7702	2,032	96.65	0.0019	435	95-100	1.0000
	PDCa	11,705	80.90	2,213	78.54	0.0110	2,548	77.79	0.0004	560	77.68	0.0669
CCBs	TAM	3,232	65.16	904	64.38	0.6926	798	66.04	0.6702	260	68.08	0.3772
	PDCp	2,106	96.72	582	96.39	0.7919	527	96.39	0.8101	177	90-95	0.2907
	PDCa	3,232	64.98	904	65.82	0.6665	798	65.29	0.9008	260	65.38	0.9477
diuretics	TAM	4,418	67.36	1,339	70.20	0.0550	1,162	63.86	0.0264	379	73.35	0.0194
	PDCp	2,976	94.72	940	95.74	0.2453	742	95.15	0.7091	278	96.04	0.4188
	PDCa	4,418	65.23	1,339	69.83	0.0020	1,162	61.79	0.0317	379	70.98	0.0275
lipid-regs	TAM	13,204	82.19	2,426	78.32	> 0.0001	2,966	81.63	0.4810	649	79.82	0.1360
	PDCp	10,853	95.68	1,900	96.00	0.5636	2,421	94.88	0.0950	518	96.91	0.2131
	PDCa	13,204	78.52	2,426	75.02	0.0001	2,966	77.28	0.1436	649	75.35	0.0616
nitrates	TAM	2,792	62.64	769	67.75	0.0103	869	61.57	0.5941	265	66.04	0.3045
	PDCp	1,749	95.88	521	96.55	0.5812	535	95.14	0.5350	175	95-100	2.4607
	PDCa	2,792	60.64	769	65.41	0.0179	869	59.38	0.5334	265	67.55	0.0323
Range across all classes		***Min***	58.84		54.50			57.65			54.39	
		Max	97.89		98.19			97.71			100.00	

Table 7.4.4 Adherence by comorbidity in the secondary prevention with treatment group at one year

p-values derived from Fisher's exact test where n < 5; In all other instances, p derived from chi-squared test. Percentages are rounded where the number of nonadherent people is < 10 to protect anonymity (while the number of nonadherent patients is not provided, it could otherwise be inferred from percentages).

Patients with neither diabetes nor depression as a comorbidity were found to be the most adherent group overall. They were the most adherent in 11 of the 30 instances studied, whereas they were only found to be the least adherent group in 3 cases: PDCa for anti-anginals, PDCa for CCBs, and PDCp for diuretics.

For the group of patients who presented with both diabetes and depression, there is some conflict in the findings. In 9 out of 30 instances, they were found to be most adherent of all four groups, however in 10 cases they were the least adherent group. Similarly, there was some inconsistency in the diabetes patients, as they were most adherent in 5 cases and least adherent in 5 cases.

Like the findings for the secondary-prevention group, adherence is never found to be highest in the patients who have depression as a comorbidity, for any drug-class or adherence measure. This matches our expectations following the literature review (**Chapter 2**) and the findings in the primary prevention and treatment groups.

On a class-by-class level there is general agreement in which drug-classes patients are most persistent to. For patients with neither comorbidity, diabetes only, or those with depression only, persistence was greatest for antiplatelets (82, 78, 82% respectively), lipid-regulators (again, rounds up to 82, 78, and 82% respectively), and BBS (81, 78, 80%). Similarly, patients who have both diabetes and depression, were most persistent to lipid-regulators (80%), ARBs (79%), and antiplatelets (79%). Notably in all cases, the differences between the drug-classes are marginal for each comorbidity group – within a range of 2% for the top three classes.

Persistence is markedly lower in alpha-blockers compared to other drug-classes, across all comorbidity sub-groups, ranging from 54-59%. Persistence is also low for; nitrates in patients with neither comorbidity and those with depression only (63% and 62% respectively); CCBs for those with diabetes only (64%); and antianginals for those with both diabetes and depression.

7.5 Comparison of Primary Prevention, Treatment, Secondary Prevention, and Secondary Prevention with Treatment

Drug Class	Adherence measure	n Patients	n adherent	% adherent	n Patients	n adherent	% adherent	p-value	n Patients	n adherent	% adherent	p-value	n Patients	n adherent	% adherent	p-value
a-blockers	TAM	46,270	24,607	53.18	12,306	7,272	59.09	> 0.0001	176	120	68.18	> 0.0001	828	481	58.09	0.0056
	PDCp	24,607	22,116	89.88	7,272	6,527	89.76	0.7797	120	108	90.00	1.0000	481	441	91.68	0.2199
	PDCa	46,270	24,097	52.08	12,306	7,049	57.28	> 0.0001	176	110	62.50	0.0072	828	483	58.33	0.0004
ACEi	TAM	242,340	155,603	64.21	73,036	54,431	74.53	> 0.0001	4,749	3755	79.07	> 0.0001	15,898	12290	77.31	> 0.0001
	PDCp	155,603	140,097	90.03	54,431	50,097	92.04	> 0.0001	3,755	3557	94.73	> 0.0001	12,290	11559	94.05	> 0.0001
	PDCa	242,340	149,389	61.64	73,036	52,855	72.37	> 0.0001	4,749	3688	77.66	> 0.0001	15,898	12262	77.13	> 0.0001
anti_anginal	TAM	2,772	1,395	50.32	27,955	17,478	62.52	> 0.0001	669	453	67.71	> 0.0001	3,647	2421	66.38	> 0.0001
	PDCp	1,395	1,221	87.53	17,478	15,585	89.17	0.0649	453	415	91.61	0.0223	2,421	2229	92.07	> 0.0001
	PDCa	2,772	1,314	47.40	27,955	16,766	59.97	> 0.0001	669	441	65.92	> 0.0001	3,647	2431	66.66	> 0.0001
antiplatelets	TAM	154,897	86,457	55.82	119,861	87,906	73.34	> 0.0001	5,964	5234	87.76	> 0.0001	20,677	16877	81.62	> 0.0001
	PDCp	86,457	69,539	80.43	87,906	75,393	85.77	> 0.0001	5,234	5086	97.17	> 0.0001	16,877	16121	95.52	> 0.0001
	PDCa	154,897	73,478	47.44	119,861	79,002	65.91	> 0.0001	5,964	5348	89.67	> 0.0001	20,677	17437	84.33	> 0.0001
ARB	TAM	90,709	65,149	71.82	30,219	23,169	76.67	> 0.0001	1,041	874	83.96	> 0.0001	4,409	3271	74.19	0.0007
	PDCp	65,149	59,563	91.43	23,169	21,564	93.07	> 0.0001	874	822	94.05	0.0070	3,271	3109	95.05	> 0.0001
	PDCa	90,709	63,159	69.63	30,219	22,733	75.23	> 0.0001	1,041	845	81.17	> 0.0001	4,409	3311	75.10	> 0.0001
BBs	TAM	272,680	110,430	40.50	98,128	72,214	73.59	> 0.0001	5,124	4427	86.40	> 0.0001	18,092	14561	80.48	> 0.0001
	PDCp	110,430	81,047	73.39	72,214	65,765	91.07	> 0.0001	4,427	4233	95.62	> 0.0001	14,561	13778	94.62	> 0.0001
	PDCa	272,680	86,902	31.87	98,128	68,756	70.07	> 0.0001	5,124	4361	85.11	> 0.0001	18,092	14462	79.94	> 0.0001
CCBs	TAM	249,336	150,974	60.55	72,004	48,594	67.49	> 0.0001	1,219	889	72.93	> 0.0001	5,610	3655	65.15	> 0.0001
	PDCp	150,974	132,059	87.47	48,594	43,507	89.53	> 0.0001	889	814	91.56	0.0003	3,655	3374	92.31	> 0.0001
	PDCa	249,336	140,628	56.40	72,004	46,033	63.93	> 0.0001	1,219	839	68.83	> 0.0001	5,610	3634	64.78	> 0.0001
diuretics	TAM	203,300	110,354	54.28	74,473	49,640	66.66	> 0.0001	1,922	1457	75.81	> 0.0001	7,898	5352	67.76	> 0.0001
	PDCp	110,354	90,229	81.76	49,640	42,469	85.55	> 0.0001	1,457	1314	90.19	> 0.0001	5,352	4805	89.78	> 0.0001
	PDCa	203,300	96,186	47.31	74,473	44,929	60.33	> 0.0001	1,922	1366	71.07	> 0.0001	7,898	5199	65.83	> 0.0001
lipid-regs	TAM	263,761	184,966	70.13	121,092	96,832	79.97	> 0.0001	5,791	5137	88.71	> 0.0001	20,466	16686	81.53	> 0.0001
	PDCp	184,966	148,761	80.43	96,832	83,168	85.89	> 0.0001	5,137	4681	91.12	> 0.0001	16,686	15206	91.13	> 0.0001
	PDCa	263,761	155,471	58.94	121,092	86,347	71.31	> 0.0001	5,791	4803	82.94	> 0.0001	20,466	15911	77.74	> 0.0001
nitrates	TAM	4,112	1,922	46.74	47,145	28,001	59.39	> 0.0001	825	565	68.48	> 0.0001	5,056	3203	63.35	> 0.0001
	PDCp	1,922	1,679	87.36	28,001	24,388	87.10	0.7688	565	506	89.56	0.1820	3,203	2900	90.54	0.0004
	PDCa	4,112	1,791	43.56	47,145	25,814	54.75	> 0.0001	825	530	64.24	> 0.0001	5,056	3107	61.45	> 0.0001
Range	**Min**			31.87			54.75				62.50				58.09	
	Max			91.43			93.07				97.17				95.52	

Table 7.5 Adherence levels between different prevention and treatment groups at one year

Across the ten drug-classes and three adherence measures, adherence ranges from 32-91% for the primary prevention group, 55-93% for the treatment group, 63-97% for the secondary prevention group, and 58-96% for the secondary-treatment group. Consistently, adherence is higher in the secondary prevention group compared with the others and is consistently lowest in the primary prevention group. Broadly, we can infer that adherence is higher overall for those who have previously suffered an MI (secondary prevention, secondary prevention with treatment) compared to those who have not (primary prevention, treatment).

The drug-classes to which patients are most or least persistent differ by patient group, however there are some consistencies. Lipid-regulatory drugs are one of the classes to which patients are most persistent (primary: 70%, treatment: 80%, secondary: 89%, secondary-treatment: 82%) and nitrates are a class to which they are all least persistent (p: 47%, t: 59%, s: 68%, s-t: 63%). Two other drug-classes that generally have low-persistence across all four groups are alpha-blockers (p: 53%, t: 59%, s: 68%, s-t: 58%) and antianginals (p: 50%, t: 63%, s: 68%, s-t: 66%). The secondary-treatment group also has comparatively lower persistence to CCBs (65%).

BBs are the class to which primary prevention patients are least persistent (40%); however, for patients who have suffered an MI (secondary prevention, secondary prevention with treatment), BBs are the class to which they are third-most persistent (s: 86%, s-t: 80%). Persistence to BBs is therefore in some way associated to the different CVD disease severities.

Persistence also differs by disease severity for some of the drugs to which patients are most persistent. Those in the primary prevention and treatment groups are, alongside lipid-regulatory drugs, most persistent to ARBs (respectively 72% and 77% for primary and treatment) and ACEi's (65% and 75%). Besides lipid-regs and BBs, the secondary and secondary-treatment group are most persistent to antiplatelets after 1 year of treatment (respectively 88% and 82%).

7.6 Discussion of adherence epidemiology

7.6.1 Sex and Age

Across all four patient groups, male sex is associated with greater adherence. There is a notable exception to this, as women tend to be more adherent to nitrate drugs compared with men. This fits-in with findings from the systematic review of reviews (**Chapter 2**).

The strong association between age and adherence observed in the primary group may be worth further consideration in the subsequent multi-variate analysis. The primary prevention group has a mean age approximately 8 years younger than the three other groups (treatment, secondary prevention, etc.) and so may impact differences between the groups. Equally, there is a higher representation of women in the younger primary prevention group compared with the other three groups (**Table 7.6**), so this may also have a confounding effect.

	Primary	Treat	Secondary	Secondary-Treatment
Age below 55, n (%)				
male	263,987 (41.8)	21,594 (54.0)	3,656 (74.4)	3,274 (74.5)
female	367,780 (58.2)	18,430 (46.0)	1,256 (25.6)	1,120 (25.5)
Age 55 – 65, n (%)				
male	201,484 (49.5)	36,413 (55.4)	4,681 (72.0)	4,383 (72.3)
female	205,821 (50.5)	29,365 (44.6)	1,818 (28.0)	1,679 (27.7)
Age over 65, n (%)				
male	251,611 (40.6)	74,477 (48.1)	7,887 (56.9)	7,726 (57.6)
female	368,883 (59.4)	80,237 (51.9)	5,985 (43.1)	5,684 (42.4)
Total, n (%)				
male	717082 (43.2)	132,484 (50.9)	16,224 (64.2)	15,383 (64.5)
female	942484 (56.8)	128,032 (49.1)	9,059 (35.8)	8,483 (35.5)

Table 7.6: Age-Sex distributions

This could also explain lower adherence to BBs in the primary prevention group as, in fact, it is one of the drug classes with the highest levels of adherence in the treatment, secondary prevention, and secondary prevention with treatment groups. This may be due to prescriptions for anxiety which have not been

identified and removed during data-cleaning steps, despite attempts to account for this (see **Chapter 4**).

Young people may be more likely to be prescribed BBs for anxiety rather than CVD, which means it may be taken to manage anxiety symptoms as they occur rather than as a daily CVD prophylactic. This could also impact lower adherence to BBs in those with depression as a comorbidity (**see Table 7.1.4**) as it may be more likely that this is due to prescriptions with an anxiety indication, rather than for CVD. As depression and anxiety often present together, this could confound results for this class of medication. As the treatment, secondary prevention, and combined groups have evidence of symptomatic CVD, it may be more likely that BB prescriptions observed here are for a CVD indication, rather than anxiety.

7.6.2 Deprivation

SIMD does not have a strong association with adherence at the univariate level, though for all patient groups there is a trend toward more-affluent (high SIMD) groups being associated with higher adherence, and for the primary prevention, secondary prevention, and secondary prevention with treatment groups, it appears to be a dose-dependent association. Notably, compared to the other characteristics studied (i.e. age, sex, etc) SIMD did not have a differential effect on adherence between the drug-classes, in that for all levels of SIMD, patients were generally found to be most or least persistent to the same drug-classes. It is possible that there is less of an effect than we may expect, as people from low-SIMD areas and who are taking medications in the first place have already accessed health services and may be more motivated, compared to those in low-SIMD areas who have been unable to access services in the first instance, and who therefore could not be observed in this study.

It is also important to note that in Scotland, there is universal, free-at-the-point-of-access healthcare. This could mean that socioeconomic factors have a lesser impact on drug adherence compared to that observed in other settings (e.g. in the US). A 2017 study found that initiation of DOACs is roughly equivalent between the different SIMD groups in Scotland[206], suggesting that

this observation may be replicated across other measures of adherence and CVD drug-classes too.

7.6.3 Comorbidities

Across the different comorbidities, findings were somewhat inconsistent. From the literature review, diabetes was associated with higher adherence to CVD medications, while depression was associated with lower adherence. This finding was replicated in the primary prevention and treatment groups and, on balance, the positive effect on adherence that diabetes was associated with seemed to cancel out the negative effect of depression, as those with both conditions were found to be slightly more adherent than those with neither condition. In the secondary prevention group, adherence was again highest for those with diabetes as a comorbidity, but those with neither comorbidity were this time more adherent than those with both. In this instance, those with depression were in fact more adherent than those with both diabetes and depression, a finding that was also replicated in the secondary prevention with treatment group.

This variation between patient groups could be due to interactions with polypharmacy. Patients with more severe CVD may be on many more medications to manage their condition. There is evidence in the literature that polypharmacy can have a negative impact on adherence[207], and may make for an interesting follow-up to this study in order to investigate this interaction.

7.6.4 Drug-classes

Adherence is generally low for nitrates, antianginals, and alpha-blockers. Compared with the other drug classes, adherence is particularly low for nitrates for all patient groups, despite excluding records labelled with ‘as-required’ from the analysis. This could be due to missing information, as the NLP algorithm may have missed records where the free-text dosage instructions used alternate phrasing or if there was insufficient information in the free-text instructions in the first place.

It is notable that there are 4,112 people in the primary prevention group investigated for adherence to nitrates, and 836 in the secondary prevention group (**Tables 7.1.1, 7.3.2**). Had classification of patients into non-symptomatic (primary and secondary prevention) and symptomatic (treatment and secondary-with-treatment) carried out in **Chapter 4** been accurate, there would be no prescriptions of nitrates or anti-anginals in these groups, as these drugs are only prescribed for angina or heart failure. This indicates possible misclassification of the patient groups, as only GTN was used to differentiate these patients, while other drugs such as isosorbide dinitrate, isosorbide mononitrate, and ivabradine may also have been considered. It is also possible that some of these patients are truly primary or secondary prevention patients who have been prescribed GTN for a non-CVD indication, namely in treating anal fissures; however, these should have been removed in data-cleaning steps as prescriptions for topical formulations of GTN were removed.

Consistently, adherence is found to be high for lipid-regulatory drugs, ACEi's, and ARBs. BBs and antiplatelets are also frequently associated with high adherence, with notable exceptions in the primary prevention group for BBs and in younger (below-55) patients for antiplatelets.

Notably, adherence to antiplatelets for the first year following an MI is higher compared to those in the primary prevention or treatment groups. This is, in a way, reassuring as clopidogrel and ticagrelor are two important antiplatelet medications, which are a key component of secondary prevention therapies. Aspirin as a prophylactic for the primary prevention and treatment groups may have lower adherence or may only appear to have lower adherence as it can be purchased readily over-the-counter and would not be picked up by PIS.

7.6.5 Adherence-measures

Overall trends show very high implementation in patients who are persistent (PDCp) suggesting that generally, patients who persist with treatment tend to implement their regimens quite well. This means that efforts to understand barriers to persistence may be more important than considering implementation. Going forward for the multi-variate analysis, TAM will be the measure used.

7.6.6 Limitations

There are some limitations to this analysis: adherence may appear higher than it truly is because this analysis excludes people who leave the patient group early; this is an issue for the secondary prevention group, as the median time spent in this group is very short - only about 4 months. As this study is comparing across 10 drug classes, it also has quite a generous definition of adherence compared to other studies that look at drugs individually. Here, people are identified as adherent if they have any prescription of that class, compared to other studies which may have more strict definitions of drug switching.

7.7 Multivariate Analysis

	Primary		Treatment		Secondary		Secondary-Treat	
	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value
ACEi								
sex female	0.7 (0.68-0.71)	p<0.001	0.72 (0.70-0.75)	p<0.001	0.62 (0.53-0.72)	p<0.001	0.84 (0.77-0.91)	p<0.001
age 55 to 65	0.98 (0.96-1.00)	p=0.076	1.11 (1.04-1.17)	p=0.001	0.87 (0.69-1.09)	p=0.230	0.86 (0.77-0.96)	p=0.009
age above 65	0.87 (0.85-0.89)	p<0.001	1.12 (1.06-1.18)	p<0.001	0.67 (0.55-0.82)	p<0.001	0.63 (0.57-0.70)	p<0.001
diabetes	1.16 (1.12-1.19)	p<0.001	1.21 (1.14-1.27)	p<0.001	1.01 (0.80-1.28)	p=0.940	0.87 (0.78-0.98)	p=0.023
depression	0.93 (0.91-0.96)	p<0.001	0.98 (0.94-1.04)	p=0.550	0.8 (0.65-0.99)	p=0.034	0.9 (0.81-1.01)	p=0.062
diabetes and depression	1.11 (1.05-1.18)	p=0.001	1.15 (1.06-1.26)	p=0.001	1.05 (0.68-1.68)	p=0.826	0.84 (0.68-1.05)	p=0.112
SIMD mid	1.04 (1.02-1.06)	p<0.001	1.04 (1.00-1.09)	p=0.062	1.01 (0.84-1.20)	p=0.943	1.04 (0.94-1.15)	p=0.449
SIMD low	1.08 (1.06-1.11)	p<0.001	1.1 (1.05-1.15)	p<0.001	1.07 (0.88-1.29)	p=0.513	1.05 (0.94-1.16)	p=0.391
Model fit (c-stat)	5.60E-01		5.52E-01		0.5911754		5.67E-01	
Antiplatelet								
sex female	0.6 (0.59-0.62)	p<0.001	0.68 (0.67-0.70)	p<0.001	0.84 (0.71-1.00)	p=0.047	0.96 (0.88-1.03)	p=0.252
age 55 to 65	2.39 (2.32-2.46)	p<0.001	1.73 (1.66-1.80)	p<0.001	1.19 (0.91-1.57)	p=0.205	0.83 (0.74-0.93)	p=0.002
age above 65	3.15 (3.07-3.24)	p<0.001	2.69 (2.59-2.79)	p<0.001	0.66 (0.52-0.83)	p<0.001	0.57 (0.52-0.64)	p<0.001

diabetes	1.07 (1.02-1.11)	p=0.002	1.24 (1.18-1.30)	p<0.001	0.82 (0.65-1.04)	p=0.091	0.81 (0.73-0.91)	p<0.001
depression	1.22 (1.18-1.25)	p<0.001	1.01 (0.98-1.05)	p=0.518	1 (0.79-1.28)	p=0.996	0.92 (0.83-1.02)	p=0.124
diabetes and depression	1.42 (1.31-1.54)	p<0.001	1.46 (1.35-1.57)	p<0.001	1.09 (0.69-1.84)	p=0.722	0.76 (0.63-0.92)	p=0.005
SIMD mid	1.07 (1.04-1.10)	p<0.001	1.07 (1.03-1.11)	p<0.001	1.05 (0.86-1.28)	p=0.637	1.06 (0.96-1.16)	p=0.235
SIMD low	1.16 (1.12-1.19)	p<0.001	1.18 (1.14-1.22)	p<0.001	0.93 (0.75-1.14)	p=0.477	1.08 (0.98-1.19)	p=0.131
Model fit	6.36E-01		6.07E-01		0.5838904		5.69E-01	
BBs								
sex female	0.73 (0.72-0.74)	p<0.001	0.73 (0.71-0.75)	p<0.001	0.92 (0.78-1.10)	p=0.372	1 (0.92-1.08)	p=0.918
age 55 to 65	2.12 (2.08-2.17)	p<0.001	1.64 (1.57-1.71)	p<0.001	1.23 (0.95-1.59)	p=0.111	0.88 (0.78-0.99)	p=0.037
age above 65	3.42 (3.35-3.50)	p<0.001	2.28 (2.19-2.37)	p<0.001	0.88 (0.70-1.10)	p=0.277	0.65 (0.59-0.73)	p<0.001
diabetes	1.38 (1.32-1.44)	p<0.001	1.26 (1.20-1.33)	p<0.001	0.88 (0.69-1.12)	p=0.285	0.85 (0.76-0.95)	p=0.005
depression	0.93 (0.91-0.95)	p<0.001	0.88 (0.84-0.91)	p<0.001	0.9 (0.71-1.16)	p=0.419	0.85 (0.76-0.95)	p=0.004
diabetes and depression	1.32 (1.23-1.42)	p<0.001	1.2 (1.10-1.30)	p<0.001	1.49 (0.87-2.80)	p=0.176	0.76 (0.62-0.94)	p=0.011
SIMD mid	1.07 (1.05-1.09)	p<0.001	1.05 (1.01-1.09)	p=0.009	1.02 (0.83-1.24)	p=0.875	1.02 (0.93-1.13)	p=0.646
SIMD low	1.1 (1.07-1.12)	p<0.001	1.17 (1.13-1.22)	p<0.001	0.91 (0.73-1.13)	p=0.403	1.03 (0.93-1.14)	p=0.593
Model fit	6.47E-01		5.95E-01		5.48E-01		5.55E-01	
Lipid-regs								
sex female	0.82 (0.81-0.84)	p<0.001	0.7 (0.68-0.72)	p<0.001	0.69 (0.58-0.82)	p<0.001	0.94 (0.87-1.02)	p=0.133
age 55 to 65	1.37 (1.34-1.40)	p<0.001	1.5 (1.43-1.57)	p<0.001	1.23 (0.93-1.62)	p=0.151	0.85 (0.76-0.96)	p=0.007
age above 65	1.39 (1.36-1.42)	p<0.001	1.91 (1.83-1.99)	p<0.001	0.76 (0.60-0.96)	p=0.025	0.66 (0.60-0.73)	p<0.001
diabetes	1.38 (1.34-1.43)	p<0.001	1.35 (1.29-1.42)	p<0.001	0.84 (0.66-1.09)	p=0.191	0.8 (0.72-0.89)	p<0.001
depression	1.05 (1.02-1.07)	p<0.001	1.09 (1.05-1.13)	p<0.001	0.89 (0.70-1.15)	p=0.380	0.92 (0.83-1.03)	p=0.146
diabetes and depression	1.66 (1.56-1.76)	p<0.001	1.6 (1.47-1.73)	p<0.001	1 (0.63-1.69)	p=0.988	0.83 (0.69-1.02)	p=0.075
SIMD mid	0.96 (0.94-0.99)	p=0.001	1 (0.97-1.04)	p=0.905	0.89 (0.71-1.10)	p=0.265	1.07 (0.97-1.17)	p=0.173
SIMD low	1 (0.97-1.02)	p=0.703	1.07 (1.03-1.11)	p=0.001	0.83 (0.66-1.04)	p=0.107	1.09 (0.99-1.20)	p=0.090
Model fit	5.53E-01		5.83E-01		0.5878772		5.55E-01	

Table 7.7: Multivariate analysis in each of the patient groups for selected drug-classes.

Table 7.7 shows the results of the multivariate analysis, and **Figure 7.1** depicts these as a forest plot. The odds-ratio here relates to the 'risk of persistence' i.e. an OR below 1 indicates that the risk factor is associated with lower levels of persistence, while an OR above 1 indicates an association with increased levels of persistence.

In all patient groups, female sex is associated with poorer persistence compared to the referent group (male). In the primary prevention and treatment groups, this is significant for all four drug-classes studied. In the secondary prevention group, this is significant for all drug-classes other than BBs, and for the secondary prevention with treatment group, this is only significant for ACEi's.

The clearest positive association between older age and higher persistence is in the treatment group. Compared to the referent (below-55 years), persistence tends to increase with increased age, as the over-65-year group has an even stronger association than that observed in the 55-65-year group. ACEi's are the one exception to this, where the positive association slightly decreases between the 55-65 and over-65-year groups. In the primary prevention group, antiplatelet drugs and BBs also show an increased association with persistence as age increases; as do lipid-regulatory drugs, but to a lesser extent. ACEi's are again an exception, where there is a non-significant difference in the association with persistence observed between the referent group and the 55-65-year group, and a reduced association with persistence observed in the over-65s compared to the below-55s.

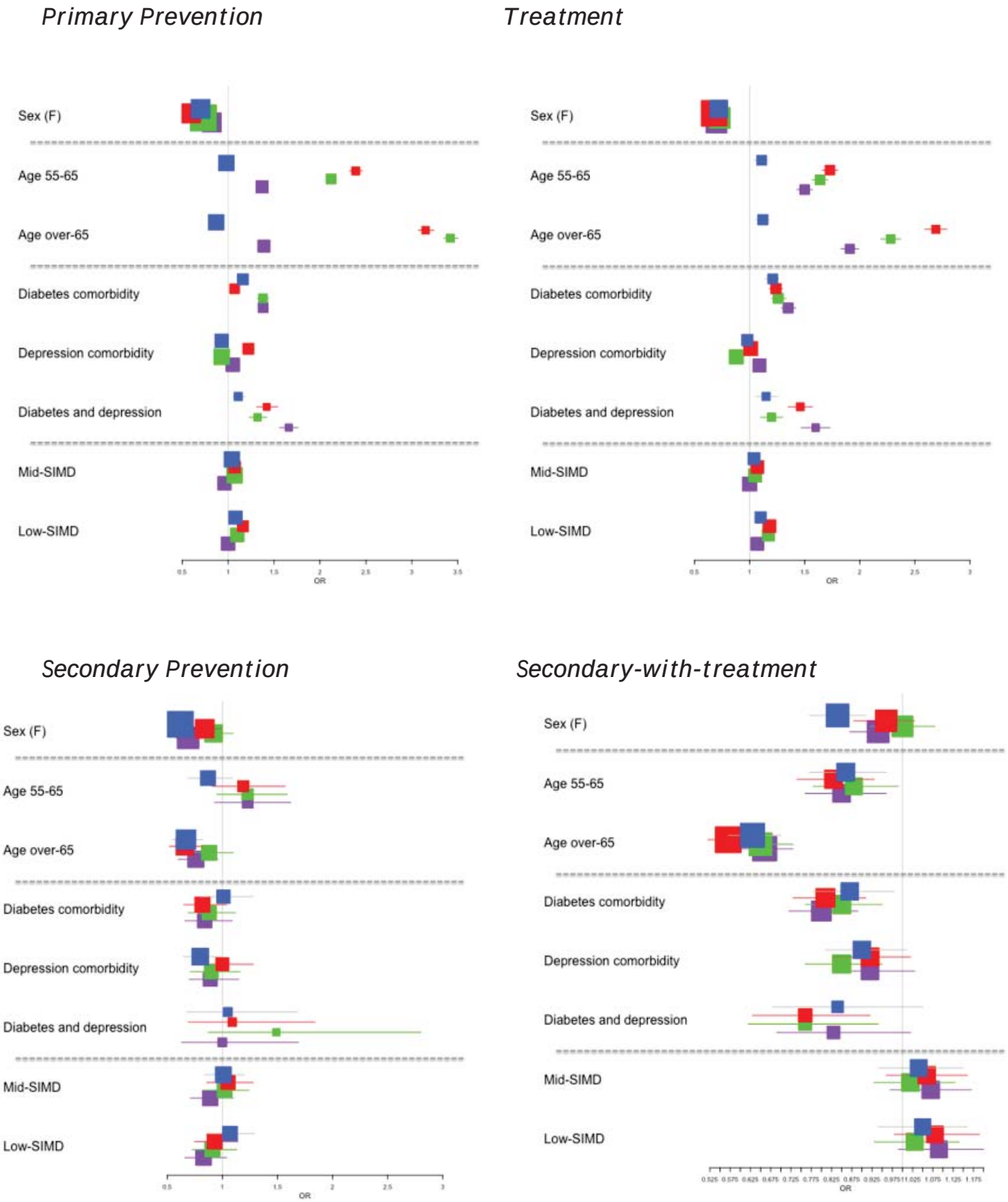

Figure 7.1: Multivariate odds-ratios of persistence to CVD drugs: blue = ACEi, red = antiplatelet, green = betablockers, purple = lipid-regulatory

In the secondary prevention group, none of the drug-classes show a significant difference between the referent (below-55) and 55-65-year group. For the group aged over-65, there is an association with reduced persistence, significant in all drug-classes other than BBs. The secondary prevention with treatment group shows almost the exact inverse of the relationship observed in the primary prevention group: all drug-classes are associated with reduced levels of persistence, and this is 'dose-dependent', with the oldest age group showing the poorest persistence.

In the primary prevention and treatment groups, diabetes as a comorbidity is associated with higher levels of persistence compared to the referent group. This is significant in all drug classes and is also true of the patients who have both diabetes and depression as comorbidities, compared to the referent group who have neither. The association between depression and persistence is less clear. In the primary prevention group, depression is associated with lower levels of persistence for ACEi's and BBs, but higher persistence for antiplatelet drugs and lipid-regulatory drugs. This is also true of the treatment group, though ACEi's and antiplatelets show non-significant differences between the persistence predicted in the referent group with the depressed group.

For secondary prevention there are no significant associations between the comorbidities studied and persistence, except for depression, which is associated with poorer persistence to ACEi's. For the secondary prevention with treatment patients, the presence of either diabetes, depression, or both diabetes and depression as a comorbidity tends to be associated with decreased persistence levels, though this is only significant for diabetes across all four drug-classes. Persistence to BBs is significantly associated with decreased persistence in those with depression and those with both depression and diabetes, while persistence to antiplatelets is significantly associated with decreased persistence only in patients with both comorbidities.

Across the four patient groups and drug-classes, there are no clear patterns between SIMD and persistence. In the primary prevention and treatment groups, there is an association with lower SIMD (i.e. most deprived) and increased persistence, for ACEi's, antiplatelet drugs and BBs. For lipid-regulatory drugs,

this is only significant in the treatment group. In the secondary prevention and secondary prevention with treatment groups, there are no significant interactions

7.8 Discussion of Multivariate Analysis

Observations of decreased persistence being associated with female sex replicates results observed in literature review (**Chapter 2**). This could be mediated through disease severity, as it is well-established that women tend to suffer less severely from CVD compared to men[202, 203]. If it follows that male patients tend to have higher blood-pressure or higher cholesterol at baseline, or that they have suffered a much more severe MI, the urgency for CVD prophylaxis may be more substantial. Furthermore, as men are generally at higher risk of CVD, and this risk is communicated to them, it could contribute to different health perceptions and an increased motivation to persist with therapy. This theory could be backed up by the fact that there is a non—significant difference between the sexes in the most severe CVD group, the secondary prevention with treatment group, indicating that patients who have both suffered an MI and have symptomatic CVD persist regardless of sex. Specifically, there is not a sex-difference for BBs and antiplatelets, which are key drug-classes recommended for use following an MI.

The relationship with age and persistence seems to flip between patients who have not suffered an MI (primary prevention and treatment) vs. those who have. This suggests that disease severity may mediate the interaction between age and persistence. Again, this may be due to health perceptions, as younger people who suffer an MI may be much more likely to persist than younger patients who have not, as this is a much more tangible interaction with ill-health than this age group might otherwise be exposed to. Those who are below-55 and are asymptomatic (i.e. have high blood pressure or high cholesterol) may choose to try to mediate their risk of CVD through diet and exercise in the first instance, as lifestyle changes may be easier to implement compared to older adults.

The association between diabetes and increased adherence in the primary prevention and treatment groups may also be mediated through the patient's perception of their health. It could also be related to drug-taking being a regular

part of their routine, especially for those with Type 1 diabetes, who will be familiar with life-long daily medication taking and the risks of non-adherence or non-persistence in this context. For those who have suffered an MI, the different interaction with diabetes may be due to poorer health overall, and possible confounding from polypharmacy, leading to difficulties in management of healthcare. Following literature review, depression may have been expected to be associated with a reduction in persistence due to lack of motivation and self-efficacy. If this were the case, it is not clear why this is observed inconsistently across drug-classes. BBs, particularly propranolol, are also prescribed for anxiety, and while I attempted to filter these out in the data-cleaning stage, it is possible that these prescriptions are still represented in some instances. As depression and anxiety often present together[208], this could mean that reduced persistence in this class could be due to the BB being prescribed for this indication rather than for CV.

While there is not a clear pattern between SIMD and persistence, it does appear that, if anything, persistence is higher in those from more deprived areas. Because access to healthcare is one of the factors used to calculate SIMD, these patients have less access to such services and may have been predicted to show lower levels of persistence. It may be that those who do access these services in the first place are more highly motivated. Or, it may be important to consider the classes of drugs where we see this interaction. The most common antiplatelet drug prescribed in our dataset is aspirin, a drug that can be purchased readily and cheaply over-the-counter. Those who appear non-persistent in the most affluent patient group (here, the referent group) may have the means to purchase drugs rather than relying on prescriptions.

7.9 Chapter Summary

The epidemiology of adherence and persistence to cardiovascular drugs in Scotland largely aligns with findings observed in the literature review, with some minor discrepancies. Particularly, adherence appears to be greatest in older, male patients, and those with more severe CVD. This suggests that national datasets in Scotland can capture population levels of persistence in a reasonably reliable way and may be useful to consider in research projects where some understanding of such patient mediation-taking behaviors are of interest.

