Determinants of medication use for the secondary prevention of cardiovascular disease

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A thesis submitted for the degree of

Doctor of Philosophy

Michaelmas 2021

Acknowledgements

There are many people to whom I am thankful for support over the four years of this DPhil. First and foremost, I am beyond grateful to my four supervisors - Boby, David, Iryna and Alastair - for their invaluable advice, guidance and continuous support. Each has steered me through this research with their insight and deep knowledge of the subject matter. Each has challenged and inspired me. I would like to offer particular thanks to Boby for her dedication, encouragement and patience, as well as for applying for NDPH and MRC funding that allowed me to undertake this DPhil in the first instance. I am also extending my thanks to David for his recommendation to use NHS Scotland data and application for BHF CRE funding that ultimately allowed me to access the data for this research. While applying for and working with the NHS Scotland data, I was extremely grateful to receive timely help from the eDRIS team, particularly Pauline. I am thankful to Nia, Mi Jun and Anna for taking the time to help me develop the search strategy and acting as reviewers for my systematic literature review. Naturally, I would also like to thank the NDPH, MRC and BHF CRE for the studentships and grant that allowed me to conduct this research. My gratitude extends to all my friends and colleagues in HERC, particularly to Patrick, and the wider NDPH, the Brasenose community and my college advisor, Eamonn, as well as my family and friends outside the office, for their unconditional support.

Abstract

Previous studies have shown that use of effective and widely recommended treatments, specifically statin and antiplatelet therapy, for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) is suboptimal. However, knowledge regarding the underlying reasons for suboptimal medication use at different treatment stages, including the role of particular individual characteristics, and the variations in medication use across different population groups and ASCVD categories, is limited.

I undertook the first systematic literature review of studies that estimated the proportions and determinants of statin and antiplatelet therapy for the secondary prevention of ASCVD among myocardial infarction and ischaemic stroke patients at every stage of the treatment pathway, namely medication prescription on discharge, initiation of treatment after discharge, adherence to and persistence with treatment. The review presented evidence of gradually increasing, yet suboptimal medication use at almost every stage of the pathway for both statin and antiplatelet therapy. Multiple patient and provider-related risk factors of suboptimal medication use were identified. Women were less likely to receive statin and antiplatelet therapy (except for aspirin) on discharge, and less likely to initiate statin. A U-shaped association was observed for risk of statin discontinuation with age, where elderly individuals aged 69 years or older and those younger than 64 years were at greater risk. Prior CVD and presence of specific physical comorbidities were associated with suboptimal statin use at various treatment stages. Most of these studies had a limited follow-up time and examined a maximum of two treatment stages, thereby limiting the ability to generalise results and insights into the full extent of suboptimal use across the entire treatment pathway and over time.

Using linked NHS Scotland administrative hospitalisation and prescription information data on all individuals in Scotland ever hospitalised for an ASCVD event since 2009 with a follow-up time of up to eight years, I estimated the extent of use and patient characteristics associated with suboptimal statin and antiplatelet therapy use. About 82% and 84% of individuals hospitalised for ASCVD event subsequently initiated statin and antiplatelet therapy, respectively, with rates varying significantly by ASCVD type. Although more than 90% of individuals who initiated statin and/or antiplatelet therapy were adherent while on medication, one quarter of individuals eventually discontinued treatment. Of those who discontinued, 50% of individuals ceased statin and/or antiplatelet therapy within 1.5 years, and 80% within 3.5 years, despite clinical guidelines recommending lifelong treatment. Among individuals who discontinued treatment, 38% and 37% of individuals re-initiated some type of statin and antiplatelet therapy at some point in time, and on average within 1.1 years since discontinuation.

Patient phenotypes that were consistently associated with higher risks of non-initiation and discontinuation of treatment included women, individuals aged below 50 years or above 70 years (compared to those aged 60 to 69 years), individuals with multiple physical morbidities, individuals with a previous record of receiving specialist mental health care, patients residing in the most deprived areas (compared to those living in the least deprived areas), and patients hospitalised in the earlier time period in study (i.e. before 2015). In addition to patient-related factors, this Thesis showed that the intensity of statins prescribed was significantly associated with market supply forces, such as the market entry of lower cost generic atorvastatin in 2012, and further accelerated via health care system demand-side measures, such as clinical guidelines and educational initiatives advocating for the use of higher intensity statin treatment. The overall prescribing budget and the notion of relative cost-effectiveness of different statin types are likely key influencing factors in prescribing decisions.

These findings will be useful to healthcare policy makers and providers in making investment and prioritisation decisions, and underline calls for interventions designed to improve drug initiation and persistence to improve health and curtail rising costs due to preventable vascular events.

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List of Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin-converting-enzyme
ACL	Adenosine triphosphate-citrate lyase
ACS	Acute coronary syndrome
AHA	American Heart Association
ARB	Angiotensin-receptor blocker
ASA	Acetylsalicylic acid (i.e. aspirin)
ASCVD	Atherosclerotic cardiovascular disease
APT	Antiplatelet therapy
ATT	Antithrombotic Treatment Trialists
BHF	British Heart Foundation
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood pressure
CABG	Coronary artery bypass graft
CCI	Charlson Comorbidity Index
CHI	Community Health Index
CI	Confidence interval
CIS	Continuous inpatient stay
CTT	Cholesterol Treatment Trialists
CVD	Cardiovascular disease
DALY	Disability-adjusted life-year
DAPT	Dual-antiplatelet therapy
DCB	Drug-coated balloons
DES	Drug-eluting stent
eDRIS	Electronic Data Research and Innovation Service
GI	Gastro-intestinal
GP	General practitioner
HDL-C	High-density lipoprotein cholesterol
HI	High-intensity

HR	Hazard ratio
ICD-10	International Classification of Diseases, 10th revision
ICD-9	International Classification of Diseases, 9th revision
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
IQR	Interquartile range
ISD	Information Services Division
ITS	Interrupted time series
LDL-C	Low-density lipoprotein cholesterol
LI/MI	Low-intensity/medium-intensity
MI	Myocardial infarction
MRC	Medical Research Council
MPR	Medication possession ratio
MTA	Multiple Technology Appraisals
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NSTEMI	Non-ST-elevation myocardial infarction
OPCS-4	Office for Population Censuses and Surveys classification of surgical operations and procedures, 4th revision
OR	Odds ratio
PAD	Peripheral arterial disease
PCA	Prescription cost analysis
PCI	Percutaneous coronary intervention
PDC	Proportion of days covered
PIS	Prescribing information system
PR	Prevalence ratio
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomised controlled trial
RR	Risk ratio
SD	Standard deviation
SDI	Socio-demographic index
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation

SMC	Scottish Medicines Consortium
STA	Single technology appraisals
STEMI	ST-Elevation Myocardial Infarction
TIA	Transient ischaemic attack
UI	Uncertainty interval
UK	United Kingdom
US	United States
WHO	World Health Organisation

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Introduction

1.1 Background

Cardiovascular disease (CVD), principally ischaemic heart disease and stroke, is the leading cause of death and disability worldwide, and in many countries accounts for a significant share of healthcare spending [1]. The global prevalence rate has increased in recent decades to 7% (2019), almost double the rate in 1990, amounting to approximately 532 million prevalent cases in 2019 [1].

CVD is mainly associated with atherosclerosis, i.e., the build-up of fatty deposits in the arteries that eventually restricts blood flow and oxygen supply to vital organs and can lead to certain types of CVD, such as heart attacks and strokes [2], [3]. Due to its high prevalence and substantial impact on health, CVD is a leading contributor to life-years lost and disability-adjusted life years. The global trends for CVD-related years of life lost have increased significantly since 1990, and years lived with disability due to CVD have doubled since 1990 to 34.4 million in 2019 [1]. Globally, 31% of all deaths, and one in every four deaths in the US and UK can be attributed to CVD [4], [5]. As a result, CVD and CVD-related mortality and morbidity constitute a substantial financial burden on healthcare systems and wider society. For example, in the UK, annual direct costs to the National Health Service (NHS) were estimated at 12.3 billion GBP in 2015, while the costs to the wider economy amounted to an estimated 14.5 billion GBP [6]–[8].

Individuals with CVD are at significantly higher risk of future vascular events than those without a history of vascular disease [9]. Low-density lipoprotein (LDL) cholesterol-lowering therapies, such as statin, and antiplatelet therapies, such as aspirin, have the potential to reduce these risks. For instance, meta-analyses of randomised controlled trials of statins have shown that major vascular events were reduced by 21% and coronary heart disease deaths by 20% per 1 mmol/L reduction in LDL cholesterol on statin therapy [9]. In the case of antiplatelet therapies, such as aspirin, relative risk reductions of 30% in vascular events and 20% in all-cause mortality were observed [10]. Given the favourable safety and cost-effectiveness profiles of these treatments, national clinical guidelines recommend the long-term use of statin and antiplatelet therapy for the secondary prevention of CVD.

Despite these recommendations, previous studies have found that statin and antiplatelet therapy use among individuals with established CVD is suboptimal [11]–[13]. However, knowledge regarding the underlying reasons for suboptimal drug use at different treatment stages, including the role of particular patient, provider and health system characteristics, and the variations in medication use across different population groups and disease categories, is limited. Policy makers, healthcare planners and providers would benefit from a more detailed understanding of the extent

of suboptimal use at different stages of the patients' treatment pathway, as well as factors associated with suboptimal use, in order to inform development of quality-improvement interventions and inform future policies. Such information can be generated from large-scale and reliable individual patient data.

1.2 Research objectives

In this Thesis, I aimed to conduct a detailed analysis of the extent and determinants associated with suboptimal use of cardioprotective medications, specifically statin and antiplatelet therapy, for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD). This was achieved by using linked and anonymised population-wide administrative NHS Scotland data for all individuals ever hospitalised for an ASCVD event in Scotland between October 2009 and July 2017. Specifically, my main objectives were to:

- Undertake the first systematic literature review of studies estimating the proportions and determinants of statin and antiplatelet therapy use for the secondary prevention of ASCVD at every single stage of the treatment pathway (i.e. prescription on discharge, initiation of treatment following discharge, adherence to the daily medical regimen that was prescribed by the treating physician, and the discontinuation of treatment).

- Estimate the extent of suboptimal statin and antiplatelet therapy use for the secondary prevention of ASCVD in Scotland overall and across subgroups of individuals defined by age, gender and ASCV type, as well as the associations between patient characteristics and cardioprotective medication use at different stages of the treatment pathway, including treatment initiation, adherence and persistence.

- Examine the role of national market supply forces and demand side measures in the types and potencies of statins used for the secondary prevention of ASCVD, specifically evaluating the UK market entry of generic atorvastatin in 2012 and the introduction of NICE clinical guideline CG181 recommending the use of more potent statins in 2014.

1.3 Structure of the Thesis

In **Chapter 2**, I present a detailed overview of the types and causes of ASCVD, focusing on the current prevalence and trends in prevalence over time, both globally and in the UK, the health and economic consequences of ASCVD, and the evidence on the safety and effectiveness of pharmacological interventions for the management and secondary prevention of ASCVD, specifically statin and antiplatelet therapy. In order to provide the necessary context for later chapters of this Thesis, I also describe the development of clinical guidelines for the secondary prevention of ASCVD published in Scotland, England and Wales, as well as changes in clinical guidelines over time.

A systematic literature review of studies estimating the proportion and determinants of individuals using statin and antiplatelet therapy for the secondary prevention of ASCVD is presented in **Chapter 3**. Estimates of proportions and determinants of medication use are examined at four different stages of the treatment pathway, namely medication prescription on discharge, initiation of treatment after discharge, adherence to and persistence with treatment. Finally, the evidence on the role of individual characteristics in the suboptimal use of statin and antiplatelet therapy for the secondary prevention of ASCVD is critically discussed.

In this Thesis I use population-wide linked administrative NHS Scotland data for the period from 2009 to 2017 to estimate the extent and determinants of suboptimal statin and antiplatelet therapy use for the secondary prevention of ASCVD. In **Chapter 4**, I describe each of the four linked NHS Scotland datasets in detail, namely the NHS Scotland General /Acute and Inpatient Day Case (SMR01), the Mental Health Inpatient and Day Case (SMR04), the National Records of Scotland (NRS) and the Prescribing Information System (PIS) dataset, highlighting the high quality, representative nature and unique properties of the data. I also present the methodology for the studies on the extent and determinants of statin and antiplatelet therapy use and report on the identification of the ASCVD study population.

In **Chapter 5**, the proportion and determinants of statin use among individuals hospitalised with ASCVD are estimated by ASCVD type and at four different stages of the treatment pathway, namely the initiation of treatment in primary care following hospital discharge, the adherence to the prescribed medical regimen, as well as the discontinuation of treatment and subsequent re-initiation. Changes in the types and potency of statins over time are examined overall and by subgroups of individuals and ASCVD conditions. Comparable analyses for antiplatelet therapy use for the secondary prevention of ASCVD are reported in **Chapter 6**.

In **Chapter 7**, I investigate the role of national market supply forces and demand side measures in the types and potencies of statins used for the secondary prevention of ASCVD over time. Specifically, two national policies are assessed, namely the UK market entry of generic atorvastatin in May 2012 and the introduction of NICE clinical guideline CG181 in July 2014. Finally, the resulting trade-off between statin potency and cost of statins made by policy and prescription decision-makers are critically discussed.

Lastly, in **Chapter 8**, I summarise and interpret the findings from the work undertaken in this Thesis in the context of other relevant research, highlight the novel contributions of the work, assess the implications for policy and healthcare planning, and discuss the limitations of the work and potential areas for future research.

1.4 Role of the author in the preparation of this Thesis

I was awarded a Medical Research Council (MRC) Doctoral Training Programme studentship and a University of Oxford Nuffield Department of Population Health (NDPH) doctoral research scholarship in 2017 to undertake the research presented in this Thesis. The studentship and scholarship applications were developed and submitted by Associate Professor Borislava Mihaylova, NDPH. In addition, I was awarded funding by the Oxford British Heart Foundation Centre of Research Excellence (BHF CRE) Pump Priming Scheme (grant RE/13/1/30181) and received research sponsorship from Clinical Trials and Research Governance (CTRG) Oxford (sponsorship PID: 13584) to conduct the retrospective observational study of cardiovascular medication use in Scotland. The BHF CRE grant application was developed with the support of NDPH, in particular the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) (Associate Professor David Preiss), and the Health Economics Research Centre (HERC) (Associate Professor Borislava Mihaylova, Dr Iryna Schlackow and Professor Alastair Gray).

I led the research presented in this Thesis, devising analysis plans, performing analyses and preparing presentations and Thesis chapters. My supervisors (Associate Professor Borislava Mihaylova, Associate Professor David Preiss, Dr Iryna Schlackow, and Professor Alastair Gray) contributed to each aspect of this process for all research presented in this Thesis.