8 Results: Outcomes of Non-persistence

Following the classification of patients in each group as persistent or non-persistent over the first year of cardiovascular drug therapy, my next aim was to investigate whether there were associations between persistence and subsequent health outcomes. Here, I look at patients who were classed as persistent with TAM at the end of year 1 (for Cox-proportional hazard analyses, this is T0) and conducted all-cause mortality over 5-years post-follow-up. To investigate some of the results further, a cardiovascular drug-count variable was included to account for polypharmacy, and analysis was repeated at 1- and 5-years post follow-up, along with additional investigations to exclude patients on beta-blockers who may have been prescribed these for anxiety, and then a comparison of specific beta-blockers and antiplatelet drugs.

8.1 All-Cause Mortality: Over 5-years follow-up

8.1.1 Primary prevention

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	63,946	9,671	-	-
	Yes	343,409	43,890	0.83 (0.81-0.84, p<0.001)	0.73 (0.71-0.75, p<0.001)
Sex	F	200,165	27,563	-	-
	M	207,190	25,998	0.91 (0.89-0.92, p<0.001)	1.18 (1.16-1.20, p<0.001)
Age group	below 55	110,446	2,825	-	-
	55 to 65	118,314	7,048	2.37 (2.27-2.48, p<0.001)	2.53 (2.42-2.65, p<0.001)
	above 65	178,595	43,688	10.83 (10.42-11.25, p<0.001)	12.40 (11.91-12.90, p<0.001)
SIMD group	high	112,937	12,496	-	-
	mid	168,295	22,145	1.20 (1.18-1.23, p<0.001)	1.20 (1.17-1.23, p<0.001)
	low	125,277	18,772	1.38 (1.35-1.42, p<0.001)	1.45 (1.42-1.49, p<0.001)
Comorbidty Status	neither	272,139	32,323	-	-
	diabetes	59,815	9,268	1.33 (1.30-1.36, p<0.001)	1.29 (1.26-1.32, p<0.001)
	depression	40,755	6,264	1.33 (1.29-1.36, p<0.001)	1.67 (1.62-1.71, p<0.001)
	both	11,343	2,114	1.63 (1.56-1.71, p<0.001)	2.09 (2.00-2.18, p<0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	75,836	13,871	-	-
	Yes	275,850	62,322	1.26 (1.23-1.28, p<0.001)	1.04 (1.02-1.06, p<0.001)
Sex	F	182,229	41,611	-	-
	M	169,457	34,582	0.88 (0.87-0.89, p<0.001)	1.07 (1.05-1.08, p<0.001)
Age group	below 55	43,050	1,777	-	-
	55 to 65	85,182	6,894	2.00 (1.90-2.11, p<0.001)	2.16 (2.04-2.28, p<0.001)
	above 65	223,454	67,522	8.54 (8.14-8.95, p<0.001)	9.96 (9.48-10.48, p<0.001)
SIMD group	high	91,812	18,014	-	-
	mid	143,694	31,195	1.12 (1.10-1.14, p<0.001)	1.15 (1.13-1.18, p<0.001)
	low	115,415	26,763	1.21 (1.18-1.23, p<0.001)	1.33 (1.31-1.36, p<0.001)
Comorbidty Status	neither	217,477	46,345	-	-
	diabetes	56,802	10,134	0.82 (0.80-0.84, p<0.001)	1.00 (0.98-1.02, p=0.972)
	depression	42,192	12,102	1.42 (1.40-1.45, p<0.001)	1.71 (1.67-1.74, p<0.001)
	both	11,527	2,611	1.07 (1.03-1.12, p<0.001)	1.61 (1.55-1.68, p<0.001)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	101,176	7,489	-	-
	Yes	257,411	36,765	1.99 (1.94-2.04, p<0.001)	0.92 (0.89-0.94, p<0.001)
Sex	F	215,483	24,724	-	-
	M	143,104	19,530	1.20 (1.18-1.23, p<0.001)	1.24 (1.22-1.26, p<0.001)
Age group	below 55	134,562	3,381	-	-
	55 to 65	83,633	5,590	2.72 (2.60-2.84, p<0.001)	2.92 (2.79-3.06, p<0.001)
	above 65	140,392	35,283	11.35 (10.96-11.76, p<0.001)	13.17 (12.66-13.69, p<0.001)
SIMD group	high	94,921	10,713	-	-
	mid	143,906	18,207	1.13 (1.10-1.16, p<0.001)	1.18 (1.15-1.21, p<0.001)
	low	118,891	15,218	1.14 (1.12-1.17, p<0.001)	1.39 (1.36-1.43, p<0.001)
Comorbidty Status	neither	230,409	28,315	-	-
	diabetes	25,858	5,144	1.69 (1.64-1.74, p<0.001)	1.32 (1.28-1.36, p<0.001)
	depression	75,370	6,833	0.73 (0.71-0.75, p<0.001)	1.40 (1.36-1.44, p<0.001)
	both	5,850	1,181	1.73 (1.63-1.83, p<0.001)	1.94 (1.83-2.06, p<0.001)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	75,410	10,490	-	-
	Yes	474,515	63,077	0.94 (0.92-0.96, p<0.001)	0.78 (0.76-0.80, p<0.001)
Sex	F	275,171	38,392	-	-
	M	274,754	35,175	0.91 (0.90-0.93, p<0.001)	1.19 (1.18-1.21, p<0.001)
Age group	below 55	107,741	3,035	-	-
	55 to 65	172,033	10,021	2.10 (2.02-2.19, p<0.001)	2.40 (2.30-2.51, p<0.001)
	above 65	270,151	60,511	8.87 (8.56-9.20, p<0.001)	11.22 (10.79-11.66, p<0.001)
SIMD group	high	146,080	16,518	-	-
	mid	223,284	29,665	1.19 (1.17-1.21, p<0.001)	1.20 (1.17-1.22, p<0.001)
	low	179,440	27,181	1.37 (1.34-1.40, p<0.001)	1.47 (1.44-1.50, p<0.001)
Comorbidty Status	neither	336,824	41,597	-	-
	diabetes	93,674	12,991	1.13 (1.11-1.15, p<0.001)	1.33 (1.30-1.35, p<0.001)
	depression	63,558	10,289	1.35 (1.32-1.38, p<0.001)	1.70 (1.66-1.74, p<0.001)
	both	20,374	3,486	1.43 (1.38-1.48, p<0.001)	2.20 (2.13-2.28, p<0.001)

Table 8.1. Mortality 5-years *after* classed as persistent or not with TAM (T0) in the primary group, across four CVD drug-classes.

In the primary prevention group, patients who were persistent at T0 with antiplatelets were, counterintuitively, at a higher hazard of death in the next 5 years, even after adjusting for sex, age, SIMD-group, and comorbidity status. For beta-blockers, persistence in the first year of therapy was associated with a reduced hazard of mortality when adjusted for the additional risk factors. For ACEi's and lipid-regulatory drugs, persistence is associated with reduced mortality in the uni- and multivariate analyses. Risk factors associated with poorer survival - male sex, older age, deprived SIMD group, and comorbidities – follow the expected pattern for all four drug-classes in the multivariable analysis, and this is especially strong for older age (above 65 years), where hazard ratios range from 9.96-13.17.

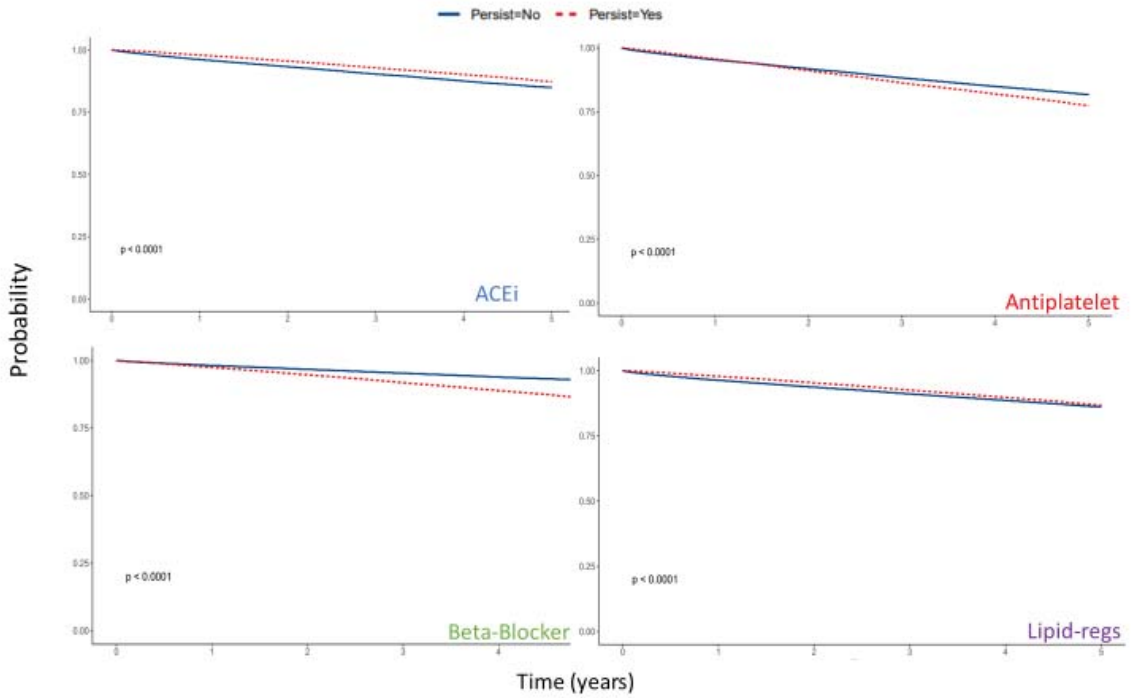

Figure 8.1 Survival Curves - 5-years *after* classed as persistent or not with TAM (T0) in the primary group, across four CVD drug-classes.

Survival analysis (**Figure 8.1**) shows a relatively low number of mortalities over 5-years following assessment of TAM, as may be expected for the relatively younger primary prevention patients. There is little difference in survival rates between those who were found to be persistent and those who were not. For anti-platelets and beta-blockers, the survival lines cross at around 2-years, indicating a failure of the cox-model assumption here. Further analysis of Schoenfeld residuals (**Appendix F**) indicates that these models may indeed be flawed.

8.1.2 Treatment

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	8,999	2,654	-	-
	Yes	59,884	13,211	0.70 (0.67-0.73, p<0.001)	0.68 (0.65-0.71, p<0.001)
Sex	F	29,131	6,723	-	-
	M	39,752	9,142	1.00 (0.97-1.03, p=0.861)	1.16 (1.12-1.20, p<0.001)
Age group	below 55	7,109	403	-	-
	55 to 65	17,511	1,869	1.94 (1.74-2.16, p<0.001)	2.00 (1.78-2.24, p<0.001)
	above 65	44,263	13,593	6.30 (5.70-6.95, p<0.001)	7.22 (6.51-8.01, p<0.001)
SIMD group	high	14,273	3,010	-	-
	mid	26,722	6,034	1.08 (1.04-1.13, p<0.001)	1.12 (1.07-1.18, p<0.001)
	low	27,770	6,786	1.18 (1.13-1.24, p<0.001)	1.33 (1.27-1.39, p<0.001)
Comorbidty Status	neither	41,818	8,986	-	-
	diabetes	10,227	2,721	1.28 (1.22-1.33, p<0.001)	1.29 (1.24-1.35, p<0.001)
	depression	8,757	2,111	1.15 (1.10-1.21, p<0.001)	1.41 (1.35-1.48, p<0.001)
	both	3,028	820	1.31 (1.22-1.41, p<0.001)	1.75 (1.63-1.88, p<0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	17,507	3,540	-	-
	Yes	111,052	24,660	1.10 (1.06-1.14, p<0.001)	0.89 (0.86-0.92, p<0.001)
Sex	F	61,899	13,538	-	-
	M	66,660	14,662	1.01 (0.98-1.03, p=0.533)	1.16 (1.13-1.19, p<0.001)
Age group	below 55	13,181	698	-	-
	55 to 65	32,148	2,983	1.79 (1.65-1.94, p<0.001)	1.91 (1.75-2.08, p<0.001)
	above 65	83,230	24,519	6.42 (5.95-6.92, p<0.001)	7.64 (7.05-8.28, p<0.001)
SIMD group	high	27,319	5,494	-	-
	mid	49,507	10,756	1.09 (1.06-1.13, p<0.001)	1.14 (1.10-1.18, p<0.001)
	low	51,504	11,877	1.17 (1.13-1.20, p<0.001)	1.33 (1.29-1.38, p<0.001)
Comorbidty Status	neither	81,104	16,773	-	-
	diabetes	14,340	3,681	1.28 (1.23-1.32, p<0.001)	1.28 (1.23-1.32, p<0.001)
	depression	19,116	4,433	1.14 (1.11-1.18, p<0.001)	1.44 (1.39-1.49, p<0.001)
	both	4,449	1,188	1.35 (1.27-1.43, p<0.001)	1.80 (1.70-1.91, p<0.001)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	11,558	2,269	-	-
	Yes	82,553	17,062	1.04 (1.00-1.09, p=0.053)	0.86 (0.82-0.90, p<0.001)
Sex	F	42,855	8,785	-	-
	M	51,256	10,546	1.01 (0.98-1.03, p=0.692)	1.16 (1.13-1.20, p<0.001)
Age group	below 55	10,046	527	-	-
	55 to 65	24,173	2,096	1.68 (1.53-1.85, p<0.001)	1.72 (1.56-1.90, p<0.001)
	above 65	59,892	16,708	6.07 (5.57-6.62, p<0.001)	6.95 (6.35-7.61, p<0.001)
SIMD group	high	21,327	4,102	-	-
	mid	36,723	7,432	1.06 (1.02-1.10, p=0.004)	1.11 (1.07-1.16, p<0.001)
	low	35,896	7,754	1.14 (1.09-1.18, p<0.001)	1.31 (1.26-1.37, p<0.001)
Comorbidty Status	neither	60,734	11,752	-	-
	diabetes	11,080	2,785	1.35 (1.29-1.40, p<0.001)	1.33 (1.27-1.38, p<0.001)
	depression	12,693	2,606	1.07 (1.03-1.12, p=0.001)	1.35 (1.30-1.41, p<0.001)
	both	2,999	800	1.46 (1.36-1.56, p<0.001)	1.91 (1.78-2.06, p<0.001)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	12,632	2,974	-	-
	Yes	119,088	25,001	0.86 (0.83-0.89, p<0.001)	0.73 (0.70-0.76, p<0.001)
Sex	F	62,502	13,061	-	-
	M	69,218	14,914	1.04 (1.01-1.06, p=0.002)	1.20 (1.17-1.23, p<0.001)
Age group	below 55	13,070	669	-	-
	55 to 65	33,643	3,107	1.84 (1.70-2.00, p<0.001)	2.01 (1.84-2.19, p<0.001)
	above 65	85,007	24,199	6.37 (5.90-6.88, p<0.001)	7.76 (7.15-8.42, p<0.001)
SIMD group	high	28,084	5,417	-	-
	mid	50,718	10,556	1.09 (1.05-1.13, p<0.001)	1.13 (1.10-1.17, p<0.001)
	low	52,699	11,935	1.20 (1.16-1.24, p<0.001)	1.36 (1.31-1.41, p<0.001)
Comorbidty Status	neither	81,940	16,162	-	-
	diabetes	15,670	4,043	1.35 (1.31-1.40, p<0.001)	1.36 (1.31-1.41, p<0.001)
	depression	19,290	4,292	1.15 (1.11-1.19, p<0.001)	1.44 (1.40-1.49, p<0.001)
	both	4,895	1,279	1.39 (1.31-1.47, p<0.001)	1.88 (1.77-1.99, p<0.001)

Table 8.2 Mortality 5-years *after* classed as persistent or not with TAM (T0) in the treatment group, across four CVD drug-classes.

For the treatment group, the hazard ratio indicates a reduced 5-year risk of mortality in patients classed as persistent at T0 across all four drug-classes in the multivariate analyses.

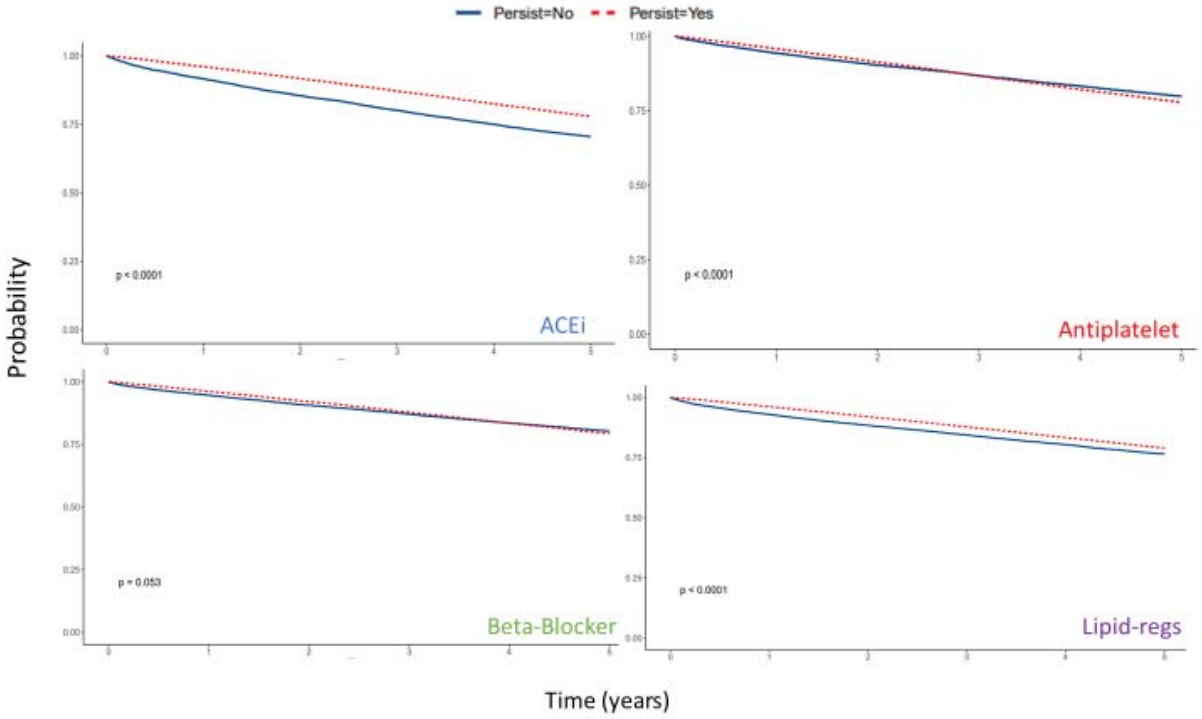

Figure 8.2 Survival Curves - 5-years after classed as persistent or not with TAM (T0) in the treatment group, across four CVD drug-classes.

Survival analyses for the treatment group (**Figure 8.2**) indicates reduced risk of mortality in persistent patients over 5-years for those on ACEi's and lipid-regulatory drugs, though little difference between persistent and non-persistent patients for those prescribed beta-blockers or antiplatelet drugs, with survival curves crossing at the 3.5-year (antiplatelet) and 4-year (beta-blocker) marks. This indicates that hazards are not proportional overtime, and the underlying assumptions of the Cox proportional hazards model have failed.

8.1.3 Secondary prevention

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	434	62	-	-
	Yes	1,908	235	0.81 (0.61-1.07, p=0.138)	0.80 (0.60-1.07, p=0.134)
Sex	F	783	132	-	-
	M	1,559	165	0.60 (0.48-0.75, p<0.001)	0.81 (0.63-1.03, p=0.089)
Age group	below 55	514	10	-	-
	55 to 65	703	46	3.46 (1.75-6.86, p<0.001)	3.89 (1.89-7.98, p<0.001)
	above 65	1,125	241	12.44 (6.61-23.41, p<0.001)	14.00 (7.16-27.35, p<0.001)
SIMD group	high	656	75	-	-
	mid	986	126	1.13 (0.85-1.51, p=0.398)	1.21 (0.90-1.63, p=0.214)
	low	694	96	1.24 (0.92-1.68, p=0.156)	1.53 (1.12-2.10, p=0.008)
Comorbidty Status	neither	1,658	174	-	-
	diabetes	252	45	1.79 (1.29-2.49, p<0.001)	1.61 (1.16-2.24, p=0.004)
	depression	291	47	1.59 (1.15-2.19, p=0.005)	1.68 (1.21-2.34, p=0.002)
	both	44	11	2.65 (1.44-4.87, p=0.002)	3.25 (1.76-5.99, p<0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	279	68	-	-
	Yes	2,588	372	0.49 (0.38-0.63, p<0.001)	0.54 (0.41-0.71, p<0.001)
Sex	F	1,019	206	-	-
	M	1,848	234	0.59 (0.49-0.72, p<0.001)	0.79 (0.65-0.97, p=0.023)
Age group	below 55	582	12	-	-
	55 to 65	793	55	3.44 (1.84-6.43, p<0.001)	3.62 (1.89-6.96, p<0.001)
	above 65	1,492	373	14.06 (7.91-24.97, p<0.001)	14.74 (8.06-26.94, p<0.001)
SIMD group	high	815	118	-	-
	mid	1,205	186	1.08 (0.86-1.36, p=0.516)	1.18 (0.92-1.50, p=0.190)
	low	840	136	1.14 (0.89-1.45, p=0.308)	1.41 (1.09-1.83, p=0.009)
Comorbidty Status	neither	1,973	245	-	-
	diabetes	322	68	1.81 (1.38-2.36, p<0.001)	1.62 (1.24-2.12, p<0.001)
	depression	367	71	1.62 (1.24-2.11, p<0.001)	1.80 (1.38-2.35, p<0.001)
	both	65	20	2.82 (1.79-4.45, p<0.001)	3.27 (2.07-5.16, p<0.001)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	296	52	-	-
	Yes	2,121	287	0.69 (0.51-0.93, p=0.014)	0.75 (0.55-1.03, p=0.078)
Sex	F	841	157	-	-
	M	1,576	182	0.59 (0.48-0.73, p<0.001)	0.79 (0.63-0.99, p=0.044)
Age group	below 55	515	10	-	-
	55 to 65	694	48	3.67 (1.86-7.26, p<0.001)	4.08 (1.99-8.36, p<0.001)
	above 65	1,208	281	13.75 (7.32-25.84, p<0.001)	14.64 (7.50-28.58, p<0.001)
SIMD group	high	668	86	-	-
	mid	1,018	148	1.15 (0.88-1.50, p=0.311)	1.27 (0.95-1.69, p=0.102)
	low	726	105	1.15 (0.86-1.53, p=0.346)	1.40 (1.03-1.90, p=0.030)
Comorbidty Status	neither	1,673	181	-	-
	diabetes	286	61	2.09 (1.57-2.80, p<0.001)	1.80 (1.34-2.40, p<0.001)
	depression	297	52	1.67 (1.23-2.28, p=0.001)	1.86 (1.36-2.54, p<0.001)
	both	50	14	2.89 (1.68-4.97, p<0.001)	3.51 (2.03-6.06, p<0.001)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	250	53	-	-
	Yes	2,537	346	0.52 (0.39-0.69, p<0.001)	0.57 (0.42-0.77, p<0.001)
Sex	F	981	184	-	-
	M	1,806	215	0.60 (0.49-0.73, p<0.001)	0.80 (0.65-0.99, p=0.037)
Age group	below 55	571	11	-	-
	55 to 65	785	53	3.59 (1.88-6.88, p<0.001)	3.84 (1.94-7.59, p<0.001)
	above 65	1,431	335	14.03 (7.69-25.58, p<0.001)	15.00 (7.97-28.24, p<0.001)
SIMD group	high	783	103	-	-
	mid	1,171	174	1.14 (0.90-1.46, p=0.279)	1.28 (0.99-1.66, p=0.058)
	low	826	122	1.15 (0.89-1.50, p=0.293)	1.38 (1.04-1.82, p=0.025)
Comorbidty Status	neither	1,926	221	-	-
	diabetes	310	61	1.82 (1.37-2.42, p<0.001)	1.60 (1.20-2.12, p=0.001)
	depression	352	65	1.66 (1.26-2.19, p<0.001)	1.82 (1.37-2.40, p<0.001)
	both	66	19	2.90 (1.81-4.63, p<0.001)	3.37 (2.11-5.38, p<0.001)

Table 8.3 Mortality 5-years *after* classed as persistent or not with TAM (T0) in the secondary group, across four CVD drug-classes.

Patients classed as persistent at T0 in the secondary-prevention group are associated with a lower risk of mortality across all four-drug classes. Unlike the primary prevention and treatment groups, adjustment for potential confounders raises hazard ratios; though these remain below 1 and remain significant for the antiplatelets and lipid-regulatory drugs. Generally, traditional risk-factors for mortality present with a hazard ratio above one in the univariable and multivariable analyses, with the notable exception of male sex, which is associated with lower levels of mortality, significant in the adjusted results for antiplatelets, beta-blockers, and lipid-regulatory drugs.

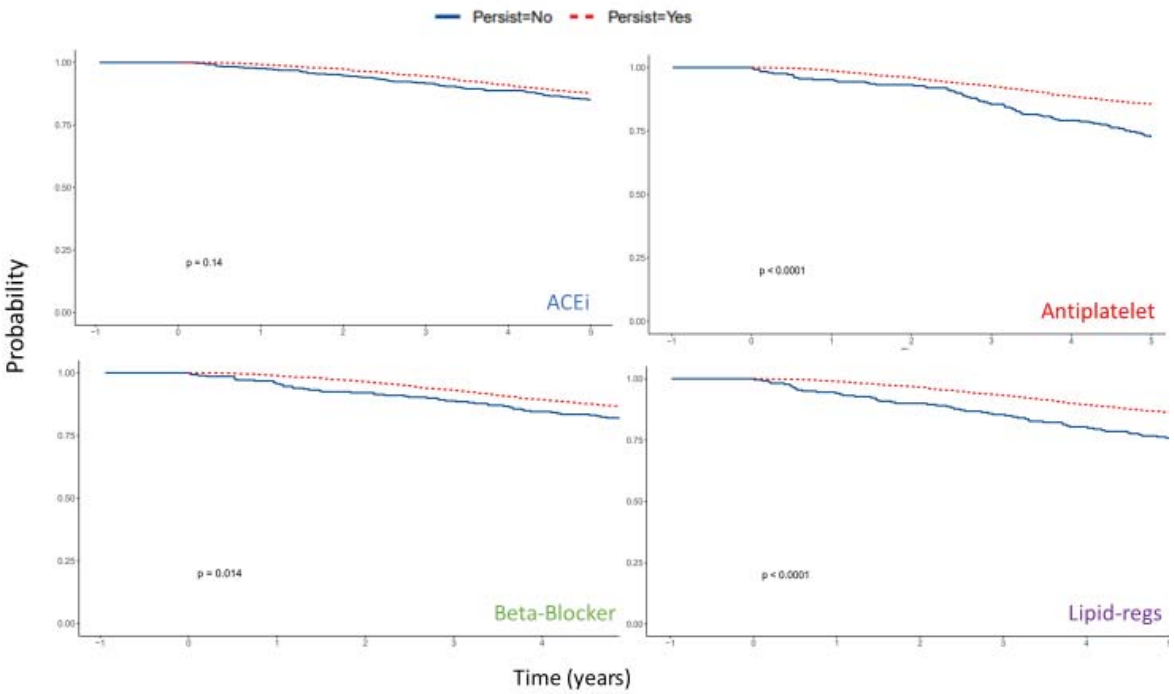

Figure 8.3 Survival Curves - 5-years after classed as persistent or not with TAM (T0) in the secondary prevention group, across four CVD drug-classes.

For all four drug-classes, survival analyses in secondary prevention patients (**Figure 8.3**) indicate an association with better survival in persistent patients compared to non-persistent patients, though this is not significant for those prescribed ACEi's ($p = 0.14$). For antiplatelets, hazards are not directly proportional overtime, as the gap between survival for persistent vs non-persistent patients widens from around 2.5 years onwards.

8.1.4 Secondary prevention progressing to treatment

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	607	156	-	-
	Yes	3,960	629	0.57 (0.48-0.68, p<0.001)	0.67 (0.56-0.81, p<0.001)
Sex	F	1,485	337	-	-
	M	3,082	448	0.61 (0.53-0.70, p<0.001)	0.90 (0.77-1.05, p=0.178)
Age group	below 55	1,139	44	-	-
	55 to 65	1,336	102	2.02 (1.42-2.88, p<0.001)	2.07 (1.43-3.01, p<0.001)
	above 65	2,092	639	9.30 (6.85-12.63, p<0.001)	10.15 (7.34-14.03, p<0.001)
SIMD group	high	992	151	-	-
	mid	1,792	290	1.08 (0.89-1.32, p=0.421)	1.15 (0.94-1.41, p=0.177)
	low	1,777	343	1.31 (1.08-1.58, p=0.006)	1.55 (1.27-1.89, p<0.001)
Comorbidty Status	neither	3,078	427	-	-
	diabetes	481	141	2.32 (1.92-2.81, p<0.001)	2.12 (1.75-2.56, p<0.001)
	depression	643	121	1.41 (1.15-1.72, p=0.001)	1.68 (1.37-2.07, p<0.001)
	both	123	34	2.16 (1.52-3.06, p<0.001)	2.21 (1.55-3.15, p<0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	396	120	-	-
	Yes	5,352	997	0.56 (0.46-0.68, p<0.001)	0.60 (0.49-0.73, p<0.001)
Sex	F	2,013	494	-	-
	M	3,735	623	0.65 (0.58-0.73, p<0.001)	0.95 (0.84-1.08, p=0.425)
Age group	below 55	1,320	58	-	-
	55 to 65	1,600	128	1.86 (1.37-2.54, p<0.001)	1.93 (1.39-2.68, p<0.001)
	above 65	2,828	931	8.95 (6.86-11.66, p<0.001)	9.94 (7.51-13.15, p<0.001)
SIMD group	high	1,297	227	-	-
	mid	2,303	436	1.10 (0.94-1.29, p=0.245)	1.18 (0.99-1.39, p=0.058)
	low	2,141	452	1.24 (1.06-1.45, p=0.009)	1.48 (1.25-1.75, p<0.001)
Comorbidty Status	neither	3,805	599	-	-
	diabetes	636	201	2.23 (1.90-2.62, p<0.001)	2.01 (1.71-2.36, p<0.001)
	depression	813	179	1.47 (1.24-1.74, p<0.001)	1.77 (1.49-2.09, p<0.001)
	both	172	54	2.21 (1.67-2.92, p<0.001)	2.27 (1.71-3.00, p<0.001)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	407	91	-	-
	Yes	4,528	837	0.79 (0.64-0.99, p=0.037)	0.76 (0.61-0.96, p=0.019)
Sex	F	1,691	407	-	-
	M	3,244	521	0.64 (0.56-0.73, p<0.001)	0.94 (0.82-1.08, p=0.413)
Age group	below 55	1,182	49	-	-
	55 to 65	1,385	110	1.96 (1.40-2.75, p<0.001)	1.96 (1.38-2.78, p<0.001)
	above 65	2,368	769	9.32 (6.99-12.45, p<0.001)	10.05 (7.44-13.58, p<0.001)
SIMD group	high	1,114	188	-	-
	mid	1,965	360	1.10 (0.93-1.32, p=0.270)	1.15 (0.95-1.38, p=0.142)
	low	1,848	378	1.24 (1.04-1.48, p=0.016)	1.48 (1.23-1.77, p<0.001)
Comorbidty Status	neither	3,294	499	-	-
	diabetes	578	182	2.33 (1.96-2.76, p<0.001)	2.06 (1.74-2.45, p<0.001)
	depression	664	141	1.46 (1.21-1.77, p<0.001)	1.76 (1.45-2.12, p<0.001)
	both	136	40	2.14 (1.55-2.96, p<0.001)	2.25 (1.62-3.12, p<0.001)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	357	103	-	-
	Yes	5,325	984	0.59 (0.48-0.73, p<0.001)	0.63 (0.51-0.78, p<0.001)
Sex	F	1,972	477	-	-
	M	3,710	610	0.65 (0.58-0.73, p<0.001)	0.96 (0.84-1.09, p=0.512)
Age group	below 55	1,310	57	-	-
	55 to 65	1,583	125	1.86 (1.36-2.54, p<0.001)	1.93 (1.39-2.68, p<0.001)
	above 65	2,789	905	8.86 (6.78-11.59, p<0.001)	9.81 (7.39-13.02, p<0.001)
SIMD group	high	1,276	211	-	-
	mid	2,285	431	1.17 (0.99-1.38, p=0.065)	1.28 (1.07-1.52, p=0.006)
	low	2,113	444	1.31 (1.11-1.54, p=0.001)	1.57 (1.32-1.86, p<0.001)
Comorbidty Status	neither	3,762	583	-	-
	diabetes	640	204	2.30 (1.96-2.70, p<0.001)	1.99 (1.69-2.33, p<0.001)
	depression	791	167	1.42 (1.19-1.68, p<0.001)	1.67 (1.40-1.99, p<0.001)
	both	166	49	2.09 (1.56-2.79, p<0.001)	2.08 (1.55-2.79, p<0.001)

Table 8.4: Mortality 5-years *after* classed as persistent or not with TAM (T0) in the secondary-with-treatment group, across four CVD drug-classes.

In secondary-with-treatment patients, persistence at T0 is significantly associated with reduced mortality over 5-years across all four drug-classes in both the univariable and multivariable analyses. Like the secondary group, adjusting for other risk factors increases the hazard ratios, except for beta-blockers where adjustment reduced the hazard ratio from 0.79 to 0.76.

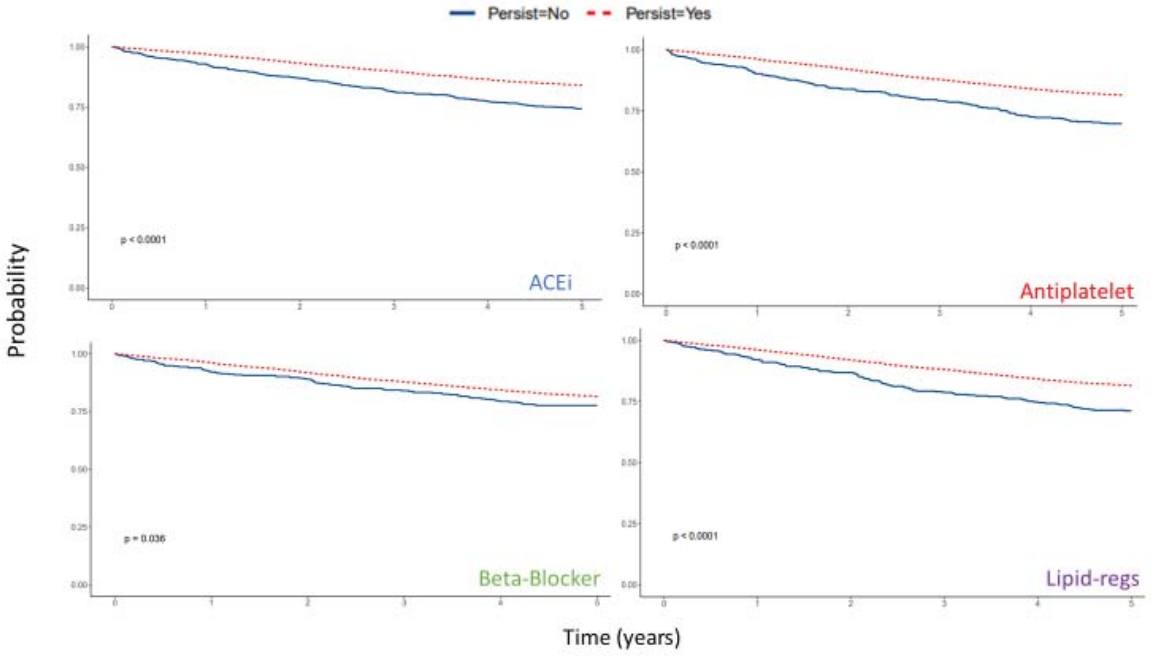

Figure 8.4 Survival Curves - 5-years after classed as persistent or not with TAM (T0) in the secondary-with-treatment group, across four CVD drug-classes.

Survival analyses for the secondary-with-treatment group indicates a significant association between persistence at T0 with 5-year survival across all four drug-classes. In this instance, hazards are roughly proportional overtime, validating the use of Cox proportional hazards models.

8.1.5 Summary: 5-year mortality

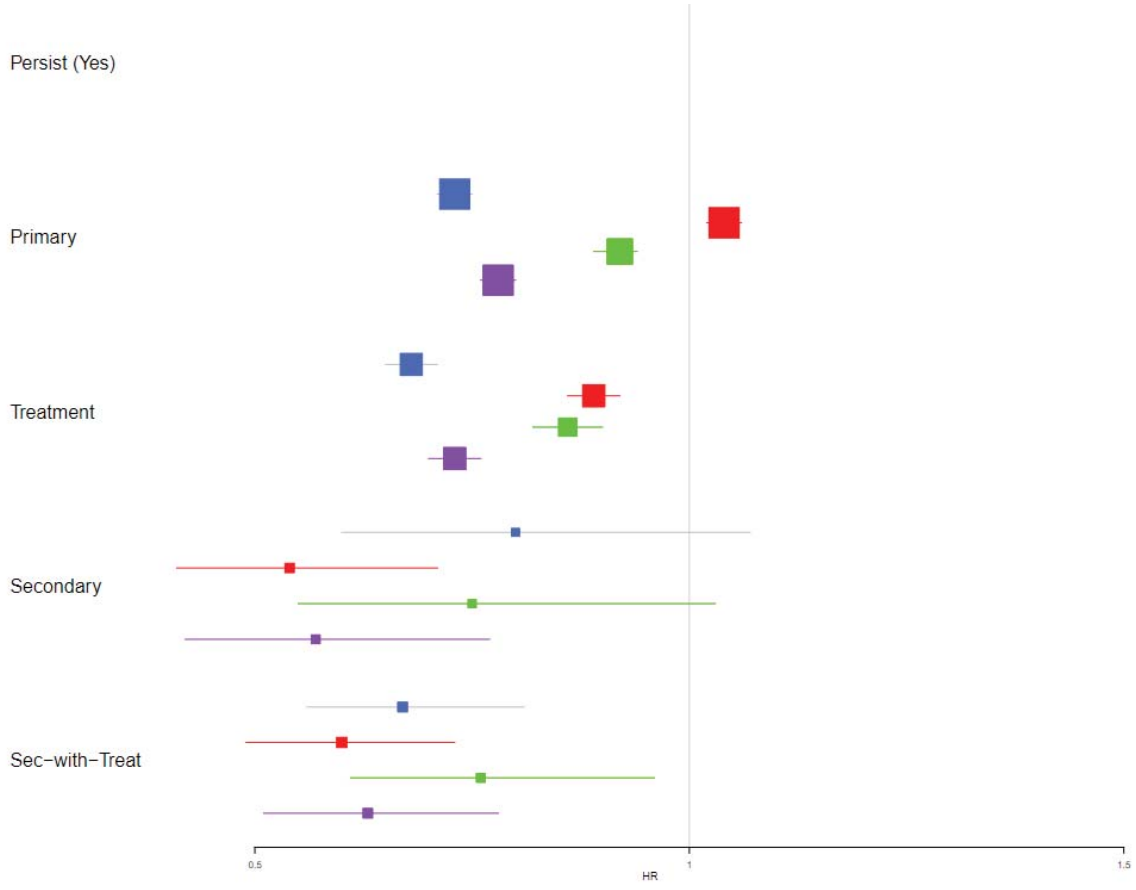

Figure 8.5: Mortality 5-years *after* classed as persistent with TAM in each of the four patient groups (Primary, Treatment, Secondary, Secondary-with-Treatment): adjusted for sex, age, SIMD, and comorbidity. Blue = ACEi, Red = Antiplatelet, Green = BBs, Purple = Lipid-regulatory.

Figure 8.5 pools together the multivariable results presented across **Tables 8.1, 8.2., 8.3, and 8.4.** From the plot, it appears that the different patient groups have similar associations between persistence at T0 and all-cause mortality five-years on from the observation period, for whom persistence is generally associated with reduced mortality. Notably, patients prescribed antiplatelet drugs in the primary prevention group are the sole outlier, with an increased risk of mortality if they have persisted to medication for their first year of prescription. As increased persistence was associated with traditional CVD risk-factors (in **Chapter 7**), there could be residual confounding from disease severity that is unaccounted for, especially as there may be misclassification of primary patients due to: some symptomatic patients never presenting at hospital and so being missed, failure to include all the relevant ICD-10 codes in our classification of CVD-history, and the possible limit of solely using GTN to identify patients

with angina symptoms. This is particularly pertinent for this class of drugs, as antiplatelets would not commonly be prescribed to those with mild evidence of CVD, and it may be that those who persist to antiplatelet drugs in this group in fact have more severe heart disease, while those who do not persist may have had a one-off prescription e.g. aspirin for pain-relief.

For the secondary prevention group, the confidence intervals cross 1 for ACEi and beta-blocker drugs, though this may be in-part due to reduced power due to the smaller group size (e.g. ACEi's include 2,342 patients total in the secondary group, vs 407,355 in the primary, and 68,663 in the treatment group).

It is also plausible that this result is nonsignificant due to residual confounding, with persistence being higher in those with worse symptoms who are also likely to have the most severe disease. In the absence of data on actual disease severity, the number of cardiovascular drugs prescribed is used as a proxy measure here. The 'drug-count' variable was used to indicate the number of different CVD drugs a patient was taking during the observation year (up until time T0), from the 10 drug-classes initially studied.

8.2 All-Cause Mortality: 5-year follow-up including a 'drug-count' variable

Addition of the drug-count variable (**Figure 8.6**) did not greatly change the associations observed (further tables included in **Appendix G**). The results also showed an inconsistent, and at times unexpected relationship with morality, as in some instances, patients with this highest drug count had lower mortality compared to those with fewer medications. This indicates that this drug-count variable may instead be working as a proxy for disease management, especially for secondary prevention patients who require a certain degree of co-prescribing for effective disease management; or it may be possible that this measure is not very meaningful in the way is has been defined. A more accurate assessment of polypharmacy and co-prescribing may be of value in future study.

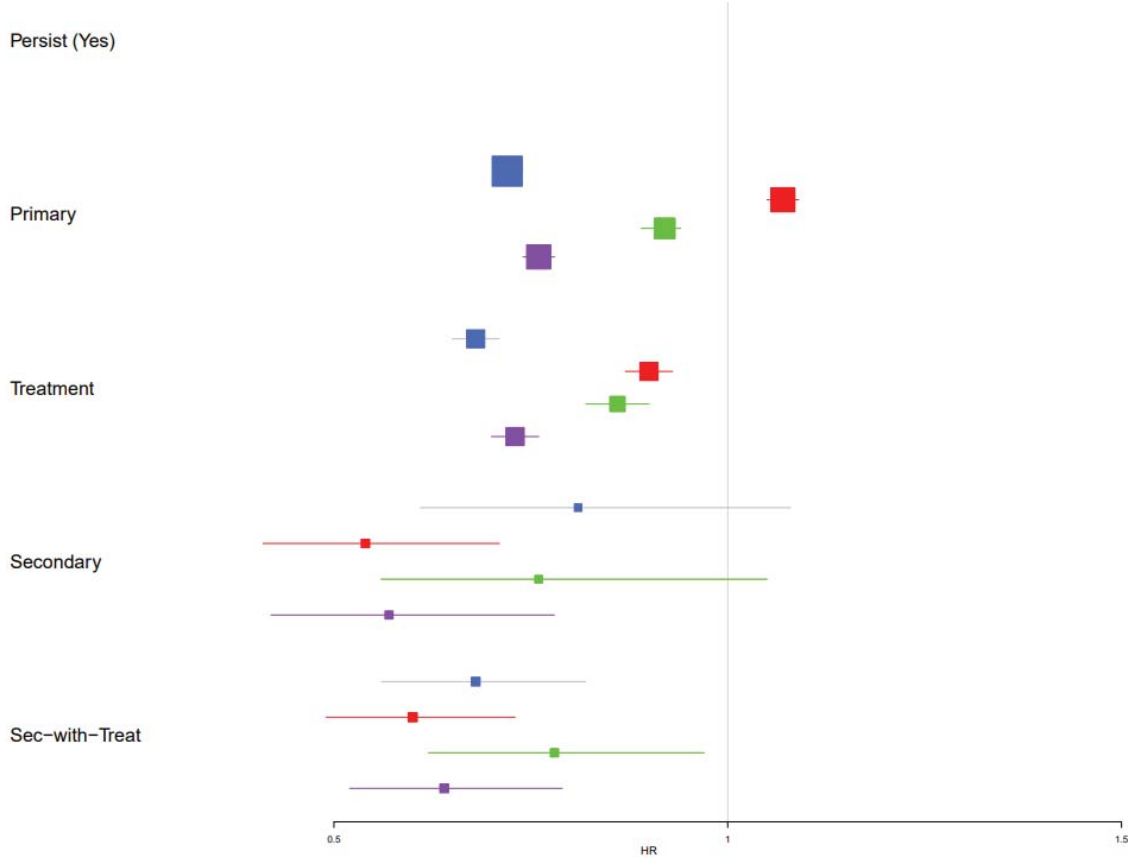

Figure 8.6: Mortality 5-years *after* classed as persistent with TAM in each of the four patient groups (Primary, Treatment, Secondary, Secondary-with-Treatment): adjusted for cvd-drug-count, sex, age, SIMD, and comorbidity. Blue = ACEi, Red = Antiplatelet, Green = BBs, Purple = Lipid-regulatory.

As persistence may have changed over the five-years on from my measurements, and as survival curves crossed for several of the drug-classes/ patient groups, additional analyses to investigate mortality 1-year on from T0 was conducted next.

8.3 All-Cause Mortality: 1-year follow-up

8.3.1 Primary prevention

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	107,759	3,302	-	-
	Yes	435,403	8,429	0.63 (0.60-0.65, p<0.001)	0.55 (0.53-0.58, p<0.001)
Sex	F	267,357	5,897	-	-
	M	275,805	5,834	0.96 (0.92-0.99, p=0.022)	1.28 (1.23-1.33, p<0.001)
Age group	below 55	167,864	721	-	-
	55 to 65	158,072	1,595	2.36 (2.16-2.57, p<0.001)	2.57 (2.34-2.82, p<0.001)
	above 65	217,226	9,415	10.29 (9.54-11.10, p<0.001)	12.23 (11.30-13.24, p<0.001)
SIMD group	high	150,732	2,731	-	-
	mid	223,917	4,851	1.20 (1.14-1.26, p<0.001)	1.21 (1.15-1.27, p<0.001)
	low	167,399	4,107	1.36 (1.29-1.43, p<0.001)	1.44 (1.37-1.52, p<0.001)
Comorbidty Status	neither	367,220	6,925	-	-
	diabetes	72,027	1,850	1.37 (1.30-1.44, p<0.001)	1.34 (1.27-1.41, p<0.001)
	depression	58,526	1,639	1.49 (1.41-1.58, p<0.001)	1.92 (1.82-2.03, p<0.001)
	both	14,008	486	1.85 (1.69-2.03, p<0.001)	2.37 (2.16-2.60, p<0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	111,889	4,577	-	-
	Yes	325,412	14,029	1.05 (1.02-1.09, p=0.003)	0.80 (0.78-0.83, p<0.001)
Sex	F	229,865	10,014	-	-
	M	207,436	8,592	0.95 (0.92-0.98, p<0.001)	1.13 (1.10-1.17, p<0.001)
Age group	below 55	70,235	533	-	-
	55 to 65	108,385	1,712	2.09 (1.90-2.30, p<0.001)	2.31 (2.08-2.56, p<0.001)
	above 65	258,681	16,361	8.58 (7.87-9.35, p<0.001)	10.62 (9.69-11.64, p<0.001)
SIMD group	high	114,570	4,395	-	-
	mid	178,072	7,609	1.12 (1.08-1.16, p<0.001)	1.15 (1.11-1.20, p<0.001)
	low	143,677	6,540	1.19 (1.15-1.24, p<0.001)	1.32 (1.27-1.38, p<0.001)
Comorbidty Status	neither	277,210	11,181	-	-
	diabetes	62,781	2,132	0.84 (0.80-0.88, p<0.001)	0.98 (0.94-1.03, p=0.422)
	depression	55,220	3,438	1.56 (1.50-1.62, p<0.001)	1.88 (1.81-1.96, p<0.001)
	both	12,932	652	1.26 (1.16-1.36, p<0.001)	1.80 (1.67-1.95, p<0.001)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	192,457	2,868	-	-
	Yes	327,018	8,471	1.75 (1.67-1.82, p<0.001)	0.78 (0.74-0.81, p<0.001)
Sex	F	316,658	6,081	-	-
	M	202,817	5,258	1.35 (1.31-1.41, p<0.001)	1.37 (1.32-1.43, p<0.001)
Age group	below 55	237,903	1,188	-	-
	55 to 65	110,746	1,491	2.71 (2.51-2.92, p<0.001)	3.08 (2.83-3.34, p<0.001)
	above 65	170,826	8,660	10.39 (9.78-11.04, p<0.001)	13.22 (12.35-14.15, p<0.001)
SIMD group	high	135,328	2,692	-	-
	mid	206,745	4,666	1.14 (1.08-1.19, p<0.001)	1.21 (1.15-1.27, p<0.001)
	low	176,013	3,953	1.13 (1.08-1.19, p<0.001)	1.43 (1.36-1.50, p<0.001)
Comorbidty Status	neither	320,793	7,027	-	-
	diabetes	31,812	1,201	1.74 (1.63-1.85, p<0.001)	1.29 (1.21-1.37, p<0.001)
	depression	128,437	2,017	0.71 (0.68-0.75, p<0.001)	1.43 (1.36-1.51, p<0.001)
	both	7,841	319	1.88 (1.68-2.10, p<0.001)	2.09 (1.87-2.34, p<0.001)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	112,741	3,557	-	-
	Yes	584,480	11,699	0.63 (0.61-0.65, p<0.001)	0.52 (0.50-0.54, p<0.001)
Sex	F	347,262	7,697	-	-
	M	349,959	7,559	0.97 (0.94-1.01, p=0.108)	1.30 (1.25-1.34, p<0.001)
Age group	below 55	152,749	773	-	-
	55 to 65	224,012	2,174	1.92 (1.77-2.09, p<0.001)	2.32 (2.13-2.53, p<0.001)
	above 65	320,460	12,309	7.72 (7.18-8.30, p<0.001)	10.60 (9.81-11.45, p<0.001)
SIMD group	high	185,127	3,303	-	-
	mid	281,948	6,219	1.24 (1.19-1.29, p<0.001)	1.24 (1.19-1.30, p<0.001)
	low	228,717	5,685	1.40 (1.34-1.46, p<0.001)	1.51 (1.45-1.58, p<0.001)
Comorbidty Status	neither	434,463	8,374	-	-
	diabetes	107,862	2,451	1.18 (1.13-1.23, p<0.001)	1.41 (1.34-1.47, p<0.001)
	depression	86,051	2,512	1.52 (1.46-1.59, p<0.001)	1.96 (1.88-2.06, p<0.001)
	both	23,822	765	1.68 (1.56-1.81, p<0.001)	2.63 (2.44-2.83, p<0.001)

Table 8.5: Mortality 1-year *after* classed as persistent or not with TAM (T0) in the primary group, across four CVD drug-classes. Including drug-count

In the primary prevention group, persistence to ACEi's and lipid-regulatory drugs at T0 is associated with significantly lower mortality over the following year in both the adjusted and unadjusted analyses. For antiplatelet and beta-blockers, persistence appears to be associated with higher mortality in the unadjusted analyses, but adjusting for sex, age, drug-count, SIMD, and comorbidity, reduces the hazard ratio below 1. This indicates reduced mortality for those who persist compared to those who do not across all four drugs.

8.3.2 Treatment

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	16,461	1,129	-	-
	Yes	86,141	3,144	0.52 (0.49-0.56, p<0.001)	0.51 (0.48-0.55, p<0.001)
Sex	F	43,811	1,785	-	-
	M	58,791	2,488	1.04 (0.98-1.11, p=0.202)	1.26 (1.18-1.34, p<0.001)
Age group	below 55	12,693	97	-	-
	55 to 65	27,196	468	2.26 (1.82-2.82, p<0.001)	2.42 (1.92-3.06, p<0.001)
	above 65	62,713	3,708	7.94 (6.49-9.72, p<0.001)	9.75 (7.86-12.10, p<0.001)
SIMD group	high	22,475	848	-	-
	mid	40,278	1,636	1.08 (0.99-1.17, p=0.076)	1.09 (1.00-1.19, p=0.040)
	low	39,687	1,781	1.19 (1.10-1.30, p<0.001)	1.34 (1.23-1.46, p<0.001)
Comorbidty Status	neither	62,425	2,328	-	-
	diabetes	14,475	706	1.32 (1.21-1.43, p<0.001)	1.33 (1.22-1.44, p<0.001)
	depression	13,631	669	1.32 (1.21-1.44, p<0.001)	1.66 (1.52-1.81, p<0.001)
	both	4,384	225	1.39 (1.21-1.59, p<0.001)	1.85 (1.61-2.12, p<0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	31,732	1,438	-	-
	Yes	149,998	6,091	0.89 (0.84-0.94, p<0.001)	0.69 (0.65-0.74, p<0.001)
Sex	F	86,593	3,545	-	-
	M	95,137	3,984	1.02 (0.98-1.07, p=0.304)	1.20 (1.14-1.26, p<0.001)
Age group	below 55	22,547	180	-	-
	55 to 65	47,831	742	1.95 (1.66-2.29, p<0.001)	2.21 (1.86-2.63, p<0.001)
	above 65	111,352	6,607	7.63 (6.58-8.85, p<0.001)	10.01 (8.54-11.73, p<0.001)
SIMD group	high	40,838	1,548	-	-
	mid	70,722	2,892	1.08 (1.02-1.15, p=0.013)	1.12 (1.05-1.19, p=0.001)
	low	69,850	3,068	1.16 (1.09-1.24, p<0.001)	1.33 (1.25-1.42, p<0.001)
Comorbidty Status	neither	113,868	4,283	-	-
	diabetes	19,583	942	1.29 (1.20-1.38, p<0.001)	1.27 (1.18-1.36, p<0.001)
	depression	28,215	1,388	1.32 (1.24-1.40, p<0.001)	1.67 (1.57-1.77, p<0.001)
	both	6,385	358	1.51 (1.36-1.68, p<0.001)	1.99 (1.78-2.21, p<0.001)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	22,811	971	-	-
	Yes	116,983	4,362	0.87 (0.81-0.93, p<0.001)	0.72 (0.67-0.78, p<0.001)
Sex	F	64,142	2,389	-	-
	M	75,652	2,944	1.05 (0.99-1.10, p=0.103)	1.24 (1.17-1.31, p<0.001)
Age group	below 55	18,213	159	-	-
	55 to 65	37,123	545	1.69 (1.41-2.01, p<0.001)	1.85 (1.53-2.24, p<0.001)
	above 65	84,458	4,629	6.43 (5.49-7.53, p<0.001)	8.18 (6.91-9.70, p<0.001)
SIMD group	high	33,156	1,179	-	-
	mid	55,146	2,104	1.07 (1.00-1.15, p=0.048)	1.12 (1.04-1.21, p=0.002)
	low	51,256	2,037	1.12 (1.04-1.20, p=0.002)	1.29 (1.19-1.39, p<0.001)
Comorbidty Status	neither	89,056	3,019	-	-
	diabetes	15,754	749	1.41 (1.30-1.53, p<0.001)	1.37 (1.27-1.49, p<0.001)
	depression	20,296	863	1.26 (1.17-1.36, p<0.001)	1.62 (1.50-1.75, p<0.001)
	both	4,568	264	1.73 (1.53-1.96, p<0.001)	2.24 (1.98-2.55, p<0.001)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	21,693	1,218	-	-
	Yes	163,070	5,763	0.62 (0.58-0.66, p<0.001)	0.51 (0.48-0.54, p<0.001)
Sex	F	86,684	3,134	-	-
	M	98,079	3,847	1.09 (1.04-1.14, p=0.001)	1.30 (1.23-1.36, p<0.001)
Age group	below 55	22,093	167	-	-
	55 to 65	49,643	752	2.01 (1.70-2.38, p<0.001)	2.37 (1.98-2.83, p<0.001)
	above 65	113,027	6,062	7.27 (6.23-8.47, p<0.001)	9.92 (8.40-11.72, p<0.001)
SIMD group	high	41,584	1,428	-	-
	mid	71,802	2,686	1.09 (1.02-1.16, p=0.008)	1.12 (1.05-1.20, p=0.001)
	low	71,073	2,851	1.17 (1.10-1.25, p<0.001)	1.32 (1.24-1.41, p<0.001)
Comorbidty Status	neither	114,097	3,803	-	-
	diabetes	21,331	981	1.39 (1.30-1.49, p<0.001)	1.40 (1.30-1.50, p<0.001)
	depression	28,181	1,269	1.36 (1.28-1.45, p<0.001)	1.74 (1.63-1.86, p<0.001)
	both	7,037	379	1.64 (1.47-1.82, p<0.001)	2.24 (2.01-2.49, p<0.001)

Table 8.6: Mortality 1-year *after* classed as persistent or not with TAM (T0) in the treatment group, across four CVD drug-classes, Including drug-count

Persistence at T0 is associated with lower mortality 1-year on in adjusted and unadjusted analysis for all four drug-classes (**Table 8.6**), with HRs ranging from 0.51-0.72 for the multivariate analyses.

8.3.3 Secondary prevention

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	913	21	-	-
	Yes	3,753	37	0.40 (0.23-0.68, p=0.001)	0.44 (0.25-0.78, p=0.004)
Sex	F	1,570	33	-	-
	M	3,096	25	0.38 (0.23-0.64, p<0.001)	0.64 (0.37-1.12, p=0.119)
Age group	below 55	929	< 5	-	-
	55 to 65	1,365	< 5	2.72 (0.30-24.37, p=0.370)	1.49 (0.13-16.42, p=0.746)
	above 65	2,372	53	21.26 (2.94-153.74, p=0.002)	21.59 (2.96-157.25, p=0.002)
SIMD group	high	1,291	13	-	-
	mid	1,937	23	1.18 (0.60-2.32, p=0.641)	1.15 (0.56-2.36, p=0.713)
	low	1,430	22	1.55 (0.78-3.07, p=0.213)	1.89 (0.93-3.84, p=0.080)
Comorbidty Status	neither	3,242	28	-	-
	diabetes	504	7	1.62 (0.71-3.72, p=0.251)	1.41 (0.61-3.24, p=0.417)
	depression	570	13	2.65 (1.37-5.12, p=0.004)	2.64 (1.35-5.16, p=0.005)
	both	123	5	4.82 (1.86-12.48, p=0.001)	4.85 (1.86-12.66, p=0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	617	24	-	-
	Yes	5,229	75	0.30 (0.19-0.48, p<0.001)	0.33 (0.20-0.54, p<0.001)
Sex	F	2,116	52	-	-
	M	3,730	47	0.51 (0.34-0.75, p=0.001)	0.69 (0.45-1.06, p=0.088)
Age group	below 55	1,060	< 5	-	-
	55 to 65	1,576	6	4.03 (0.48-33.44, p=0.197)	2.19 (0.23-21.06, p=0.497)
	above 65	3,210	92	31.34 (4.37-224.90, p=0.001)	29.60 (4.11-213.27, p=0.001)
SIMD group	high	1,619	20	-	-
	mid	2,445	43	1.43 (0.84-2.43, p=0.188)	1.50 (0.86-2.63, p=0.157)
	low	1,774	36	1.66 (0.96-2.87, p=0.068)	1.96 (1.10-3.49, p=0.022)
Comorbidty Status	neither	3,962	48	-	-
	diabetes	662	17	2.17 (1.25-3.77, p=0.006)	1.89 (1.09-3.29, p=0.024)
	depression	744	18	2.00 (1.17-3.44, p=0.012)	1.95 (1.12-3.38, p=0.017)
	both	169	6	3.02 (1.29-7.06, p=0.011)	3.66 (1.56-8.58, p=0.003)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	602	19	-	-
	Yes	4,424	69	0.43 (0.26-0.71, p=0.001)	0.45 (0.26-0.77, p=0.003)
Sex	F	1,765	41	-	-
	M	3,261	47	0.62 (0.40-0.93, p=0.023)	0.90 (0.58-1.42, p=0.661)
Age group	below 55	954	0	-	-
	55 to 65	1,382	5	18877916.22 (0.00-Inf, p=0.994)	13945918.14 (0.00-Inf, p=0.995)
	above 65	2,690	83	166150525.31 (0.00-Inf, p=0.994)	192166658.44 (0.00-Inf, p=0.994)
SIMD group	high	1,384	18	-	-
	mid	2,112	38	1.38 (0.79-2.42, p=0.259)	1.39 (0.77-2.49, p=0.270)
	low	1,524	32	1.63 (0.92-2.91, p=0.096)	1.88 (1.03-3.43, p=0.039)
Comorbidty Status	neither	3,448	44	-	-
	diabetes	577	17	2.33 (1.33-4.09, p=0.003)	1.98 (1.13-3.46, p=0.017)
	depression	608	14	1.81 (0.99-3.30, p=0.054)	1.93 (1.05-3.55, p=0.034)
	both	134	5	3.00 (1.19-7.57, p=0.020)	3.64 (1.44-9.20, p=0.006)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	548	23	-	-
	Yes	5,131	68	0.26 (0.16-0.42, p<0.001)	0.28 (0.17-0.46, p<0.001)
Sex	F	2,020	45	-	-
	M	3,659	46	0.56 (0.37-0.84, p=0.005)	0.84 (0.54-1.30, p=0.430)
Age group	below 55	1,043	< 5	-	-
	55 to 65	1,556	6	4.02 (0.48-33.35, p=0.198)	2.27 (0.24-21.82, p=0.478)
	above 65	3,080	84	29.36 (4.09-210.88, p=0.001)	29.56 (4.10-213.20, p=0.001)
SIMD group	high	1,562	18	-	-
	mid	2,373	40	1.46 (0.84-2.55, p=0.180)	1.50 (0.83-2.72, p=0.178)
	low	1,735	33	1.68 (0.94-2.98, p=0.078)	2.03 (1.10-3.72, p=0.023)
Comorbidty Status	neither	3,861	47	-	-
	diabetes	633	14	1.84 (1.01-3.34, p=0.045)	1.52 (0.84-2.77, p=0.170)
	depression	717	14	1.61 (0.88-2.92, p=0.119)	1.56 (0.85-2.86, p=0.154)
	both	169	7	3.58 (1.62-7.91, p=0.002)	3.88 (1.75-8.61, p=0.001)

Table 8.7: Mortality 1-year *after* classed as persistent or not with TAM (T0) in the secondary group, across four CVD drug-classes. Including drug-count

In the secondary prevention patient group, persistence is strongly associated with lower mortality in adjusted and unadjusted analysis for all drug classes. While adjustment for known risk-factors increases HRs toward 1, the association between persistence and reduced mortality remains stark, with HRs ranging from 0.28-0.45.

The association observed between mortality and various demographic variables differs from the results seen in primary and treatment groups. In the unadjusted analysis, male sex is associated with better survival – though in multivariate analysis this is not significant.

8.3.4 Secondary prevention progressing to treatment

ACEI		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	1,867	106	-	-
	Yes	12,204	345	0.49 (0.39-0.61, p<0.001)	0.58 (0.46-0.73, p<0.001)
Sex	F	4,400	200	-	-
	M	9,671	251	0.57 (0.47-0.68, p<0.001)	0.80 (0.66-0.98, p=0.030)
Age group	below 55	3,343	23	-	-
	55 to 65	4,156	44	1.54 (0.93-2.55, p=0.093)	1.83 (1.07-3.11, p=0.027)
	above 65	6,572	384	8.71 (5.72-13.27, p<0.001)	9.88 (6.27-15.57, p<0.001)
SIMD group	high	3,221	75	-	-
	mid	5,658	192	1.46 (1.12-1.91, p=0.005)	1.51 (1.15-1.99, p=0.003)
	low	5,177	183	1.53 (1.17-2.00, p=0.002)	1.71 (1.30-2.27, p<0.001)
Comorbidty Status	neither	9,287	230	-	-
	diabetes	1,540	84	2.24 (1.74-2.87, p<0.001)	1.97 (1.54-2.54, p<0.001)
	depression	2,025	80	1.61 (1.25-2.08, p<0.001)	1.89 (1.45-2.45, p<0.001)
	both	408	25	2.52 (1.66-3.80, p<0.001)	2.47 (1.63-3.74, p<0.001)
Antiplatelets		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	1,333	120	-	-
	Yes	16,753	613	0.39 (0.32-0.48, p<0.001)	0.45 (0.37-0.55, p<0.001)
Sex	F	6,204	331	-	-
	M	11,882	402	0.63 (0.54-0.73, p<0.001)	0.90 (0.77-1.05, p=0.174)
Age group	below 55	3,898	21	-	-
	55 to 65	5,018	66	2.45 (1.50-4.01, p<0.001)	2.84 (1.68-4.81, p<0.001)
	above 65	9,170	646	13.51 (8.75-20.86, p<0.001)	16.06 (10.03-25.73, p<0.001)
SIMD group	high	4,274	130	-	-
	mid	7,367	328	1.47 (1.20-1.81, p<0.001)	1.65 (1.34-2.04, p<0.001)
	low	6,426	274	1.41 (1.14-1.74, p=0.001)	1.67 (1.34-2.08, p<0.001)
Comorbidty Status	neither	11,757	380	-	-
	diabetes	2,018	117	1.82 (1.48-2.24, p<0.001)	1.58 (1.28-1.95, p<0.001)
	depression	2,666	145	1.71 (1.41-2.07, p<0.001)	2.00 (1.65-2.43, p<0.001)
	both	563	41	2.30 (1.67-3.18, p<0.001)	2.39 (1.73-3.30, p<0.001)
Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	1,314	79	-	-
	Yes	14,446	539	0.61 (0.48-0.77, p<0.001)	0.66 (0.52-0.85, p=0.001)
Sex	F	5,289	258	-	-
	M	10,471	360	0.70 (0.60-0.82, p<0.001)	1.00 (0.85-1.19, p=0.975)
Age group	below 55	3,458	22	-	-
	55 to 65	4,424	48	1.71 (1.03-2.83, p=0.037)	2.01 (1.16-3.49, p=0.013)
	above 65	7,878	548	11.29 (7.37-17.28, p<0.001)	14.62 (9.11-23.46, p<0.001)
SIMD group	high	3,713	112	-	-
	mid	6,420	265	1.38 (1.10-1.72, p=0.005)	1.50 (1.19-1.89, p=0.001)
	low	5,610	240	1.43 (1.14-1.79, p=0.002)	1.68 (1.33-2.13, p<0.001)
Comorbidty Status	neither	10,282	322	-	-
	diabetes	1,850	105	1.84 (1.47-2.29, p<0.001)	1.58 (1.27-1.97, p<0.001)
	depression	2,229	109	1.58 (1.27-1.96, p<0.001)	1.91 (1.53-2.39, p<0.001)
	both	477	34	2.33 (1.64-3.32, p<0.001)	2.46 (1.72-3.51, p<0.001)
Lipid-regulators		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	1,329	89	-	-
	Yes	16,560	595	0.52 (0.42-0.65, p<0.001)	0.55 (0.44-0.70, p<0.001)
Sex	F	6,013	304	-	-
	M	11,876	380	0.63 (0.54-0.73, p<0.001)	0.88 (0.75-1.03, p=0.121)
Age group	below 55	3,868	24	-	-
	55 to 65	4,979	61	1.98 (1.24-3.18, p=0.005)	2.37 (1.42-3.96, p=0.001)
	above 65	9,042	599	11.00 (7.32-16.55, p<0.001)	13.45 (8.59-21.06, p<0.001)
SIMD group	high	4,244	125	-	-
	mid	7,274	306	1.44 (1.17-1.77, p=0.001)	1.57 (1.26-1.94, p<0.001)
	low	6,353	253	1.36 (1.10-1.68, p=0.005)	1.56 (1.25-1.95, p<0.001)
Comorbidty Status	neither	11,635	349	-	-
	diabetes	2,030	120	2.00 (1.63-2.47, p<0.001)	1.72 (1.40-2.12, p<0.001)
	depression	2,603	126	1.63 (1.33-2.00, p<0.001)	1.91 (1.56-2.35, p<0.001)
	both	557	42	2.57 (1.87-3.54, p<0.001)	2.64 (1.91-3.64, p<0.001)

Table 8.8: Mortality 1-year *after* classed as persistent or not with TAM (T0) in the secondary-with-treatment group, across four CVD drug-classes. Including drug-count.

In the treatment following secondary prevention group, persistence at T0 is associated with higher 1yr-survival across all drug-classes in uni- and multivariate analysis, with HRs ranging from 0.45-0.66. Unlike the primary prevention and treatment groups, adjusting for other risk factors increases HRs toward 1, indicating an increased risk of mortality once factoring these in. Counterintuitively, for ACEi's male sex is significantly associated with better survival in multivariate analysis, while other variables such as age, SIMD, and comorbidity status are more in line with expectations.

8.3.5 Summary: 1-year mortality with CVD drug-count

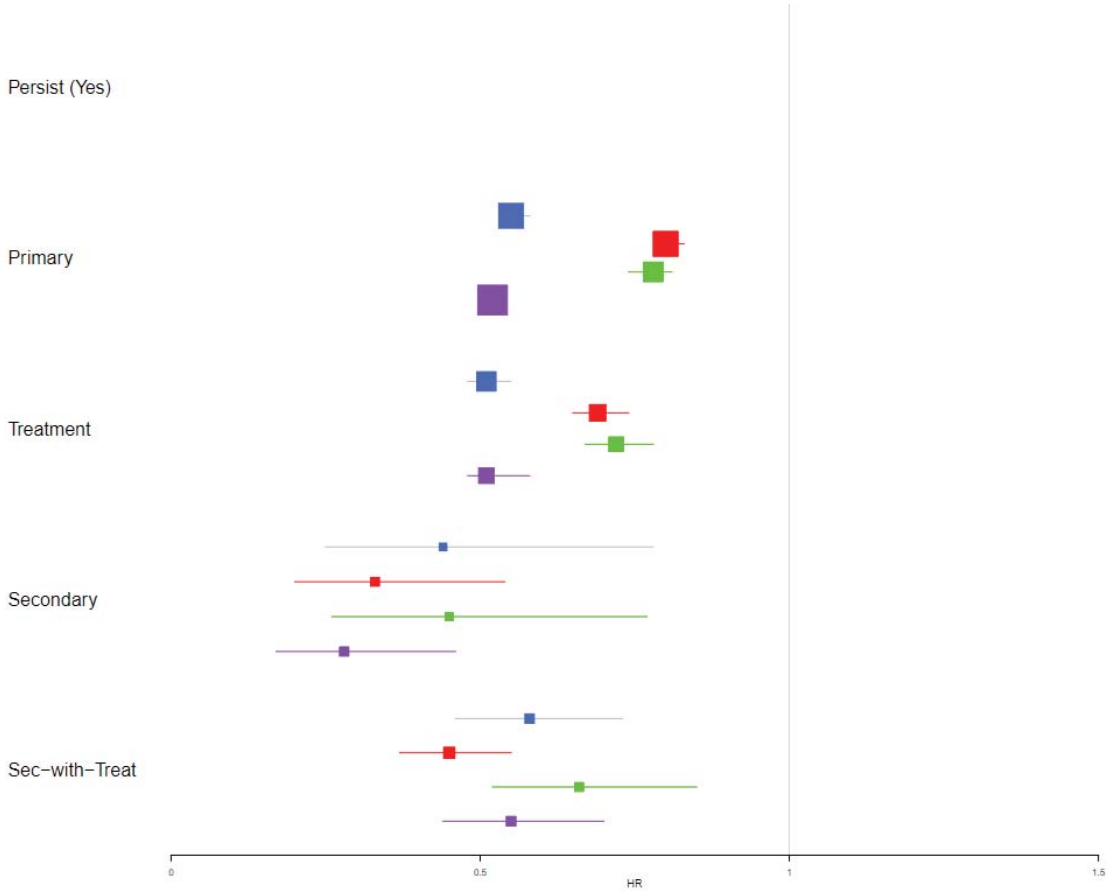

Figure 8.7: Mortality 1-year *after* classed as persistent with TAM in each of the four patient groups (Primary, Treatment, Secondary, Secondary-with-Treatment): adjusted for cvd-drug-count, sex, age, SIMD, and comorbidity. Blue = ACEi, Red = Antiplatelet, Green = BBs, Purple = Lipid-regulatory.