Nia Roberts from the Knowledge Centre at the Bodleian Libraries, University of Oxford, contributed to the research presented in **Chapter 3** by providing guidance in the development of the electronic search strategy for the systematic literature review. Mi Jun Keng, from HERC, University of Oxford, and Anna Strampelli from the Department of Life Sciences, Imperial College London, were the second and third reviewers for the systematic literature review presented in **Chapter 3**. The Electronic Data Research and Innovation Service (eDRIS) Team, National Services Scotland, supported this Thesis through their involvement in obtaining approvals, provisioning and linking NHS Scotland data and the use of the secure analytical platform within the National Safe Haven.

I am first author and presenter of the presentations held at the Health Economists' Study Group (HESG) Conference in Newcastle in January 2020, and the virtual European Society of Cardiology (ESC) Congress in September 2020. The funders had no role in study design, data collection and analysis, or preparation of this Thesis, and the views expressed are those of the author and not necessarily of the NHS, the BHF CRE, the MRC or the NDPH.

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2

Background to medication use for the secondary prevention of cardiovascular disease

2.1. Definition and burden of cardiovascular disease (CVD)

2.1.1. Definition of CVD

Cardiovascular disease (CVD) is a term encompassing conditions that affect the structure or function of the heart or blood vessels [1]. It is mainly associated with atherosclerosis, i.e. the build-up of fatty deposits (plaques) made of cholesterol and other cellular products inside the arteries, causing the hardening and narrowing of the inner walls of blood vessels that eventually lead to the restriction of blood flow and oxygen supply to vital organs [2]. Plaque rupture can lead to thrombosis and blockage of an artery providing blood to part of the heart or brain. While some individuals will experience angina in the case of moderate to severe atherosclerosis of the coronary arteries, there is an absence of symptoms in most cases, and affected individuals may be unaware of the condition until they experience life-threatening cardiovascular events such as heart attacks or stroke [2].

There are various key risk factors for CVD including high cholesterol, high blood pressure, diabetes, being overweight or obese, smoking and other tobacco use, family history of early heart disease[1] and physical inactivity. Other risk factors affecting the risk of developing CVD include age (i.e., the risk of developing CVD increases with age), sex (i.e., men are more likely to develop ischaemic heart disease (IHD) than women); diet (i.e., unhealthy diet can lead to high cholesterol and high blood pressure), and alcohol (i.e., use of alcohol can increase blood pressure levels, and contribute to weight gain) [1].

Lipids play a key role in atherosclerotic plaque formation. Studies by Windhaus (1910) and Anitschkow (1913) demonstrated, respectively, that cholesterol forms a component of atherosclerotic plaques and that cholesterol plays a causal role in the pathogenesis of atherosclerosis [3], [4]. There is abundant evidence that lowering cholesterol, specifically low-density lipoprotein cholesterol (LDL-C), reduces CVD risk. Findings from studies on monogenic conditions like familial hypercholesterolaemia (FH; a condition that can lead to extremely high LDL-C levels) showed that individuals with FH had a substantially increased risk of CVD [5]. Further direct associations of high blood cholesterol levels and risk of cardiovascular events were recognised in epidemiological studies, such as the Framingham Study and the Seven Countries Study, clinical trials (e.g.,

[1] According to the National Health Service (NHS) an individual is considered to have a family history of CVD if either (1) their father or brother were diagnosed with CVD before the age of 55 or (b) their mother or sister were diagnosed with CVD before the age of 65.

Multiple Risk Factor Intervention Trial (MRFIT)), and Mendelian randomisation studies (e.g., Allara and colleagues (2019)) [6]–[9]. In particular, further investigation showed that the described association was mainly related to LDL-C, whilst high-density lipoprotein cholesterol (HDL-C) appeared to be conversely associated with a reduced risk in CVD-related mortality and morbidity [10]–[12][2]. These findings were paramount to the start of a new era of lipid-lowering therapeutics in the management and prevention of CVD, discussed in **Section 2.2**.

While there are other causes of CVD, such as congenital heart disease or damage to arteries, this thesis focusses on atherosclerotic cardiovascular diseases (ASCVD), the main form of CVD [13]. There are different types of ASCVD, and the three main manifestations are presented in **Table 2.1**.

[2] Even though observational studies have shown that LDL-C and HDL-C have opposing associations with CVD risk, these types of studies cannot distinguish between a causal role in the pathological process and a marker of the underlying pathophysiology. Mendelian randomisation studies have shown that some genetic mechanisms which increase plasma HDL-C do not appear to lower the risk of myocardial infarction (MI), challenging the concept that a raise in HDL-C will uniformly translate into reduced risks of MI [10].

Table 2.1 Overview of the three main types of atherosclerotic cardiovascular disease [1]

ASCVD type	**Ischaemic heart disease (IHD)** (also known as coronary artery disease and coronary heart disease)	**Ischaemic stroke and transient ischaemic attack (TIA)**	**Peripheral arterial disease (PAD)**
Definition	Blockage or reduction of oxygen-rich blood flow to the heart muscle. This can lead to certain types of coronary artery disease, such as myocardial infarction in the case of acute blood flow blockage, or angina caused by blood flow restriction.	Blood supply cut-off to part of the brain (ischaemic stroke), or temporary disruption of blood flow to brain (TIA).	Blockage (critical ischaemia) or reduction (claudication) of oxygen-rich blood flow to the limbs, most commonly the legs.
Interventional procedures to treat/prevent ASCVD	Coronary angioplasty (percutaneous transluminal coronary angioplasty (PTCA)) or coronary angioplasty with stenting (percutaneous coronary intervention (PCI)) to widen blocked/narrowed coronary arteries. Coronary artery bypass graft (CABG) to divert blood around narrowed/ clogged parts of arteries	Intravenous drug treatment with tissue plasminogen activator (tPa) to dissolve a blood clot. Thrombectomy (i.e. removal of a blood clot under image guidance). Carotid endarterectomy to scrape out plaque. Carotid angioplasty and stenting to widen carotid artery.	Peripheral angioplasty +/- stenting to open vessels. Drug coated balloons (DCB) to expand artery and release medicine for blockage prevention. Arterial thrombectomy to remove clot from artery. Peripheral atherectomy to cut through plaque in blood vessels.

2.1.2. Global burden of CVD

Cardiovascular diseases, primarily ischaemic heart disease and stroke, are the leading cause of death and major drivers of disability worldwide [14]. Using estimates from the Global Burden of Disease (GBD) study 2019, the prevalence rate of total CVD increased from 5.3% (95% uncertainty interval (UI): 4.9% - 5.5%) in 1990 to 7% (6.8%-7.4%) in 2019, amounting to approximately 523 million prevalent cases in 2019, almost double since 1990 [14]. The prevalence rates vary across countries (e.g. in 2019, UK: 10.3% (9.7%-10.8%); USA: 12.8% (12.3%-13.2%)), and are higher in high socio-demographic index (SDI) countries (2019: 11.6% (11.1%-12.1%)), compared to middle SDI (2019: 6.7% (6.4%-7.1%)) and low SDI countries (2019: 3.7% (3.4%-4%)) [15]. Nearly 19 million CVD deaths were recorded in 2019 (95% UI: 17.1 to 19.7 million), i.e. 31% of all global deaths, and one in every four deaths in the US and UK can be attributed to CVD [16], [17]. While the overall decline in age-standardised rates of prevalent CVD cases and death (e.g., such as in the UK and Europe) indicate that population growth and aging play a significant role in the rise in total CVD cases, an alarming rise in the age-standardised rate of CVD was observed in some locations where it was previously declining, including some states in the US[3] [14].

Furthermore, CVD morbidity remains a major issue for health and social care. The global trends for CVD-related disability-adjusted life years (DALYs) and years of life lost have increased significantly since 1990, while years lived with disability doubled throughout the same time period to 34.4 million (95% UI: 24.0 to 43.6 million) in 2019. In addition, sex differences in total CVD DALYs were observed across different age groups[4]. For instance, among individuals aged 80 to 84 years, CVD was a cause of more DALYs in men than in women of the same age group. However, the relationship reverses with age, with higher DALYs observed in women aged 84 years or older compared to men [14].

As a result, CVD and CVD-related morbidity constitute a considerable financial burden on healthcare systems and wider society. For example, in the US, the CVD-related annual direct costs[5] were estimated at 216 billion USD (i.e., 156 billion GBP) in 2016/17, with additional indirect costs due to lost productivity estimated at 147 billion USD (i.e. 106

[3] The study by Roth and colleagues (2020) calculated percent change in age-standardised CVD death and prevalent CVD case rate from 2010 to 2019.
[4] The study by Roth and colleagues (2020) calculated DALYs for 23 age groups, with a 4-year grouping (e.g., age 1 to 4, 5 to 9, (…), 90 to 94, and 95 plus years).
[5] Direct costs include the cost of physicians and other professionals, hospital services, prescribed medications, and home health care; excluding the cost of nursing home care [18].

billion GBP) [18]. In the UK, annual direct costs to the National Health Service (NHS) were estimated at 12.3 billion GBP in 2015, while the costs to the wider economy amounted to an estimated 14.5 billion GBP [19]–[21]. The global CVD-related economic and social costs are expected to rise further in future, particularly due to population aging.

2.2. Prevention of cardiovascular disease

2.2.1. Overview of primary and secondary prevention strategies

It is estimated that 34% of deaths due to ischaemic heart disease could potentially be prevented by addressing modifiable risk factors, such as hypertension, hyperlipidaemia, diabetes, smoking, poor diet and sedentary lifestyle [22]. These risk factors, in addition to psychosocial and somatic factors, were also collectively associated with approximately 90% of the population-attributable risks of stroke in each major region in the world [23]. As a result, policy makers have aimed to address these risk factors through primary and secondary prevention strategies[6], in order to reduce the risks of CVD morbidity and mortality. Primary prevention encompasses a combination of CVD risk assessment[7], lifestyle changes (e.g., diet, physical activity, smoking, alcohol use) and pharmacotherapy (e.g. lipid- and blood pressure-lowering pharmacotherapies, depending on an individual's risk of ASCVD and the presence of specific risk factors). In the case of secondary prevention, all individuals are considered at high risk of recurring CVD events and mortality, and therefore CVD risk assessments are not recommended to guide allocation of therapies like statin and aspirin. Instead, secondary prevention focuses on pharmacotherapy, accompanied with lifestyle changes, as outlined in more detail in **Table 2.2** [24]. This thesis focusses on the use of lipid-lowering and antiplatelet therapies (further described in **Sections 2.2.2-2.2.3)** among individuals with established ASCVD.

[6] Primary prevention is defined as interventions designed to prevent the onset of a specific disease, while secondary prevention focusses on interventions that are implemented after the onset of disease e.g. to prevent future acute events.

[7] CVD risk assessment: assessment of risk factors and 10-year risk using risk scores, such as those calculated via the QRisk and JBS3 risk calculators in the UK.

Table 2.2 Broad overview of secondary prevention interventions for CVD/ASCVD [1], [24]

	Interventions used in the secondary prevention of CVD/ASCVD
Pharmacotherapy	
Antiplatelet therapy	Antiplatelet therapy is recommended to reduce the risk of blood clots, and therapies include aspirin and P2Y12 inhibitors.
LDL-C-lowering therapy	Statin therapy (typically high-intensity) is recommended to decrease LDL-C levels. Complementary and alternative cholesterol-lowering drugs include ezetimibe and PCSK9 inhibitors.
Blood pressure-lowering therapy	Blood-pressure (BP) lowering drugs are recommended to decrease BP levels, and include ACE inhibitors, angiotensin-2 receptor blockers (ARBs), calcium channel blockers, beta blockers.
Lifestyle interventions	
Smoking cessation	Education, assessment of triggers, counselling and pharmacotherapy are used to reduce cigarette/tobacco use.
Diet/weight management	A healthy diet high in fresh fruits and vegetables, and low in salt and sugar is recommended, as well as the monitoring of individual's body mass index (BMI).
Physical exercise	Moderate-vigorous exercise is recommended, while sitting or sedentary time should be reduced.

2.2.2. Lipid-lowering therapies

Overview of lipid-lowering therapies

Low-density lipoprotein (LDL) cholesterol-lowering therapies are a group of medicines that reduce circulating LDL particles in the circulation and are central to the prevention of vascular events. Therapies include statins or HMG-CoA Reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin), NPC1L1 inhibitors (ezetimibe), PCSK9 inhibitors (alirocumab and evolocumab), bile acid sequestrants also called resins (cholestyramine, colestipol, colesevelam hydrochloride) and adenosine triphosphate-citrate lyase (ACL) inhibitors (bempedoic acid) [25]. In addition, fibrates (gemfibrozil, fenofibrate, clofibrate), which reduce triglyceride levels and modestly reduce LDL-C, may on occasion be added to statin therapy[8]. Statins are the most commonly prescribed type of lipid-lowering treatment for the prevention of ASCVD, and the only class recommended for secondary prevention in all affected patients, and constitute the focus of this section and thesis [26].

Overview of statin therapy

Statins, or HMG-CoA Reductase inhibitors, first launched in 1987, inhibit the production of cholesterol in the liver by blocking the enzyme HMG-CoA-Reductase. As a result, hepatocytes increase expression of the LDL receptor, leading to increased uptake of LDL-C from the circulation and a decline in circulating LDL-C levels, which subsequently reduces the risks for heart disease and stroke [27]. There are currently five types of statins available on prescription and over-the-counter[9] in the UK (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin; which constitute the focus of this thesis) and seven types in the US (lovastatin and pitavastatin in addition to those listed prior) that vary in their potency based on the type and dose of statin [28]. Based on a meta-analysis of 164 randomised controlled trials, the yields in absolute LDL-C reduction (mmol/l) depend on a particular statin and dose used, and range from 10% (e.g. fluvastatin 5mg) to 58% (e.g. rosuvastatin 80mg; although not used in clinical care) (see **Table 2.3**). With each doubling of the dose of a particular statin, LDL-C levels decrease by approximately 6% compared to the current dose [29]. According to the National Institute for Health and Care

[8] Please not, the US Food and Drug Administration (FDA) has withdrawn previous approval for the use of fibrates and niacin in addition to statin therapy to treat high cholesterol due to lack of evidence of cardiovascular benefit in 2016.

[9] Out of all statins available in the UK, only low-strength simvastatin 10mg is available over the counter.

Excellence (NICE) in England and Wales, statins that reduce LDL-C by ≤40% are classified as low/medium intensity, while those reducing LDL-C by more than 40% are classed as high intensity therapy. In contrast, the American College of Cardiology (ACC) and American Heart Association (AHA) have set a higher classification threshold, defining statin therapy as high-intensity if the selected statin and dose will reduce LDL-C by more than 50% on average, moderate-intensity if the expected reduction in LDL-C is between 30% and 50%, and low-intensity if the expected reduction is less than 30% (**Table 2.3**) [30].

Table 2.3 Overview of yields in LDL-C reduction by statin type and dose (mg/day), based on Law et al. (2003) [29]

Organisation	**Classification of intensity**						
NICE	Low-intensity statin		Medium-intensity statin		High-intensity statin		
ACC/AHA	Low-intensity statin		Medium-intensity statin				High-intensity statin
Statin therapy	**Reduction in LDL cholesterol**						
	21-24%	**27-29%**	**31-33%**	**37-38%**	**42-45%**	**48-49%**	**53-58%**
Atorvastatin				10mg	20mg	40mg	80mg
Rosuvastatin				5mg	10mg	20mg	40mg
Simvastatin		10mg	20 mg	40mg	80mg*		
Fluvastatin	20mg	40mg	80mg				
Pravastatin	20mg	40mg					

*Please note, simvastatin 80mg is seldom used in clinical care due to myopathy risk.

Clinical benefits of statin therapy in secondary prevention of CVD

Individuals with established CVD are at substantially higher absolute risk of future vascular events than those without a history of vascular disease. For instance, a large meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration (based on patient-level data from 170,000 participants across 26 randomised trials of statin therapy) showed that the annual rate of major vascular events among statin-untreated individuals was 5.6% in those with established coronary heart disease, compared to 1.8% in individuals without CVD [31]. The meta-analysis of individual patient data from randomised, placebo-controlled, double-blinded, as well as open-label trials of statins has shown that non-fatal myocardial infarctions were reduced by around 27%, major vascular events by 21% and coronary heart

disease deaths by 20% per 1 mmol/L reduction in LDL-C on statin therapy over a median of five years [31].

A meta-analysis of cardiovascular outcomes trials has demonstrated that, compared to moderate-intensity statin treatment, higher-intensity therapy yielded a 16% risk reduction in coronary death or myocardial infarction, as well as a 16% risk reduction of coronary death or any cardiovascular event [31], [32]. The statin-related proportional reduction in the risk of vascular events per mmol/L reduction in LDL-C is similar across most major categories of patients (including by sex, age, levels of total cholesterol and LDL-C, systolic and diastolic blood pressure and smoking status), and therefore individuals at high absolute cardiovascular risk, such as those with established CVD, achieve the greatest absolute risk reduction from statins and benefit more from intensive lipid lowering, as the absolute risk reduction is a function of the initial level of risk [31], [33].

Safety of statin therapy

Based on a comprehensive review of all statin trials to date conducted by a Task Force of the US National Lipid Association [34], and further confirmations by the CTT Collaboration [33], [35], there is strong evidence for the safety of statins. No increased risk of cancer or non-cardiovascular mortality has been observed in statin trials [31], [33]. Fewer than 1% of participants treated with statins[10] (typically high dose atorvastatin) experienced raised levels of liver enzymes, a state that is reversible upon treatment withdrawal.

Cases of myopathy, where individuals experience muscle weakness due to dysfunction of muscle fibres, and rhabdomyolysis, a potentially life-threatening condition caused by muscle breakdown and muscle death, are very rare [31], and increase in the case of statin interactions with a number of other medications (e.g. gemfibrozil, nicotinic acid, amiodarone, verapamil, diltiazem) [36], [37]. For instance, one meta-analysis including 13 major statin trials came to the conclusion that treatment of 10,000 patients for five years with an effective regimen (e.g. atorvastatin 40mg daily) would cause about five cases of myopathy, one of which might progress to rhabdomyolysis if the therapy is not stopped. Muscle pain or weakness may be caused in up to about 50 to 100 patients (0.5%-1% absolute harm) per 10,000 treated for five years [38]. Therefore, the review demonstrates that the vast majority of the symptomatic adverse events attributed to statin therapy in routine practice represent misattribution and are not actually caused by statins. In addition,

[10] With the exception of atorvastatin at max. 80mg and combination statin and ezetimibe therapy, where levels were higher.

the large-scale evidence available from randomised trials indicates that large absolute excesses in other serious adverse events that still await discovery are unlikely [38]. Based on evidence from a small number of studies, 70% to 90% of patients reporting statin intolerance, such as muscle pain or other apparent side effects, were able to use some form of statin upon rechallenge [39]–[41].

Based on data on up to 223,463 individuals from 43 genetic studies, an increased risk of type 2 diabetes was observed with statins, which was at least partially explained by the inhibition of the intended drug target (i.e. HMGCR). In 129,170 individuals in randomised trials, moderate-intensity statin use increased the relative odds of new-onset type 2 diabetes by 11% compared to placebo or standard care [42]. Individuals using high dose statins had 12% higher odds of developing new-onset type 2 diabetes compared to individuals who received moderate dose [42], [43]. At present there is insufficient evidence to establish whether statins impact on the development of diabetes-related microvascular complications. Statins should also be avoided in individuals with active liver disease and pregnant women and those breastfeeding [44].

Overall, the benefits of statin use heavily outweigh the potential risks of harm. Based on a study by Collins and colleagues, the treatment of 2,000 patients with established CVD for five years would prevent 200 major vascular events (or 100 events in the case of high-risk individuals without a history of CVD), while causing one case of myopathy, one to two haemorrhagic strokes and 10 to 20 new cases of diabetes [31], [38]. Given the large-scale evidence available from randomised trials, any further findings that could emerge about the effects of statin therapy would not be expected to alter materially the balance of benefits and harms [38].

2.2.3. Antiplatelet therapies

Overview of antiplatelet therapies

Antiplatelet therapies are a class of medicines that decrease the risk of platelet aggregation and inhibit blood clot formations in the arterial circulation that could otherwise lead to the narrowing or blockage of arteries during plaque rupture and result in life-threatening conditions, such as heart attacks or stroke [45]. Antiplatelet therapies interfere with the binding of platelets, and include thromboxane inhibitors (aspirin), adenosine diphosphate (ADP) receptor antagonists (or P2Y12 inhibitors) such as thienopyridines (clopidogrel and prasugrel) and the nonthienopyridines (ticagrelor, cangrelor), as well as nucleoside transport inhibitors (dipyridamole) [46]. Depending on the type of CVD, the inhibitors are

either prescribed as (1) monotherapies or (2) as dual antiplatelet therapies (DAPT) typically by combining aspirin with one of the listed P2Y12 inhibitors or dipyridamole, which provides more intense platelet inhibition resulting in incremental reductions in the risk of thrombotic events compared to monotherapy (see **Table 2.4** for indications based on CVD type) [47]. The most commonly used antiplatelet agents are aspirin and clopidogrel, which are discussed in more detail in the sections below on clinical benefit and safety of antiplatelet therapies. An overview of the respective indications for each antiplatelet therapy outside of the acute care setting is presented in **Table 2.4**.

Table 2.4 Overview of antiplatelet therapies and indications according to the British National Formulary (BNF) [45]

Antiplatelet therapy	Indication
Aspirin	▪ Secondary prevention in patients with CVD (including previous MI, ischaemic stroke, coronary artery bypass surgery, percutaneous coronary intervention, stable angina) (long-term use)
Clopidogrel	▪ Secondary prevention in ischaemic stroke patients (long-term use) ▪ Dual-antiplatelet therapy (DAPT) with aspirin for non-ST-elevation myocardial infarction (NSTEMI) patients (3 months from acute event) ▪ DAPT with aspirin for ST-elevation myocardial infarction (STEMI) patients (4 weeks from acute event) ▪ DAPT with aspirin for patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) (for up to 12 months since PCI) ▪ Patients with atrial fibrillation for whom warfarin sodium is unsuitable ▪ As an alternative in patients with aspirin hypersensitivity or intolerance
Prasugrel	▪ DAPT with aspirin for patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) (for up to 12 months since PCI)
Ticagrelor	▪ DAPT with aspirin for patients with acute coronary syndrome (for up to 12 months from acute event)
Cangrelor	▪ Patients with coronary artery disease undergoing PCI for whom other P2Y12 inhibitors are unsuitable
Dipyridamole	▪ DAPT with aspirin for secondary prevention of ischaemic stroke and TIA, as an alternative to clopidogrel

Clinical benefits of antiplatelet therapy in secondary prevention of CVD

In the case of secondary prevention of CVD, there is strong and well-documented evidence of the clinical benefits of aspirin. The Antithrombotic Trialist's (ATT) Collaboration conducted meta-analyses based on 282 studies involving 135,000 patients, which show a relative risk reduction of 18% in all-cause mortality, 20% in strokes, 30% in myocardial infarctions and 30% in other vascular events among individuals treated with prolonged aspirin therapy for two years following a CVD event compared to placebo, with low dose aspirin (i.e. 75-150mg/day) being at least as effective as higher daily doses [48]. As a result, daily aspirin is routinely offered to patients with established atherosclerotic disease, and while there is no clinical trial evidence on treatment beyond a few years, aspirin is usually continued for life due to the likely ongoing benefits [49]. Notably, a meta-analysis based on six primary and 16 secondary prevention trials concluded that the proportional reductions in a combined outcome measure for serious vascular events are similar for men and women [50]. Aspirin monotherapy is indicated in CVD patients, including those with previous MI, ischaemic stroke (as an alternative to clopidogrel), coronary artery bypass surgery, percutaneous coronary intervention and stable angina [45].

The use of clopidogrel monotherapy yielded comparable relative risk reductions in cardiovascular outcomes to aspirin monotherapy in the secondary prevention of vascular events among patients with ischaemic heart disease and ischaemic stroke [51], and is currently indicated as monotherapy for the secondary prevention of CVD among patients with stroke or TIA who do not have atrial fibrillation [45]. A recent meta-analysis observed further relative risk reductions in myocardial infarction when using clopidogrel monotherapy compared to aspirin monotherapy, but concluded that this additional benefit is of debatable clinical relevance due to the high number needed to treat to obtain the benefits and the absence of any effects on all-cause and vascular mortality [52]. Stroke and TIA patients with clopidogrel intolerance are prescribed DAPT with dipyridamole and aspirin as an alternative, and stroke/TIA patients using this combination therapy had a 20% relative risks reduction in stroke and vascular events compared to aspirin monotherapy [53].

DAPT with clopidogrel, prasugrel or ticagrelor, which is prescribed short-term (e.g., for up to 12 months in patients treated with PCI to reduce risks of stent thrombosis, and those with acute coronary syndrome (ACS) due to higher thrombotic risks, particularly in the first three months after acute event; up to 3 weeks in NSTEMI patients and 4 weeks in STEMI patients from acute event) provides more intense platelet inhibition resulting in

incremental reductions in the risk of thrombotic events after PCI or ACS [47]. A large randomised placebo-controlled trial of about 45,000 individuals found that the use of DAPT with clopidogrel in these patients produced a significant 9% proportional reduction in death, reinfarction or stroke compared to aspirin monotherapy [54]. Using a prasugrel or ticagrelor DAPT combination yielded even higher relative risk reductions compared to a clopidogrel DAPT combination, however, at a cost of increased risk of bleeding [55], [56].

Safety of antiplatelet therapy

Low-dose aspirin, i.e. the dose routinely used in CVD management, can increase the risks of major gastrointestinal (GI), intracranial and extracranial bleeds. The ATT Collaboration conducted meta-analyses and noted that the benefits of antiplatelet therapy significantly outweighed the excess risk of major extracranial bleeding, which was estimated to be about three additional major extracranial bleeds per 1,000 patients allocated prolonged antiplatelet therapy, i.e., an excess of about 1 such bleed per 1,000 patients per year than placebo for patients with myocardial infarction [48]. The analysis reported consistent findings for patients with stroke, and a detailed analysis of the International Stroke Trial suggested that much of this excess occurred when antiplatelet therapy was used in conjunction with heparin. Furthermore, in stroke patients, antiplatelet therapy produced an absolute excess of 1.9 haemorrhagic strokes per 1,000 patients, which was however counterbalanced by an absolute reduction of 6.9 fewer ischaemic strokes per 1,000 patients [48], [50]. Findings from meta-analyses of observational studies are comparable to those reported in randomised trials, reporting a relative risk of 1.4 for GI bleeds and 1.4 for intracranial haemorrhage (ICH) [50], [57], [58]. Therefore, the benefits of antiplatelet therapy are greater than any hazards, unless the absolute risk of bleeding is high, such as among haemodialysis patients, or the absolute risk of a vascular event is low, such as among apparently healthy individuals [48].

However, bleeding risks differ between antiplatelet therapy types. For example, a meta-analysis of benefits and risks of long-term clopidogrel versus aspirin monotherapy after ischaemic stroke noted that the risk of any bleeding was lower for clopidogrel compared to aspirin (risk ratio: 0.57, 95% confidence interval: 0.45, 0.74), whilst no difference in the rate of all-cause mortality between the two groups was found [59]. In addition, a multicentre, double-blind randomised trial in 18,000 patients with acute coronary syndrome (ACS) observed no significant difference in the rates of major bleeding between ticagrelor and clopidogrel (11.6% and 11.2%, respectively; P=0.43), although

ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, P=0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types [55]. When comparing prasugrel with clopidogrel monotherapy in 13,000 ACS patients, one study observed an increase in relative risks of major bleeding in patients receiving prasugrel (hazard ratio, 1.32 [95% CI, 1.03 -1.68]; P=0.03) [56].

Differences in bleeding risks between DAPT and monotherapy use in secondary stroke prevention were assessed in a meta-analysis of randomised controlled trials based on 27,000 patients from all major studies that compared the efficacy and safety of DAPT versus monotherapy, which showed that DAPT increased the relative risk of major bleeding compared to monotherapy (relative risk: 2.17 [95% CI, 1.45–3.25]) [60].

2.2.4. Cost-effectiveness of statin and antiplatelet therapy for the secondary prevention of CVD

A systematic review and meta-analysis used by NICE, an independent national advisory body, has shown that based on evidence from randomised controlled trials (published up until the year 2004) that recorded the efficacy of statins in the prevention of recurring CVD events and deaths (as outlined in **Section 2.2.2**), statin therapy was clinically effective and cost-effective for people with clinical evidence of CVD. The incremental cost-effectiveness ratios (ICERs) varied between £10,000 and £17,000 per quality adjusted life year (QALY) between ages 45 and 85 [61]. Therefore, the ICERs were below the cost-effectiveness threshold range of £20,000 to £30,000 used by NICE, i.e. the maximum amount a decision-maker is willing to pay for a unit of health [62]. With costs of statin therapies having decreased over time, particularly in 2006 when generic simvastatin entered the UK market and became a cheaper alternative to another widely used statin (i.e. atorvastatin) (see **Chapter 7** for an overview of changes in prices of different statin therapies over time and market entry of generic versions), the ICER of statin therapy has decreased as well, with statins becoming a highly cost-effective therapy for the secondary prevention of CVD.

A review produced by the Health Technology Assessment Group, an advisory body to the NHS, in 1999 found that the cost-effectiveness of aspirin for the secondary prevention of CVD was estimated to be £53 per life year saved [63]. Other antiplatelet therapies, as well as dual-antiplatelet therapies, were also determined to be clinically

effective and cost-effective following an evidence review by NICE's Appraisal Committee in 2010 [64].

Similarly, NICE's Appraisal Committee has reviewed evidence on the use of antiplatelet therapies for the secondary prevention of CVD and concluded that antiplatelet therapies are clinically effective and cost-effective. For example, in the case of MI, a treatment strategy of aspirin followed by clopidogrel had an ICER of £2,000 per QALY gained compared to aspirin alone. Among individuals with aspirin intolerance, clopidogrel monotherapy had an ICER of £2,000 per QALY gained compared with no preventative treatment. For ischaemic stroke, a treatment strategy of clopidogrel followed by aspirin had an ICER of £4,000 per QALY gained compared with aspirin alone [64].