Compared to the 5-year mortality summary, hazard ratios after 1-year shift left, indicating reduced mortality is associated with persistent patients compared to non-persistent patients. In the primary prevention group, and to a lesser-extent in the treatment group, there seems to be a split between the HRs for ACEi's

and lipid-regulatory drugs, which are approximately 0.25 lower than the HRs for antiplatelets and beta-blockers. This further implies a difference in the patients making-up these groups, and suggests that those thought as having "milder" CVD, and thus classified as primary prevention or treatment, may be being prescribed these drugs for different reasons.

8.4 Further investigating confounding

8.4.1 Beta-blockers

Sensitivity analysis was performed on beta-blockers, as it was suspected that some of these patients had been prescribed beta-blockers for anxiety and not for a CVD indication, despite excluding records that stated 'anxiety' in the dosage information line during data-cleaning steps. This seemed especially pertinent to the primary prevention group, as patients in this group are most likely to be asymptomatic; for example, hypertension is estimated to affect 28-40% of adults in Scotland (according to the 2017 Scottish Health Survey[209]) and this rarely presents with symptoms[210]. Using guidance from a clinician, it was suggested that for a CVD indication, beta-blockers would usually be prescribed alongside an ACEi or a CCB drug, so all patients with either of these drugs prescribed in their first year of beta-blocker therapy were identified, and analysis was repeated on this subgroup.

Beta-blockers		All (n)	Deaths (n)	HR (univariable)	HR (multivariable)
Persist	No	22,249	3,474	-	-
	Yes	121,508	20,752	1.01 (1.00-1.03, p=0.054)	0.97 (0.96-0.98, p<0.001)
Sex	F	74,973	12,926	-	-
	M	68,784	11,300	0.99 (0.98-1.00, p=0.102)	1.02 (1.01-1.04, p<0.001)
Age group	below 55	25,881	989	-	-
	55 to 65	38,479	2,911	1.04 (1.02-1.05, p<0.001)	1.05 (1.03-1.06, p<0.001)
	above 65	79,397	20,326	1.26 (1.25-1.28, p<0.001)	1.29 (1.27-1.31, p<0.001)
SIMD group	high	38,635	5,826	-	-
	mid	59,301	10,218	1.02 (1.01-1.04, p<0.001)	1.03 (1.01-1.04, p<0.001)
	low	45,556	8,122	1.03 (1.02-1.04, p<0.001)	1.05 (1.03-1.06, p<0.001)
Comorbidty	neither	97,204	15,426	-	-
	diab	18,644	3,798	1.05 (1.04-1.07, p<0.001)	1.05 (1.03-1.06, p<0.001)
	dep	15,836	2,700	1.01 (1.00-1.03, p=0.102)	1.06 (1.04-1.08, p<0.001)
	both	3,498	766	1.07 (1.04-1.11, p<0.001)	1.11 (1.07-1.15, p<0.001)

Table 8.9. Mortality 5-years *after* classed as persistent or not with TAM (T0) in the primary prevention group, for beta-blockers; limited to only include patients with a concurrent prescription of either ACEi's or CCB's during the observation period.

Compared to the previous analysis, removing patients who cannot be confirmed as having been prescribed beta-blockers for CVD attenuates the level of risk observed, from 1.99 down to 1.01 in the univariable analysis, though raises the risk for the multivariate model from 0.92 to 0.97 (**Tables 8.1 and 8.9**). This indicates that misclassification of patients who received medication for other non-cardiac interactions does not appear to have a significant impact on associations observed between persistent patients and survival.

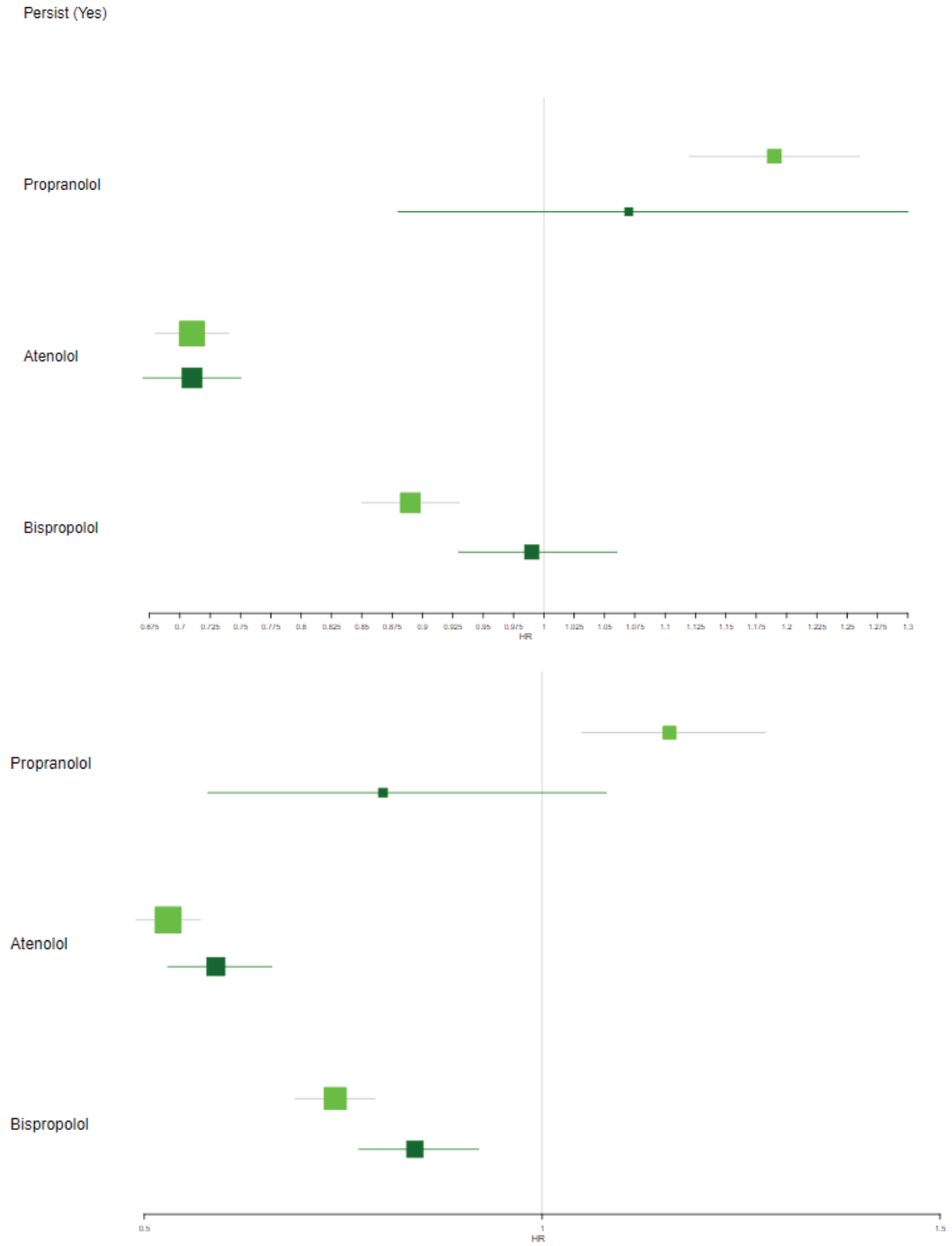

Figure 8.8: Mortality 5-years (top) and 1-year (bottom) *after* classed as persistent with TAM to three different beta-blocker drugs, in the Primary (green) and Treatment (dark green) patient groups: adjusted for CVD-drug-count, sex, age, SIMD, and comorbidity.

Persistence to atenolol and bisoprolol at T0 was associated with a reduced risk of mortality after 1- and 5-years (**Figure 8.8**), for patients in both the primary prevention, though for bisoprolol this is not significant in the treatment group after 5 years.

The opposite is true of propranolol: persistence to this beta-blocker drug is associated with increased mortality 1 and 5-years on from T0, significant in the primary prevention group. This may be related to residual confounding for propranolol due to its use for several other non-cardiac indications (including migraine, anxiety, cirrhosis, and portal hypertension[211]). This may explain the differential findings for this drug compared with the other beta-blockers, as these non-CVD indications may still be included in the analyses. Bisoprolol is licensed for heart failure[22] and its use in primary prevention patients may indicate misclassification, due to failure to include the relevant ICD-10 code (I50) when categorising patient groups. Atenolol is more limited to its use as an antihypertensive agent, so is likely to be prescribed for this indication.

8.4.2 Anti-platelets

Persistence to aspirin at T0 is associated with increased 5-year mortality rate in the primary prevention group, though for treatment patients, aspirin persistence is associated with reduced mortality (**Figure 8.9**). For clopidogrel, the hazard ratios show the opposite effect: as primary preventions are associated with lower levels of mortality while treatment patients are non-significantly associated with higher mortality. There is a non-significant relationship between dipyridamole and 5-year mortality for primary prevention patients, though a protective association is observed for those classed as treatment. For all the 1-year analyses, persistence was associated with better survival. The difference in findings between the 1- and 5-year analyses may indicate failure of the cox proportional hazards models, as risk appears to change with time.

Some of these Cox analyses present with very wide confidence intervals. This is due to very small patient numbers, as we may expect for the primary prevention and treatment groups, as antiplatelets are usually recommended for prescription following an MI, and evidence of an MI would exclude patients from being eligible for inclusion in these groups.

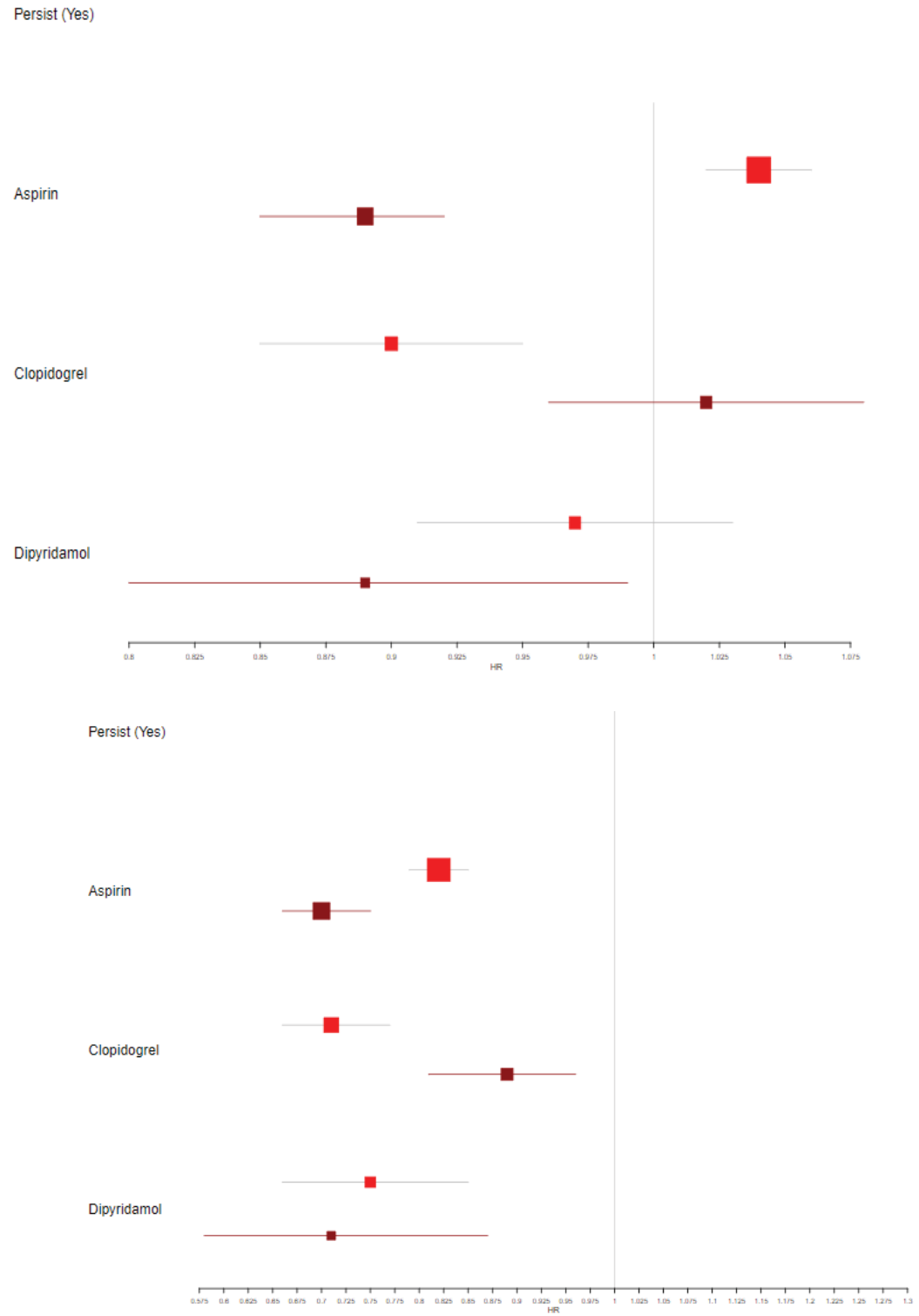

Figure 8.9: Mortality 5-years (top) and 1-year (bottom) *after* classed as persistent with TAM to four different antiplatelet drugs, in the Primary prevention (red) and Treatment (dark red) patient groups: adjusted for CVD-drug-count, sex, age, SIMD, and comorbidity.

8.5 Discussion

8.5.1 Overall conclusions

Adjusting for traditional CVD risk factors has a differential effect on HR depending on whether patients have suffered an MI previously: in the primary

and treatment groups, adjusting for these risk factors reduced mortality risk observed, while in the secondary and secondary-with-treatment groups, adjustment increased the risk.

However, in almost all instances, persistence with medications was found to correlate with a decreased risk of mortality. While this finding may be line with expectations for this study, it is important to acknowledge the flaw in using Cox models here when the model assumptions failed, due to survival lines crossing overtime (**Figures 8.1-8.4**) and results from plotting Schoenfeld Residuals (**Appendix F**). A revision of these methods must be considered for these results to be taken as legitimate.

8.5.2 Cardiovascular polypharmacy

Polypharmacy has previously been associated with increased mortality[212, 213], so a drug-count variable was added to the analyses to ascertain CVD drug polypharmacy and to create a proxy of disease severity. However, addition of this variable did not have a clear effect on HRs, and direct associations between the number of CVD drugs prescribed and mortality was often counterintuitive. This may be due to the broad approach taken here: some CVD polypharmacy may be acceptable and indeed important in preventing or treating disease and therefore may be indicative of good disease management. Identifying 'acceptable polypharmacy' for each patient may provide deeper insights and use of a drug-count variable as a proxy for good CVD management could be considered/ validated for future studies.

8.5.3 Comparing specific CVD drugs

In the primary and treatment groups, persistence to antiplatelet and beta-blocker drugs tended to be associated with higher HRs compared to ACEi's and lipid-regulatory drugs, so further investigation was carried out for these classes. It was expected that persistence may differ by specific drug; for example, persistence to aspirin may not be as important as persistence to other antiplatelet drugs, due to the availability of this as an over-the-counter medicine which could mean patients who appear non-persistent here are in fact purchasing aspirin themselves; or, due to propranolol being commonly

prescribed as an anxiolytic and for other non-CVD indications, that there may be important differences between specific drugs within these classes.

These analyses showed there were different drug-specific interactions to observe. For beta-blockers, persistence to atenolol and bisoprolol was associated with reduced mortality while persistence to propranolol was associated with increased mortality for primary prevention patients (NS for treatment patients). Here, persistence may act as a proxy for disease severity: for example, for propranolol, patients who are non-persistent may not be true CVD patients. This confounding is not observed for atenolol persistence, as this drug is only used for management of hypertension, hence the reduced risk of mortality for those who persist.

To break down drug-classes into their individual drugs to study persistence differences in depth could be a valuable follow-up but would require further clinical information to define different drug indications, identify and validate allowed gap-lengths, and to define acceptable drug-switches for each.

8.6 Chapter Summary

Secondary databases can have value for estimating population level adherence and persistence, and to some extent can be used for estimating the outcomes associated with good persistence. These results, while intuitive, should be considered with a degree of caution due to issues in fulfilling the assumptions that underpin Cox proportional hazards models, and the influence of known and unknown confounders. Residual confounding presents a limitation in using secondary data for such analyses, as all CVD risk factors cannot be accounted for with the data available.

9 Discussion

9.1 Study context

In Scotland, morbidity and mortality related to CVD exceeds the levels observed in the rest of the UK and other similar European countries. There are already a host of interventions with proven efficacy against CVD, including pharmaceutical prevention and treatment. Improving management of such interventions could be crucial in addressing excess CVD burden in Scotland. Adherence, whether it is the initiation, implementation, or persistence to a therapy, is an important aspect of chronic disease management and understanding the epidemiology of this in Scotland may be a key feature of future public health interventions.

However, previous studies have found that adherence and persistence can be challenging to assess, and both have been inconsistently defined in the literature. The different ways of measuring and recording adherence, different assumptions made about the data, and different analyses run can all lead to different findings, highlighting the importance in clearly and accurately reporting on the methods used and the justifications for these, within the limits of the available data.

Scotland has access to anonymised, population-level pharmacy data, which can be readily linked to hospitalisation and death data, and therefore provides a valuable tool for adherence research. When using secondary data, it is important to be aware of its limitations for defining a behavioural trait such as adherence and the lack of granularity when compared to methods such as electronic-monitoring, while also highlighting the potential value secondary data can have for identifying general trends across the population.

9.1.1 What was previously known: cardiovascular adherence

A 2003 report by The World Health Organisation suggested that adherence to long-term therapy was particularly problematic for chronic diseases, with adherence estimated at 50% for patients in developed countries[214]. This trend was replicated in a 2008 study of patients prescribed antihypertensive drugs,

which found that half had discontinued their drug within 1 year[215]. Studies in LMICs have found that adherence levels are suboptimal here too[216].

Different risk factors have previously been identified as being associated with adherence in cardiovascular disease, and these are defined across five key domains: disease factors, therapy factors, healthcare factors, patient factors, and social factors[76, 214]. From systematic review (**Chapter 2**), higher levels of adherence in cardiovascular disease were associated with secondary prevention (compared with primary prevention), diabetes comorbidity (compared to no comorbidity), ARBs (compared to other drug-classes), higher SES, male sex, and lower dosing frequencies. Mixed findings were associated with ACEi's and CCBs, complex dosing regimens, and age, which had a 'u' shaped relationship with nonadherence. Younger patients, below the age of 50, are generally less-adherent than older adults; however, over the age of 80 adherence once again decreases in prevalence[217].

My review of systematic reviews also indicated that adherence was associated with improved clinical and economic outcomes in the majority of reviews; however, there was some mixed evidence across the primary studies. Good adherence was generally associated with a reduction in CVD risk and all-cause mortality[11, 123], as well as a reduction in overall healthcare costs[118, 124].

9.2 Main findings

Risk Factor	Association with adherence	
	Systematic review	In Scotland (using PIS)
Secondary prevention (vs primary)	↑	↑
Male sex (vs female)	↑	↑
Older age (vs below 55 yrs) • 55-65 • 65+	↑ –	↑ ↑
SIMD (vs low) • High	↑	↑
Comorbidity • Diabetes • Depression • Diabetes & depression	↑ ↓ –	– ↓ –

Table 9.1: Comparison of the associations between different risk factors and levels of adherence, observed in systematic review vs findings in this thesis

The epidemiology of adherence to cardiovascular drugs in Scotland is largely similar to that observed in my literature review (**Table 9.1**). Notably, the systematic review conducted included studies which used a range of methods for measuring adherence (self-report, EMS, secondary databases), as well as across many different countries and contexts. This helps validate the potential utility of using PIS as a tool for estimating adherence at the population level. It also suggests that the epidemiology of adherence to cardiovascular drugs in Scotland is not especially different to other countries and contexts previously studied.

This broad summary table does not provide granular information that may be important. Patients over 65 years are more adherent than those aged below 55 or aged 55-65 years in my cohort, but in my literature review it was found that patients over the age of 85 years tend to be less adherent. It may be important for future studies to further subdivide older age groups to investigate this, as geriatric care for people living in residential nursing homes or assisted living facilities, and with increased comorbidities and polypharmacy, may have very different interactions with adherence. Around 60% of people living in care-homes are aged over 85 years[218], highlighting the heterogeneity of people included in our over-65-year group. Relevant to this, the secondary prevention group is the

one patient group where 55-65-year-olds are more likely to be adherent or persistent than over-65s.

Drug Class	Association with implementation/ persistence			
	Primary	Treatment	Secondary	Sec-Treat
Alpha-blockers	↓	↓	–	↓
ACEi	–	↑	↑	↑
Antianginal	↓	–	–	–
Antiplatelet	↓	–	↑↑	↑↑
ARB	↑	↑	↑↑	↑
Beta-blockers	↓↓	↑	↑↑	↑↑
CCBs	–	–	↑	–
Diuretic	↓	–	↑	–
Lipid-regulatory	↑	↑	↑↑	↑
Nitrates	↓	↓	–	–

Table 9.2 Summary of levels of persistence and implementation observed across different drug-classes and patient groups. (Adapted from Table 7.7).

My analyses comparing the primary prevention, treatment, secondary prevention, and secondary-prevention-with-treatment provided valuable insights into how adherence may vary by drug class. Adherence is best for lipid-regulatory drugs and ARBs across all four patient groups, while adherence to ACEi's and beta-blockers is high across treatment, secondary, and secondary-with-treatment only. Conversely, the drug to which primary prevention patients are least adherent to are beta-blockers, and this may be due to a higher rate of prescriptions with an anxiolytic indication in this group, despite efforts to minimise this through data-cleaning. Similarly, antiplatelet adherence is higher for those patients who have suffered an MI compared to those who have not.

Adherence is consistently lowest across alpha-blockers, anti-anginal drugs, and nitrates. Despite excluding records with 'as required' in the dosage instructions, it is likely that many prescriptions of nitrates are for symptom management of angina, and therefore adherence cannot be ascertained.

Notably, implementation and persistence were associated with traditional CVD risk-factors in the primary and treatment groups, but this effect was attenuated in the secondary prevention group (**Chapter 7, Figure 7.1 and Table 7.7**) – possibly due to the fact that all patients had a clear CVD risk which was tangible to the patient.

Drug Class	Association between persistence and outcomes			
	Primary	Treatment	Secondary	Sec-Treat
ACEi	↑	↑	–	↑
Antiplatelet	–	↑	↑	↑
Beta-blocker	↑	↑	–	↑
Lipid-regulatory	↑	↑	↑	↑

Table 9.3 Summary of associations between persistence and outcomes, across different drug-classes and patient groups (adapted from 5-year and 1-year Cox survival analyses, Chapter 8).

Results observed for the associations between persistence and survival (**Table 9.3**) showed that, generally, persistence was associated with reduced mortality. There were several exceptions to this: in the primary prevention group, patients found to be persistent to antiplatelet drugs were associated with increased mortality over 5-years of follow-up compared to those who did not persist, though this was not replicated in the 1-year follow-up analyses. In the secondary prevention group, association with persistence and reduced mortality were non-significant for ACEi and beta-blocker drugs, though this may be in part due to the smaller sample size of this group. Follow-up time was very limited in the secondary prevention group, and many patients will have been excluded from

investigations into levels of persistence (Chapter 7) if they did not fulfil the eligibility criteria for inclusion in this group for the entire year. This may introduce bias as it could be possible that the least adherent patients have the poorest outcomes and may have already suffered a subsequent MI or death within this timeframe. It is important to note also that this reduced time is due to limitations in the definition of secondary prevention patients, which ought to be revised for future study.

The assumptions of the Cox proportional hazards models, namely that risk is proportional for the duration of follow-up, was not met for all of these analyses, and therefore the results may need to be considered with caution. There are also certain limitations in study design (discussed further in section **9.3.3**) which may allow for residual confounding that has not been accounted for.

Another dimension of adherence that was not considered was a comparison of initiators from non-initiators. Patients who suffered an MI but did not collect a prescription within the defined time period were excluded from analyses, as the PIS data provided here does not include non-initiators who were prescribed drugs but who did not collect their first script. It is also important to note that persistence tends to change overtime. An adherence study which is more detailed may benefit from a longer follow-up period, comparing different outcomes for patients who persist after 6-months, 1-year, 2-years, and so on. Future analysis may benefit from additionally investigating the association between persistence with subsequent MI for primary or treatment patients.

9.2.1 What this study adds

This is the first study to provide a population-level perspective of adherence across a range of CVD drug-classes in Scotland. Previous studies using these Scottish datasets have provided an in depth analysis of individual classes, including statins[219] and anticoagulants[199], whereas this study provided a much broader epidemiological approach across ten different CVD drug-classes.

It also highlights the possibilities of using PIS as a tool for estimating population-level adherence. Findings here tend to replicate those observed in literature review: traditional CVD risk factors were associated with higher levels of

adherence. This suggests that PIS is comparable to other validated databases as a tool for conducting adherence research, whilst suggesting that there may be potential confounding issues that require further study.

As much time in this project was spent identifying the data cleaning steps needed to be taken, and deciding on adherence and persistence measures that were possible with the data available, a paper to lay out the framework used here to estimate adherence with PIS, SMR, and NRS records could be of methodological value for future studies, as it would allow for adherence measures to be included more readily.

9.2.2 Future research

A longitudinal follow-up of adherence and persistence over time, beyond the first year of therapy, would provide interesting insights, particularly as adherence tends to decline overtime[39, 88, 91]. This was limited here due to the secondary prevention group having very short follow-up time, less than 4 months. Further analysis of this in patients taking medications for primary prevention or treatment, especially as these patients may receive CVD medication for many years before suffering an MI, may provide valuable insights into the long-term management of CVD. This is pertinent as patients who discontinue statins are at an elevated risk, with one study citing a 33% increase in CVD hospital admissions in patients over the age of 75 who did not persist with statins for primary prevention[220].

Additionally, studying adherence at specific points in time could be a valuable follow-up study, particularly in response to changes in policy: for example, introduction of new drugs (as has been previously studied when DOACs were first licensed in Scotland[206]), changes to guidelines, or introduction of new interventions to improve adherence. This would be particularly valuable as a longitudinal study, to observe changes in behaviours in response to public health policy. Some of the more beneficial and cost-effective interventions to improve management of adherence include the introduction of combination pills/ therapies[221, 222], especially for secondary-prevention patients who have a higher pill burden, and automated phone-call reminders[221]. As electronic-pill-bottles and blister-packs come off patent, these could also to useful to help patients to

monitor their own medication-use in real-time and is also relatively cost-effective, and in one study improved adherence by 27%[222]. As health services are under particular strain in the context of the global coronavirus pandemic, the opportunity to invest in options such as increased consultations with clinicians and pharmacists and developing disease co-management plans (which has been found to be effective[221]) may be limited, but should be considered as a future goal.

Due to the scale of this study, comparing across various drug-classes and patient groups, a general adherence and persistence measure was used. For more nuanced study, adherence measures and acceptable gaps between prescriptions ought to be validated for specific drugs, for example, based on the specific pharmacokinetics.

This study also used narrow age-bands of age groups and comorbidity status, and a future project looking at this in more detail would be valuable. Grouping age into further categories and/ or including it as a continuous variable could provide useful insights, and particularly subdividing the over-65s age group to explore adherence patterns in geriatric patients could be pertinent. Exploring patient pathways into care facilities and interactions with CVD adherence may be insightful, especially considering how adherence may change due to onset of cognitive decline and other diseases of ageing. There is also a great loss of information in the way comorbidity is assessed here, as study of comorbidities was limited to diabetes and depression. While these comorbidities were deemed relevant from findings in literature review (**Chapter 2**) it does not negate the impact of other comorbidities that could have important implications: for example, a patient diagnosed with cancer may be briefly prescribed an antiplatelet drug due to clotting as a side-effect of chemotherapy, and may be classed as nonadherent to CVD drugs when it has been discontinued for legitimate clinical reasons; a patient diagnosed with a stomach ulcer may cease therapy with aspirin due to contraindication; or a patient with Alzheimer's disease may require additional support to maintain their medication regimen. Analyses including use of a multimorbidity measure, such as the Charlson Index[223] or the Elixhauser score[224], would be a valuable follow-up.

A complementary study to this, including a qualitative dimension conducted in a sub-group of patients, could add value in order to more fully understand patient adherence behaviours and the factors that influence them.

There could be relevance here to COVID-19, the disease caused by the novel coronavirus SARS-CoV-2. Patients with pre-existing conditions such as CVD and diabetes are at a particular risk from the virus, though the exact mechanism is unknown[225]. Respiratory viruses are known to put added strain on the cardiovascular system so this could explain the increased risk, or a systemic immune response could affect organs such as the heart and kidneys. Another theory involves the ACE2 receptor, by which the virus enters the cells. Notably the ACE2 receptor interacts with drugs studied here; specifically, ACEi's and ARBs[225]. Using PIS, identifying patients prescribed these drugs, and estimating their adherence using the methods within this thesis could be an interesting way of seeing a population level picture. Comparing adherent patients to nonadherent patients, and comparing patients prescribed ACEi's and ARBs to patients prescribed other CVD drugs, and then linking this to records of patients with positive tests, ICU admissions, and deaths from COVID-19 could present a worthwhile exploratory analysis of any possible relationship between this and the virus. It may also be important to consider how adherence behaviours changed during national lockdown, particularly as shielding individuals may have had new barriers to accessing medications.

9.3 Challenges and limitations

9.3.1 Using secondary records

Access to secondary data in Scotland depends on application through eDRIS, and approval via Public Benefit and Privacy Panel. While this can be a time-consuming process, it is important in ensuring safe and proper use of patient data. For conducting this PhD project, the benefit of this process was that it forced an early focus on deciding key aims and developing the basis and value of such research early on. From the date of PBPP approval to receiving the majority of the data output took 6 months, though with some added delay to dosage instruction information arriving.

As per the PBPP request, all prescriptions for each drug listed in the whole of Scotland between the years of 2009-early 2017 were included in the data output. This produced a considerable sized dataset and created a need for efficient data management in order to reduce burden on computer memory. However, these challenges are outweighed by the value in having access to a population-level dataset for epidemiological study.

At a fundamental level, all routinely collected data will carry inherent flaws, and quality assessment is vitally important in any research project which attempts to use it, as understanding where these flaws occur and how to counter them is an important aspect of study design. In Chapter 4, quality assessment of the PIS dataset highlighted issues with the dispensed date variable, where 55% of records defaulted to the end of the month (**Figure 4.1**). This led to selection of the prescribed date variable instead, which was more complete. However, this variable continues to be imperfect as 11% of records defaulted to the end of the month. Communicating such issues back to data providers is crucial, as it allows steps to be taken to improve these datasets, and for details of such issues to be communicated to future users of these data.

There were some other issues with data quality observed at the data-cleaning steps. While some of these issues were clearly erroneous (for example, patients who attended hospitals following their registered date of death; prescriptions of tablets with dosing quantities of mg/ml, etc.) it leaves the possibility of other, less obvious, errors being present that cannot be identified in the data.

9.3.2 Defining Patient Groups

Using hospitalisation and prescribing data to characterise patient groups depends on certain assumptions being made about patient characteristics. Here, despite certain flaws, it seems that the definitions used to separate primary prevention patients from the treatment group and secondary prevention groups did work reasonably well, as the resulting groups did differ in ways we may expect; for example, with the average age being lower in the primary group and higher levels of polypharmacy in the treatment and secondary groups. CVD is a disease that lends itself reasonably well to secondary database study, due to clear clinical endpoints such as MI. While previous studies have validated ICD10 codes

as having high sensitivity and specificity for identifying MIs[226], this is still imperfect. The ICD disease code R074 indicates the diagnosis of 'unspecified chest pain,' and this was seen to be a common cause of hospitalisation in our cohort (**Chapter 6**). This could relate to angina or even an MI, especially as there is increasing evidence that female patients present with atypical symptoms and are often misdiagnosed or delayed in treatment[227]; however, the R074 code may not relate to any CVD indication at all and cannot be presumed as such. Studies using secondary data to observe CVD clinical endpoints may need to consider this in sensitivity analysis, and to investigate if there is a sex bias in MI reporting.

However, there remains further potential for classification bias due to researcher error, particularly if selection of ICD-10 codes is flawed. Here, patients with atrial fibrillation (I48), heart failure (I50), and peripheral vascular disease (I73) may have erroneously been classified as primary prevention, due to the omission of these codes when characterising key groups. Additionally, those with angina may not always present at hospital and therefore may not be captured, also allowing for misclassification as primary prevention patients. GTN was used here instead to separate symptomatic from non-symptomatic CVD patients, but this may be misleading, particularly for those who have suffered an MI (secondary, secondary-with-treatment) as these patients are advised to collect GTN spray as a precautionary measure, even in the absence of symptoms. These flaws likely explain the high number of "primary" prevention patients prescribed nitrate drugs, and the very short follow up times observed in the secondary group, due to the majority going on to collect their recommended GTN spray, and is an error that ought to be rectified for any future publications.

9.3.3 Reflecting on study design

The challenge of taking on a vast dataset and attempting to carry out analyses across a series of risk factors has led to some oversights in study design, particularly in grouping of key variables. Despite overall demographics of the patient groups falling somewhat in line with expectations, there is clear evidence that some misclassification occurred, particularly with the secondary prevention group. While some degree of misclassification is unavoidable when using secondary data, further discussions with clinicians – particularly with

General Practitioner's and Cardiologist's - would have been invaluable in improving these analyses and could have given greater credibility to this research.

Other important factors to improve the study design here include rethinking the age bands, as the very narrow bands (effectively 18-55, 55-65, and 65-100) will obscure some of the rich epidemiological insights that this dataset could have provided. Equally, limiting comorbidity to diabetes and depression will have failed to make full use of the information available.

A missed opportunity in the original data request to PBPP was the exclusion of anticoagulants, particularly as the novel DOACS were introduced during the years of the study period. While these have been included in other high quality research studies using Scottish datasets[199, 206], it does not negate the relevance it would have had for this project.

It is also important to note that co-prescribing was not included in the models here. Instead of taking such a vast, big picture, attempt at describing adherence, a more meaningful project of CVD adherence may have looked at this in a more refined approach. For example, assessing patient pathways, e.g. patients moving from ACEi's to ARBs and adherence levels between switchers and non-switchers, could have provided more clinically interesting analyses than a range of adherence levels between classes. Importantly, effective management of cardiovascular disease often requires a regimen of multiple drugs, such as ACD prescribing (ACEi/ ARB, CCB, Diuretic) for management of hypertension, or a combination therapy which is standard care following an MI. While a goal of this project was to consider if there were differences in adherence between specific drug-classes, it is important to note that differences are most likely to occur between individuals rather than between different drugs. Understanding which questions are most clinically relevant and likely to provide the most epidemiologically insightful findings should be considered when designing a research study.