2.3. Clinical guidelines for the secondary prevention of CVD

Given the vast evidence on the benefits of using statin and antiplatelet therapy in individuals with established CVD, both treatments are routinely offered long-term to CVD patients to prevent recurrent vascular events, as recommended by national and international clinical guidelines, including those issued by the American College of Cardiology, the European Society of Cardiology, the National Institute for Health and Care Excellence for England and Wales and the Scottish Intercollegiate Guidelines Network Consortium. As the research presented in this thesis is based on Scottish national healthcare data 2009-2017, with a focus on the use of statin and antiplatelet therapy for the secondary prevention of ASCVD, taking into consideration national policies and clinical guidelines issued in Great Britain, the following section will outline clinical guidelines for the secondary prevention of CVD published by NICE and SIGN during the study period, as well as the latest guidelines published after 2017.

SIGN, which is part of the Evidence Directorate of Healthcare Improvement Scotland, was founded in 1993, prior to NICE's creation in 1999 in England. However, certain types of NICE guidance and related outputs have formal application in Scotland. For instance, technology appraisals were formally applicable after validation by the NHS Quality Improvement Scotland up until 2016/17, when single technology appraisals (STAs; as of 2016) and Multiple Technology Appraisals (MTAs; as of 2017) lost status in NHS Scotland, and NHS Scotland Boards were required to consider Scottish Medicines Consortium (SMC) advice since [65]. Public health programme/intervention guidance issued by NICE are evaluated by NHS Health Scotland in the context of Scotland's policy, infrastructure, practice and developments, who issue a commentary on NICE's

recommendation [66]. In the case of clinical guidelines, NICE recommendations are not formally applicable in Scotland and SIGN remains the source of clinical guidelines for Scotland. Nevertheless, NICE publications may be used by health professionals in Scotland as sources of evidence when considering clinical topics or issues [66].

Tables 2.5-2.7 below provide an overview of all changes in clinical guideline recommendations ever issued by NICE and SIGN for the secondary prevention of CVD. In the case of statin therapy, recommendations have been consistent across different CVD types. Up until 2014, both NICE and SIGN had recommended moderate intensity statin therapy for long-term use, specifically simvastatin 40mg/day, taking into account lower doses or different statin types in the case of intolerance, drug interactions of high risk of adverse effects (see **Table 2.3**). The guidelines also advocated for the use of statins of low acquisition cost [67], [68]. NICE issued new guidelines in 2014 (CG181)[11] endorsing high-intensity instead of moderate intensity statin treatment, in particular atorvastatin 80mg/day, considering factors listed prior, as well as patient preferences [69]. These recommendations were carried over to the publication of the latest guidelines (NICE NG128 (2019), NG185 (2020), and SIGN 149 (2017)) [49], [70], [71].

In the case of antiplatelet therapy, recommendations vary by CVD type. For myocardial infarction, since 2008 NICE and SIGN have been advising the long-term use of low-dose aspirin monotherapy (75 mg/day) or clopidogrel monotherapy, unless patients experience intolerance or have an indication for anticoagulation [49], [67]–[69], [72], [73]. In the 2020 update to the National Guidance on acute coronary syndromes (ACS), NICE began recommending the use of DAPT for 12 months from acute event, before proceeding with APT monotherapy indefinitely (**Table 2.5**) [70]. In line with clinical evidence summarised in **Section 2.2.3**, the recommendations for the management of ischaemic stroke advise long-term use of clopidogrel monotherapy (75mg/day) or DAPT with dipyridamole and low-dose aspirin, with guidelines remaining unchanged since 2008 (**Table 2.6**) [49], [67]–[69], [71], [74]. Recommendations also vary for PAD, other ASCVD and individuals treated with PCI. In 2012, NICE issued guideline CG147 for the management of PAD, recommending the long-term use of clopidogrel (75mg/day) or DAPT with dipyridamole and low-dose aspirin [75]. Prior to this, NICE and SIGN recommended aspirin monotherapy (75mg/day), and the latest SIGN guideline (SIGN 149, 2017) continues to recommend long-term aspirin monotherapy, except for patients experiencing intolerance, in which case clopidogrel monotherapy is recommended. This

[11] SIGN officially updated their guideline in 2017 (i.e. SIGN 149) to recommend high-intensity statin [49].

medical regimen (i.e. long-term aspirin monotherapy and clopidogrel monotherapy for individuals with aspirin intolerance) also applies to individuals with established cardiovascular disease since 2007 and remains unchanged in the latest guidelines (**Table 2.7**) [49], [68]. Lastly, for patients treated with PCI, the NICE guidelines CG172 (2013) and CG167 (2013), as well as appraisal guidance 317 in 2014 (consistent with guidance in Scotland following an evaluation by Healthcare Improvement Scotland) and NICE NG185 (2020), recommend DAPT with prasugrel and aspirin, or clopidogrel and aspirin, for up to 12 months after the index procedure. In the case of patients aged 75 years or older, ticagrelor or clopidogrel should be considered if the risk of bleeding outweighs its effectiveness (**Table 2.7**) [49], [68], [70], [72], [73], [76], [77].

Table 2.5 Comparison of current and previous clinical guidelines for the secondary prevention of CVD following myocardial infarction issued by NICE (England and Wales) and SIGN (Scotland) [49], [67]–[70], [72], [73]

	Myocardial Infarction				
	England/Wales			**Scotland**	
Time period / clinical guidelines	**2008 – 2013** CG67 (2008)	**2013 – 2020** CG172 (2013) CG181 (2014)	**2020 – Present** NG185 (2020)	**2007 – 2017** SIGN97 (2007)	**2017 – Present** SIGN148 (2016) SIGN 149 (2017)
Lipid-lowering therapy[12]					
Simvastatin 40mg/day, indefinitely	✓			✓	
Atorvastatin 80mg/day (i.e., high-intensity statin therapy), indefinitely		✓	✓	All patients should be considered for more intensive therapy	✓
Consider lower dose or other statin type if potential drug interactions, high risk of adverse effects	✓	✓ *Consider patient preference	✓ *Consider patient preference	✓	✓
Use a statin of low acquisition cost	✓	✓		✓[13]	✓[13]
Do not delay statin treatment to treat modifiable risk factors		✓			✓
Antiplatelet therapy					
Aspirin or clopidogrel monotherapy, indefinitely (unless intolerant or indication for anticoagulation)	✓	✓	✓	✓	✓
DAPT for 12 months from acute event, unless separate indication for anticoagulation			✓		

Note: Empty cells mean that no explicit recommendation was made in the guidelines.

[12] Applicable to all statins: do not prescribe in patients with active liver disease except for mild NAFLD; women who are pregnant/ breastfeeding; simvastatin 80mg (risk of myopathy); with gemfibrozil or drugs influencing cytochrome P450.

[13] Not explicitly stated in the guidelines, however, the SMC refers to NICE CG67 (2008) and CG181 (2014) and their recommendations to use a statin with low acquisition cost when conducting a health technology assessment (HTA) of statins and recommending their use within NHS Scotland (e.g. cited in SMC's HTA of Crestor (2011) [78].

Table 2.6 Comparison of current and previous clinical guidelines for the secondary prevention of CVD following ischaemic stroke issued by NICE (England and Wales) and SIGN (Scotland) [49], [67]–[69], [71], [74]

	Ischaemic Stroke				
	England/Wales			**Scotland**	
Time period / clinical guidelines	2008 – 2014 CG67 (2008) CG68 (2008)	2014 – 2019 CG181 (2014)	2019 – Present NG128 (2019)	2007 – 2017 SIGN 97 (2007)	2017 – Present SIGN149 (2017)
Lipid-lowering therapy[14]					
Simvastatin 40mg/day, indefinitely	✓			✓	
Atorvastatin 80mg/day (i.e. high-intensity statin therapy), indefinitely		✓	✓	All patients should be considered for more intensive therapy	✓
Consider lower dose or other statin type if potential drug interactions, high risk of adverse effects	✓	✓ *Consider patient preference	✓ *Consider patient preference	✓	✓
Use a statin of low acquisition cost	✓	✓		✓[15]	✓[14]
Do not delay statin treatment to treat modifiable risk factors		✓			✓
Antiplatelet therapy					
Clopidogrel 75mg/day or DAPT with low-dose aspirin and dipyridamole, indefinitely[16]	✓	✓		✓	✓

Note: Empty cells mean that no explicit recommendation was made in the guidelines.

[14] Applicable to all statins: do not prescribe in patients with active liver disease except for mild NAFLD; women who are pregnant/ breastfeeding; simvastatin 80mg (risk of myopathy); with gemfibrozil or drugs influencing cytochrome P450.

[15] Not explicitly stated in the guidelines, however, the SMC refers to NICE CG67 (2008) and CG181 (2014) and their recommendations to use a statin with low acquisition cost when conducting a health technology assessment (HTA) of statins and recommending their use within NHS Scotland (e.g. cited in SMC's HTA of Crestor (2011) [78].

[16] Information complemented with treatment summaries outlined on NICE Clinical Knowledge Summaries (CKS) and the British National Formulary [79], [80].

Table 2.7 Comparison of current and previous clinical guidelines for the secondary prevention of CVD following peripheral arterial disease and other CVD and procedures issued by NICE (England and Wales) and SIGN (Scotland) [49], [67]–[70], [72], [73], [75], [76], [78], [81]

	Peripheral Arterial Disease and Other CVD & procedures				
	England/Wales			**Scotland**	
Time period / clinical guidelines	2008 – 2013 CG67 (2008) TA210(2010) CG147(2012)	2013 – Present CG172 (2013) CG167 (2013) CG181 (2014)	2020 – Present NG185 (2020) **PCI*	2007 – 2014 SIGN97 (2007) SMC Appraisal 317 (2014)[17]	2014 – Present SIGN148 (2016) SIGN149 (2017)
Lipid-lowering therapy					
Simvastatin 40mg/day, indefinitely	✓			✓	
Atorvastatin 80mg/day (i.e. high-intensity statin therapy), indefinitely		✓	✓	All patients should be considered for more intensive therapy	✓
Consider lower dose or other statin type if potential drug interactions, high risk of adverse effects	✓	✓ *Consider patient preference	✓ *Consider patient preference	✓	✓
Use a statin of low acquisition cost	✓	✓		✓[18]	✓[17]
Antiplatelet therapy[19]					
PAD Clopidogrel 75mg/day or DAPT with low-dose aspirin and dipyridamole, indefinitely	✓	✓	Guideline not applicable to PAD		✓ or aspirin 75mg daily
Other CVD Aspirin 75 mg daily (alternatively, Clopidogrel if intolerance)	✓	✓	Guideline not applicable to other CVD	✓	✓
PCI DAPT prasugrel or clopidogrel +aspirin; if 75+ years consider ticagrelor or clopidogrel for up to 12months since index event		✓	✓	✓	✓

Note: Empty cells mean that no explicit recommendation was made in the clinical guidelines.

[17] Healthcare Improvement Scotland evaluated NICE Multiple Technology Appraisal Guidance 317 on prasugrel in PCI and noted the recommendations of NICE and the Scottish Medicines Consortium (SCM) are consistent (2014) [77].

[18] Not explicitly stated in the guidelines, however, the SMC refers to NICE CG67 (2008) and CG181 (2014) and their recommendations to use a statin with low acquisition cost when conducting a health technology assessment (HTA) of statins and recommending their use within NHS Scotland (e.g. cited in SMC's HTA of Crestor (2011) [78].

[19] Information complemented with treatment summaries outlined on NICE Clinical Knowledge Summaries (CKS) and the British National Formulary [79], [80].

2.4. Suboptimal medication use for the secondary prevention of CVD

Although there is substantial evidence that statin and antiplatelet therapies are clinically efficacious and cost-effective in reducing recurrent vascular events in high-risk individuals with established CVD, as presented in **Sections 2.2.2-2.2.3**, numerous studies have shown that their use, particularly in the long-term, remains suboptimal. Addressing the challenges in the secondary prevention of CVD and implementation of evidence-based clinical guidelines is essential to improve the management of disease and decrease the high burden and associated costs of CVD that have been outlined in **Section 2.1.2**. However, knowledge regarding the underlying reasons for suboptimal drug use at different treatment stages is limited and fragmented [82], [83]. The next chapter (**Chapter 3**) provides an in-depth overview of the published research to date examining the rates, trends and determinants of suboptimal statin and antiplatelet therapy use for the secondary prevention of CVD across different treatment stages, countries and time periods.

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3

Systematic literature review of studies estimating the rates and determinants of statin and antiplatelet therapy use for the secondary prevention of ASCVD

Summary

This chapter constitutes the first systematic literature review to investigate both the proportions and determinants of statin and antiplatelet therapy use for the secondary prevention of ASCVD, specifically among patients who experienced myocardial infarction and ischaemic stroke, at every single stage of the treatment pathway (i.e. prescription on discharge, initiation of treatment following discharge, adherence to the daily medical regimen that was prescribed by the treating physician, and the discontinuation of treatment). An electronic search strategy was developed, which yielded 34,842 records from EMBASE, MEDLINE, CINAHL and PsycINFO. Following the removal of duplicates (n=5,390), and screening and exclusion by abstracts and titles (n=29,452), 398 publications underwent full-text review. Of these, 47 studies met the eligibility criteria and were included for data extraction. The quantitative pooling and qualitative summary of proportions of medication use at all treatment stages showed that the proportions of individuals using statin and antiplatelet therapies have been increasing over time. However, treatment gaps remained at every stage of the treatment pathway: the average rate of statin prescription on hospital discharge was 87%, followed by 67% for statin initiation. The average proportion of individuals classified as being adherent while on statin treatment was 75%, while statin discontinuations rates within 12 months since initiation averaged 21%. Antiplatelet therapy prescriptions, specifically aspirin, among MI patients have been consistently high since the early 2000s, averaging 93%. Initiation rates of any antiplatelet therapy among MI patients ranged from 39% to 94%, and between 67% and 81% of initiators were considered adherent in the first year since treatment initiation. Antiplatelet therapy discontinuation rates within 24 months since initiation ranged from 22% to 36%, depending on calendar period and country.

The review also identified multiple patient and provider-related risk factors that were associated with suboptimal statin and antiplatelet therapy use at different stages of the treatment pathway. Amongst these, women were less likely to receive statin therapy and antiplatelet therapy (except for aspirin) on discharge, and less likely to initiate statin, but also had a lower risk of both statin and antiplatelet therapy discontinuation. A U-shaped association was observed for risk of statin discontinuation with age, where elderly individuals aged 69 years or older and those younger than 64 years were at greater risk. Prior CVD and presence of specific physical comorbidities were associated with suboptimal statin use at various treatment stages. The factors identified need to be considered in the development of policies that aim to address the treatment gap and improve the management of ASCVD.

3.1. Background

Previous systematic reviews of the published literature have identified consistent evidence that adherence to and persistence with cardioprotective treatment is suboptimal, and have collated existing evidence on the underlying factors for suboptimal use (see **Appendix A.1**). Fifteen systematic reviews were retrieved (published up to 10 April 2018) that examined the association between specific factors and statin and antiplatelet therapy use for the secondary prevention of CVD. Of these, one review studied factors associated with statin or antiplatelet therapy prescription and two reviews investigated factors associated with statin or antiplatelet therapy adherence, while the remaining twelve reviews focussed on adherence within a single drug class (i.e. statin adherence (n=11) and aspirin adherence (n=1)).