9.3.4 Prescribing data

Prescribing data has value for defining CVD patients, as many of the drugs here have a clear indication and are not used regularly for other indications. This could be a challenge for other drug classes; for example, when attempting to define patients with depression as a comorbidity, it was important to look at other prescriptions received by the patient and to curate a list of medications which allowed a patient to be classed as having suspected depression vs. those who did not. Some patients (those prescribed only <75mg amitriptyline, duloxetine, flupentixol, moclobemide, reboxetine, agomelatine, phenelzine, tranylcypromine, and tryptophan) were omitted from the analysis, due to the fact their comorbidity status could not be confidently defined. Some of these drugs are used in management of pain, and patients should not be incorrectly classified in the analysis if this is the indication for which drugs were prescribed. While this may minimise some misclassification, it may also miss some people who were prescribed these drugs for a depression indication, reducing the sample size and leading to a loss of information.

It is also not true that all CVD medications have one clear indication. Beta-blockers were an issue here, as propranolol is commonly prescribed for anxiety. Results observed in the levels of implementation and persistence in the primary prevention group are likely to have been confounded by this, despite attempts to remove prescriptions for anxiety at the data-cleaning stage.

Similarly, GTN, used to define our treatment group, may also be prescribed for another indication; management of anal fissures. In this instance, it is dispensed as a cream rather than as a spray formulation. Understanding this allowed a distinction to be made between patients who did not have GTN prescribed for angina from those who did.

All of this underpins the importance in thoroughly understanding the drugs included in such analyses. Understanding different drug-indications, and how these can possibly be teased out, is crucial to improve the reliability of the assumptions made. For some medications, it may not be possible to make these distinctions, and without additional clinical information, this type of study may not be possible.

9.3.5 Adherence research

Adherence is one of the more complicated drug-utilisation interactions to study, and this has led to numerous guidelines in assessing and reporting on it[43, 142] being developed. Even within these frameworks, there is not a clear gold-standard, and there is much room for variation in measures, dependent on the data available[44] and specific study aims. When using PIS for this project, considerable data-cleaning was required to estimate the 'days-coverage' value from the dosage information variable, and from this, to estimate adherence. Here, simple implementation and persistence measures were used as these are more readily assessed, but further validation of adherence measures could add value for future study.

Furthermore, adherence is a complex behaviour, which can be difficult to quantify as there are many unexpected and potentially unmeasurable confounders. An anecdote given by a leading adherence researcher during their presentation at the European Drug Utilisation Research Group (EuroDURG) Conference in 2017 summed this up nicely: using EMS monitoring, a patient consistently took their medication at the same time every evening and then suddenly stopped. Upon patient interview, it was determined that this change in behaviour was related to their television-set breaking, as they had previously used the start of the evening news as a reminder to take their medication. To truly understand patient interactions with their medications, qualitative research gives much greater depth; however, individual quirks such as this could never feasibly considered in any epidemiological study.

However, there are other interactions with adherence that could be more broadly considered. Clinicians, district nurses, and social workers have many anecdotes of arriving at a patient's house to find that, while they have been collecting their medication regularly, they have stockpiled these extensively. Additionally, there are more recent social events that may lead to stockpiling and may create challenges in measurements: news around potential drug shortages after the UK left the European Union, and concerns around access to pharmacies in the midst of the COVID-19 pandemic are two notable recent events that led to increased demand seen in pharmacies[228]. Conversely, public perceptions of drugs could also lead to changes in adherence. There is some

debate about statin use in primary prevention of CVD[229], especially for those in low-risk groups, due to the benefit: cost ratio for the associated side-effects such as myopathy[229]. Similarly, confusion around the interaction between SARS-CoV-2 with ACEi's and ARB's could lead to patients choosing to stop taking these drugs without consulting a doctor or pharmacist if they have not been clearly informed on this, particularly as research is on-going.

To study this nuance at a population level could create substantial noise in the data. An understanding of general levels of adherence in a population, such as those identified within this PhD study, could be valuable in order to allow future investigation into the impact of such changes in response to current affairs.

9.3.6 Unexpected challenges

This PhD was a sideways step from my previous study in virology and medical genetics, but I choose this project as I was keen to learn transferable data-analysis skills and to dip my toe into public health research. This was harder than I had expected, and I had a steep learning curve with R. On reflection, starting out with such a large dataset certainly did not help as I found myself constantly crashing R in the early days of data-cleaning. Working out what to look for during data-cleaning while learning to implement the code at the same time was challenging and I was lucky to receive help from Kevin Ross, a researcher with previous experience of PIS data, and to have my supervisor's expertise throughout. A valuable resource could be developed by data controllers and researchers using secondary datasets such as PIS, SMR, and NRS in the form of a 'living document', which can be updated regularly to highlight quirks of the datasets to look out for.

The years of my PhD were strange times, bookended by the Brexit referendum the summer before I started and a global pandemic to round things off. There were two general elections during my study, and I found myself easily distracted by the political turbulence that characterised the UK in these years. Losing my flat toward the end of my PhD and moving back in with my parents to complete my write-up in the midst of COVID-19 presented other unexpected challenges, not least because the dogs want me to let them in and out of the garden every five minutes. It is worth noting that, while inconvenient, getting up and down

from my seat constantly must have a cardioprotective effect for me and I should be grateful.

9.4 Conclusions

Scottish datasets offer great potential for studying drug use at the population level, but there are important considerations in the data cleaning steps and assumptions made when conducting such study. The epidemiology of cardiovascular drug adherence in Scotland is largely related to traditional cardiovascular risk-factors, as has been observed previously, and therefore it is hard to use this data to make any conclusions about the long-term outcomes that may be related to adherence compared to nonadherence.

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Appendices

Appendix A: Literature Review Supplementary Tables

Supplementary Table 1: Data Extraction for factors associated with adherence

Review Author (year)	Aim	Setting	No. of studies included (participants)	Search Strategy	Adherence Measurement	Quality tool used	Factors contributing to nonadherence	Adherence operational measure	QA (from AMSTAR)
Al-Noumani et al. (2019)	Review health beliefs and associations with adherence to hypertension	Not geographically limited. Includes Canada, Brazil, South Africa, NI, etc.	30 studies (8414)	PubMed, CINHAL, EMBASE, and PsycINFO	93% of studies used self-report (mostly MMAS). Also MEMs and refills.	QATSO guide	Perceived barriers associated with nonadherence	Not specified	(+)
Bahiru et al (2017)	Effects of fixed-dose combo drug on mortality, etc (includes adherence)	Not geographically restricted.	13 trials in review plus update (9,059)	CENTRAL, MEDLINE, Embase, ISI Web of Science, and DARE, HTA, and HEED, plus clinical trial registries.	Self report, pill count, and pharmacy data	GRADE approach	FDC associated with 44% improvement in adherence compared with usual care (4 trials, 3835 participants); However, discontinuation higher in FDC group = 12% versus 10%,	Not specified	(++)
Cheen et al (2019)	Identify primary non-adherence (i.e. non-initiating) across six different diseases and associated factors.	Europe, USA, Canada	33 studies (539, 156). (studies of hypertension, 15 of hyperlipidaemia	MEDLINE, Embase, Cochrane Library, CINAHL and PsycINFO. 2008-18, English only.	Derived primary non-adherence (i.e. initiator y/n)? From study data.	Cochrane ROB, Newcastle-Ottawa Scale, National Heart, Lung and Blood Institute Quality Assessment	Factors associated with nonadherence in HTN/ Hlip: perceive good health at baseline, older age (inconsistent), co-payment, sex (inconsistent), comorbidity and disability	Binary initiate vs non-initiate	(++)
Du et al (2018)	Impact of FDC on adherence to hypertensive meds	Not specified	9 studies (62,481)	MEDLINE and Embase; Jan 2000-Jun 2017; no language restriction	Range of measures included	Newcastle-Ottawa Scale	Adherence 14.92% higher FDC vs free-equivalent; FDC more likely to persist, RR 1.84	MPR or PDC	(++)

Durand et al (2017)	Prevalence of non-adherence in resistant hypertension, and risk-factors	Predominantly Europe and US	24 studies	PsycINFO, PubMed, Embase, Web of Science, and CINAHL	Range of measures; include physical test (e.g. urine sample), MEMS, DOT, self-report, prescription refill	Sanderson guidelines	Pooled prevalence of nonadherence 31.2%. Age, sex, race, income, socioeconomic indicators, and heart rate all associated with nonadherence in resistant hypertension	Range (includes MPR)	(+)
Hope, et al (2019)	Review associated predictors/ risk-factors for use of statins in CVD primary prevention	Predominantly Europe and US	19 studies	PubMed, PsycINFO, Embase and CINAHL, Jan 1984-May 2017	10 studies used refill date; 5 used self-reported measure; 1 electronic monitoring	adapted from Sanderson guidelines	more "traditional" CVD risk factors = more adherent to statins. E.g. males, older age	MPR/ PDC and other. Most common, 80% cut-off	(+)
Ju et al (2018)	Describe patient perspectives to statin adherence	Eight different countries; predominantly US and Europe	32 studies (888)	PsycINFO, CINAHL, Embase, MEDLINE, PhD theses; no date cut-off to present	Interviews/ focus groups/ questionnaires	COREQ reporting criteria	Barriers across several themes: confidence in prevention; routinising into daily life; questioning utility; medical distrust; threatening health; signifying sickness; financial strain	Not specified	(-)
Kawalec et al (2018)	Assess differences in FDC and free-equivalents in managing hypertension	Not specified	12 studies in meta-analysis and 3 in narrative	PubMed, Web of Science, and Cochrane	Not specified	Newcastle-Ottawa Scale and Delhpi scale	FDCs associated with higher adherence compared with free-equivalent doses.	PDC (1 study) and MPR (8 studies)	(++)
Kraft et al (2017)	Investigate role of telemedicine in secondary prevention following stroke/ TIA	Not specified	13 studies (2672)	MEDLINE, Cochrane, reference lists of articles identified; until 2016	Not specified	Cochrane ROB tool	No significant change in adherence associated with telemedicine (in one trial- more research needed?)	Not specified	(++)
Kristina and Wulandari (2020)	Assess self-reported adherence in chronic disease	Not geographically restricted.	16 papers in total, range of diseases. 6 HTN, 1 angina.	PubMed, Science Direct, Google Scholar; 2008-18; English language	Mostly self-repot/ MMAS	GRADE approach	SES, personal factors (confidence/ behaviour), healthcare factors(staff knowledge) all impacted	Not specified	(-)

Lemstra, (2018)	Analyse primary nonadherence/ non-initiation in chronic disease	N. America and Europe	24 papers (relates to a pooled 550,485 prescriptions)	CINAHL, Cochrane,Embase, MEDLINE, ProQuest, PsycINFO, PubMed, Scopus	Mostly prescription fills/administrative records.	Cochrane ROB, Newcastle-Ottawa Scale	Evidence of considerable burden on non-initiation in chronic disease; highest in lipid-regulatory drugs (20.8%). Lack of social support associated with reduced adhere	Initiator yes/no	(++)
Miguel-Cruz et al (2019)	Assess evidence for use of electronic-pill boxes	Not specified	22 studies included; 3 HTN, 1 HF	Scopus, Pubmed, Embase, Medline-Ovid, Medline-Ebsco, IEEE Explore, ISI Web of Sciences, Ebsco Host	Electronic pillboxes (range of designs)	Physiotherapy Evidence Database (PeDro) Scale	Weak evidence that pill-boxes may be associated with improved adherence in hypertension/ chronic disease	Range; includes 80% cut-off, persistence, timing adherence	(+)
Ofori-Asenso et al (2018)a	To review risk-factors for statin-nonadherence in people aged 65 or over	13 countries	45 articles, (1.8M)	Medline, Embase, CINAHL, PsycINFO, NHSEED, DARE and Cochrane; Published up until Dec 2016; English language	Not specified	NIH Quality Assessment tool for observational studies; Joanna Briggs Institute's checklist for RCT	Factors associated with nonadherence: black/non-white race; female gender; current smoker; higher co-payments; new user; lower number of concurrent cardiovascular medications; primary prevention; comorbidity of respiratory disorders, depression, cancer, dementia; not having; lower income status; higher number of medications; and not having hypertension, renal disease, or diabetes	Majority (80%) of adherence studies used PDC; Majority of persistence studies used gap methods.	(+)
Ofori-Asenso, R., et al. (2018)b	To review patterns of statin-nonadherence in people aged 65 or over	40 countries	82 studies (>3M)	Medline, Embase, PsycINFO, CINAHL, DARE, NHSEED, CENTRAL; Published up until Dec 2016; English language	Studied adherence and persistence	NIH Quality Assessment tool for observational studies	At 1 year, 47.9% of primary prevention group & 62.3% secondary prevention. Adherence reduced in >75yrs compared to 65-75yrs. At 3 years, adhere drops to 55%; at 10 years, 28 %	Adherence: MPR and PDC; Persistence: most used permissible gap	(+)

Oori, et al (2019)	Identify rates of statin adherence in Iran	Iran	17 studies (7941)	MagIran, Barakat Knowledge Network System, Scientific Information Database (SID), Web of Sciences, PubMed, Science Direct, Google Scholar; Years 2000-2018; English and Persian	Self-report: MMAS-8, HBMA; researcher tools; self-care tools	Developed a 15-item scale	Overall prevalence of adherence = 33%.Highest adherence rates observed in older, married people (vs. younger/ single)	Score high/ moderate/ low	(++)
Schneider et al. (2018)	Investigate relationship between aspects of drug-therapy and non-adherence	Not geographically restricted.	31 studies (27,441)	PubMed, LILACS, Academic Search and CINAHL; Jan 1960-Dec2015	Mostly self-repot/ MMAS	Strobe criteria	Non adherence associated with lack of access to insurance/ medication coverage and dosing freq 2 or more per day	Cut-off score/ adherent yes or no	(++)
Shahin et al (2019)	Investigate effect of personal/ cultural beliefs on adherence in chronic conditions (including HTN)	Majority US, though not geographically restricted	25 studies, majority looked at HTN and DM	PubMed, CINAHL, EMBASE and PsychINFO	Mostly self-repot/ MMAS/ MARS (some with language adaptations)	None specified	Factors studied: perception of illness, health literacy, cultural beliefs, self-efficacy, spiritual and religious beliefs, and illness knowledge. 80% of studies found significance but direction of association inconsistent	Not specified	(+)
Van Der Laan et al (2017)	Identify risk-factors associated with non-adherence to antihypertensives	Majority US	44 studies	MEDLINE, EMBASE, PsycINFO, Cochrane; Jan 1960-Jul 2016	Half of the studies used pharmacy refill	Quality assessment tool based on that of Effective Public Health Practice Project	Higher co-payment, side effects and poor patient-provider relationship were associated with nonadherence	MPR most commonly used/ 80% cut-off	(-)

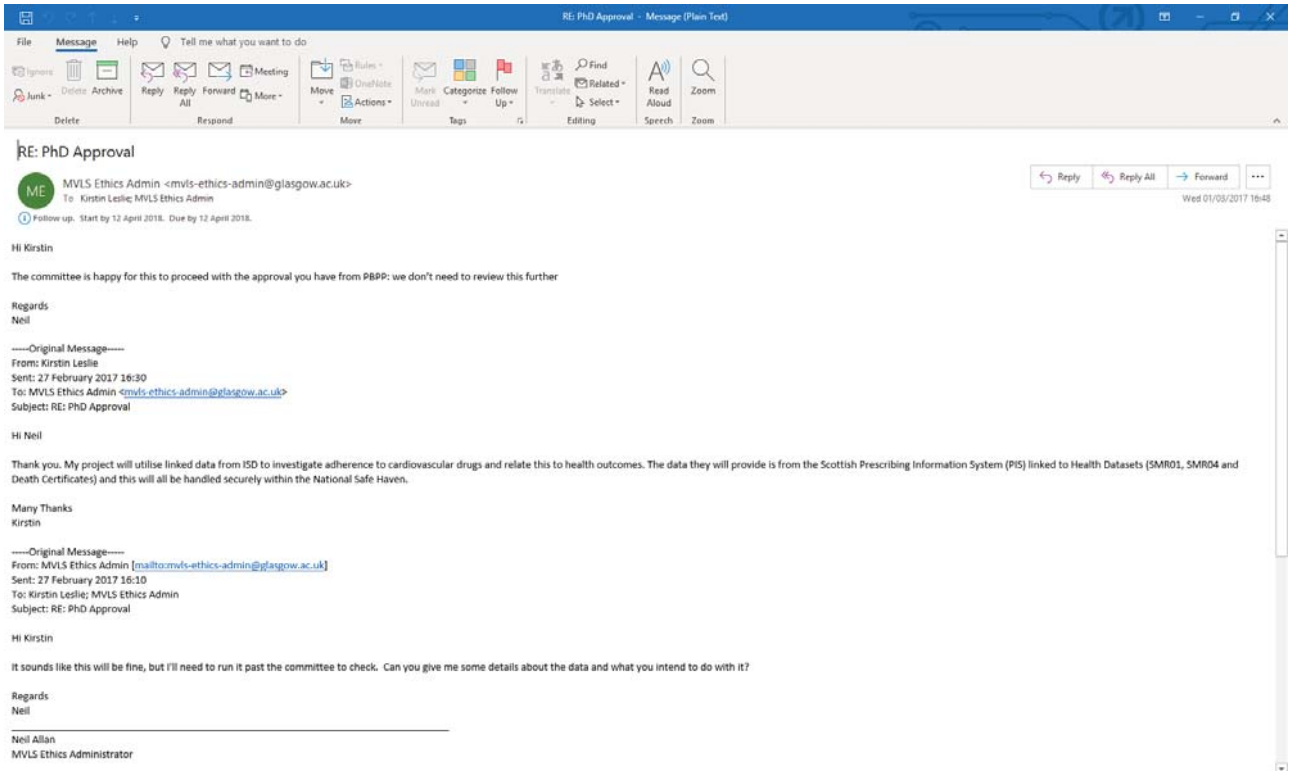
Papers included here were identified in updated search, Feb 2020. Papers identified in original search can be downloaded as Supplementary Table 1 from: 10.1093/pubmed/fdy088

Supplementary Table 2: Data Extraction for outcomes associated with non-adherence

Review Author (year)	Aim	Setting	No. of studies included (participants)	Search Strategy	Adherence Measurement	Quality tool used	Outcomes (and factors if included)	Adherence operational measure	Quality Score (from AMSTAR tool)
Martin-Ruiz et al (2018)	Assess risk of nonadherence to statins in primary prevention of CVD events/ mortality	Predominantly Europe and US	17 studies	MEDLINE, Trip database; articles published up until Dec 2016; limited to English and Spanish language	Mix; tablets received/ treatment visits/ pharmacy refills	Newcastle-Ottawa Scale	Pooled across studies: 18% reduced risk associated with CVD outcome and 49% reduced risk of mortality adherence vs nonadherence.	Two methods: split into adherence levels/ compare relative risk against ref (worst adherers); arbitrary 80% cut-off/ compare 'good' to 'bad	(++)
Murali et al (2017)	Evaluate how adherence/persistence assessed in trials, and their association with CVD outcomes/ mortality for dialysis patients	Not specified	22 trials (19,322); 5 measured adherence	MEDLINE, EMBASE and Cochrane CENTRAL; searched RCTs published 2005-2015; English	Not specified	None specified	Inconclusive; in five trials which studied this, appears that outcomes for these patients are negatively associated with poor adherence. More research needed.	Only defined in one trial; used 80% cut-off	(+)
Xu, et al (2017).	Identify association between adherence and stroke risk	Majority US or Europe	15 studies	MEDLINE, EMBASE	Not specified	Newcastle-Ottawa Scale	Increased adherence associated with reduced stroke risk, significant in 12 of 15 studies. Pooled RR of 0.77.	PDC and MPR	(++)

Papers included here were identified in updated search, Feb 2020. Papers identified in original search can be downloaded as Supplementary Table 2 from: 10.1093/pubmed/fdy088

Appendix B: Ethics Approvals



RE: PhD Approval - Message (Plain Text)

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Delete Respond Move Tags Editing Speech Zoom

RE: PhD Approval

ME MVLS Ethics Admin <mvls-ethics-admin@glasgow.ac.uk>
To Kirstin Leslie; MVLS Ethics Admin

Reply Reply All Forward
Wed 01/03/2017 16:48

Follow up. Start by 12 April 2018. Due by 12 April 2018.

Hi Kirstin

The committee is happy for this to proceed with the approval you have from PBPP: we don't need to review this further

Regards
Neil

-----Original Message-----
From: Kirstin Leslie
Sent: 27 February 2017 16:30
To: MVLS Ethics Admin <mvls-ethics-admin@glasgow.ac.uk>
Subject: RE: PhD Approval

Hi Neil

Thank you. My project will utilise linked data from ISD to investigate adherence to cardiovascular drugs and relate this to health outcomes. The data they will provide is from the Scottish Prescribing Information System (PIS) linked to Health Datasets (SMR01, SMR04 and Death Certificates) and this will all be handled securely within the National Safe Haven.

Many Thanks
Kirstin

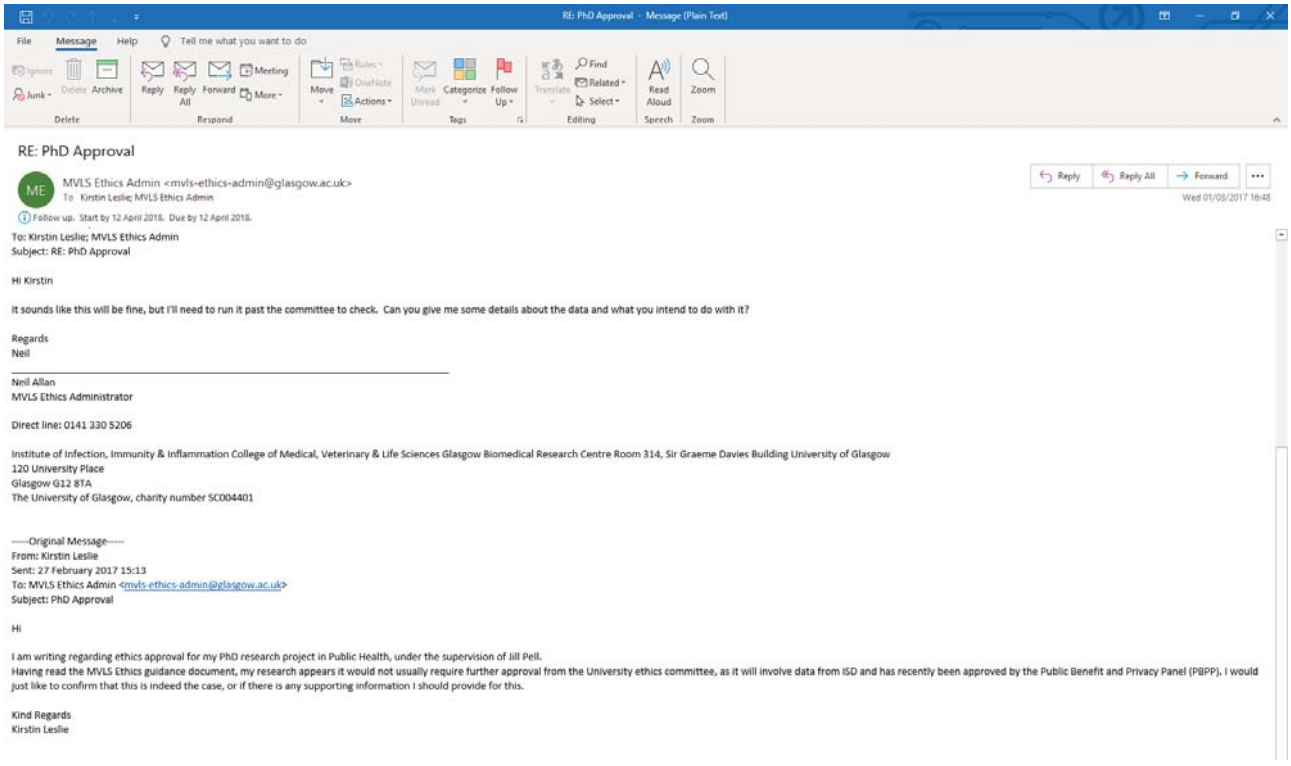
-----Original Message-----
From: MVLS Ethics Admin [mailto:mvls-ethics-admin@glasgow.ac.uk]
Sent: 27 February 2017 16:10
To: Kirstin Leslie; MVLS Ethics Admin
Subject: RE: PhD Approval

Hi Kirstin

It sounds like this will be fine, but I'll need to run it past the committee to check. Can you give me some details about the data and what you intend to do with it?

Regards
Neil

Neil Allan
MVLS Ethics Administrator



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Delete Respond Move Tags Editing Speech Zoom

RE: PhD Approval

ME MVLS Ethics Admin <mvls-ethics-admin@glasgow.ac.uk>
To Kirstin Leslie; MVLS Ethics Admin

Reply Reply All Forward
Wed 01/03/2017 16:48

Follow up. Start by 12 April 2018. Due by 12 April 2018.

To: Kirstin Leslie; MVLS Ethics Admin
Subject: RE: PhD Approval

Hi Kirstin

It sounds like this will be fine, but I'll need to run it past the committee to check. Can you give me some details about the data and what you intend to do with it?

Regards
Neil

Neil Allan
MVLS Ethics Administrator

Direct line: 0141 330 5206

Institute of Infection, Immunity & Inflammation College of Medical, Veterinary & Life Sciences Glasgow Biomedical Research Centre Room 314, Sir Graeme Davies Building University of Glasgow
120 University Place
Glasgow G12 8TA
The University of Glasgow, charity number SC004401

-----Original Message-----
From: Kirstin Leslie
Sent: 27 February 2017 15:13
To: MVLS Ethics Admin <mvls-ethics-admin@glasgow.ac.uk>
Subject: PhD Approval

Hi

I am writing regarding ethics approval for my PhD research project in Public Health, under the supervision of Jill Pell.
Having read the MVLS Ethics guidance document, my research appears it would not usually require further approval from the University ethics committee, as it will involve data from ISD and has recently been approved by the Public Benefit and Privacy Panel (PBPP). I would just like to confirm that this is indeed the case, or if there is any supporting information I should provide for this.

Kind Regards
Kirstin Leslie

Appendix C: PBPP Form

Public Benefit and Privacy Panel for Health and Social Care

Application Form

Application Control *Applicants should not fill out this section*			
Application Coordinator	David Bailey		
Application Number	1617-0221	Submitted Date	
Applicant Name	Kirstin Leslie		
Proposal Name	Scotland-wide study of adherence with cardiovascular medication		

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Note to Applicants

Prior to completing your application form you should:

- Contact the eDRIS Team, who will assist you - Nss.edris@nhs.net or by phone on 0131 275 7333
- Read and understand the separate Guidance for Applicants

Your application should be typed, not handwritten. Your eDRIS application coordinator will inform you how to submit your application form and any supporting evidence. Before submitting your completed application, you should ensure that:

- All relevant sections of the application are complete
- Relevant supporting evidence is attached
- Individuals named on the form have read and approved its submission

Please note that submitted applications may be circulated to panel members, administrative colleagues, NHSScotland information governance and information security colleagues, Caldicott Guardians, the CHI Advisory Group and, where appropriate, non-NHS Scotland colleagues from a variety of participating partner bodies, in the course of processing. You must make your eDRIS application coordinator aware of any confidential or sensitive information contained in your application which you would consider inappropriate for circulation in such a manner. Your application could be subject to disclosure or partial disclosure under the Freedom of Information (Scotland) Act, and will be retained in line with NHSScotland information policy.

Section 1 – People

1.1	**Applicant** *Please read section 1.1 of the guidance*	
1.1.01	Full Name:	Kirstin Leslie
1.1.02	Title:	Ms
1.1.03	Position:	PhD student
1.1.04	Professional Registration No.:	*If applicable*
1.1.05	Organisation Name:	University of Glasgow
1.1.06	Address:	Institute of Health and Wellbeing, 1 Lilybank Gardens, Glasgow
1.1.07	Postcode:	G12 8RZ
1.1.08	Telephone Number:	0141 330 4072
1.1.09	Email:	k.leslie.1@research.gla.ac.uk
1.1.10	Do you have an NHS contract/honorary contract?	No
1.1.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if you have undertaken any of those listed	
	Name of course:	MRC Research Data and Confidentiality e-learning
	Link to course content:	http://www.byglearning.co.uk/mrcrsc-lms/login/index.php
	Institution:	Medical Research Council
	Date completed:	30/11/2016

1.2	**Clinical Sponsor/Lead** *Please read section 1.2 of the guidance*	
1.2.01	Full Name:	Jill Pell
1.2.02	Title:	Professor & Doctor
1.2.03	Position:	Director of the Institute of Health and Wellbeing
1.2.04	Professional Registration No.:	3259687
1.2.05	Organisation Name:	University of Glasgow
1.2.06	Address:	1 Lilybank Gardens, Glasgow
1.2.07	Postcode:	G12 8RZ
1.2.08	Telephone Number:	0141 330 3239
1.2.09	Email:	Jill.pell@glasgow.ac.uk

1.2.10	Does this person have an NHS contract/honorary contract?	Honorary Consultant in Public Health NHS Greater Glasgow and Clyde
1.2.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if this person has undertaken any of those listed	
	Name of course:	MRC Research Data and Confidentiality e-learning
	Link to course content:	http://www.byglearning.co.uk/mrcrsc-lms/login/index.php
	Institution:	Medical Research Council
	Date completed:	15/05/2015

1.3	**Information/Data Custodian** *Please read section 1.3 of the guidance*	
1.3.01	Full Name:	Jill Pell
1.3.02	Title:	Professor & Doctor
1.3.03	Position:	Director of the Institute of Health and Wellbeing
1.3.04	Professional Registration No.:	3259687
1.3.05	Organisation Name:	University of Glasgow
1.3.06	Address:	1 Lilybank Gardens, Glasgow
1.3.07	Postcode:	G12 8RZ
1.3.08	Telephone Number:	0141 330 3239
1.3.09	Email:	Jill.pell@glasgow.ac.uk
1.3.10	Does this person have an NHS contract/honorary contract?	Honorary Consultant in Public Health NHS Greater Glasgow and Clyde
1.3.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if this person has undertaken any of those listed	
	Name of course:	MRC Research Data and Confidentiality e-learning
	Link to course content:	http://www.byglearning.co.uk/mrcrsc-lms/login/index.php
	Institution:	Medical Research Council
	Date completed:	15/05/2015

1.4 Others with access to identifiable or potentially identifiable data *Please read section 1.4 of the guidance*

Complete this section if applicable – for each additional person			
Full Name:	Alex Marshall	Telephone/ Email:	a.marshall.1@research.gla.ac.uk
Organisation:	Robertson Centre for Biostatistics (RCB), University of Glasgow	Position:	PhD Research Student
Professional Registration No:	n/a	NHS contract/ honorary contract?	No

IG Training - Name of course:	MRC Research Data and Confidentiality e-learning		
IG Training - Link to course:	http://www.byglearning.co.uk/mrcrsc-lms/login/index.php		
IG Training - Institution:	Medical Research Council	Date completed:	26/09/2016

1.4 Others with access to identifiable or potentially identifiable data Please read section 1.4 of the guidance			
Complete this section if applicable – for each additional person			
Full Name:	Professor Jill Pell	Telephone/ Email:	0141 330 3239 Jill.Pell@glasgow.ac.uk
Organisation:	University of Glasgow	Position:	Director of Institute of Health and Wellbeing
Professional Registration No:	3259687	NHS contract/ honorary contract?	Honorary Consultant in Public Health – NHS Greater Glasgow and Clyde

IG Training - Name of course:	MRC Research Data and Confidentiality e-learning		
IG Training - Link to course:	http://www.byglearning.co.uk/mrcrsc-lms/login/index.php		
IG Training - Institution:	Medical Research Council	Date completed:	15/05/2015

1.4 Others with access to identifiable or potentially identifiable data *Please read section 1.4 of the guidance*			
Complete this section if applicable – for each additional person			
Full Name:	Colin McCowan	Telephone/ Email:	0141 330 3319 Colin.McCowan@Glasgow.ac.uk

Organisation:	RCB, University of Glasgow	Position:	Professor of Health Informatics
Professional Registration No:		NHS contract/ honorary contract?	Yes *Honorary Contract with NHS GGC HB*
IG Training - Name of course:	MRC Research Data and Confidentiality e-learning		
IG Training - Link to course:	http://www.byglearning.co.uk/mrcrsc-lms/login/index.php		
IG Training - Institution:	Medical Research Council	Date completed:	05/01/2015

1.4 Others with access to identifiable or potentially identifiable data Please read section 1.4 of the guidance			
Complete this section if applicable – for each additional person			
Full Name:	Kevin Ross	Telephone/ Email:	0141 330 5188
Organisation:	University of Glasgow	Position:	Data Analyst
Professional Registration	No	NHS contract/ honorary contract?	No
IG Training - Name of course:	MRC Research Data and Confidentiality e-learning course		
IG Training - Link to course:	https://byglearning.com/mrcrsc-lms/course/index.php?categoryid=1		
IG Training - Institution:	Medical Research Council	Date completed:	18/02/2016

1.5 Others *Please read section 1.5 of the guidance*			
Complete this section if applicable – for each additional person			
Full Name:		Involvement in Proposal:	
Organisation:		Position:	

Section 2 – Organisations & Bodies

2.1	**Organisation or Body Leading Proposal** *Please read section 2.1 of the guidance*	
2.1.01	Organisation or Body Name:	University of Glasgow
2.1.02	Is this organisation or body a registered data controller? If 'Yes', provide Data Protection Registration Number:	Yes Z6723578
2.1.03	Is this a commercial organisation or body?	No
2.1.03a	If 'Yes', please provide a full explanation of the organisation or body's activity and industry sector, including any previous experience of using NHSScotland data - append supporting documentation as appropriate	*If applicable*
2.1.04	Is this organisation or body wholly funding or paying for the costs of conducting the proposal?	No

2.2	**Organisation or Body Funding Proposal** *Please read section 2.2 of the guidance*	
Complete the following section if you answered 'No' to question 2.1.4		
2.2.01	Organisation or Body Name:	University of Glasgow Joint MRC Doctoral Training Programme (with Edinburgh University)
2.2.02	Is this organisation or body a registered data controller? If 'Yes', provide Data Protection Registration Number:	Yes Z6723578
2.2.03	Is this organisation or body a commercial organisation?	No
2.2.03a	If 'Yes', please provide a full explanation of the organisation or body's activity and industry sector, including any previous experience of using NHSScotland data - append supporting documentation as appropriate	**N/A**

2.3 Other Relevant Organisations or Bodies *Please read section 2.3 of the guidance*		
Complete this section if applicable		
Organisation Name	Nature of Business/Sector	Nature of interest in proposal

Section 3 – Overview

3.1	**Proposal Essentials** *Please read section 3.1 of the guidance*	
3.1.01	Proposal title/name:	Scotland-wide study of adherence with cardiovascular medication
3.1.02	Is this proposal an extension or renewal of an existing approval (for example to conduct a study over a wider geographic area or for a longer period of time)? Please provide details, include the reference number of the original approval, and summarise the changes requested	No
3.1.03	Is this new proposal related to a previous application (approved or not)? Please give details, indicate if this is a resubmission, including the reference number of the original submission	No
3.1.04	What is(are) the substantive purpose(s) of the proposal? (tick all that apply) ☐ Patient Care ☒ Research ☐ Audit ☐ Performance Monitoring/Management ☐ Service Planning/Improvement ☐ Health/Social Care Administration ☐ Systems Implementation/Testing ☐ Training/Education ☐ Quality (Clinical, Educational, etc)	
	If other clearly defined purpose, please give details:	
3.1.05	Does the proposal require the use of information which can identify or potentially identify individuals?	No
3.1.06	Access is being requested to data from which sources? (tick as many as are relevant)	

	☐ A single NHS Scotland Board (excluding NSS) x NHS National Services Scotland ☐ More than one NHS Scotland Board x A national NHS Scotland system/database ☐ More than one NHS Scotland system/database ☐ Community Health Index (CHI) database ☐ NHS Central Registry
	If other, please give details:
3.1.07	Provide a full, clear concise outline of the proposal background – describe why it is needed, aims and objectives and envisaged benefits to the public and/or patients: Over the past century there has been a large shift in disease burden within the developed world, with chronic diseases now occurring much more frequently when compared to acute and infectious diseases (*Sabaté E, 2003*). Additionally, there is an improved rate of survival from such conditions and people are generally living longer, meaning they tend to remain on prescriptions for a much longer period of time and are much more likely to develop multiple, co-morbid disorders requiring multiple prescriptions. There has also been a change in medical practice, leading to an increased use in drugs for primary prevention of disease, particularly with lipid-lowering statins in prevention of cardiovascular diseases. As such, many more long-term self-care prescriptions are administered and it has become increasingly important to consider what happens to these prescriptions once the patient takes it home. Adherence, also referred to as compliance, is defined by World Health Organization as "*the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*." There have been recent efforts to move away from the use of the term "compliance" as this implies a lack of patient autonomy, though both terms are recognised within the literature. It is a huge issue, and it is commonly cited that adherence to medication regimens for long-term treatment averages at 50% (*Nichol et al 1999, Nieuwlaat et al 2014, Sabaté E 2003*). Without effective adherence, it is unlikely that drugs can reach their therapeutic range and hence optimally treat the disease affecting the patient. For example, antihypertensive drugs are used in both the primary and secondary prevention of cardiovascular disease (CVD), and despite efficacy shown in trials, this has not translated to the clinic (*Grassi et al 2011*). There are a number of contributing factors to this, and the lower rate of adherence in the community setting compared with a highly-motivated and monitored trial population is likely to be one of them. In a US study, patients who were good compliers (defined as patients who collected $\geq 80\%$ of the medication prescribed in a given period) were 45% more likely to reach their target blood pressure than those classed as medium or low compliers (*Grassi et al 2011*), and this was also associated with a reduced risk of hospital admissions. In Scotland, heart disease has a particularly high prevalence, and so research into adherence to antihypertensive drugs could be hugely valuable in this setting.