Determinants influencing the prescription of both statin and antiplatelet treatment were assessed in one systematic review that limited the analysis to socioeconomic factors only [1]. In the case of adherence, some statin-related reviews investigated the role of specific determinants of adherence, including gender and ethnicity [2], and urban-rural factors [3]. The majority of studies analysed statin adherence in specific populations, for example among elderly patients aged 65 years or older [4], patients with hypercholesterolemia [5], studies based on US data only [6]; as well as in specific types of study designs, such as qualitative [7], [8] or prospective studies like clinical trials [9]. Four studies evaluated a broad range of determinants of statin adherence reported in publications up to 2012 [10]–[13], however, few studies summarised rates of statin use. In the case of antiplatelet therapy, two systematic reviews of statin adherence outlined above also examined barriers to aspirin adherence [9], [12], in addition to a third review which assessed adherence to DAPT specifically after coronary stenting [14].

Previous systematic reviews typically limited their analyses to a single treatment stage, such as prescription of or adherence to cardioprotective drugs, or specific types of determinants. Substantial variations in search strategies and study eligibility criteria create further barriers to the analysis of common determinants across the entire treatment pathway. As a result, this study sought to be the first systematic review to investigate the relevance of both patient- and healthcare provider-related characteristics to statin and antiplatelet therapy use for the secondary prevention of CVD at every stage of the treatment pathway, including the prescription, initiation of, adherence to and persistence with pharmacotherapies. By applying a unified search strategy aimed at the identification

of a broad range of determinants across all treatment stages, this review is able to expand the comparison and identification of recurrent drivers of suboptimal medication use across different steps of the treatment pathways.

Previous studies have reported significant variations in statin use between individual healthcare providers and settings (e.g. Jortveit and Halvorsen, 2017 [15]). The review presented in this chapter focuses on publications with larger study samples of individual participant data (i.e. 10,000 individuals or more), in order to capture (1) regional and national trends and (2) more generalisable populations as opposed to populations derived from discrete settings. Furthermore, clinical trials and other study designs that may not reflect real world practices (e.g. due to structured monitoring of adherence) were excluded from this review. For the purpose of this study, the review focused on adult populations aged 18 years or older and specifically on patients with myocardial infarction (MI) and stroke, as international clinical guidelines published from inception have explicitly recommended long-term low-density lipoprotein (LDL) cholesterol-lowering and antiplatelet treatment in these patient categories for the secondary prevention of cardiovascular disease. Furthermore, this study extends previous systematic reviews that included publications up until the year 2016 by including published literature up to 2018 and summarising statin and antiplatelet therapy utilisation rates across different treatment stages to investigate the degree of and global trends in cardioprotective medication use for the secondary prevention of ASCVD. The findings are presented by type of drug class, where **Part A** presents findings on statin rates and determinants at every stage of the treatment pathway (i.e. prescription, initiation, adherence and persistence), followed by **Part B,** which focusses on antiplatelet therapy in a similar structure, and subsequently reviewed and summarised in **Section 3.6** (i.e. discussion) and **Section 3.7** (i.e. conclusions).

3.2. Systematic literature review: methods

3.2.1. Search strategy

MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and PsycINFO databases were searched from inception to 7 June 2018. The search was restricted to studies published in English and tagged as human studies, however no geographical restrictions were applied to study settings. A PROSPERO research protocol (CRD42018117179) was published on 29 November 2018, outlining the Patient

Intervention Comparison Outcome (PICO) search methodology and strategy for this study:

(P) Individuals with clinical or self-reported diagnosis of MI or stroke, excluding children and adolescents under 18 years of age;

(I) Individuals with a history of MI or stroke using (i.e. being prescribed, initiating, adhering to or persisting with) statin and/or antiplatelet therapy for the secondary prevention of cardiovascular disease;

(C) Individuals with a history of MI or stroke, who do not use (i.e. were not prescribed or did not initiate, adhere or persist with) statin and/or antiplatelet therapy;

(O) Any measure of prescription, initiation, utilisation, persistence and adherence rates reported separately for statin and antiplatelet therapy; as well as factors (i.e. barriers and facilitators) that are associated with statin and/or antiplatelet therapy uptake and use.

The review is based on a broad electronic search strategy, including terms that describe the interventions, outcome measures, individuals' characteristics and disease areas, and was developed in consultation with an information specialist[20]. Search terms include for example: statins; aspirin; prescription; initiation; adherence: persistence; socioeconomic status; lifestyle; cardiovascular diseases, and searched in MeSH subject heading fields, title fields, abstracts and substance fields. The search strategy is presented in full in **Appendix A.2**.

3.2.2. Study eligibility criteria

Following the exclusion of duplicate records, titles, abstracts and full texts were screened. Studies were excluded at each stage of the screening process if they did not meet the following eligibility criteria:

Inclusion criteria

- Peer-reviewed, full-text, English language research
- Any type of observational study
- Studies with a sample size of 10,000 individuals or more

[20] Nia Roberts, Outreach Librarian, Konwledge Centre, Bodleian Libraries, University of Oxford.

- Studies that report interventions and outcomes of interest (see **Section 3.2.1**) specifically for individuals with a history of MI or stroke.

Exclusion criteria

- Randomised controlled trials (RCTs)
- Study data on children and adolescents under 18 years of age
- Studies that report outcomes of interest for populations different than myocardial infarction and ischaemic stroke (e.g., haemorrhagic stroke and/or transient ischaemic attacks (TIAs))
- Abstracts, conference abstracts, poster presentations, editorials.

In addition, reference lists of all included studies were screened to identify and cross-reference any further eligible research not captured in the database search. Studies using the same dataset were retained for data extraction. In the case that both dataset and time periods overlapped, only one of the studies was used for the summary of quantitative results. I completed the study screening and selection to identify studies meeting all eligibility criteria for full-text review. A second reviewer (AS)[21] independently assessed a random subsample of 10% (i.e. 38 studies) of the potentially eligible studies retrieved for full text review.

3.2.3. Quality assessment

The quality of individual studies was formally assessed using a reduced version of Downs and Black's 27-item checklist for the assessment of the methodological quality of randomised and non-randomised studies of health care interventions [16] (please see **Appendix A.3** for an overview of the reduced checklist). The reduced checklist, which was modified to specifically assess the quality of observational studies and used in previous literature [17], contains nine 'yes'-or-'no' questions across three sections, excluding sections and questions from the original checklist that specifically apply to the assessment of randomised controlled trials. Each section consists of two to four questions to help assess the (1) quality of reporting, (2) external validity (i.e. generalisability of study findings and risk of selection bias due to sampling), and (3) internal validity (i.e. risk of measurement, validity of causality, information bias (specifically treatment of missing data) and confounding bias).

[21] Anna Strampelli, Researcher, Department of Life Sciences, Imperial College London.

Based on the reviewers' examination of the overall risk of bias, a numeric score out of a possible 9 points is calculated to classify studies as being of good (9-7), fair (6-4) or poor (3-0) quality. The quality assessment tool was applied to all studies meeting the inclusion criteria by the main reviewer, and a second reviewer (MK)[22] independently performed the assessment for 10% of studies (i.e. four studies). Disagreements on the overall quality assessments (i.e. at the three-category level described above) were resolved through discussion. Where applicable, the findings of the quality assessment were used in sensitivity analyses to report findings following the removal of studies of low quality.

3.2.4. Data extraction

For studies meeting the eligibility criteria, detailed information was extracted on: source (e.g. author, year of publication); study population and setting (e.g. population description and source, location, type of setting); study methodology (e.g. aims, design); participant demographics and baseline characteristics; outcome measures and times of measurement; results (e.g. level of adjustment, response rates, missing data); information for assessment of quality of reporting and risk of bias. Please see **Appendix A.3** for the complete list of items included in the data extraction form.

I extracted data from each selected study into a standardised, pre-piloted form (the form was piloted on three studies) in order to assess the quality of studies and to allow synthesis of evidence. A second reviewer (MK) independently extracted data from a 10% random subsample of studies (i.e. four studies).

3.2.5. Data analysis

Quantitative synthesis

The studies were grouped on the basis of (1) the type of intervention (i.e. statin or antiplatelet therapy) and (2) the type of outcome (described below) and corresponding metric (e.g. measure of proportions of medication use or identification of factors associated with intervention use). Studies contributed to one of the following five outcomes based on the following definitions, irrespective of the terms used in studies to describe their outcome measure (e.g. some studies use the term 'adherence' interchangeably with 'persistence').

[22] Mi Jun Keng, DPhil Candidate, Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford.

- **Prescription on discharge** refers to patients being discharged from hospital and provided with/prescribed a supply of statin and/or antiplatelet therapy by hospital staff on (the day of) discharge.
- **Initiation** describes the first prescription fill/dispense/use of statins and/or antiplatelet therapy within a specified time period (usually no longer than 180 days) since index discharge.
- **Adherence** is defined as the degree to which patients follow the agreed recommendations and prescription instructions from a healthcare provider. It is measured using the medication possession ratio (MPR) or the proportion of days covered with medication (PDC), which calculate the ratio of the number of days the patient is covered by the medication in a period to the total number of days in the period or the total number of days in the period that the patient is eligible to have the medication on hand.
- **Persistence** refers to the act of continuing and refilling treatment over time. Persistence can be defined as the time from the start of medication use to discontinuation of treatment, where discontinuation can either be measured as (1) the start of the first continuous medication treatment gap of an arbitrary number of days (e.g. 60 days) since initiation or (2) as the proportion of individuals not dispensing/not filling prescription/not reporting the use of a drug at a specific point in time or a specific number of times in a given time period since initiation.
- **Utilisation** refers to patients dispensing/filling prescriptions/reporting the use of statins and/or antiplatelet therapy at a non-specified point in time since index discharge. For example, the number of patients in a given year that use a specific drug.

Quantitative synthesis of proportions of medication use

Studies were included in the quantitative summary of results if mean rates of the above-defined outcomes were reported. Rates of non-prescribing, non-initiation, and non-adherence were re-calculated as rates of prescribing, initiation and adherence by subtracting the reported rate from the whole population (i.e. 1-A). Where rates were reported by subpopulation groups (e.g. age, gender) or across different calendar years,

average rates for the overall population or time period weighted by size of the group were manually calculated (if possible) to allow for a more uniform comparisons between studies.

A quantitative summary of mean proportions of medication prescription, initiation, adherence and persistence was provided if at least two studies reported results for the same outcome and used the same outcome measure (e.g. studies measuring adherence via the PDC vs. the MPR). If two or more studies used identical datasets and overlapping time periods for the same outcome measure, only one of the studies (i.e. the study reporting more recent time periods or providing the largest amount of information) was included in the analysis of proportions of medication use. As all studies estimating adherence in this review used the same threshold of ≥ 80% for the proportion of prescribed doses taken to indicate adherence, the rates were comparable across studies. In the case of persistence, results were grouped and analysed by time to discontinuation as defined in the respective studies, irrespective of differences in the length of treatment gaps.

Quantitative synthesis of predictors

Individual estimates of effect sizes were pooled using random-effects meta-analysis with study sample size weighting in Stata version 15. The I^2 statistic was used to evaluate the proportion of variance across the studies attributable to study heterogeneity. Quantitative pooling of predictors corresponding to one of the above-defined outcomes was performed if there were at least three studies that investigated the same or similar predictor using the same data format (e.g. age measured as categorical vs. continuous data) for the same outcome measure (e.g. odds ratio, risk ratio).

Where two or more studies used identical datasets and time periods for the same outcome measure, the study providing the most information was included. Studies that presented data in subgroups only and conducted analyses of distinct populations were treated as separate cohorts within the same publication and not combined. If cohorts were stratified by age, then effects and sample sizes of the different strata were included as separate effects in the meta-analysis. Where studies used a reference group that was different to the one reported in the majority of studies and also provided information on case numbers, the unadjusted crude rate was manually calculated.

Qualitative synthesis of proportions and predictors

If proportion and predictor data did not meet the criteria for quantitative pooling, pooled data estimates had high levels of heterogeneity ($I^2 > 50\%$) or could not be synthesised conceptually, a qualitative synthesis was performed.

Sensitivity analysis

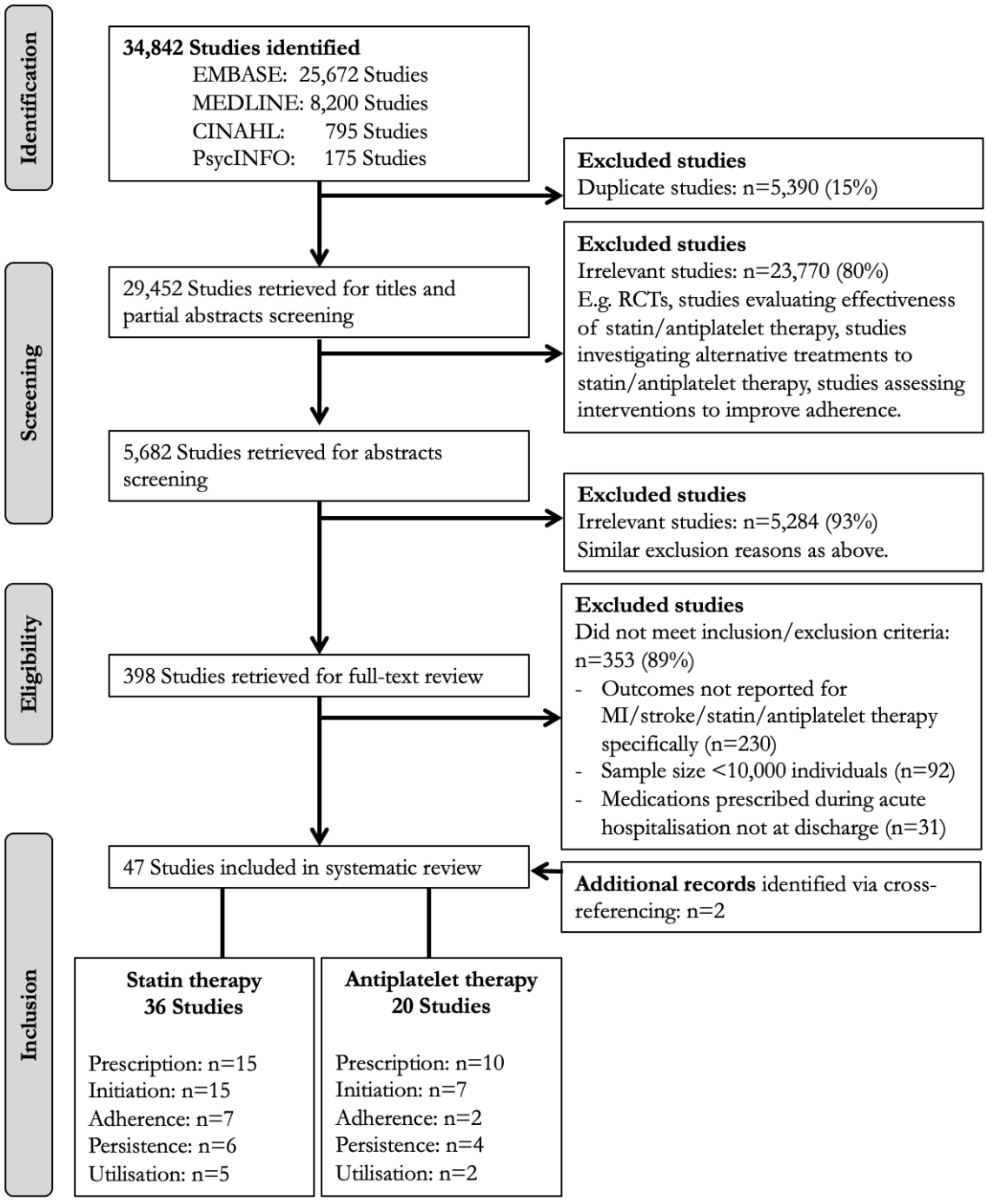
As none of the publications included in the systematic review were judged to be of poor quality based on the quality assessment using the reduced version of Downs and Black's 27-item checklist (i.e., score of 0 to 3; see **Section 3.2.3**), no sensitivity analysis was performed by excluding studies with a low quality score.