Despite the known risks, there are many reasons patients fail to comply with a drug regimen: forgetfulness, side-effects, complex dosage regimens, a perception that the drug is not working, and a lack of understanding. Complex dosing may be difficult to avoid in particular classes of medication, especially if they are fast-acting drugs. It has also been found that the longer a patient is on a drug, the more likely they are to become non-compliant (*Jin et al 2008*), either by increasingly erratic dosing (*Cramer JA 2002*) or non-persistence. Furthermore, some sub-groups of patients are more likely to struggle with adherence than others. Adherence generally improves with age, and adolescents are notoriously poor compliers. However, elderly patients may also struggle to adhere, for example if they have a co-morbid disorder affecting their cognition, making it difficult for them to understand instructions. Social demographics, such as level of deprivation may also have an impact.

Need for Study: Despite advances, there is still a lack of quality research in this field; a 2014 Cochrane Review of 182 studies found that only 17 had an acceptably low risk of bias (*Nieuwlaat et al 2014*). For years research into medical adherence has been plagued by a lack of standardized methodology and failure of researchers to clearly define the terms 'adherence' or 'compliance,' as well as the different metrics used to study this, making it difficult for comparison in meta-analyses. This is the first study of its kind: A longitudinal, Scotland-wide, retrospective study of adherence in anti-hypertensive therapy, covering all ages and socioeconomic classes, giving greater insight into potential risk factors, and allowing us to identify unmodifiable risk factors, or particular patient groups requiring extra support. We will also consider other key patient and disease factors, and whether different drug classes (e.g. lipid-lowering drugs, beta-blockers, etc.) has a major impact on adherence.

Aim: To study the epidemiology of non-adherence to cardiovascular medication in Scotland and its subsequent effect on outcomes

Objectives:

- To determine the level of adherence with cardiovascular medication within Scotland
- To determine the factors associated with adherence, including drug group, dosage and prescribing regimen, sociodemographic factors, type of usage (treatment vs primary prevention vs secondary prevention), as well as co-morbidity and polypharmacy.
- To determine the outcomes of poor adherence by linking prescription data to medical records to assess future hospitalisations and deaths

Benefits to public: Failure to adhere to medication can contribute to reduced clinical effectiveness, reduced cost effectiveness, poorer overall health and health inequalities. Identifying national levels of adherence as well as identifying sub-groups of the population who do not comply and why is fundamental to developing interventions to improve adherence and, thereby, population health.

	References: Cramer JA. 2002. Effect of Partial Compliance on Cardiovascular medication effectiveness. *Heart*; 88:203-206 Grassi G, Seravalle G, Mancia G. 2011. Cardiovascular consequences of poor compliance to antihypertensive therapy. *Blood Pressure*. 20:4, 196-203 Jin J, Sklar GE, Oh VMS, Li SC. 2008. Factors affecting therapeutic compliance: a review from the patients perspective. *Therapeutics and Clinical Risk Management*: 4(1) 269-286 Nichol MB, Venturini F, Sung JCY. 1999. A Critical Evaluation of the Methodology of the Literature on Meciation Compliance. *The Annals of Pharmacotherapy*; 33:531-40 Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. 2014. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*, Issue 11. Art. No.: CD000011. DOI: 10.1002/14651858.CD000011.pub4. Sabaté E, editor. , ed. 2003. Adherence to Long-Term Therapies: Evidence for Action. Geneva, Switzerland: *World Health Organization.*
3.1.08	Provide a full, clear and concise outline of the proposal design, listing: data sources; sample size ; inclusion/exclusion criteria (eg involvement in trial/survey; health event, etc); relevant date range; need for identifiable or potentially identifiable data; requirement for a matched control cohort etc. **Data Sources:** • PIS (2009-most recent) – for prescribing information; PIS data for all items prescribed to members of our cohort will be used to identify polypharmacy • SMR01 (1999-most recent) – record of admissions to acute hospitals • SMR04 (1999-most recent) – record of admissions to psychiatric hospitals • Death Certificates (NRS Deaths) (2009-most recent) PIS will be used to identify all individuals prescribed one or more of the following medications from January 2009 onwards (including individuals who did not collect some/all of the prescriptions): - Lipid-regulating drugs (BNF 2.12) - Diuretics (BNF 2.2) - Alpha-blockers (BNF 2.3.4) - Beta-blockers (BNF 2.4) - ACE inhibitors (BNF 2.5.5.1) - Angiotensin-2-receptor blockers (BNF 2.5.5.2) - Nitrates (BNF 2.6.1) - Calcium Channel Blockers (BNF 2.6.2) - Other antianginal agents (2.6.3)

	- Antiplatelet drugs (BNF 2.9) For these individuals we require linkage to all SMR01, SMR04 and death data for the time periods listed above. SMR01 data will be used to categorise use of these medications into secondary prevention (commencement within 30 days of acute myocardial infarction), treatment (commencement of anti-anginal medication within 10 years of ischaemic heart disease code) and primary prevention (neither). SMR01, SMR04 and death data will be used to derive outcomes: • All-cause hospitalisations • Cause-specific hospitalisations • All-cause mortality • Cause-specific mortality SMR01 and SMR04 records in the 10 years prior to prescription of the listed drugs will be used to ascertain comorbidities based on the ICD-10 coding as this is likely to be an important factor for levels of adherence. PIS data will be used to identify polypharmacy in terms of the number and types of additional drugs prescribed at the same time as the drug of interest. PIS data on prescribed medications based on written prescription, encashed medication based on that dispensed by the pharmacist and dosage instructions will be used to assess adherence in a number of ways, including percentage of actual prescriptions dispensed and medication possession ratio which examines the actual encashed medications over the period of use. We will investigate whether adherence varies by the following and undertake sub-group analyses where relevant. • age, • sex, • socioeconomic deprivation, • drug category • prescribing regimen • use of medication for primary versus secondary prevention treatment • presence / absence and level of comorbidity / multimorbidity • presence / absence and level of polypharmacy
3.1.09	Does the proposal have implications for, or target, sensitive groups or vulnerable populations? Please give details

	No
3.1.10	Does the proposal seek to use information exclusively about deceased persons? Please give details
	No
3.1.11	Have any members of the public/lay representatives been involved in the proposal design? Please give details
	No
3.1.12	Has any peer review of the proposal been undertaken? Please give details (for example formal review by a peer organisation or funding body, informal internal review, review by a third party)
	Yes the project was subjected to internal peer review as part of the MRC Doctoral Training Programme – all proposals were reviewed, ranked and shortlisted.
3.1.13	Is there *any* commercial aspect or dimension to the proposal or its outcomes? Please give details
	No

3.2 Proposal Geography *Please read section 3.2 of the guidance*
☐ Local/Regional (relating to one or more specific areas within Scotland)
X National (relating to the whole of Scotland)
☐ UK-wide (relating to the whole of the UK, or to UK regions outside Scotland)
☐ International (relating to areas within the EEA)

☐ International (relating to areas beyond the EEA)

3.3	**Proposal Duration and Frequency** *Please read section 3.3 of the guidance*	
3.3.01	What is the proposed duration of the proposal?	4 years
3.3.02	Does the proposal require updates of information at regular intervals? Please give details	No
3.3.03	Are you seeking approval to iterate the proposal (ie the *whole* project, audit or study) at regular intervals? Please give details	No

3.4	**Statutory and Regulatory Context** *Please read section 3.4 of the guidance*	
3.4.01	Does your proposal have a statutory or regulatory justification - is the proposal responding to a statutory or regulatory instruction, duty or order? Please give details	*No*
3.4.02	Which Data Protection Act schedule 2 and schedule 3 conditions are relevant? (a list of conditions can be found at Appendix B)	Schedule 2:(6) "legitimate interests pursued by the Data Controller or the third party." Schedule 3: (8), "processing is necessary for "medical purposes"…includes the purposes of medical research…"
3.4.03	Are there any relevant information sharing agreements, protocols or contracts in place which support your proposal? Please give details and attach as supporting documentation if available	*No – all datasets are held by ISD*
3.4.04	Has a Privacy Impact Assessment been carried out which supports your proposal? Please give details and attach as supporting documentation if available	*Not applicable – see attached document which applies screening criteria to the need for an application*
3.4.05	Has local Caldicott approval been given for your proposal at a local level? Please give details	*Not applicable*

3.4.06	Are approvals from Caldicott Guardians outside Scotland pending or received? Please give details	*Not applicable*

3.5	**Research and Ethics Governance** *Please read section 3.5 of the guidance*	
3.5.01	Has your proposal sought research/ethics approval?	No –not applicable as the project would fall under the pre-arranged Ethics Approval for eDRIS studies analysed within the National Safe Haven
3.5.01a	If yes, please provide committee details and status of approval (ie pending, approved, etc). Please attach as supporting documentation if available	*If applicable*
3.5.01b	If no, please explain why research/ethics approval is not sought:	*If applicable*

3.6	**Safe Havens** *Please read section 3.6 of the guidance*	
3.6.01	Do you intend to access the data requested exclusively through a safe haven listed at Appendix A? Please provide details of which safe haven/s	Yes *If you have answered 'Yes' you do not need to complete sections 5.2 or 5.3*
3.6.02	If you applying to use NHS NSS data and you do not intend to do this through the National Safe Haven, please explain why	*If applicable*

Section 4 – Data & Data Subjects

4.1 Data yet to be collected *Please read section 4.1 of the guidance*		
Dataset/source Name	Collection by (whom)?	Explicit consent sought? If Yes, describe how explicit consent being sought – provide copies of participant consent/registration forms, etc. If No, explain why consent is not being sought (eg impractical, risk associated with seeking consent, etc)
N/A		

4.2 All Other Datasets / sources *Please read section 4.2 of the guidance*		
Dataset/source Name	Data Controller (Organisation)	Original purpose compatible with proposal?
SMR 01	NSS	• Outcomes (cause specific and all cause hospitalisations) • Differentiate between primary or secondary prevention and treatment • Identify comorbid conditions
SMR 04	NSS	• Outcomes (all-cause hospitalisations) • Identify comorbid conditions
Deaths	NRS	• Outcomes
PIS	NSS	• Exposure (adherence to medication) • Modifying factors (drug category, polypharmacy, doseage regiment) • Comorbidity • Confirmation of date of first usage

How were individuals originally informed of the use of their data? (if known)		
We are requesting a download of data collected and collated by NHS Scotland. Patients attending / accessing NHS healthcare services are provided with leaflets informing them that data will be collected and the uses to which they they will be put. No written consent is obtained. We are not involved in this process		
For existing dataset/sources for which the data controller is not an NHSScotland board, please append evidence of the data controllers permission to use the data We are using an anonymised extract of data collected by the NHS and already collated and held by ISD.		

4.3 Data Variables *Please read section 4.3 of the guidance*			
Dataset/source Name	Variable	Time Period/Range	Processing only?
SMR 01	Unique Patient ID Full admission date Full discharge date Continuous Inpatient Stay (CIS) marker (including GLS) Location Health Board of Treatment Specialty Significant Facility Admission Type Admission Reason Admission transfer from Admission transfer from desc Discharge type Discharge transfer to Discharge transfer to desc main_condition other_condition_1	Jan 1999 onwards	Yes

	other_condition_2 other_condition_3 other_condition_4 other_condition_5 main_operation_date main_operation_a main_operation_b other_operation_1_a other_operation_1_b other_operation_2_a other_operation_2_b other_operation_3_a other_operation_3_b Inpatient/Day Case MarkerSIMD Scotland Quintile (2012) SIMD Scotland Decile (2012) D.O.B (mm/yyyy) Length of Stay		
SMR 04	Unique Patient ID Full admission date Full discharge date Continuous Inpatient Stay (CIS) marker (including GLS) Location Health Board of Treatment Specialty Significant Facility Admission Type Admission Reason Admission transfer from Admission transfer from desc Discharge type	2009 Onwards	Yes

	Discharge transfer to Discharge transfer to desc main_condition other_condition_1 other_condition_2 other_condition_3 other_condition_4 other_condition_5 main_operation_date main_operation_a main_operation_b other_operation_1_a other_operation_1_b other_operation_2_a other_operation_2_b other_operation_3_a other_operation_3_b Inpatient/Day Case Marker SIMD Scotland Quintile (2012) SIMD Scotland Decile (2012) Age in years Length of Stay		
NRS Death Registrations	Unique Patient ID Age at Death Date of Death Underlying Cause of Death Code Cause of Death Code 0 Cause of Death Code 1 Cause of Death Code 2 Cause of Death Code 3 Cause of Death Code 4 Cause of Death Code 5	2009 Onwards	Yes

	Cause of Death Code 6 Cause of Death Code 7 Cause of Death Code 8 Cause of Death Code 9 Place of Occurrence Code		
PIS	Unique Patient ID Gender Age D.O.B (mm/yyyy) Patient Postcode Sector (5 digit) SIMD Scotland Quintile (2012) SIMD Scotland Decile (2012) Patient Health Board Patient CHP Patient Local Authority Anonymised Prescribing GP practice code Prescribing Health Board Paid date (full date) Dispensed date (full date) Prescribed Date (full date)) PI Drug approved name PI Item Description PI Product Description PI Drug Formulation PI Strength/UOM BNF Item BNF root drug	2009 Onwards	

	Number of Items Dispensed/ Paid Quantity dispensed/ paid Number of Defined Daily Doses dispensed for all prescribed drugs listed in 3.1.8 ePR native dose instructions for drugs listed in 3.1.8. (Dose variable information extracted from Dose Instructions using NLP)		

Please justify your need for identifiable or potentially identifiable variables:

Full dates of death, admission and discharge are requested to allow for accurate modelling of clinical and economic outcomes.
GP Practice code and Patient Postcode Sector have been requested to group patients by these categories and examine whether practice or location are associated with different outcomes.

4.4	**NRS/NHSCR Data Sources** *Please read section 4.4 of the guidance*	
Complete this section if access to NHSCR is required, or if there is any National Records of Scotland involvement		
4.4.01	Does the proposal require access to NHS Central Registry as a sampling frame for cohorts?	No
4.4.02	Does the proposal involve flagging of individuals on the NHSCR for long term follow up?	No
4.4.03	If yes, is flagging necessary: ☐ To trace and contact individuals throughout the UK? ☐ To be informed of fact and cause of death? ☐ To be informed of the incidence of on-going cancers? ☐ To be informed of emigrations prospectively and retrospectively?	

4.4.04	Is any other NRS involvement required? Please provide details	No

4.5	**Making Contact with Individuals** *Please read section 4.5 of the guidance*				
4.5.01	Is any direct contact with any group of individuals required? If Yes, please provide details below				No
	Contact Group and Method of contact				Contact by (whom)
	☐ Hospital Consultants	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Other NHSS Staff	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ General Practitioners	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Patients/Public	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Relatives of participants	☐ Letter	☐ Phone	☐ Other (specify):	
	☐ Others (please specify):	☐ Letter	☐ Phone	☐ Other (specify) :	
4.5.02	Please explain why contact is being made – append copies of relevant correspondence as supporting evidence				
	If applicable				

4.6	**Community Health Index (CHI) Database** *Please read section 4.6 of the guidance*
Complete this section if access to CHI Database is required	

4.6.01	What monitoring and audit of the use of CHI is planned? Please provide details	
4.6.02	What technical method will be used to access CHI (online read-only, download, other extract, anonymised extract, etc)? Please provide details	
4.6.03	Have any risks been identified in the proposal which relate specifically to CHI?	

Section 5 – Methodology & Data Processing

5.1	**Methodology** *Please read section 5.1 of the guidance*	
5.1.01	Does the proposal require any of the following: x Data matching/linking x Single anonymised data extract ☐ Use of matched controls Other (please specify):	
5.1.02	Who is carrying out any indexing/ linkage/anonymisation, and where?	ISD Indexing team
5.1.03	Which data sources listed at section 4.1 and 4.2 will NSS/NRS receive identifiers for linkage purposes?	*If applicable*
5.1.04	What variables will be provided for linkage? ☐ CHI Number ☐ Forename ☐ Surname ☐ Date of Birth ☐ Address or Postcode ☐ NHS Number Other Please Specify: N/A	

5.2	**Access** *Please read section 5.2 of the guidance*	
Complete the following section if you answered 'No' to question 3.6.1		
5.2.01	At what location is identifiable or potentially identifiable data being accessed?	N/A
5.2.02	Please provide details of security policy/procedure governing access to this physical and technical environment – append supporting documentation	N/A
5.2.03	Does this policy/procedure cover password policy in detail? Please provide details/ append supporting documentation	N/A
5.2.04	Does this policy/procedure cover user account management, including review or removal of access to	N/A

	sensitive/personal data, in detail? Please provide details/ append supporting documentation	
5.2.05	Will individuals with access to data have individual or shared accounts?	N/A
5.2.06	Will the data be accessed by staff working off site eg staff working from home at any time during the duration of the proposal?	Choose an item.
5.2.06b	If yes, are policies/procedures in place to facilitate, monitor and audit this access? Please provide details/ append supporting documentation	*If applicable*
5.2.07	Provide any additional detail of how data is protected from unauthorised access	*If applicable*

5.3	**Store & Use** *Please read section 5.3 of the guidance*	
Complete the following section if you answered 'No' to question 3.6.1		
5.3.01	Where is data being stored and used? (location, organisation, address – refer to addresses in previous sections if appropriate)	N/A
5.3.02	Data Protection Registration Number	*If applicable*
5.3.03	ISO 27001 Cert. No.	*If applicable*
5.3.04	Please provide details of security policy/procedure governing storage and use of data within this physical and technical environment – append supporting documentation	N/A
5.3.05	Does this policy/procedure cover the implementation of up-to-date controls for the detection and prevention of malware? Please provide details/ append supporting documentation	N/A
5.3.06	Does this policy/procedure cover access control and auditing of system administrator activity? Please provide details/ append supporting documentation	N/A

5.3.07	Does this policy/procedure cover the production of backups and the controls in place around these? Please provide details/ append supporting documentation	N/A
5.3.08	Does this policy/procedure describe the controls in place to prohibit unauthorised copying of data? Please provide details/ append supporting documentation	N/A
5.3.09	Does this policy/procedure describe physical and site controls? Please provide details/ append supporting documentation	N/A
5.3.10	Does this policy/procedure cover hardware repair, replacement or disposal and protection of data from inappropriate access during such procedures? Please provide details/ append supporting documentation	N/A
5.3.11	Describe the systems, software and security used to store and use data - please provide details/ append supporting documentation	N/A
5.3.12	Is outsourced IT in use? Please give details	N/A
Please repeat section 5.3 above for each relevant location in the proposal – see guidance		

5.4	**Transfer** *Please read section 5.4 of the guidance*	
5.4.01	Please provide details of security policy/procedure to ensure that data will be transferred in such a way that it is protected from inappropriate or unauthorised access (mention email encryption, secure file transfer protocols SFTP, device encryption, physical controls, etc, as appropriate) - append supporting documentation	All data transfers will only be required within eDRIS procedures including hosting on National Safe Haven
5.4.02	At what intervals/ trigger points will data transfer take place?	Single transfer
5.4.03	Will any identifiable or potentially identifiable data be transferred outside of the UK?	No
5.4.03b	If yes, please provide details of the country of destination, the method of transfer, the proposed location and method	*If applicable*

	of storage outside of the UK, and details of any further onward transfer	
5.4.04	Other than initial transfers from source systems, is there any copying of data required within the proposal? Please give details	No

5.5	**Dissemination** *Please read section 5.5 of the guidance*	
5.5.01	Will proposal findings be published or disseminated beyond the proposal team?	Yes *If you have answered 'No', go directly to section 5.6*
5.5.01a	If yes, how will proposal findings be published or disseminated, to what audience and in what format? Please give details	Dissemination to researchers through high quality, peer reviewed journals, conference presentations, and publication in PhD Thesis. To general audiences, accessible summary articles will be presented.
5.5.01b	If yes, what steps will be taken to ensure that persons cannot be identified in published findings (eg disclosure control procedures (safe haven), use of aliases, numbers, avoidance of small geographical areas, avoidance of small numbers , etc)? Please give details	Only aggregated data presented
5.5.01c	If yes, are there any circumstances where a living or dead individual would be cited? (eg where a person consented to their data being used as a case study)? Please give details	No
5.5.01d	If yes, were any permissions to publish data required or sought (for example from data controllers)? Please provide details	No

5.6	**Retain/Dispose** *Please read section 5.6 of the guidance*	
5.6.01	Which information/data/records retention policy will you be applying to the proposal data (details of the policy and the organisation to which it belongs)?	NHS NSS Retention Policy
5.6.02	How long do you intend to retain identifiable or potentially identifiable data after the conclusion of the proposal (including archive/backup copies)?	2 years
5.6.03	Who will retain the data and where?	As per NSS Safe Haven PoI
5.6.04	What is the purpose for retaining the data for the specified time?	To re-visit analysis/ make amendments, write up of papers, answer journal questions and write-up of and Thesis
5.6.05	What method of disposal or destruction will be used when this period has expired (including archive/backup copies)?	As per eDRIS User Agreement.
5.6.06	What evidence will be obtained that destruction has occurred (eg IT supplier certificate of destruction, etc)?	As per eDRIS User Agreement.

5.7	**Review** *Please read section 5.7 of the guidance*	
5.7.01	Describe how the mechanisms which safeguard data security will be audited and reviewed at regular intervals to ensure their continued efficacy	As per eDRIS User Agreement.
5.7.02	Describe any resource implications to any of the proposed measures for the protection of physical or technical security of information which are unresolved at the time of this application? (for example encryption of devices is an intention not yet fulfilled, training is not yet undertaken, etc)	As per eDRIS User Agreement.
5.7.03	Describe the breach reporting mechanisms to be invoked in the event of any inappropriate access to data or other information security incident	As per eDRIS User Agreement.

Section 6 – Declaration

- I DECLARE THAT this application is accurate, and that, should it be successful, any health data made accessible will be used for no other purpose, and in no other way, than as described above.
- I UNDERTAKE TO notify the Public Benefit and Privacy Panel of any future changes to the purpose or manner in which data is processed in accordance with this application.
- I UNDERSTAND THAT any future applications by me, or my employing or sponsoring organisation, may be refused should any health data made accessible be used for any other purpose or in any other way than that described above.
- I CERTIFY THAT all those who have access to health data in this proposal are aware of the requirements of confidentiality and understand that any breach (eg disclosure of confidential information to a person not authorised to receive it) will be reported to the data controller, and in the case of NHS Scotland originated data to Scottish Government eHealth division.
- I GUARANTEE THAT no publication will appear in any form in which an individual may be identified without the written permission of that individual, and that I will apply appropriate disclosure control when planning publications involving the data requested.
- I UNDERSTAND THAT the Data Controller, and agents acting on its behalf, reserves the right to inspect the data on the sites where it is being processed.

To be signified by the APPLICANT

Name (in Capitals): KIRSTIN LESLIE	Date: 22/12/2016

- I DECLARE THAT (the applicant named above) is a *bona fide* worker engaged in a reputable project and that the data he/she asks for can be entrusted to him/her in the knowledge that he/she will conscientiously discharge his/her obligations, including in regard to confidentiality of the data, as stated in the declaration above.

To be signified by the INFORMATION CUSTODIAN named in Section 1.3 above (where the Information Custodian is not the applicant).

Name (in Capitals): JILL PELL	Date: 22/12/2016

Section 7 - Supporting Evidence

Supporting Evidence *Please read section 7 of the guidance*
Please list each piece of supporting evidence which you have included with your application in the box below – the name of each should clearly indicate what the document/file/reference is about
1617-0221 - Privacy Impact Assessment – comparison of application against the criteria listed in the ICO Code of Practice Report 1617-0221 – Certificate of Completion - MRC Research Data and Confidentiality e-learning – Kirstin Leslie 1617-0221 – Certificate of Completion - MRC Research Data and Confidentiality e-learning – Alex Marshall

Appendix A – Reference lists for applicants

1. Examples of Existing Datasets and Data Sources	
SMR 00 Outpatients	SMR 04 Mental Health
SMR 01 Inpatients and Day Cases	SMR 06 Cancer Registration
SMR 02 Maternity	SMR 11/SBR Neonatal/Scottish Birth Records
Scottish Drugs Misuse Database (SDMD)	Birth Registrations
A&E – Accident & Emergency	Stillbirth Registrations
PIS Prescribing Information	Death Registrations
CHSP-PS/CHSP-S/SIRS – Child Health Surveillance and Immunisation	SCI-DC
NHS National Service Scotland's Information Services Division (ISD) maintains a National Dataset Catalogue (NDC) containing details of all health and health related datasets that are held by ISD. The Administrative Data Liaison Service (ADLS) publishes further information on key NHSScotland datasets	

2. Common Identifiable Variables		
Forename	Middle Name	Surname
CHI Number	Date of Birth	UK NHS Birth Registration Number
Gender	Postcode	

3. Recognised Safe Havens
NHS NSS ISD Electronic Data Research Innovation Service (@Farr Institute)
NHS Research Scotland South East (ACCORD)
NHS Research Scotland East (TASC)
NHS Research Scotland North (DaSH)
NHS Research Scotland West
University of Dundee Health Informatics Centre (HIC)
National Records Scotland Scottish Longitudinal Study (SLS)
Robertson Centre @ Glasgow University

4. Research and Information Governance Training
MRC Research Data and Confidentiality online module
University of Edinburgh SHIP Information Governance training
NHS Health and Social Care Information Centre On-line Information Governance training
NHSScotland Information Governance eLearning: • Safe Information Handling (Foundation Level) • Information Handling in Practice (Intermediate Level)

5. Sensitive Data Categories		
Abortion	Mental health	Contraception
Pregnancy in age < 16 years	Drugs and alcohol misuse	Crime related statistics
Sexually transmitted disease	Suicide	Ethnicity
Assisted conception		

6. Vulnerable Populations	
Adults with Incapacity	Drugs users
Minority ethnic groups	Specific religious affiliation

Appendix B –The Caldicott Principles & the Data Protection Principles (& Schedules)

1. Caldicott Principles
1. **Justify the purpose(s)** Every single proposed use or transfer of patient identifiable information within or from an organization should be clearly defined and scrutinized, with continuing uses regularly reviewed, by an appropriate guardian.
2. **Don't use patient identifiable information unless it is necessary** Patient identifiable information items should not be included unless it is essential for the specified purpose(s) of that flow. The need for patients to be identified should be considered at each stage of satisfying the purpose(s).
3. **Use the minimum necessary patient-identifiable information** Where use of patient identifiable information is considered to be essential, the inclusion of each individual item of information should be considered and justified so that the minimum amount of identifiable information is transferred or accessible as is necessary for a given function to be carried out.
4. **Access to patient identifiable information should be on a strict need-to-know basis** Only those individuals who need access to patient identifiable information should have access to it, and they should only have access to the information items that they need to see. This may mean introducing access controls or splitting information flows where one information flow is used for several purposes.
5. **Everyone with access to patient identifiable information should be aware of their responsibilities** Action should be taken to ensure that those handling patient identifiable information - both clinical and non-clinical staff - are made fully aware of their responsibilities and obligations to respect patient confidentiality.
6. **Understand and comply with the law** Every use of patient identifiable information must be lawful. Someone in each organization

handling patient information should be responsible for ensuring that the organization complies with legal requirements.

7. **The duty to share information can be as important as the duty to protect patient confidentiality**
   Health and social care professionals should have the confidence to share information in the best interests of their patients within the framework set out by these principles. They should be supported by the policies of their employers, regulators and professional bodies.

2. Data Protection Principles
1. Personal data shall be processed fairly and lawfully and, in particular, shall not be processed unless – (a) at least one of the conditions in Schedule 2 is met, and (b) in the case of sensitive personal data, at least one of the conditions in Schedule 3 is also met
2. Personal data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes
3. Personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed
4. Personal data shall be accurate and, where necessary, kept up to date
5. Personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes
6. Personal data shall be processed in accordance with the rights of data subjects under this Act
7. Appropriate technical and organizational measures shall be taken against unauthorized or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data

8. Personal data shall not be transferred to a country or territory outside the European Economic Area unless that country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data

3. Data Protection Schedule 2 & 3 Conditions
Schedule 2 – Conditions for Processing any Personal Data
1. The data subject has given his **consent** to the processing
2. The processing is necessary— (a) for the **performance of a contract** to which the data subject is a party, or (b) for the taking of steps at the request of the data subject with a view to entering into a contract
3. The processing is necessary for compliance with any **legal obligation** to which the data controller is subject, other than an obligation imposed by contract
4. The processing is necessary in order to protect the **vital interests** of the data subject
5. The processing is necessary— (a) for the administration of **justice**, (aa) for the exercise of any functions of either **House of Parliament**, (b) for the exercise of any functions conferred on any person by or under any **enactment**, (c) for the exercise of any functions of the **Crown, a Minister of the Crown or a government department**, or (d) for the exercise of any other functions of a **public nature exercised in the public interest** by any person
6. (1) The processing is necessary for the purposes of **legitimate interests** pursued by the data controller or by the third party or parties to whom the data are disclosed, except where the processing is unwarranted in any particular case by reason of prejudice to the rights and freedoms or legitimate interests of the data subject. (2) The Secretary of State may by order specify particular circumstances in which this condition is, or is not, to be taken to be satisfied
Schedule 3 – Conditions for Processing any Sensitive Personal Data
1. The data subject has given his **explicit consent** to the processing of the personal data

2. (1) The processing is necessary for the purposes of exercising or performing any right or obligation which is conferred or imposed by law on the data controller in connection with **employment**
3. The processing is necessary— (a) in order to protect the **vital interests** of the data subject or another person, in a case where— (i) **consent cannot be given** by or on behalf of the data subject, or (ii) the data controller **cannot reasonably be expected to obtain the consent** of the data subject, or (b) in order to protect the **vital interests** of another person, in a case where **consent** by or on behalf of the data subject has been **unreasonably withheld**
4. The processing— (a) is carried out in the course of its **legitimate activities** by any body or association which— (i) is **not established or conducted for profit**, and (ii) exists for political, philosophical, religious or trade-union purposes, (b) is carried out with appropriate safeguards for the rights and freedoms of data subjects, (c) relates only to individuals who either are members of the body or association or have regular contact with it in connection with its purposes, and (d) does not involve disclosure of the personal data to a third party without the consent of the data subject
5. The information contained in the personal data has been **made public** as a result of steps deliberately taken **by the data subject**
6. The processing— (a) is necessary for the purpose of, or in connection with, any **legal proceedings** (including prospective legal proceedings), (b) is necessary for the purpose of obtaining **legal advice**, or (c) is otherwise necessary for the purposes of establishing, exercising or defending **legal rights**
7. (1) The processing is necessary— (a) for the **administration of justice**, (aa) for the exercise of any functions of either **House of Parliament**, (b) for the exercise of any functions conferred on any person by or under an **enactment**, or

(c) for the exercise of any functions of the **Crown, a Minister of the Crown or a government department**

(2)The Secretary of State may by order—

(a) exclude the application of sub-paragraph (1) in such cases as may be specified, or

(b) provide that, in such cases as may be specified, the condition in sub-paragraph (1) is not to be regarded as satisfied unless such further conditions as may be specified in the order are also satisfied

7A. (1) The processing—

(a) is either—

(i) the disclosure of sensitive personal data by a person as a member of an **anti-fraud** organisation or otherwise in accordance with any arrangements made by such an organisation; or

(ii) any other processing by that person or another person of sensitive personal data so disclosed; and

(b) is necessary for the purposes of preventing fraud or a particular kind of fraud

(2) In this paragraph "an anti-fraud organisation" means any unincorporated association, body corporate or other person which enables or facilitates any sharing of information to prevent fraud or a particular kind of fraud or which has any of these functions as its purpose or one of its purposes

8. (1) The processing is necessary for **medical purposes** and is undertaken by—

(a) a health professional, or

(b) a person who in the circumstances owes a duty of confidentiality which is equivalent to that which would arise if that person were a health professional

(2) In this paragraph "medical purposes" includes the purposes of preventative medicine, medical diagnosis, medical research, the provision of care and treatment and the management of healthcare services

9. (1) The processing—

(a) is of sensitive personal data consisting of information as to **racial or ethnic origin**,

(b) is necessary for the purpose of identifying or keeping under review the existence or absence of **equality of opportunity** or treatment between persons of different racial or ethnic origins, with a view to enabling such equality to be promoted or maintained, and

(c) is carried out with appropriate safeguards for the rights and freedoms of data subjects

(2) The Secretary of State may by order specify circumstances in which processing falling within sub-paragraph (1)(a) and (b) is, or is not, to be taken for the purposes of sub-paragraph (1)(c) to be carried out with appropriate safeguards for the rights and freedoms of data subjects
10. The personal data are processed in circumstances specified in an order made by the Secretary of State for the purposes of this paragraph