3.3. Systematic literature review: results

3.3.1. Search strategy

The systematic search yielded 34,842 records (25,672 from EMBASE; 8,200 from MEDLINE; 795 from CINAHL; and 175 from PsycINFO), of which 5,390 (15%) duplicates were removed. Following screening and exclusion by abstracts and titles, 398 studies were included in the full-text review, of which 47 met all inclusion criteria. Two additional studies were identified and included following review of the reference lists of included articles. In total, 47 individual publications were included in the systematic review (i.e. 45 derived from the electronic search and 2 studies identified via cross-referencing), some of which provided information on both interventions of interest (i.e. statin and antiplatelet therapy), leading to a total of 36 (respectively 20) studies examining rates and/or predictors of statin (respectively antiplatelet) therapy use. These studies were then grouped into one or more outcome categories: prescription on discharge, initiation, utilisation, adherence and persistence. See **Figure 3.1** for a complete overview of the search results.

Figure 3.1 Overview of the study selection process and search results[23]



[23] Please note that the total number of included studies across all outcome measures is greater than the total number of studies reported by medication type and the total number of studies included in the review. This is because some studies provided information on both statin and antiplatelet therapy, as well as more than one outcome measure.

3.4. PART A: STUDIES REPORTING RATES AND DETERMINANTS OF STATIN USE

3.4.1. Overall characteristics and methods of included studies

The review consists of 36 individual retrospective studies using primarily patient-level data, with only two studies using health board or hospital-level summary data [15], [18]. The characteristics of the included studies are summarised overall in **Table 3.1** and by outcome measure in **Appendices A.4** and **A.5**, **Tables A.5-A.9**. Studies that reported findings for multiple outcome measures (n=12) or countries (n=2) contributed separate cohorts to the analyses, thus increasing the total number of cohorts from which data was extracted to 50 (**Figure 3.1**).

Most studies (n=21, 55%) were based on individuals resident in Europe, with the remaining studies being located in North America (n=16, 42%) and one in Asia[24]. The median sample size across all studies was 34,874 (interquartile range: 19,969 to 70,791), with almost a third of studies (n=11) capturing information on more than 50,000 individuals. The majority of studies (n=31, 86%) sampled entire national populations or general, but not necessarily representative, adult populations; other studies focused on elderly individuals aged 65 years or older. Only six studies (16%) investigated statin use in stroke populations. Cohort follow-up information was collected for a full year at a minimum and frequently over several years, the median length being five years (interquartile range: three to eight years). Rates of statin use at different treatment stages were reported by all studies but one, with approximately half of studies also investigating associations between a range of factors, such as patient or provider characteristics, and one of the five outcome measures. In total, 31 studies[25] contributed results (either for a single or multiple outcome measures) to the main summary of estimates. Further details on characteristics and analytical methods of studies included in the quantitative synthesis are described by outcome measure in **Appendix A.5**, **Tables A.5-A.9**.

[24] One study reported findings for three different regions, therefore the total number of studies amounts here to 38 instead of 36 [19].
[25] Four studies were excluded due to the use of identical datasets and time periods.

Table 3.1 Characteristics of studies reporting on rates and determinants of statin use included in the systematic review by study quality

Study characteristics	All studies	Study quality[26]	
		Good	Fair
Number of studies (N contributing to quantitative summary) **Total number of cohorts due to some studies reporting multiple outcome measures or countries*	36 (32) **50*	25 (23)	11 (9)
Region			
Europe	21 (19)	16 (13)	5 (5)
North America	16 (13)	10 (8)	6 (4)
Asia	1 (1)	1 (1)	0 (0)
Study population			
All adults	29 (27)	22 (21)	7 (6)
Elderly	7 (4)	3 (1)	4 (3)
CVD condition			
MI	30 (26)	19 (17)	11 (9)
Stroke	6 (5)	6 (5)	0 (0)
Sample size			
Median (IQR)	34,874 (19,969, 70,791) (34,735 (19,368, 72,352))	33,421 (16,433, 59,824) (32,599 (16,433, 59,117))	35,012 (21,077, 57,888) (32,749 (18,345, 39,344))
≥ 50,000 participants	11 (9)	8 (7)	3 (2)
10,000 – 49,999 participants	25 (22)	17 (16)	8 (7)
Outcome measure			
Prescription on discharge	15 (14)	12 (12)	3 (2)
Initiation	15 (13)	10 (10)	5 (3)
Adherence	7 (6)	4 (4)	3 (2)
Persistence	6 (5)	3 (2)	3 (3)
Utilisation[27]	5 (0)	2 (0)	3 (0)
Determinants reported			
Yes	19 (0)	14 (0)	5 (0)
**Some studies report multiple outcomes*:			
Prescription on discharge	7 (0)	7 (0)	0 (0)
Initiation	5 (0)	3 (0)	2 (0)
Utilisation	0 (0)	0 (0)	0 (0)
Adherence	4 (0)	2 (0)	2 (0)
Persistence	4 (0)	3 (0)	1 (0)

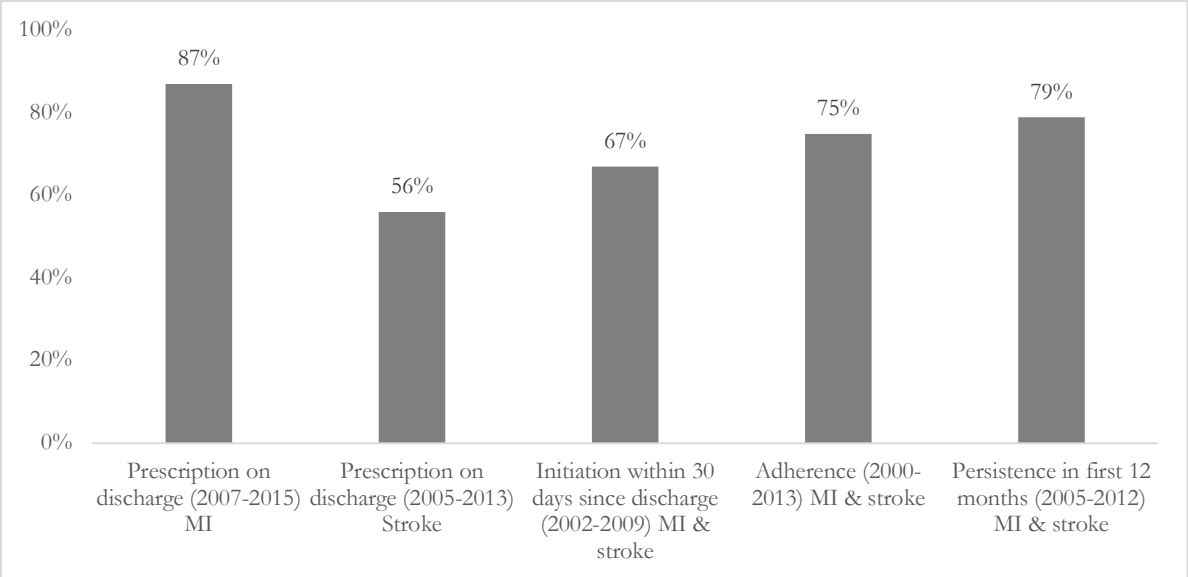
[26] No study was classified as of 'poor quality'.
[27] Summaries of study characteristics and findings are reported in **Appendix A.6**.

3.4.2. Average proportion of statin use at different stages of the treatment pathway

The quantitative pooling of proportions of statin use at different stages of the treatment pathway highlights that there are treatment gaps at every single step of the pathway and that investigating or targeting a single stage is not sufficient to address the suboptimal use of statin therapy (see **Figure 3.2**). The average rate of statin prescription on hospital discharge is 87%, followed by 67% for statin initiation within 30 days since discharge. The average proportion of individuals classified as being adherent while on statin treatment is 75%, and the average proportion of individuals continuing treatment in the first 12 months since initiation is 79%, meaning that 21% of individuals discontinued therapy. **Sections 3.4.4-3.4.8** describe the characteristics of the included studies and detailed findings by treatment stage.

In addition, five studies investigated rates of statin utilisation among individuals with a history of myocardial infarction (MI) or stroke in a specific calendar year. As these study populations combine individuals that are at different stages in their treatment journey (e.g. recently discharged for MI vs. individuals who experienced an MI more than five years ago), it is difficult to analyse and contextualise the reported proportions of statin utilisation. The summary of characteristics and findings of studies investigating statin utilisation can be found in the **Appendix A.6**.

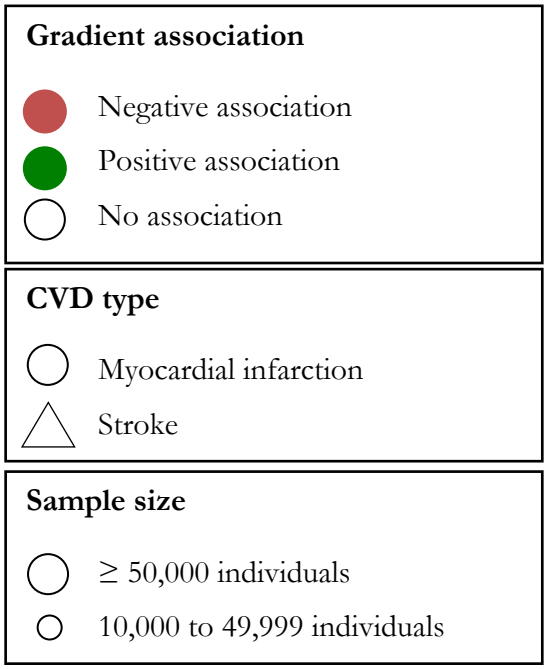
Figure 3.2 Average proportions of statin use at different stages of the treatment pathway



3.4.3. Overview of determinants associated with statin use at different stages of the treatment pathway

The pooling of risk factors by treatment stage and type of risk factor shows that a number of demographic, socioeconomic, clinical, provider and lifestyle factors are significantly associated with an increased risk of suboptimal prescription on discharge, initiation, adherence to and persistence with statin therapy (**Figure 3.3**). Furthermore, some risk factors, such as gender[28], play a significant role at every stage of the treatment pathway. **Figure 3.3** (below) provides a high-level overview of specific patient- and provider-related factors, as well as calendar years, and shows how these are related to the use of statin treatment at different stages of the pathway. A more detailed visualisation, which further breaks down categories such as history of CVD and medication use into the respective associations with specific conditions and medication types, can be found in the **Appendix A.7**. Furthermore, **Sections 3.4.4-3.4.8** in this chapter describe the characteristics of studies and detailed findings by treatment stage.

Key to **Figure 3.3**[29]



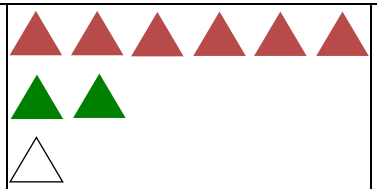
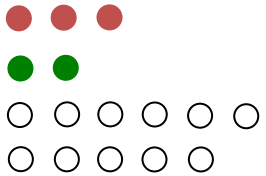
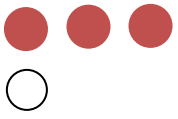
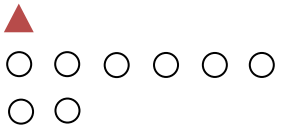
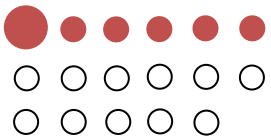
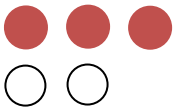
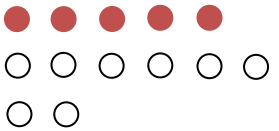
[28] Please note that the term gender (i.e., socio-economic, family role nuances related to sex) is used interchangeably with sex (i.e., biological risk) from here onwards.

[29] Outcomes from studies that performed separate regression analyses for multiple datasets or different population groups were treated as different cohorts.

Figure 3.3 Overview of factors associated with statin use at different stages of the treatment pathway

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Demographic				
Women (vs. men)	▲ ● ●	● ● ● ●	●[30] ●[31]	● ▲
Older age groups, i.e., 69 years or older (vs. < 69 years)/increasing age in years	▲	● ○ ○	○	● ● ●
Younger age groups, i.e., 64 years or younger (vs. > 65 years)				● ● ●
Black/African American ethnicity/race (reference: White)		● ● ○	● ●	
Asian ethnicity/race (reference: White)[32]		●	○ ○	
Other ethnicity/race (reference: White)[33]	▲	○ ○ ○	● ●	
Socioeconomic status				
Lower (household) income/ low income/ low-income subsidy/Medicare Part D/Dual Medicare and Medicaid coverage[34]		● ● ○	●	

[30] Please note that the association between being female and experiencing greater odds of adherence was only significant in the case of White women compared to White men. Black, Hispanic, and Asian women were each less likely to be adherent compared respective category of men, though statistical significance was not reported.
[31] Please note that the study focussed on adherence to high-intensity statin therapy vs. low/medium-intensity statin therapy.
[32] Initiation: statistically significant for female Asians only.
[33] 'Other' is here defined as any ethnic group except for 'White'.
[34] The results refer specifically to US patients with dual Medicare and Medicaid coverage with lower socioeconomic status, however, are as a result covered by federal health insurance and therefore do not have to pay any prescription medication-related charges.

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Clinical history				
Previous history of CVD[35]				
Physical comorbidities[36]				
Depression				
Mental health problems (other than depression)/Low mood				
Operations/Procedures				
Prosthetic heart valve				
In-hospital revascularisation procedures, angiography (during index hospitalisation), stent during index hospitalisation				
Cardiac surgery (during index hospitalisation)				

[35] Types of CVD reported in studies: myocardial infarction, stroke, coronary heart disease, coronary artery disease, cerebrovascular disease, atrial fibrillation, (congestive) heart failure, cardiac dysrhythmias, carotid stenosis, peripheral arterial disease, hypertension, dyslipidaemia. For a more detailed breakdown of associations, please see **Appendix A.7, Figure A.1**.