Appendix D: Dataset Assumptions

Variable Name	Description	Derivation/Assumptions
PatID	Anonymous patient identifier	ID number assigned between 1 and xxx.
Sex	Sex	sex taken from PIS records (if gender changed at any point, took most commonly occurring value)
postcode_sector	Postcode sector of residence at index date	Postcode sector taken from first dispensation of drug of interest. If multiple recorded on same date, most commonly occurring value used.
simd12_dec	SIMD decile at index date	SIMD 2012 decile taken from first dispensation of drug of interest. If multiple recorded on same date, most commonly occurring value used.
simd12_quint	SIMD quintile at index date	SIMD 2012 quintile taken from first dispensation of drug of interest. If multiple recorded on same date, most commonly occurring value used.
DOB	Date of birth	Date of birth derived from mm/YYYY values provided in PIS. All set to first date of month i.e. YYYY-mm-01
Age	Age at index prescription	Age calculated from DOB and date of first dispensation of drug of interest.
PatIndexDate	Entry date	First/minimum date in study period where drug of interest was dispensed for individual patient.
PatEndDate	End Date	Last/ maximum date in study period where drug of interest dispensed for individual patient.
Length	Length of time between first and last dispensation of drug of interest.	Subtract to find interval between PatIndexDate and PatEndDate. Number of days between first and last dispensation.
FirstGTN	First date of GTN prescription dispensed (NA for those who are never prescribed GTN)	Relevant GTN prescription identified by PIBNFRootDrugDescription == 'GLYCERYL TRINITRATE" and grepl("^020601F0", PIBNFItemCode) and min dispensed date.
LastGTN	Last date of GTN prescription dispensed (NA for those who are never prescribed GTN)	Relevant GTN prescription identified by PIBNFRootDrugDescription == 'GLYCERYL TRINITRATE" and grepl("^020601F0", PIBNFItemCode) and max dispensed date.
date_of_death	Date of death	field from NRS Deaths record
Age_at_death	Age of death	Calculated from DOB and date of death variable with lubridate package.
primary	Field to differentiate those who fulfil criteria for primary participants at any point in time. "Y" indicates	Ascertained dependent on primary inclusion criteria, outlined in Chapter 4.

	primary, NA if not.	
primary_start_date	Date of first prescription dispensed for all primary subjects.	Taken from pat_index_date for all subjects where primary == "Y".
primary_end_date	Date at which patient no longer counted as primary subject (may have changed status to secondary or treatment, or may be excluded from study after this point).	Create long dataset with all end_reasons in a column and respective dates. Group_by patID, arrange dates in chronological order and use: slice(which.min(end_reason)) to identify which end reason occurs first.
primary_end_reason	Character variable, indicates reason for leaving primary group. May be following: end of follow up, death, reach age 100, GTN prescribed, hospital admission for CVD	End reason which corresponds to earliest date for each patID.
primary_age	Age at primary_start_date	Use lubridate package to identify interval between dob & primary start: round(interval(start = dob, end =primary_start_date/ duration(num=1, units="years)
primary_length	Day difference between inclusion to primary group and end of primary.	No. days between primary start and end date: length(as.numeric(primary_end_date – primary_start_date)
treatment	Field to differentiate those who fulfil criteria for treatment participants at any point in time. "Y" indicates treatment, NA if not..	Ascertained dependent on treatment inclusion criteria, outlined in Chapter 4.
treat_start_date	Date of first GTN prescription within the study period.	Taken from date of first GTN for all pats where treatment ="Y"
treat_end_date	Date at which patient no longer counter as a treatment subject (may have changed status to secondary or may be excluded from study after this point).	Create long dataset with all end_reasons in a column and respective dates. Group_by patID, arrange dates in chronological order and use: slice(which.min(end_reason)) to identify which end reason occurs first.
treat_end_reason	Character variable, indicates reason for leaving treatment group. May be following: end of follow up, death, reach age 100, hospital admission for MI.	End reason which corresponds to earliest date for each patID.
treat_age	Age at treat_start_date	Use lubridate package to identify interval between dob and treat_start: round(interval(start = dob, end =treat_start_date/ duration(num=1, units="years)
treat_length	Day difference between inclusion to treatment group and end of treatment.	No. days between treatment start and end date: length(as.numeric(treat_end_date – treat_start_date)
secondary	Field to differentiate those who fulfil criteria for	Ascertained dependent on secondary inclusion criteria, outlined in

	secondary participants at any point in time. “Y” indicates secondary, NA if not.	Chapter 4.
sec_start_date	Date of first prescription following MI during study period (between 2009-2017). Must be within 42 days.	Taken from date of first presc following MI for all pats where secondary = “Y”
sec_end_date	Date at which patient no longer counted as secondary subject (excluded from study after this point).	Create long dataset with all end_reasons in a column and respective dates. Group_by patID, arrange dates in chronological order and use: slice(which.min(end_reason)) to identify which end reason occurs first.
sec_end_reason	Character variable, indicates reason for leaving secondary group. May be following: end of follow up, death, reach age 100, GTN prescribed (move to sec-with-treat), subsequent hospital admission for MI.	End reason which corresponds to earliest date for each patID.
sec_age	Age at sec_start_date	Use lubridate package to identify interval between dob and sec_start: round(interval(start = dob, end =sec_start_date/ duration(num=1, units=”years)
sec_length	Day difference between inclusion to secondary group and end of secondary.	No. days between secondary start and end date: length(as.numeric(sec_end_date – sec_start_date)
secondary_treatment	Field to differentiate those who fulfil criteria for sec-treatment participants at any point in time. “Y” indicates treatment, NA (or 0? “N”).	Ascertained dependent on secondary-treatment inclusion criteria, outlined in Chapter 4.
sec_treat_start_date	Date of first GTN prescription following inclusion in secondary group (move to this group on this date).	Taken from date of first GTN prescribed after inclusion in secondary group, for all pats where secondary_treatment = “Y”
sec_treat_end_date	Date at which patient no longer counts as a secondary-treatment subject (excluded from study after this).	Create long dataset with all end_reasons in a column and respective dates. Group_by patID, arrange dates in chronological order and use: slice(which.min(end_reason)) to identify which end reason occurs first.
sec_treat_end_reason	Character variable, indicates reason for leaving group. May be following: end of follow up, death, reach age 100, hospital admission for MI.	End reason which corresponds to earliest date for each patID.
sec_treat_age	Age at sec_treat_start_date	Use lubridate package to identify interval between dob & start: round(interval(start = dob, end =sec_treat_start_date/ duration(num=1, units=”years)
sec_treat_length	Day difference between inclusion to treatment group and end of treatment.	No. days between treatment start and end date: length(as.numeric(sec_treat_end_date – sec_treat_start_date)

Appendix E: Multivariable Models *Odds Ratios of persistance*

ACEi

	Primary		Treatment		Secondary		Secondary-Treat	
		p value		p value		p value		p value
Model 1								
sex female	0.69 (0.68-0.70)	p<0.001	0.73 (0.70-0.75)	p<0.001	0.62 (0.54-0.72)	p<0.001	0.83 (0.76-0.89)	p<0.001
age 55 to 65	0.97 (0.95-0.99)	p=0.012	1.10 (1.04-1.16)	p<0.001	0.89 (0.71-1.11)	p=0.296	0.86 (0.77-0.96)	p=0.007
age above 65	0.86 (0.84-0.88)	p<0.001	1.10 (1.05-1.16)	p<0.001	0.67 (0.55-0.82)	p<0.001	0.62 (0.56-0.68)	p<0.001
Model fit (c-stat)	5.56E-01		5.42E-01		0.5863263		5.66E-01	
Model 2								
sex female	0.70 (0.68-0.71)	p<0.001	0.73 (0.70-0.75)	p<0.001	0.62 (0.53-0.72)	p<0.001	0.84 (0.77-0.91)	p<0.001
age 55 to 65	0.98 (0.96-1.00)	p=0.033	1.10 (1.04-1.16)	p=0.001	0.86 (0.69-1.08)	p=0.200	0.85 (0.76-0.96)	p=0.007
age above 65	0.87 (0.85-0.88)	p<0.001	1.10 (1.05-1.16)	p<0.001	0.67 (0.54-0.82)	p<0.001	0.62 (0.56-0.69)	p<0.001
cm diabetes	1.16 (1.13-1.20)	p<0.001	1.21 (1.15-1.27)	p<0.001	1.02 (0.81-1.28)	p=0.896	0.88 (0.78-0.98)	p=0.026
cm depression	0.94 (0.92-0.96)	p<0.001	0.99 (0.94-1.04)	p=0.785	0.80 (0.65-0.99)	p=0.042	0.90 (0.81-1.01)	p=0.071
cm both	1.12 (1.06-1.19)	p<0.001	1.16 (1.07-1.27)	p=0.001	1.06 (0.69-1.70)	p=0.793	0.84 (0.68-1.05)	p=0.126
Model fit (c-stat)	5.59E-01		5.50E-01		0.5915414		5.67E-01	
Model 3								

sex female	0.69 (0.68-0.70)	p<0.001	0.72 (0.70-0.75)	p<0.001	0.62 (0.53-0.72)	p<0.001	0.82 (0.76-0.89)	p<0.001
age 55 to 65	0.98 (0.96-1.00)	p=0.04	1.11 (1.05-1.17)	p<0.001	0.90 (0.72-1.12)	p=0.340	0.86 (0.77-0.96)	p=0.010
age above 65	0.87 (0.85-0.88)	p<0.001	1.12 (1.07-1.18)	p<0.001	0.68 (0.56-0.83)	p<0.001	0.62 (0.56-0.69)	p<0.001
SIMD mid	1.05 (1.02-1.07)	p<0.001	1.05 (1.00-1.09)	p=0.043	1.00 (0.84-1.18)	p=0.980	1.04 (0.95-1.15)	p=0.389
SIMD low	1.09 (1.07-1.12)	p<0.001	1.11 (1.06-1.16)	p<0.001	1.06 (0.88-1.28)	p=0.535	1.05 (0.95-1.16)	p=0.370
Model fit (c-stat)	5.58E-01		5.46E-01		5.86E-01		5.67E-01	
Model 4								
sex female	0.70 (0.68-0.71)	p<0.001	0.72 (0.70-0.75)	p<0.001	0.62 (0.53-0.72)	p<0.001	0.84 (0.77-0.91)	p<0.001
age 55 to 65	0.98 (0.96-1.00)	p=0.076	1.11 (1.04-1.17)	p=0.001	0.87 (0.69-1.09)	p=0.230	0.86 (0.77-0.96)	p=0.009
age above 65	0.87 (0.85-0.89)	p<0.001	1.12 (1.06-1.18)	p<0.001	0.67 (0.55-0.82)	p<0.001	0.63 (0.57-0.70)	p<0.001
cm diabetes	1.16 (1.12-1.19)	p<0.001	1.21 (1.14-1.27)	p<0.001	1.01 (0.80-1.28)	p=0.940	0.87 (0.78-0.98)	p=0.023
cm depression	0.93 (0.91-0.96)	p<0.001	0.98 (0.94-1.04)	p=0.550	0.8 (0.65-0.99)	p=0.034	0.9 (0.81-1.01)	p=0.062
cm both	1.11 (1.05-1.18)	p=0.001	1.15 (1.06-1.26)	p=0.001	1.05 (0.68-1.68)	p=0.826	0.84 (0.68-1.05)	p=0.112
SIMD mid	1.04 (1.02-1.06)	p<0.001	1.04 (1.00-1.09)	p=0.062	1.01 (0.84-1.20)	p=0.943	1.04 (0.94-1.15)	p=0.449
SIMD low	1.08 (1.06-1.11)	p<0.001	1.1 (1.05-1.15)	p<0.001	1.07 (0.88-1.29)	p=0.513	1.05 (0.94-1.16)	p=0.391
Model fit (c-stat)	5.60E-01		5.52E-01		0.5911754		5.67E-01	

Antiplatelet

	Primary	p value	Treatment	p value	Secondary	p value	Secondary-Treat	p value
Model 1								
sex female	0.62 (0.61-0.64)	p<0.001	0.69 (0.67-0.71)	p<0.001	0.85 (0.73-1.00)	p=0.055	0.95 (0.88-1.02)	p=0.173
age 55 to 65	2.27 (2.21-2.34)	p<0.001	1.69 (1.63-1.76)	p<0.001	1.19 (0.91-1.56)	p=0.200	0.82 (0.73-0.92)	p=0.001
age above 65	2.95 (2.88-3.03)	p<0.001	2.58 (2.49-2.68)	p<0.001	0.64 (0.51-0.79)	p<0.001	0.56 (0.51-0.62)	p<0.001
Model fit (c-stat)	6.28E-01		6.00E-01		0.5801964		5.62E-01	
Model 2								
sex female	0.60 (0.59-0.62)	p<0.001	0.69 (0.67-0.71)	p<0.001	0.84 (0.71-1.00)	p=0.047	0.96 (0.89-1.04)	p=0.283
age 55 to 65	2.36 (2.29-2.43)	p<0.001	1.70 (1.64-1.77)	p<0.001	1.19 (0.91-1.56)	p=0.210	0.82 (0.73-0.93)	p=0.001
age above 65	3.11 (3.03-3.19)	p<0.001	2.63 (2.53-2.73)	p<0.001	0.66 (0.53-0.83)	p=0.001	0.57 (0.51-0.63)	p<0.001
cm diabetes	1.07 (1.03-1.12)	p=0.001	1.25 (1.20-1.31)	p<0.001	0.82 (0.65-1.04)	p=0.089	0.82 (0.74-0.91)	p<0.001
cm depression	1.23 (1.20-1.27)	p<0.001	1.03 (0.99-1.07)	p=0.126	1.00 (0.79-1.28)	p=0.980	0.93 (0.84-1.03)	p=0.159
cm both	1.44 (1.33-1.56)	p<0.001	1.49 (1.38-1.61)	p<0.001	1.08 (0.68-1.82)	p=0.745	0.76 (0.63-0.93)	p=0.006
Model fit (c-stat)	6.34E-01		6.04E-01		0.5814488		5.67E-01	
Model 3								
sex female	0.62 (0.61-0.64)	p<0.001	0.68 (0.66-0.70)	p<0.001	0.85 (0.73-1.00)	p=0.056	0.95 (0.88-1.02)	p=0.151
age 55 to 65	2.31 (2.24-2.37)	p<0.001	1.72 (1.66-1.79)	p<0.001	1.19 (0.91-1.56)	p=0.195	0.82 (0.73-0.92)	p=0.001

age above 65	3.01 (2.93-3.09)	p<0.001	2.66 (2.57-2.76)	p<0.001	0.63 (0.50-0.79)	p<0.001	0.57 (0.51-0.63)	p<0.001
SIMD mid	1.08 (1.05-1.11)	p<0.001	1.08 (1.05-1.12)	p<0.001	1.05 (0.86-1.26)	p=0.652	1.04 (0.95-1.14)	p=0.417
SIMD low	1.18 (1.15-1.22)	p<0.001	1.21 (1.17-1.25)	p<0.001	0.94 (0.76-1.15)	p=0.536	1.06 (0.96-1.16)	p=0.237
Model fit (c-stat)	6.30E-01		6.04E-01		5.84E-01		5.64E-01	
Model 4								
sex female	0.6 (0.59-0.62)	p<0.001	0.68 (0.67-0.70)	p<0.001	0.84 (0.71-1.00)	p=0.047	0.96 (0.88-1.03)	p=0.252
age 55 to 65	2.39 (2.32-2.46)	p<0.001	1.73 (1.66-1.80)	p<0.001	1.19 (0.91-1.57)	p=0.205	0.83 (0.74-0.93)	p=0.002
age above 65	3.15 (3.07-3.24)	p<0.001	2.69 (2.59-2.79)	p<0.001	0.66 (0.52-0.83)	p<0.001	0.57 (0.52-0.64)	p<0.001
cm diabetes	1.07 (1.02-1.11)	p=0.002	1.24 (1.18-1.30)	p<0.001	0.82 (0.65-1.04)	p=0.091	0.81 (0.73-0.91)	p<0.001
cm depressio n	1.22 (1.18-1.25)	p<0.001	1.01 (0.98-1.05)	p=0.518	1 (0.79-1.28)	p=0.996	0.92 (0.83-1.02)	p=0.124
cm both	1.42 (1.31-1.54)	p<0.001	1.46 (1.35-1.57)	p<0.001	1.09 (0.69-1.84)	p=0.722	0.76 (0.63-0.92)	p=0.005
SIMD mid	1.07 (1.04-1.10)	p<0.001	1.07 (1.03-1.11)	p<0.001	1.05 (0.86-1.28)	p=0.637	1.06 (0.96-1.16)	p=0.235
SIMD low	1.16 (1.12-1.19)	p<0.001	1.18 (1.14-1.22)	p<0.001	0.93 (0.75-1.14)	p=0.477	1.08 (0.98-1.19)	p=0.131
Model fit (c-stat)	6.36E-01		6.07E-01		0.5838904		5.69E-01	

Beta-blockers

	Primary	p value	**Treatment**	p value	**Secondary**	p value	**Secondary-Treat**	p value
Model 1								
sex female	0.73 (0.71-0.74)	p<0.001	0.72 (0.70-0.74)	p<0.001	0.93 (0.78-1.10)	p=0.365	0.97 (0.89-1.05)	p=0.402
age 55 to 65	2.14 (2.10-2.19)	p<0.001	1.62 (1.56-1.69)	p<0.001	1.25 (0.97-1.61)	p=0.081	0.89 (0.79-1.00)	p=0.042
age above 65	3.48 (3.41-3.55)	p<0.001	2.26 (2.18-2.35)	p<0.001	0.87 (0.70-1.08)	p=0.208	0.67 (0.60-0.74)	p<0.001
Model fit (c-stat)	6.44E-01		5.84E-01		5.45E-01		5.46E-01	
Model 2								
sex female	0.73 (0.72-0.74)	p<0.001	0.73 (0.71-0.76)	p<0.001	0.92 (0.77-1.10)	p=0.356	1.00 (0.92-1.08)	p=0.958
age 55 to 65	2.11 (2.07-2.16)	p<0.001	1.61 (1.54-1.69)	p<0.001	1.23 (0.95-1.59)	p=0.110	0.88 (0.78-0.99)	p=0.035
age above 65	3.40 (3.33-3.48)	p<0.001	2.23 (2.14-2.32)	p<0.001	0.89 (0.71-1.11)	p=0.315	0.65 (0.59-0.72)	p<0.001
cm diabetes	1.39 (1.33-1.44)	p<0.001	1.28 (1.21-1.34)	p<0.001	0.87 (0.69-1.12)	p=0.280	0.85 (0.76-0.95)	p=0.005
cm depression	0.94 (0.92-0.96)	p<0.001	0.89 (0.86-0.93)	p<0.001	0.90 (0.71-1.16)	p=0.416	0.86 (0.77-0.96)	p=0.005
cm both	1.34 (1.25-1.43)	p<0.001	1.22 (1.12-1.32)	p<0.001	1.49 (0.86-2.79)	p=0.181	0.77 (0.63-0.95)	p=0.013
Model fit (c-stat)	6.46E-01		5.92E-01		0.5473879		5.53E-01	
Model 3								
sex female	0.73 (0.71-0.74)	p<0.001	0.71 (0.69-0.73)	p<0.001	0.93 (0.78-1.10)	p=0.386	0.96 (0.89-1.04)	p=0.366
age 55 to 65	2.16 (2.11-2.20)	p<0.001	1.65 (1.58-1.72)	p<0.001	1.25 (0.97-1.61)	p=0.082	0.89 (0.79-1.00)	p=0.045

age above 65	3.51 (3.44-3.58)	p<0.001	2.32 (2.23-2.41)	p<0.001	0.86 (0.69-1.07)	p=0.181	0.67 (0.60-0.74)	p<0.001
SIMD mid	1.08 (1.05-1.10)	p<0.001	1.06 (1.02-1.10)	p=0.003	1.01 (0.83-1.23)	p=0.924	1.00 (0.91-1.10)	p=0.998
SIMD low	1.10 (1.08-1.13)	p<0.001	1.17 (1.13-1.22)	p<0.001	0.92 (0.74-1.13)	p=0.411	1.02 (0.93-1.13)	p=0.648
Model fit (c-stat)	6.46E-01		5.89E-01		5.48E-01		5.47E-01	
Model 4								
sex female	0.73 (0.72-0.74)	p<0.001	0.73 (0.71-0.75)	p<0.001	0.92 (0.78-1.10)	p=0.372	1 (0.92-1.08)	p=0.918
age 55 to 65	2.12 (2.08-2.17)	p<0.001	1.64 (1.57-1.71)	p<0.001	1.23 (0.95-1.59)	p=0.111	0.88 (0.78-0.99)	p=0.037
age above 65	3.42 (3.35-3.50)	p<0.001	2.28 (2.19-2.37)	p<0.001	0.88 (0.70-1.10)	p=0.277	0.65 (0.59-0.73)	p<0.001
cm diabetes	1.38 (1.32-1.44)	p<0.001	1.26 (1.20-1.33)	p<0.001	0.88 (0.69-1.12)	p=0.285	0.85 (0.76-0.95)	p=0.005
cm depression	0.93 (0.91-0.95)	p<0.001	0.88 (0.84-0.91)	p<0.001	0.9 (0.71-1.16)	p=0.419	0.85 (0.76-0.95)	p=0.004
cm both	1.32 (1.23-1.42)	p<0.001	1.2 (1.10-1.30)	p<0.001	1.49 (0.87-2.80)	p=0.176	0.76 (0.62-0.94)	p=0.011
SIMD mid	1.07 (1.05-1.09)	p<0.001	1.05 (1.01-1.09)	p=0.009	1.02 (0.83-1.24)	p=0.875	1.02 (0.93-1.13)	p=0.646
SIMD low	1.1 (1.07-1.12)	p<0.001	1.17 (1.13-1.22)	p<0.001	0.91 (0.73-1.13)	p=0.403	1.03 (0.93-1.14)	p=0.593
Model fit (c-stat)	6.47E-01		5.95E-01		5.48E-01		5.55E-01	

Lipid-regulatory

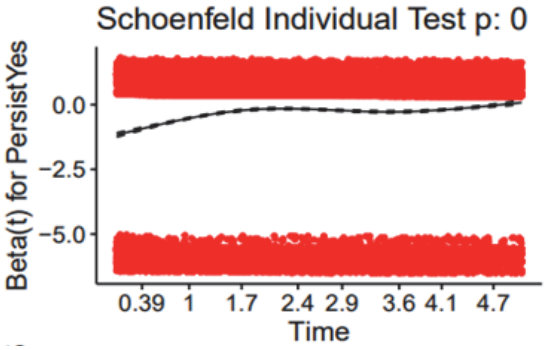
	Primary	p value	**Treatment**	p value	**Secondary**	p value	**Secondary-Treat**	p value
Model 1								
sex female	0.82 (0.81-0.83)	p<0.001	0.71 (0.69-0.73)	p<0.001	0.70 (0.60-0.83)	p<0.001	0.93 (0.86-1.00)	p=0.055
age 55 to 65	1.31 (1.28-1.34)	p<0.001	1.48 (1.41-1.54)	p<0.001	1.21 (0.92-1.59)	p=0.167	0.85 (0.76-0.94)	p=0.003
age above 65	1.31 (1.28-1.34)	p<0.001	1.84 (1.77-1.91)	p<0.001	0.73 (0.58-0.92)	p=0.009	0.65 (0.59-0.72)	p<0.001
Model fit (c-stat)	5.40E-01		5.72E-01		0.5816041		5.49E-01	
Model 2								
sex female	0.82 (0.81-0.84)	p<0.001	0.70 (0.68-0.72)	p<0.001	0.69 (0.58-0.82)	p<0.001	0.94 (0.87-1.02)	p=0.151
age 55 to 65	1.37 (1.34-1.40)	p<0.001	1.49 (1.42-1.56)	p<0.001	1.23 (0.93-1.63)	p=0.147	0.85 (0.76-0.95)	p=0.004
age above 65	1.39 (1.36-1.42)	p<0.001	1.89 (1.82-1.97)	p<0.001	0.77 (0.61-0.98)	p=0.034	0.66 (0.59-0.73)	p<0.001
cm diabetes	1.38 (1.34-1.42)	p<0.001	1.36 (1.29-1.43)	p<0.001	0.83 (0.65-1.08)	p=0.162	0.81 (0.73-0.90)	p<0.001
cm depression	1.05 (1.02-1.07)	p<0.001	1.10 (1.05-1.14)	p<0.001	0.89 (0.70-1.15)	p=0.356	0.93 (0.84-1.03)	p=0.167
cm both	1.65 (1.56-1.75)	p<0.001	1.61 (1.49-1.75)	p<0.001	0.99 (0.62-1.67)	p=0.974	0.84 (0.69-1.03)	p=0.094
Model fit (c-stat)	5.52E-01		5.82E-01		0.5842169		5.54E-01	
Model 3								
sex female	0.82 (0.81-0.83)	p<0.001	0.70 (0.68-0.72)	p<0.001	0.71 (0.60-0.84)	p<0.001	0.93 (0.86-1.00)	p=0.046

age 55 to 65	1.31 (1.28-1.34)	p<0.001	1.49 (1.43-1.56)	p<0.001	1.21 (0.92-1.59)	p=0.173	0.85 (0.76-0.95)	p=0.005
age above 65	1.31 (1.29-1.34)	p<0.001	1.87 (1.80-1.94)	p<0.001	0.72 (0.57-0.91)	p=0.006	0.66 (0.59-0.72)	p<0.001
SIMD mid	0.98 (0.96-1.00)	p=0.021	1.02 (0.98-1.06)	p=0.254	0.89 (0.72-1.09)	p=0.264	1.04 (0.95-1.14)	p=0.415
SIMD low	1.02 (1.00-1.04)	p=0.126	1.10 (1.06-1.14)	p<0.001	0.83 (0.67-1.04)	p=0.104	1.07 (0.98-1.18)	p=0.136
Model fit (c-stat)	5.41E-01		5.75E-01		5.87E-01		5.50E-01	
Model 4								
sex female	0.82 (0.81-0.84)	p<0.001	0.7 (0.68-0.72)	p<0.001	0.69 (0.58-0.82)	p<0.001	0.94 (0.87-1.02)	p=0.133
age 55 to 65	1.37 (1.34-1.40)	p<0.001	1.5 (1.43-1.57)	p<0.001	1.23 (0.93-1.62)	p=0.151	0.85 (0.76-0.96)	p=0.007
age above 65	1.39 (1.36-1.42)	p<0.001	1.91 (1.83-1.99)	p<0.001	0.76 (0.60-0.96)	p=0.025	0.66 (0.60-0.73)	p<0.001
cm diabetes	1.38 (1.34-1.43)	p<0.001	1.35 (1.29-1.42)	p<0.001	0.84 (0.66-1.09)	p=0.191	0.8 (0.72-0.89)	p<0.001
cm depression	1.05 (1.02-1.07)	p<0.001	1.09 (1.05-1.13)	p<0.001	0.89 (0.70-1.15)	p=0.380	0.92 (0.83-1.03)	p=0.146
cm both	1.66 (1.56-1.76)	p<0.001	1.6 (1.47-1.73)	p<0.001	1 (0.63-1.69)	p=0.988	0.83 (0.69-1.02)	p=0.075
SIMD mid	0.96 (0.94-0.99)	p=0.001	1 (0.97-1.04)	p=0.905	0.89 (0.71-1.10)	p=0.265	1.07 (0.97-1.17)	p=0.173
SIMD low	1 (0.97-1.02)	p=0.703	1.07 (1.03-1.11)	p=0.001	0.83 (0.66-1.04)	p=0.107	1.09 (0.99-1.20)	p=0.090
Model fit (c-stat)	5.53E-01		5.83E-01		0.5878772		5.55E-01	

Appendix F Schoenfeld Residual Plots

Primary: Schoenfeld Residuals of survival 5yrs after persistence analysis

ACEI



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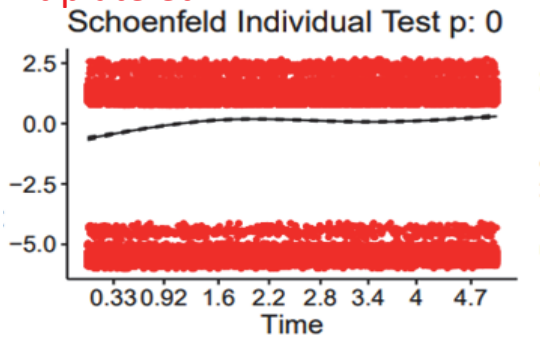
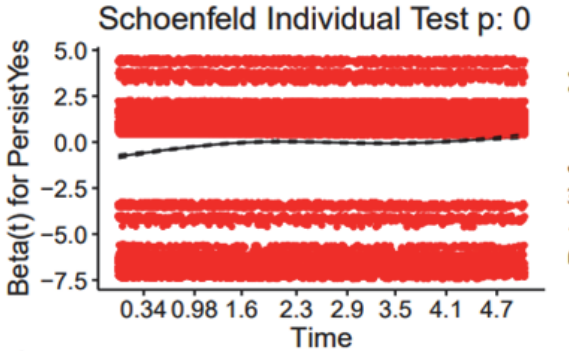
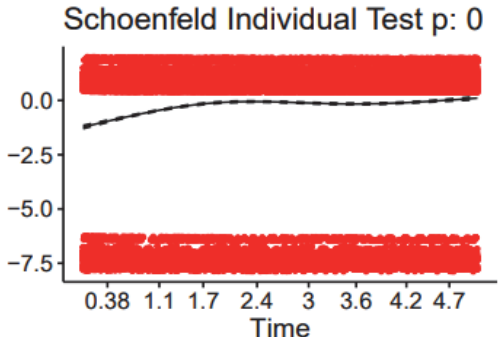


Beta-blockers

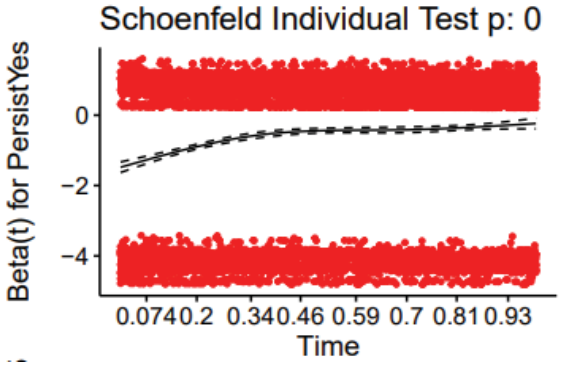


Lipid-regulatory



Primary: Schoenfeld Residuals of survival 1yr after persistence analysis

ACEI



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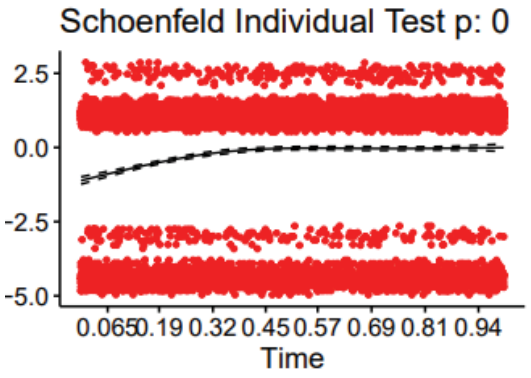

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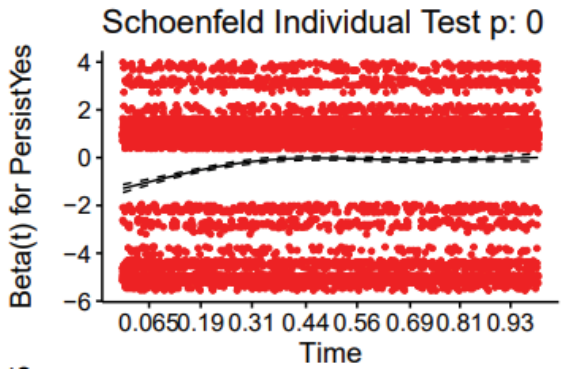
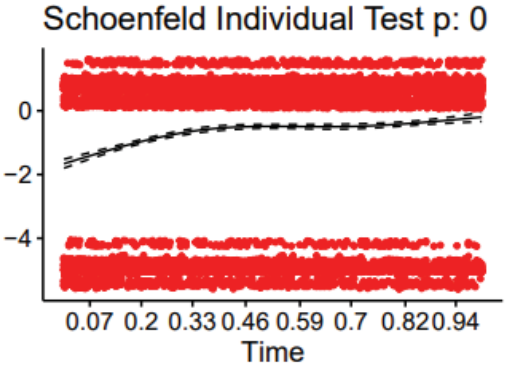


Lipid-regulatory



Treatment: Schoenfeld Residuals of survival 5yrs after persistence analysis

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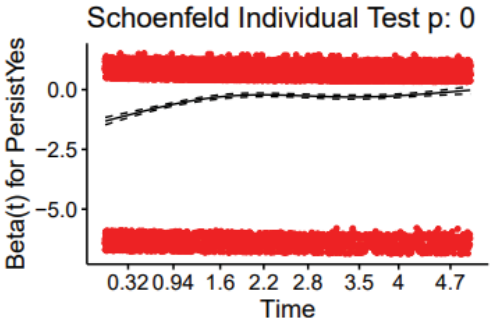

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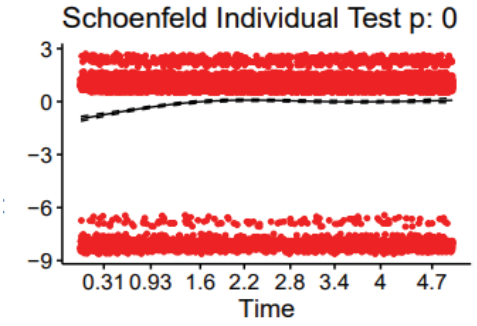

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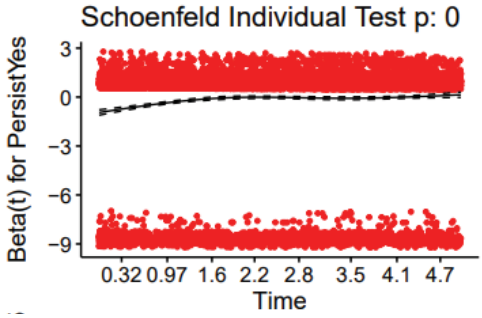
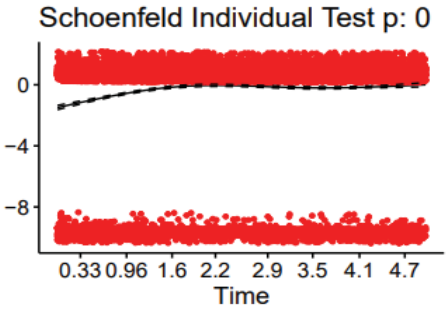


Lipid-regulatory



Treatment: Schoenfeld Residuals of survival 1yr after persistence analysis

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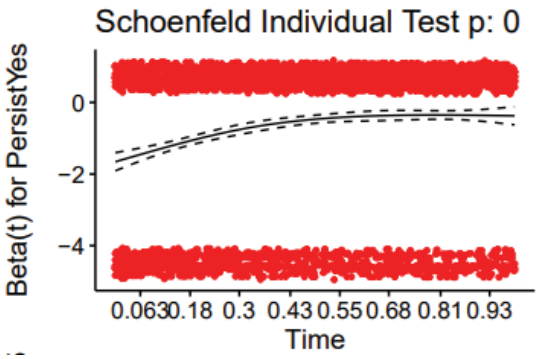

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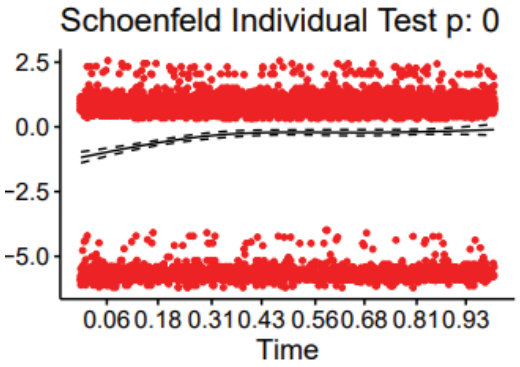

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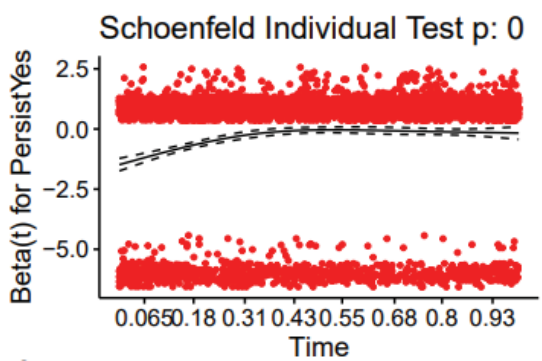
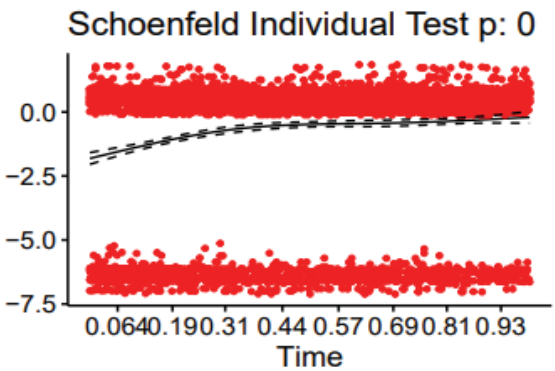