[36] Types of physical comorbidities reported in studies: diabetes, chronic kidney disease, renal disease, dialysis, chronic pulmonary disease, COPD, malignancy, cancer, dementia, rheumatoid arthritis, any previous hospitalisations, Charlson Comorbidity Index (reference: zero). For a more detailed breakdown of associations, please see **Appendix A.7, Figure A.1.**

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Medication use[37]				
Increasing number of medications taken/polypharmacy		● ●	●	
Previous lipid-lowering medication use	▲			▲
High-intensity statin (vs. low intensity)			● ●	●
Moderate-intensity statin (vs. low intensity)			○	●
Acute care				
Hospitals with higher numbers of annual stroke discharges	▲			
Hospital type: academic teaching status (vs. non-academic)	▲			
Increasing length of hospitalisation		●		● ○
Aftercare/Post-hospitalisation				
Post-MI Cardiac rehabilitation			●	
Cardiologist (vs. physician care)				● ○
Increasing number of outpatient visits			● ●	△
Institutional living (vs. living at home)				▲
Lifestyle/Behaviour				
Smoking	▲			
Alcohol abuse		●		
Time effects				
Later calendar years	▲	●		● ● ○

[37] Please see **Appendix A.7, Figure A.1** for a breakdown of types of medications and changes in statin intensity.

3.4.4. Statin prescription on discharge

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.4.4.1. Rates of statin prescription on discharge

The proportion of individuals being issued with a statin prescription on hospital discharge ranged from 30.8% to 91% for MI patients (**Figure 3.4**) and from 34.5% to 79.2% for stroke patients (**Figure 3.5**). In the case of MI patients, the wide variation in prescription rates can be partly explained by changes in prescribing patterns over calendar time, influenced by the increasing publication of clinical trial results and changes in clinical guidelines and recommendations for the use of statins in the secondary prevention of CVD[38]. For instance, the average reported prescription rates between 1994 and 2006 were 44%, increasing to an average of 87.2% for the time period 2007-2015.

Calendar time effects were also found to be significant in the case of stroke, as reported in a study investigating improvement in adherence to performance measures in acute ischaemic stroke care in China [20]. Rates increased from 42.6% in 2007/2008 to 66.3% in 2012/2013. However, time effects only partly explained the wide variation in prescribing practices among stroke patients. Rates in Sweden were almost half of those reported in the US for a relatively similar time period (i.e. 2005-2006 vs. 2005-2007). Some heterogeneity will have arisen due to the characteristics of the sample and study design. For instance, proportions for the U.S. were derived from hospitals that were part of the Get-With-The-Guidelines-Stroke in-hospital programme for stroke care improvement, which promotes consistent adherence to the latest scientific treatment guidelines [21].

[38] UK example: 1998: Joint British recommendations on prevention of coronary heart disease in clinical practice recommends all patients with CHD and LDL-C ≥ 3mmol/l use statins; 2000: the Coronary Heart Disease National Service Framework recommends statins for all patients with CHD regardless of LDL-C level; 2006: NICE Technology Appraisal (TA94) approves statins for the prevention of cardiovascular events; 2007: NICE CG48 recommends statin use in both primary and secondary care for patients following a myocardial infarction; 2008: NICE CG67 recommends Simvastatin 40mg and statins with a low acquisition cost for primary and secondary prevention of CVD; 2014: NICE recommends high-intensity statin use for the secondary prevention of CVD.

Figure 3.4 Proportion of MI patients being issued a statin on discharge (1994-2015) [15], [19], [22]–[31]

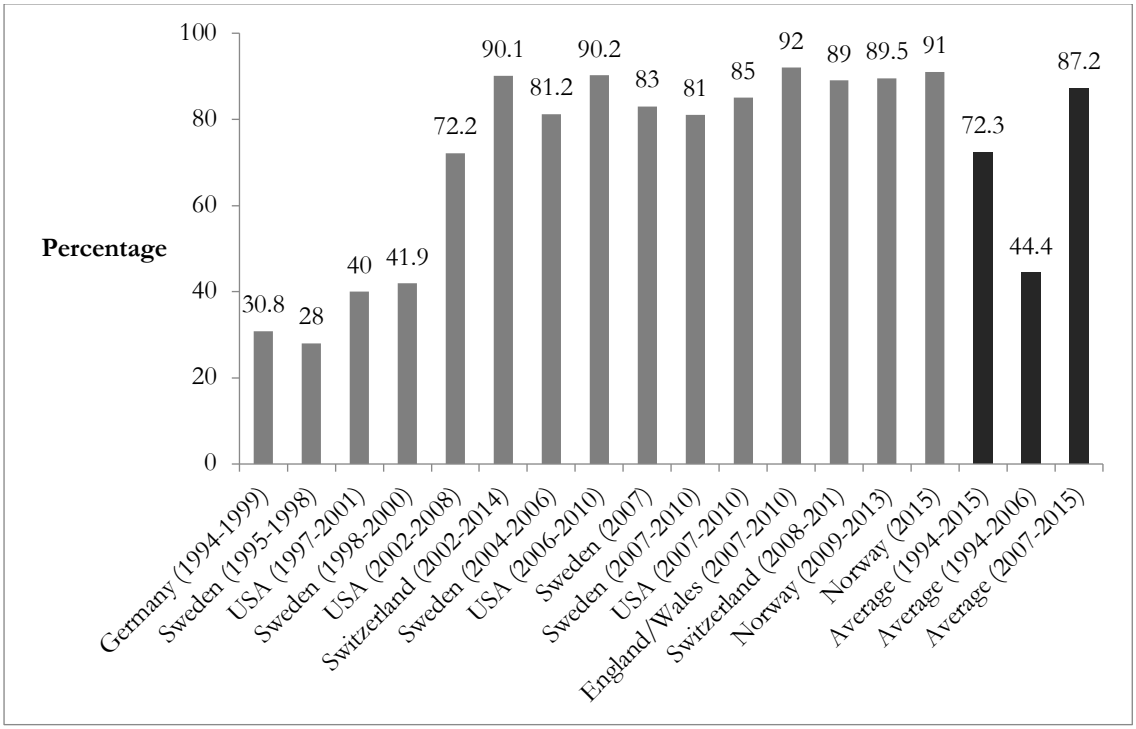
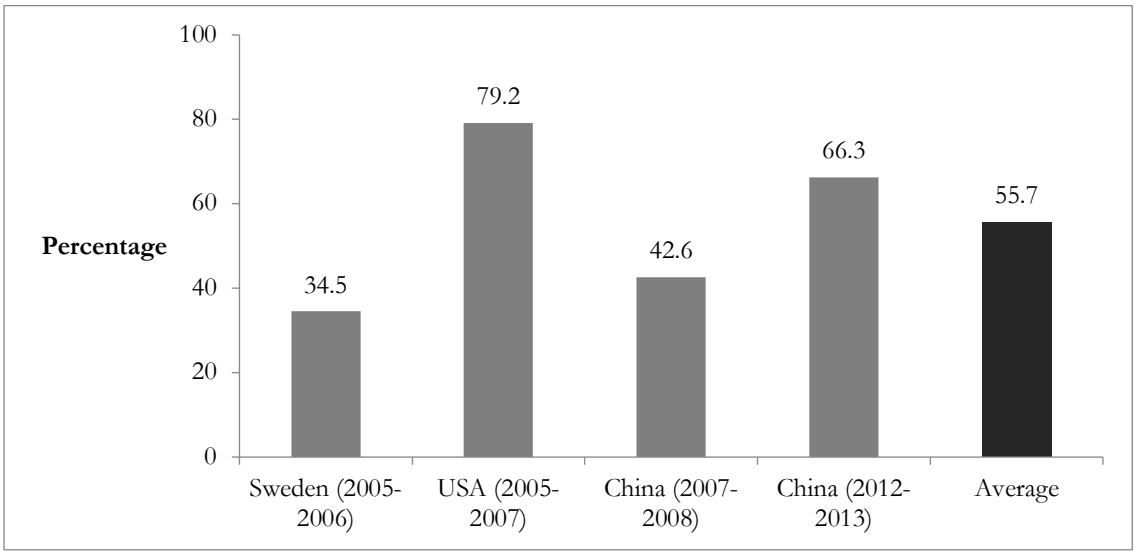


Figure 3.5 Proportion of stroke patients being issued a statin on discharge (2005-2013) [20], [21], [32]



3.4.4.2. Determinants of statin prescription on discharge

Gender

Three studies based in the US (n=173,284), Sweden (n=48,118), and Switzerland (n=21,620) examined gender as a predictor of statin prescription, and found that compared to men, women were less likely to be prescribed treatment on discharge after hospitalisation for MI (OR 0.81, 95% CI 0.77-0.96), STEMI (OR 0.67, 95% CI 0.56-0.81) and stroke (OR 0.86, 95% CI 0.85-0.88) [21], [28], [29]. A quantitative pooling of the individual estimates of the effect sizes was attempted, yielding an overall odds ratio of 0.86 (95% CI 0.84-0.88), however, the I^2 value of 84.2% indicated high levels of between-study heterogeneity that could not be explained by sampling error alone (**Appendix A.8, Figure A.2)**.

Age and Race

One large stroke registry study from the US (n=173,284) reported a negative association between age and statin prescriptions on discharge, with elderly patients being less likely to be prescribed statins (OR 0.93, 95% CI 0.91-0.94) [21]. All other studies included age in their regression models as an adjustor and did not report effect sizes. The same study also examined the relationship between race and prescribing, showing that White patients were less likely to receive statins than Americans of other races (OR 0.87, 95% CI 0.82-0.92).

CVD type and clinical history

Two studies provided information on the association between patients' clinical history and statin prescribing on discharge. One US study compared STEMI to NSTEMI patients (n=72,352) who were treated at one of 237 hospitals participating in the Get-With-The-Guidelines-CAD in-hospital programme and found that STEMI patients were almost twice as likely to be discharged on statin than those diagnosed with NSTEMI (OR 1.71, 95% CI 1.56-1.86) [30].

Another US study examining statin prescriptions at hospitals participating in the counterpart in-hospital programme for stroke (GWTG-Stroke) showed that stroke patients (n=173,284) with a previous history of stroke, CAD, MI, AF, PVD or a prosthetic heart valve were less likely to receive statins on discharge than those without a history of such events, while those with a history of hypertension, dyslipidaemia, carotid stenosis, as well as those taking cholesterol-lowering treatment at admission and smokers, were more likely to be discharged on statin therapy than those without the listed comorbidities or

prior use of cholesterol-lowering drugs [21] (please see **Appendix A.9, Table A.10** for effect sizes).

Outpatient vs. inpatient myocardial infarction onset

One longitudinal study from Switzerland spanning twelve years (n=33,421) investigated the relationship between the location of acute MI onset and subsequent prescription on hospital discharge, and found that patients who were admitted to hospital for other reasons and subsequently experienced an in-hospital MI were half as likely to receive statins than those being admitted to hospital with an outpatient-onset MI (OR 0.51, 95% CI 0.41-0.63) [22].

Hospital characteristics

Several hospital characteristics evaluated in a large stroke registry study from the US (n=173,284) were associated with a lower likelihood of statin prescription on discharge, including hospitals with academic teaching status (vs. non-academic hospitals: OR 0.74, 95% CI 0.67-0.83), lower annual number of stroke discharges (i.e. comparing hospitals with a total of 0-100 stroke discharges to those with more than 301 discharges: OR 0.67, 95% CI 0.57-0.78; although no difference was observed when comparing hospitals with 101 to 300 annual stroke discharges to those with more than 301 discharges), as well as region (i.e. hospitals located in Midwest and South US compared to those in the West). Hospitals with a higher number of hospital beds were slightly more likely to discharge their patients on statin (OR 1.03, 95% CI 1.00-1.06 per 100 bed unit change) [21]. Please see **Appendix A.9, Table A.10** for a detailed overview of the effect sizes.

Management initiatives and publication of clinical trial results

Two publications studied how external factors may influence statin prescription rates among stroke patients after adjusting for patient and hospital-related factors. For instance, one study (n=31,777) assessed the introduction of nationwide stroke quality initiatives in 2009 to improve adherence to guideline-recommended ischaemic stroke performance metrics in China and reported that the same hospitals assessed over two separate time periods were almost three times as likely to prescribe statins on discharge in the later than in the earlier time period (OR 3.05, 95% CI 2.73-3.40; comparing all hospitals in general: OR 2.72, 95% CI 2.02-3.65) [20]. Another U.S. study used patient data (n=173,284) from hospitals participating in the Get-With-The-Guidelines-Stroke in-hospital programme for stroke care improvement, which promotes consistent adherence to the latest scientific

treatment guidelines [21]. No evidence was found that nationwide trends in discharge statin treatment changed in response to the dissemination of The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial results (OR 0.99, 95%CI 0.98-1.01).

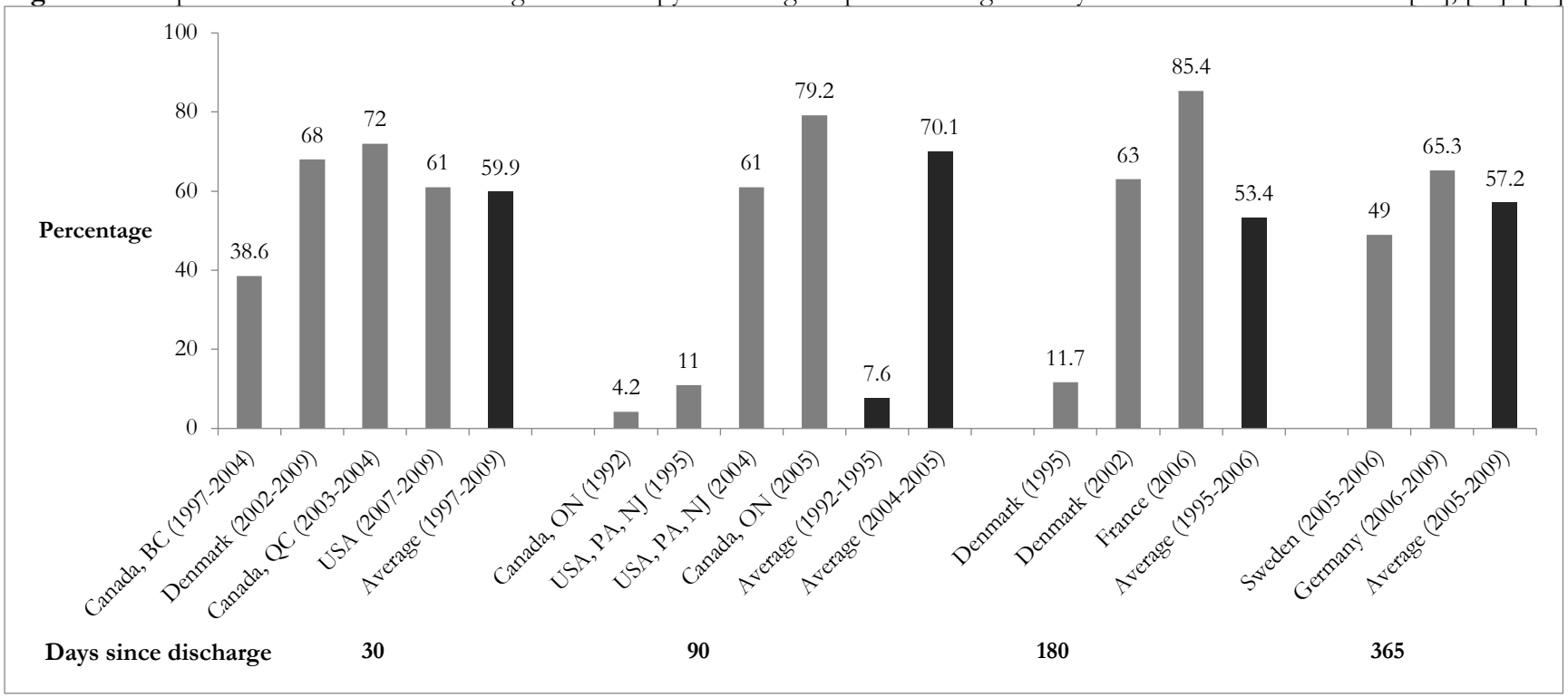
3.4.5. Statin initiation

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.4.5.1. Rates of statin initiation

The proportion of individuals initiating statin treatment within 30 days since hospital discharge ranged from 38.6% to 72%. Studies that allowed for a time period of 90 or 180 days since discharge reported initiation rates from 4.2% and 11.7% in the 1990s to 79.2% and 85.4% in the years 2005/6, respectively. Two studies assessed the number of initiations within a year since discharge and observed initiation rates that ranged from 49% in 2005/6 in Sweden to 65.2% for the years 2006 to 2009 in Germany. Rates varied across time periods, as well as between countries for similar population groups and time periods. For instance, 79.2% of MI patients aged 65 years or older in Ontario, Canada, initiated statin therapy in 2005 compared to 61% of community-dwelling elderly patients in Pennsylvania and New Jersey, U.S., in 2004.