Lipid-regulatory



Secondary: Schoenfeld Residuals of survival 5yrs after persistence analysis

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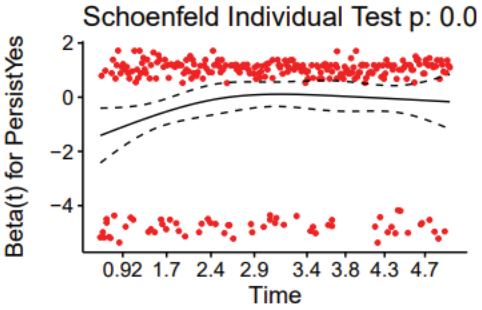

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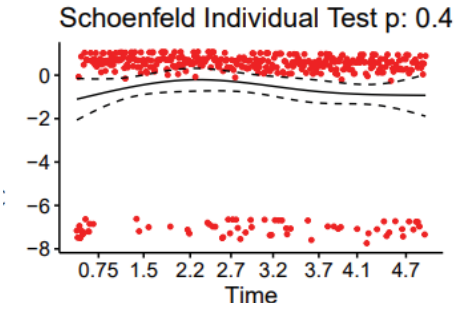

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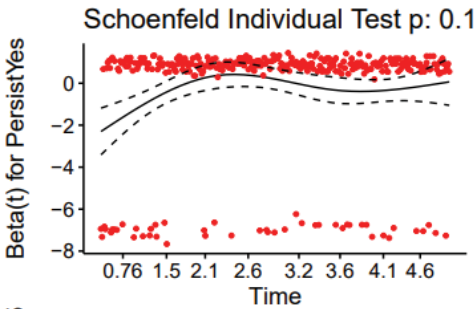
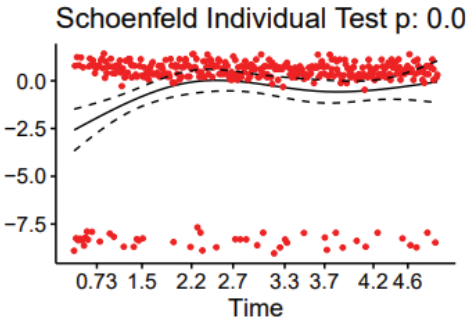
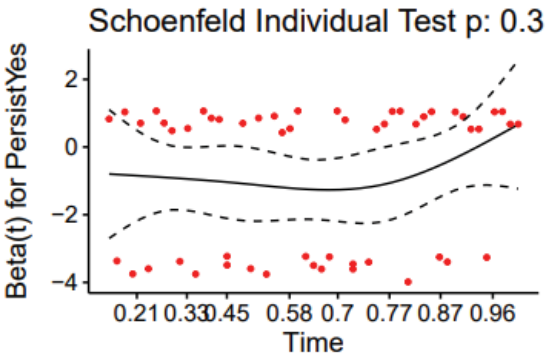


Lipid-regulatory



Secondary: Schoenfeld Residuals of survival 1yr after persistence analysis

ACEI



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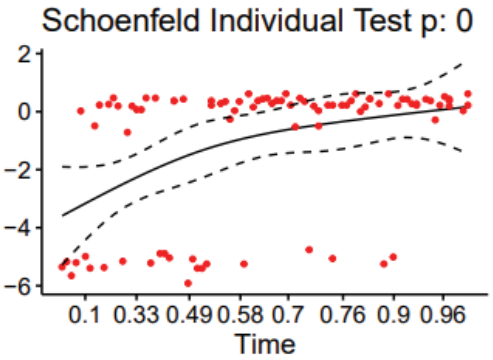

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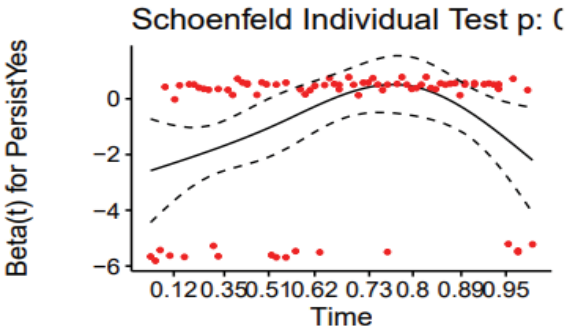
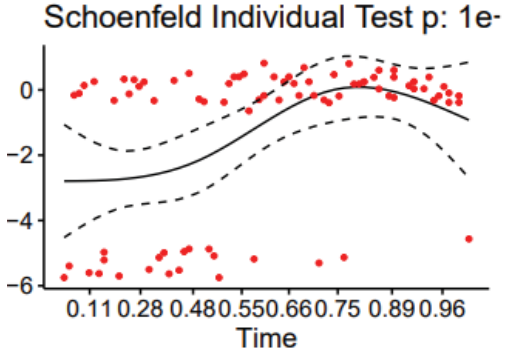


Lipid-regulatory



Secondary-Treatment: Schoenfeld Residuals of survival 5yrs after persistence analysis

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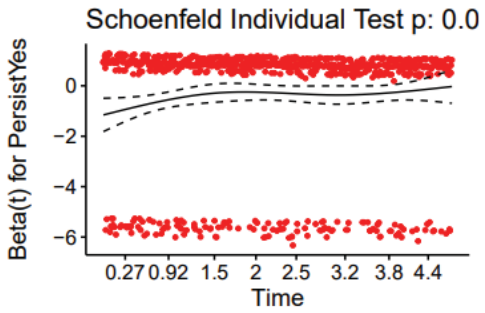

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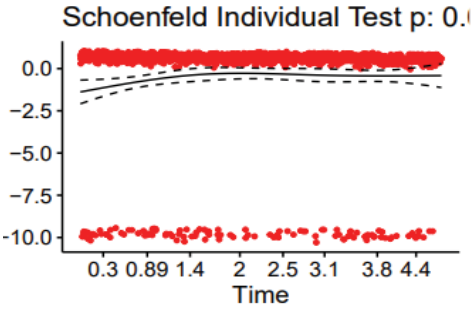

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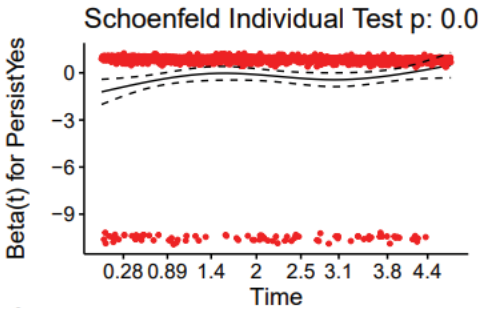
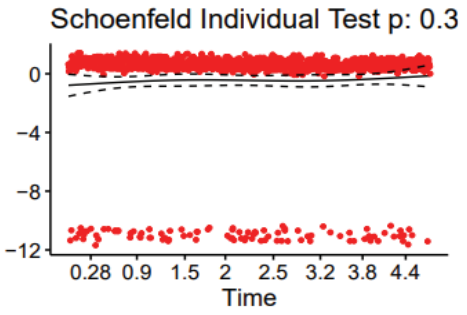
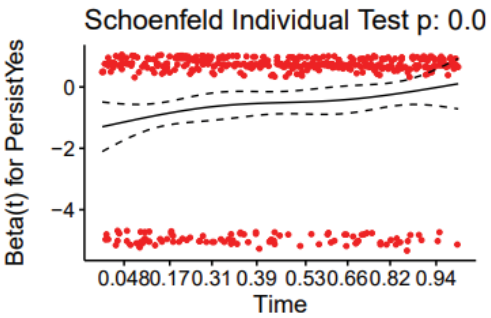


Lipid-regulatory



Secondary-Treatment: Schoenfeld Residuals of survival 1yr after persistence analysis

ACEI



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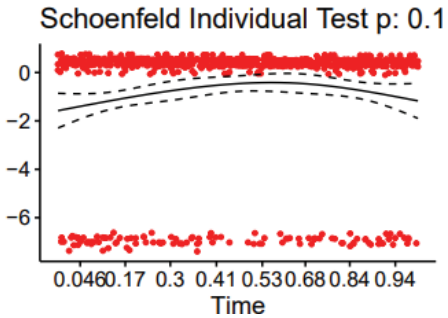

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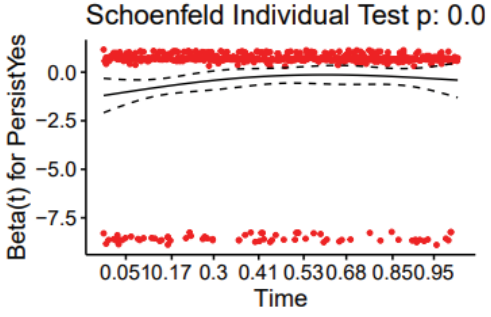
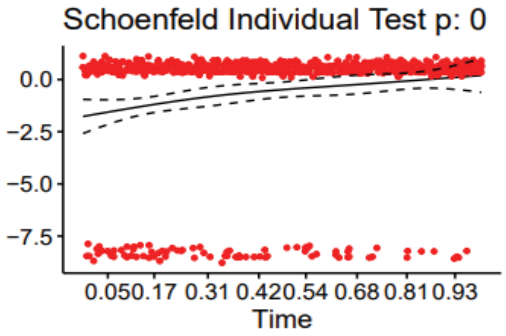


Lipid-regulatory



Appendix G: All-Cause Mortality: 5-year follow-up including a 'drug-count' variable

1.1.1 Primary

ACEi		All (n)	HR (univariable)	HR (multivariable)
Persist	No	63,946	-	-
	Yes	343,409	0.83 (0.81-0.84, p<0.001)	0.72 (0.71-0.74, p<0.001)
Sex	F	200,165	-	-
	M	207,190	0.91 (0.89-0.92, p<0.001)	1.18 (1.15-1.20, p<0.001)
Age group	below 55	110,446	-	-
	55 to 65	118,314	2.37 (2.27-2.48, p<0.001)	2.50 (2.39-2.62, p<0.001)
	above 65	178,595	10.83 (10.42-11.25, p<0.001)	12.11 (11.63-12.60, p<0.001)
SIMD group	high	112,937	-	-
	mid	168,295	1.20 (1.18-1.23, p<0.001)	1.20 (1.17-1.23, p<0.001)
	low	125,277	1.38 (1.35-1.42, p<0.001)	1.45 (1.41-1.48, p<0.001)
Comorbidity status	neither	272,139	-	-
	diabetes	59,815	1.33 (1.30-1.36, p<0.001)	1.27 (1.24-1.30, p<0.001)
	depression	40,755	1.33 (1.29-1.36, p<0.001)	1.67 (1.62-1.71, p<0.001)
	both	11,343	1.63 (1.56-1.71, p<0.001)	2.05 (1.96-2.15, p<0.001)
Drug count	1 to 3	310,760	-	-
	4 to 7	96,321	1.62 (1.59-1.65, p<0.001)	1.11 (1.09-1.14, p<0.001)
	8 to 10	274	2.27 (1.79-2.87, p<0.001)	1.39 (1.08-1.78, p=0.010)
Antiplatelet		All (n)	HR (univariable)	HR (multivariable)
Persist	No	75,836	-	-
	Yes	275,850	1.26 (1.23-1.28, p<0.001)	1.07 (1.05-1.09, p<0.001)
Sex	F	182,229	-	-
	M	169,457	0.88 (0.87-0.89, p<0.001)	1.07 (1.05-1.08, p<0.001)
Age group	below 55	43,050	-	-
	55 to 65	85,182	2.00 (1.90-2.11, p<0.001)	2.20 (2.08-2.32, p<0.001)
	above 65	223,454	8.54 (8.14-8.95, p<0.001)	10.23 (9.72-10.75, p<0.001)
SIMD group	high	91,812	-	-
	mid	143,694	1.12 (1.10-1.14, p<0.001)	1.15 (1.13-1.18, p<0.001)
	low	115,415	1.21 (1.18-1.23, p<0.001)	1.33 (1.31-1.36, p<0.001)
Comorbidity status	neither	217,477	-	-
	diabetes	56,802	0.82 (0.80-0.84, p<0.001)	1.03 (1.00-1.05, p=0.023)
	depression	42,192	1.42 (1.40-1.45, p<0.001)	1.69 (1.66-1.73, p<0.001)
	both	11,527	1.07 (1.03-1.12, p<0.001)	1.64 (1.58-1.71, p<0.001)
Drug count	1 to 3	245,735	-	-
	4 to 7	105,674	0.91 (0.89-0.92, p<0.001)	0.81 (0.80-0.83, p<0.001)
	8 to 10	277	1.30 (1.04-1.62, p=0.021)	1.21 (0.96-1.51, p=0.106)
Beta-blockers		All (n)	HR (univariable)	HR (multivariable)
Persist	No	101,176	-	-
	Yes	257,411	1.99 (1.94-2.04, p<0.001)	0.92 (0.89-0.94, p<0.001)
Sex	F	215,483	-	-
	M	143,104	1.20 (1.18-1.23, p<0.001)	1.24 (1.22-1.26, p<0.001)
Age group	below 55	134,562	-	-
	55 to 65	83,633	2.72 (2.60-2.84, p<0.001)	2.93 (2.80-3.06, p<0.001)
	above 65	140,392	11.35 (10.96-11.76, p<0.001)	13.21 (12.70-13.74, p<0.001)
SIMD group	high	94,921	-	-
	mid	143,906	1.13 (1.10-1.16, p<0.001)	1.18 (1.15-1.21, p<0.001)
	low	118,891	1.14 (1.12-1.17, p<0.001)	1.39 (1.36-1.43, p<0.001)
Comorbidity status	neither	230,409	-	-
	diabetes	25,858	1.69 (1.64-1.74, p<0.001)	1.32 (1.28-1.36, p<0.001)
	depression	75,370	0.73 (0.71-0.75, p<0.001)	1.40 (1.36-1.44, p<0.001)
	both	5,850	1.73 (1.63-1.83, p<0.001)	1.94 (1.83-2.06, p<0.001)
Drug count	1 to 3	279,349	-	-
	4 to 7	78,959	1.83 (1.79-1.87, p<0.001)	0.98 (0.96-1.00, p=0.132)
	8 to 10	279	2.57 (2.03-3.24, p<0.001)	1.22 (0.96-1.55, p=0.104)
Lipid-regulators		All (n)	HR (univariable)	HR (multivariable)
Persist	No	75,410	-	-
	Yes	474,515	0.94 (0.92-0.96, p<0.001)	0.76 (0.74-0.78, p<0.001)
Sex	F	275,171	-	-
	M	274,754	0.91 (0.90-0.93, p<0.001)	1.19 (1.18-1.21, p<0.001)
Age group	below 55	107,741	-	-
	55 to 65	172,033	2.10 (2.02-2.19, p<0.001)	2.36 (2.26-2.46, p<0.001)
	above 65	270,151	8.87 (8.56-9.20, p<0.001)	10.81 (10.40-11.24, p<0.001)
SIMD group	high	146,080	-	-
	mid	223,284	1.19 (1.17-1.21, p<0.001)	1.19 (1.17-1.22, p<0.001)
	low	179,440	1.37 (1.34-1.40, p<0.001)	1.46 (1.44-1.49, p<0.001)
Comorbidity status	neither	336,824	-	-
	diabetes	93,674	1.13 (1.11-1.15, p<0.001)	1.30 (1.27-1.32, p<0.001)
	depression	63,558	1.35 (1.32-1.38, p<0.001)	1.71 (1.67-1.74, p<0.001)
	both	20,374	1.43 (1.38-1.48, p<0.001)	2.16 (2.09-2.24, p<0.001)
Drug count	1 to 3	422,320	-	-
	4 to 7	127,290	1.58 (1.56-1.61, p<0.001)	1.20 (1.18-1.22, p<0.001)
	8 to 10	315	2.48 (2.01-3.07, p<0.001)	1.73 (1.40-2.15, p<0.001)

Table G1: Mortality 5-years *after* classed as persistent or not with TAM (T0) in the primary group, across four CVD drug-classes. Including drug-count.

1.1.2 Treatment

ACEi		All (n)	HR (univariable)	HR (multivariable)
Persist	No	8,999	-	-
	Yes	59,884	0.70 (0.67-0.73, p<0.001)	0.68 (0.65-0.71, p<0.001)
Sex	F	29,131	-	-
	M	39,752	1.00 (0.97-1.03, p=0.861)	1.16 (1.12-1.20, p<0.001)
Age group	below 55	7,109	-	-
	55 to 65	17,511	1.94 (1.74-2.16, p<0.001)	2.00 (1.79-2.24, p<0.001)
	above 65	44,263	6.30 (5.70-6.95, p<0.001)	7.23 (6.51-8.02, p<0.001)
SIMD group	high	14,273	-	-
	mid	26,722	1.08 (1.04-1.13, p<0.001)	1.12 (1.07-1.18, p<0.001)
	low	27,770	1.18 (1.13-1.24, p<0.001)	1.33 (1.27-1.39, p<0.001)
Comorbidity status	neither	41,818	-	-
	diabetes	10,227	1.28 (1.22-1.33, p<0.001)	1.29 (1.24-1.35, p<0.001)
	depression	8,757	1.15 (1.10-1.21, p<0.001)	1.41 (1.35-1.48, p<0.001)
	both	3,028	1.31 (1.22-1.41, p<0.001)	1.75 (1.63-1.88, p<0.001)
Drug count	1 to 3	25,590	-	-
	4 to 7	42,158	0.99 (0.96-1.03, p=0.651)	0.98 (0.95-1.02, p=0.373)
	8 to 10	1,135	1.15 (1.02-1.29, p=0.021)	1.01 (0.90-1.15, p=0.816)
Antiplatelet		All (n)	HR (univariable)	HR (multivariable)
Persist	No	17,507	-	-
	Yes	111,052	1.10 (1.06-1.14, p<0.001)	0.90 (0.87-0.93, p<0.001)
Sex	F	61,899	-	-
	M	66,660	1.01 (0.98-1.03, p=0.533)	1.16 (1.13-1.19, p<0.001)
Age group	below 55	13,181	-	-
	55 to 65	32,148	1.79 (1.65-1.94, p<0.001)	1.91 (1.75-2.09, p<0.001)
	above 65	83,230	6.42 (5.95-6.92, p<0.001)	7.67 (7.08-8.31, p<0.001)
SIMD group	high	27,319	-	-
	mid	49,507	1.09 (1.06-1.13, p<0.001)	1.14 (1.10-1.18, p<0.001)
	low	51,504	1.17 (1.13-1.20, p<0.001)	1.33 (1.29-1.38, p<0.001)
Comorbidity status	neither	81,104	-	-
	diabetes	14,340	1.28 (1.23-1.32, p<0.001)	1.28 (1.24-1.33, p<0.001)
	depression	19,116	1.14 (1.11-1.18, p<0.001)	1.44 (1.39-1.49, p<0.001)
	both	4,449	1.35 (1.27-1.43, p<0.001)	1.81 (1.70-1.92, p<0.001)
Drug count	1 to 3	53,062	-	-
	4 to 7	73,970	0.98 (0.95-1.00, p=0.050)	0.93 (0.91-0.96, p<0.001)
	8 to 10	1,527	1.20 (1.08-1.32, p<0.001)	1.03 (0.93-1.15, p=0.523)
Beta-blockers		All (n)	HR (univariable)	HR (multivariable)
Persist	No	11,558	-	-
	Yes	82,553	1.04 (1.00-1.09, p=0.053)	0.86 (0.82-0.90, p<0.001)
Sex	F	42,855	-	-
	M	51,256	1.01 (0.98-1.03, p=0.692)	1.16 (1.13-1.20, p<0.001)
Age group	below 55	10,046	-	-
	55 to 65	24,173	1.68 (1.53-1.85, p<0.001)	1.73 (1.56-1.91, p<0.001)
	above 65	59,892	6.07 (5.57-6.62, p<0.001)	6.96 (6.36-7.62, p<0.001)
SIMD group	high	21,327	-	-
	mid	36,723	1.06 (1.02-1.10, p=0.004)	1.11 (1.07-1.16, p<0.001)
	low	35,896	1.14 (1.09-1.18, p<0.001)	1.31 (1.26-1.37, p<0.001)
Comorbidity status	neither	60,734	-	-
	diabetes	11,080	1.35 (1.29-1.40, p<0.001)	1.33 (1.27-1.38, p<0.001)
	depression	12,693	1.07 (1.03-1.12, p=0.001)	1.35 (1.30-1.41, p<0.001)
	both	2,999	1.46 (1.36-1.56, p<0.001)	1.91 (1.78-2.05, p<0.001)
Drug count	1 to 3	35,695	-	-
	4 to 7	57,074	1.05 (1.02-1.08, p=0.002)	0.98 (0.95-1.01, p=0.133)
	8 to 10	1,342	1.34 (1.20-1.49, p<0.001)	1.11 (0.99-1.24, p=0.072)
Lipid-regulators		All (n)	HR (univariable)	HR (multivariable)
Persist	No	12,632	-	-
	Yes	119,088	0.86 (0.83-0.89, p<0.001)	0.73 (0.70-0.76, p<0.001)
Sex	F	62,502	-	-
	M	69,218	1.04 (1.01-1.06, p=0.002)	1.20 (1.17-1.23, p<0.001)
Age group	below 55	13,070	-	-
	55 to 65	33,643	1.84 (1.70-2.00, p<0.001)	2.00 (1.83-2.19, p<0.001)
	above 65	85,007	6.37 (5.90-6.88, p<0.001)	7.72 (7.12-8.38, p<0.001)
SIMD group	high	28,084	-	-
	mid	50,718	1.09 (1.05-1.13, p<0.001)	1.13 (1.09-1.17, p<0.001)
	low	52,699	1.20 (1.16-1.24, p<0.001)	1.36 (1.31-1.40, p<0.001)
Comorbidity status	neither	81,940	-	-
	diabetes	15,670	1.35 (1.31-1.40, p<0.001)	1.35 (1.31-1.40, p<0.001)
	depression	19,290	1.15 (1.11-1.19, p<0.001)	1.45 (1.40-1.50, p<0.001)
	both	4,895	1.39 (1.31-1.47, p<0.001)	1.87 (1.76-1.98, p<0.001)
Drug count	1 to 3	54,882	-	-
	4 to 7	75,332	1.11 (1.09-1.14, p<0.001)	1.05 (1.02-1.07, p<0.001)
	8 to 10	1,506	1.33 (1.21-1.47, p<0.001)	1.15 (1.03-1.28, p=0.011)

Table G2: Mortality 5-years *after* classed as persistent or not with TAM (T0) in the treatment group, across four CVD drug-classes. Including drug count.

1.1.3 Secondary

ACEi		All (n)	HR (univariable)	HR (multivariable)
Persist	No	434	-	-
	Yes	1,908	0.81 (0.61-1.07, p=0.138)	0.81 (0.61-1.08, p=0.153)
Sex	F	783	-	-
	M	1,559	0.60 (0.48-0.75, p<0.001)	0.80 (0.63-1.03, p=0.079)
Age group	below 55	514	-	-
	55 to 65	703	3.46 (1.75-6.86, p<0.001)	3.86 (1.88-7.92, p<0.001)
	above 65	1,125	12.44 (6.61-23.41, p<0.001)	13.92 (7.12-27.20, p<0.001)
SIMD group	high	656	-	-
	mid	986	1.13 (0.85-1.51, p=0.398)	1.22 (0.90-1.64, p=0.198)
	low	694	1.24 (0.92-1.68, p=0.156)	1.54 (1.12-2.11, p=0.007)
Comorbidity status	neither	1,658	-	-
	diabetes	252	1.79 (1.29-2.49, p<0.001)	1.58 (1.13-2.20, p=0.007)
	depression	291	1.59 (1.15-2.19, p=0.005)	1.69 (1.21-2.34, p=0.002)
	both	44	2.65 (1.44-4.87, p=0.002)	3.26 (1.77-6.00, p<0.001)
Drug count	1 to 3	649	-	-
	4 to 7	1,683	0.93 (0.72-1.19, p=0.548)	0.96 (0.74-1.25, p=0.768)
	8 to 10	10	2.62 (0.83-8.30, p=0.100)	2.30 (0.72-7.39, p=0.162)
Antiplatelet		All (n)	HR (univariable)	HR (multivariable)
Persist	No	279	-	-
	Yes	2,588	0.49 (0.38-0.63, p<0.001)	0.54 (0.41-0.71, p<0.001)
Sex	F	1,019	-	-
	M	1,848	0.59 (0.49-0.72, p<0.001)	0.80 (0.65-0.97, p=0.025)
Age group	below 55	582	-	-
	55 to 65	793	3.44 (1.84-6.43, p<0.001)	3.63 (1.89-6.98, p<0.001)
	above 65	1,492	14.06 (7.91-24.97, p<0.001)	14.78 (8.08-27.02, p<0.001)
SIMD group	high	815	-	-
	mid	1,205	1.08 (0.86-1.36, p=0.516)	1.17 (0.92-1.50, p=0.200)
	low	840	1.14 (0.89-1.45, p=0.308)	1.41 (1.09-1.83, p=0.009)
Comorbidity status	neither	1,973	-	-
	diabetes	322	1.81 (1.38-2.36, p<0.001)	1.63 (1.24-2.14, p<0.001)
	depression	367	1.62 (1.24-2.11, p<0.001)	1.80 (1.38-2.35, p<0.001)
	both	65	2.82 (1.79-4.45, p<0.001)	3.29 (2.08-5.20, p<0.001)
Drug count	1 to 3	831	-	-
	4 to 7	2,022	1.02 (0.83-1.26, p=0.850)	1.01 (0.81-1.25, p=0.945)
	8 to 10	14	0.95 (0.24-3.86, p=0.947)	0.69 (0.17-2.84, p=0.611)
Beta-blockers		All (n)	HR (univariable)	HR (multivariable)
Persist	No	296	-	-
	Yes	2,121	0.69 (0.51-0.93, p=0.014)	0.76 (0.56-1.05, p=0.094)
Sex	F	841	-	-
	M	1,576	0.59 (0.48-0.73, p<0.001)	0.79 (0.63-0.99, p=0.044)
Age group	below 55	515	-	-
	55 to 65	694	3.67 (1.86-7.26, p<0.001)	4.08 (1.99-8.35, p<0.001)
	above 65	1,208	13.75 (7.32-25.84, p<0.001)	14.63 (7.50-28.56, p<0.001)
SIMD group	high	668	-	-
	mid	1,018	1.15 (0.88-1.50, p=0.311)	1.29 (0.97-1.71, p=0.084)
	low	726	1.15 (0.86-1.53, p=0.346)	1.41 (1.04-1.91, p=0.028)
Comorbidity status	neither	1,673	-	-
	diabetes	286	2.09 (1.57-2.80, p<0.001)	1.78 (1.33-2.39, p<0.001)
	depression	297	1.67 (1.23-2.28, p=0.001)	1.87 (1.37-2.56, p<0.001)
	both	50	2.89 (1.68-4.97, p<0.001)	3.61 (2.09-6.25, p<0.001)
Drug count	1 to 3	683	-	-
	4 to 7	1,722	0.81 (0.64-1.02, p=0.067)	0.81 (0.64-1.03, p=0.085)
	8 to 10	12	1.66 (0.53-5.23, p=0.386)	1.11 (0.27-4.59, p=0.881)
Lipid-regulators		All (n)	HR (univariable)	HR (multivariable)
Persist	No	250	-	-
	Yes	2,537	0.52 (0.39-0.69, p<0.001)	0.57 (0.42-0.78, p<0.001)
Sex	F	981	-	-
	M	1,806	0.60 (0.49-0.73, p<0.001)	0.80 (0.65-0.99, p=0.036)
Age group	below 55	571	-	-
	55 to 65	785	3.59 (1.88-6.88, p<0.001)	3.81 (1.93-7.54, p<0.001)
	above 65	1,431	14.03 (7.69-25.58, p<0.001)	14.92 (7.92-28.09, p<0.001)
SIMD group	high	783	-	-
	mid	1,171	1.14 (0.90-1.46, p=0.279)	1.28 (0.99-1.66, p=0.058)
	low	826	1.15 (0.89-1.50, p=0.293)	1.38 (1.04-1.82, p=0.025)
Comorbidity status	neither	1,926	-	-
	diabetes	310	1.82 (1.37-2.42, p<0.001)	1.59 (1.20-2.12, p=0.001)
	depression	352	1.66 (1.26-2.19, p<0.001)	1.82 (1.37-2.41, p<0.001)
	both	66	2.90 (1.81-4.63, p<0.001)	3.38 (2.11-5.40, p<0.001)
Drug count	1 to 3	1,000	-	-
	4 to 7	1,773	0.87 (0.71-1.07, p=0.193)	0.93 (0.75-1.15, p=0.495)
	8 to 10	14	1.96 (0.73-5.29, p=0.184)	1.29 (0.41-4.11, p=0.666)

Table G3: Mortality 5-years *after* classed as persistent or not with TAM (T0) in the secondary group, across four CVD drug-classes. Including drug count.

1.1.4 Secondary-treatment

ACEi		All (n)	HR (univariable)	HR (multivariable)
Persist	No	607	-	-
	Yes	3,960	0.57 (0.48-0.68, p<0.001)	0.68 (0.56-0.82, p<0.001)
Sex	F	1,485	-	-
	M	3,082	0.61 (0.53-0.70, p<0.001)	0.90 (0.77-1.05, p=0.179)
Age group	below 55	1,139	-	-
	55 to 65	1,336	2.02 (1.42-2.88, p<0.001)	2.07 (1.43-3.00, p<0.001)
	above 65	2,092	9.30 (6.85-12.63, p<0.001)	10.07 (7.29-13.93, p<0.001)
SIMD group	high	992	-	-
	mid	1,792	1.08 (0.89-1.32, p=0.421)	1.15 (0.94-1.42, p=0.168)
	low	1,777	1.31 (1.08-1.58, p=0.006)	1.55 (1.27-1.89, p<0.001)
Comorbidity status	neither	3,078	-	-
	diabetes	481	2.32 (1.92-2.81, p<0.001)	2.09 (1.73-2.54, p<0.001)
	depression	643	1.41 (1.15-1.72, p=0.001)	1.68 (1.37-2.07, p<0.001)
	both	123	2.16 (1.52-3.06, p<0.001)	2.21 (1.55-3.15, p<0.001)
Drug count	1 to 3	1,163	-	-
	4 to 7	3,360	0.87 (0.74-1.02, p=0.076)	0.96 (0.81-1.13, p=0.611)
	8 to 10	44	2.15 (1.29-3.57, p=0.003)	1.32 (0.79-2.21, p=0.286)
Antiplatelet		All (n)	HR (univariable)	HR (multivariable)
Persist	No	396	-	-
	Yes	5,352	0.56 (0.46-0.68, p<0.001)	0.60 (0.49-0.73, p<0.001)
Sex	F	2,013	-	-
	M	3,735	0.65 (0.58-0.73, p<0.001)	0.95 (0.84-1.08, p=0.422)
Age group	below 55	1,320	-	-
	55 to 65	1,600	1.86 (1.37-2.54, p<0.001)	1.93 (1.39-2.67, p<0.001)
	above 65	2,828	8.95 (6.86-11.66, p<0.001)	9.89 (7.48-13.09, p<0.001)
SIMD group	high	1,297	-	-
	mid	2,303	1.10 (0.94-1.29, p=0.245)	1.18 (1.00-1.39, p=0.057)
	low	2,141	1.24 (1.06-1.45, p=0.009)	1.48 (1.25-1.75, p<0.001)
Comorbidity status	neither	3,805	-	-
	diabetes	636	2.23 (1.90-2.62, p<0.001)	2.00 (1.71-2.35, p<0.001)
	depression	813	1.47 (1.24-1.74, p<0.001)	1.76 (1.49-2.09, p<0.001)
	both	172	2.21 (1.67-2.92, p<0.001)	2.26 (1.70-3.00, p<0.001)
Drug count	1 to 3	1,360	-	-
	4 to 7	4,314	0.94 (0.82-1.08, p=0.419)	0.95 (0.82-1.09, p=0.453)
	8 to 10	74	1.98 (1.34-2.95, p=0.001)	1.08 (0.72-1.63, p=0.696)
Beta-blockers		All (n)	HR (univariable)	HR (multivariable)
Persist	No	407	-	-
	Yes	4,528	0.79 (0.64-0.99, p=0.037)	0.78 (0.62-0.97, p=0.027)
Sex	F	1,691	-	-
	M	3,244	0.64 (0.56-0.73, p<0.001)	0.95 (0.83-1.09, p=0.449)
Age group	below 55	1,182	-	-
	55 to 65	1,385	1.96 (1.40-2.75, p<0.001)	1.96 (1.38-2.78, p<0.001)
	above 65	2,368	9.32 (6.99-12.45, p<0.001)	9.95 (7.36-13.45, p<0.001)
SIMD group	high	1,114	-	-
	mid	1,965	1.10 (0.93-1.32, p=0.270)	1.15 (0.95-1.38, p=0.147)
	low	1,848	1.24 (1.04-1.48, p=0.016)	1.48 (1.23-1.78, p<0.001)
Comorbidity status	neither	3,294	-	-
	diabetes	578	2.33 (1.96-2.76, p<0.001)	2.04 (1.72-2.42, p<0.001)
	depression	664	1.46 (1.21-1.77, p<0.001)	1.74 (1.44-2.11, p<0.001)
	both	136	2.14 (1.55-2.96, p<0.001)	2.20 (1.59-3.06, p<0.001)
Drug count	1 to 3	1,107	-	-
	4 to 7	3,767	0.76 (0.66-0.89, p<0.001)	0.83 (0.72-0.97, p=0.020)
	8 to 10	61	1.80 (1.17-2.76, p=0.007)	1.17 (0.75-1.81, p=0.495)
Lipid-regulators		All (n)	HR (univariable)	HR (multivariable)
Persist	No	357	-	-
	Yes	5,325	0.59 (0.48-0.73, p<0.001)	0.64 (0.52-0.79, p<0.001)
Sex	F	1,972	-	-
	M	3,710	0.65 (0.58-0.73, p<0.001)	0.96 (0.84-1.09, p=0.506)
Age group	below 55	1,310	-	-
	55 to 65	1,583	1.86 (1.36-2.54, p<0.001)	1.92 (1.38-2.67, p<0.001)
	above 65	2,789	8.86 (6.78-11.59, p<0.001)	9.73 (7.34-12.92, p<0.001)
SIMD group	high	1,276	-	-
	mid	2,285	1.17 (0.99-1.38, p=0.065)	1.28 (1.08-1.52, p=0.005)
	low	2,113	1.31 (1.11-1.54, p=0.001)	1.57 (1.32-1.87, p<0.001)
Comorbidity status	neither	3,762	-	-
	diabetes	640	2.30 (1.96-2.70, p<0.001)	1.97 (1.68-2.31, p<0.001)
	depression	791	1.42 (1.19-1.68, p<0.001)	1.66 (1.40-1.98, p<0.001)
	both	166	2.09 (1.56-2.79, p<0.001)	2.06 (1.54-2.77, p<0.001)
Drug count	1 to 3	1,620	-	-
	4 to 7	3,997	0.86 (0.76-0.98, p=0.026)	0.92 (0.80-1.05, p=0.210)
	8 to 10	65	2.05 (1.37-3.08, p=0.001)	1.17 (0.77-1.77, p=0.474)

Table G4: Mortality 5-years *after* classed as persistent or not with TAM (T0) in the secondary-treatment group, across four CVD drug-classes. Including drug-count.