Figure 3.6 Proportion of individuals initiating statin therapy following hospital discharge for myocardial infarction or stroke [18], [33]–[42]



3.4.5.2. Determinants of statin initiation

Gender

Three longitudinal U.S. studies (n=119,663), encompassing three elderly and one general population cohort, examined the relationship between gender and the initiation of statin treatment after hospital discharge [40], [43], [44]. One study covering two cohorts observed that male Medicare and MarketScan beneficiaries were more likely to initiate high-intensity statin therapy than female beneficiaries (Medicare: RR 1.06, 95% CI 1.02-1.10; MarketScan: RR 1.09, 95% CI 1.04-1.13) [43]. In contrast, an earlier U.S. study (1995-2004) focused on elderly MI patients and found the relationship to be the reverse, with men having a higher risk of not initiating treatment compared to women (RR 0.85, 95CI 0.82-0.89) [40]. A third large U.S. study (n=85,017) analysing initiation patterns amongst elderly patients reported no difference in odds of White women and White men initiating treatment following adjustment for demographic, clinical and baseline characteristics (OR 0.98, 95% CI 0.95-1.02) [44]. (**Appendix A.8, Figure A.3**).

Ethnicity

Three longitudinal U.S. studies (n=113,360) comprising elderly population cohorts (i.e. individuals aged 65 years or older) contained information on ethnicity and its association with (high-intensity) statin initiation [40], [43], [44]. An older study using data for the years 1995-2004 showed a statistically significant relationship, in which Black or African American patients were less likely to initiate treatment (RR 0.86, 95% CI 0.80-0.93) [40]. Two additional studies did not find any differences in likelihood of initiating statin therapy between Black and African American patients and individuals of White ethnic backgrounds [43], [44]. Lauffenburger and colleagues tested for associations between several race/ethnicity-gender groups and statin initiation and reported that Asian women were significantly more likely to initiate therapy than White men (OR 1.20, 95% CI 1.02-1.41), while not finding any significant differences between other ethnicity-gender groups compared to White men [44] (see **Appendix A.8, Figure A.4** for an overview of effect sizes).

Clinical history

The role of several co-morbidities in the uptake of statin therapy amongst the elderly (i.e. individuals aged 65 years or older) was examined in three U.S. studies (n=113,360) [38], [40], [43]. The following concomitant medical conditions in addition to MI or stroke were

associated with a lower likelihood of statin initiation (compared to the absence of such condition): atrial fibrillation, chronic pulmonary diseases, malignancy, dementia, mental disorders, dialysis and heart failure [40], although no statistically significant association was observed for heart failure and dementia in a second study [43]. Two studies found the presence of CHD in addition to MI and stroke to be associated with lower initiation rates of statins amongst the elderly, however, the association was not found to be significant when analysing a population encompassing individuals from age 18 and onwards for the same time period [40]. Additionally, one study specifically examined statin initiation amongst patients with both MI and rheumatoid arthritis and noted that RA patients had a significantly lower likelihood of treatment initiation compared with MI-only patients (OR 0.69, 95% CI 0.58-0.82) [38].

In contrast, the following concomitant conditions and procedures were associated with greater odds of initiation: hypertension, angiography during index hospitalisation and cerebrovascular disease [40]. A second study examining a similar population cohort in later time periods did not find any associations between history of stroke and statin initiation post myocardial infarction [43].

Independent of the presence of co-morbidities, the total number of medications taken by individuals had an association with the intensity of statin therapy initiated in both elderly and general population cohorts with MI, as reported in one U.S. study (n=15,278) [43]. The greater the number of drugs, the higher the risk of initiating low/medium intensity statin than high-intensity therapy.

Age

One U.S. study (elderly patients; n=19,368) reported a statistically significant association between patients' age and statin initiation with older age associated with an increased risk of non-initiation in the period from 1995 to 2004 (RR 0.97, 95% CI 0.97-0.97) [40]. A more recent US study did not observe any statistically significant relationship between age and the initiation of high-intensity versus low/medium intensity statins among elderly patients [43].

Socioeconomic status

One longitudinal study including 28,216 individuals from British Columbia, Canada, investigated the association between socioeconomic status (SES) and statin initiation, where SES was based on household income levels for 80% of the population and validated area-level measures of mean neighbourhood income for the remainder [45]. After

adjustment and stratification by gender, the study reported initiation rates to be significantly higher in higher SES quintile groups (i.e. Q4 and Q5) compared to the lowest quintile (i.e. Q1). When analysing results by gender, men in the highest SES quintile were almost twice as likely (OR 1.71, 95% CI 1.53-1.90), while women were 1.32 times more likely (95% CI 1.12-1.54) to initiate statin treatment than respective individuals in the lowest SES group. A relatively more recent study from the U.S. did not find any association between SES and the initiation of high-intensity statin compared to other statin intensities among elderly Medicare patients (n=8,975), using the receipt of a low-income subsidy under Medicare Part D and dual eligibility for Medicare/Medicaid as markers of low socioeconomic status [43].

Other factors

One U.S. study (n=15,278) investigated the role of further factors, including the length of MI hospitalisation, alcohol abuse and whether patients were treated in cardiologist care in the year prior to their MI, and found these to be associated with an increased risk of not initiating high-intensity statin treatment compared to low/medium-intensity statins [43]. However, the association with prior history of cardiologist care reported above was not found to be significant in an earlier U.S. study that examined the initiation of statins in general [40].

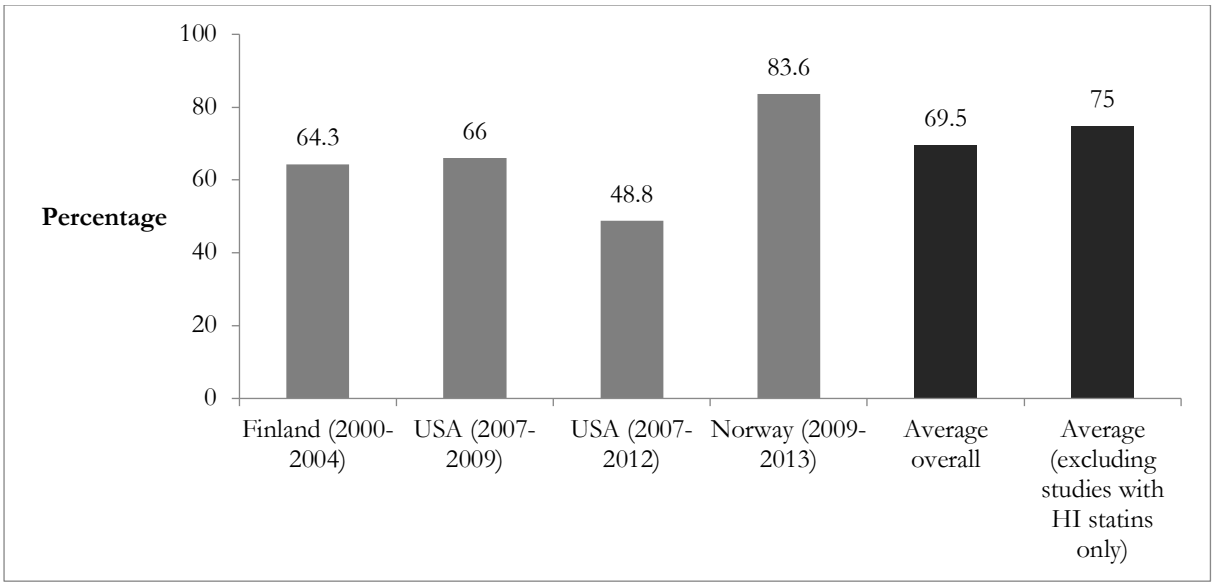
3.4.6. Statin adherence

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.4.6.1. Rates of statin adherence

Adherence rates, defined as the proportion of individuals with a PDC of ≥80%, ranged from 64.3% to 83.6% after one year since statin initiation (**Figure 3.7**). One U.S. study investigated adherence rates specifically amongst elderly high-intensity statin users and reported that 48.8% of high-intensity users were adherent to high-intensity treatment, while the remainder were not adherent. As such, the total average proportion of adherent patients with MI or stroke was 75% if excluding studies with high-intensity-only statin adherence rates, and 69.5% for all included studies. In addition, one U.S. study examined adherence rates in an elderly population cohort after re-initiation of statin therapy since the first reported treatment discontinuation gap and reported an average adherence rate of 45.8%. As the rates are reported across different countries, time periods and population cohorts, it is difficult to discern if rates also vary across similar time periods and countries with similar population groups.

Figure 3.7 Proportion of statin users with PDC ≥ 80% at 12 months since initiation [24], [44], [46], [47]



3.4.6.2. Determinants of statin adherence

Gender

Two large U.S. studies based on elderly population cohorts (n=98,061) and with overlapping time periods analysed the association between gender and statin adherence after one or two years. Of these, one study, which stratified analyses by gender and ethnicity, reported that White women were 1.05 times more likely to adhere to treatment at 12 months since initiation than White men (OR, 95% CI 1.01-1.09), though associations differed in other ethnic categories [44]. In another study, Colantonio and colleagues found that the proportion of women adhering to high-intensity statin therapy at 24 months is 9% lower compared to men (Prevalence Ratio (PR) 0.91, 95% CI 0.88-0.94) [34]. The study adjusted for ethnicity, however, interactions were not investigated.

Ethnicity

The relationship between ethnicity or race and statin adherence was investigated in two U.S. Medicare study cohorts including individuals aged 65 years or older (n=98,061). Regardless of whether results were reported by gender and ethnicity or ethnicity alone, the findings suggest that Black, Hispanic and other non-White ethnicities or races are significantly less likely to adhere to statin therapy after 12 and 24 months since initiation, compared to White patients (or White men) [34], [44]. Neither study found significant differences in adherence between Asian and White patients with MI. Please see **Appendix A.9, Table A.12** for an overview of effect sizes.

Clinical history

One large U.S. study (n=45,876) examining adherence in elderly patients aged 65 years or older found that individuals with a greater number of co-morbidities as defined by the Charlson Comorbidity Index, and specifically diabetes, stroke and coronary heart disease were less likely to be adherent to statin therapy. The findings also applied to individuals with any prior hospitalisations, recurrent MI and those using multiple medications (i.e. polypharmacy) [34]. Please see **Appendix A.9, Table A.12** for an overview of effect sizes.

Socioeconomic status

The association between socioeconomic status and adherence to high-intensity statin therapy following MI was evaluated in one large U.S. study of Medicare patients aged 65 years or older (n=45,876), using a patient's dual eligibility for Medicare/Medicaid as a

marker of low socioeconomic status. The findings suggest that individuals with dual Medicare/Medicaid coverage were more likely to take high-intensity statins with high adherence within two years since initiation compared to individuals without dual coverage (Prevalence Ratio (PR) 1.09, 95% CI 1.06-1.13) [34]. It must be noted that similarly to Medicare patients, patients with dual eligibility for Medicare and Medicaid are covered by federal health insurance. However, patients who receive dual coverage are entitled to more services and no or even lower co-payments than individuals who receive Medicare alone. As a result, it is not possible to differentiate if the findings are reflective of the role of socioeconomic status or the role of patients' cost burdens due to the presence of co-pay in the degree of statin adherence.

Urban-rural location

One longitudinal U.S. study, which assessed adherence to high-intensity statin therapy in elderly Medicare patients aged 65 years or older (n=45,876) reported that patients with rural residence were slightly more likely to be adherent to high-intensity statins after MI compared to individuals living in non-rural areas who initiated high-intensity statin after MI discharge (Prevalence Ratio (PR) 1.03, 95% CI 1.00-1.06) [34].

Statin intensity and type

The relevance of statin intensity to treatment adherence was studied in one U.S. Medicare cohort consisting of MI patients aged 65 years or older (n=13,132). When analysing statin adherence after re-initiation of statin therapy, the study found that individuals re-initiating high-intensity statin were at greater risk of being non-adherent compared to those re-initiating low-intensity statins (RR 0.80, 95% CI 0.75-0.86). Individuals who down-titrated treatment at re-initiation, were more likely to be adherent than those who did not modify their treatment intensity (RR 1.10, 95% CI 1.05-1.16). Furthermore, those who discontinued statin treatment and subsequently re-initiated a different statin type were also at lower risk of statin non-adherence than those who remained on the treatment throughout (RR for adherence: 1.10, 95% CI 1.06-1.14) [47].

Myocardial infarction post-discharge care

One large U.S. study (n=45,876) examined a number of factors related to MI aftercare and found that, after multivariable adjustment, the proportion of individuals continuing to take a high-intensity statin with high adherence at two years after discharge was higher among individuals attending cardiac rehabilitation (OR 1.10, 95% CI 1.06-1.15), and those with

greater number of outpatient or outpatient cardiologist visits (per 5 visits: OR 1.02, 95% CI 1.01-1.03) after index hospital discharge [34].

Time effects

Colantonio and colleagues noted that the proportion of U.S. Medicare patients (n=45,876) being adherent to high-intensity statins increased significantly between 2007 and 2012, with a prevalence ratio of 1.07 for the year 2008 (95% CI 1.01-1.14) and up to 1.46 for the year 2012 (95% CI 1.39-1.54) [34].

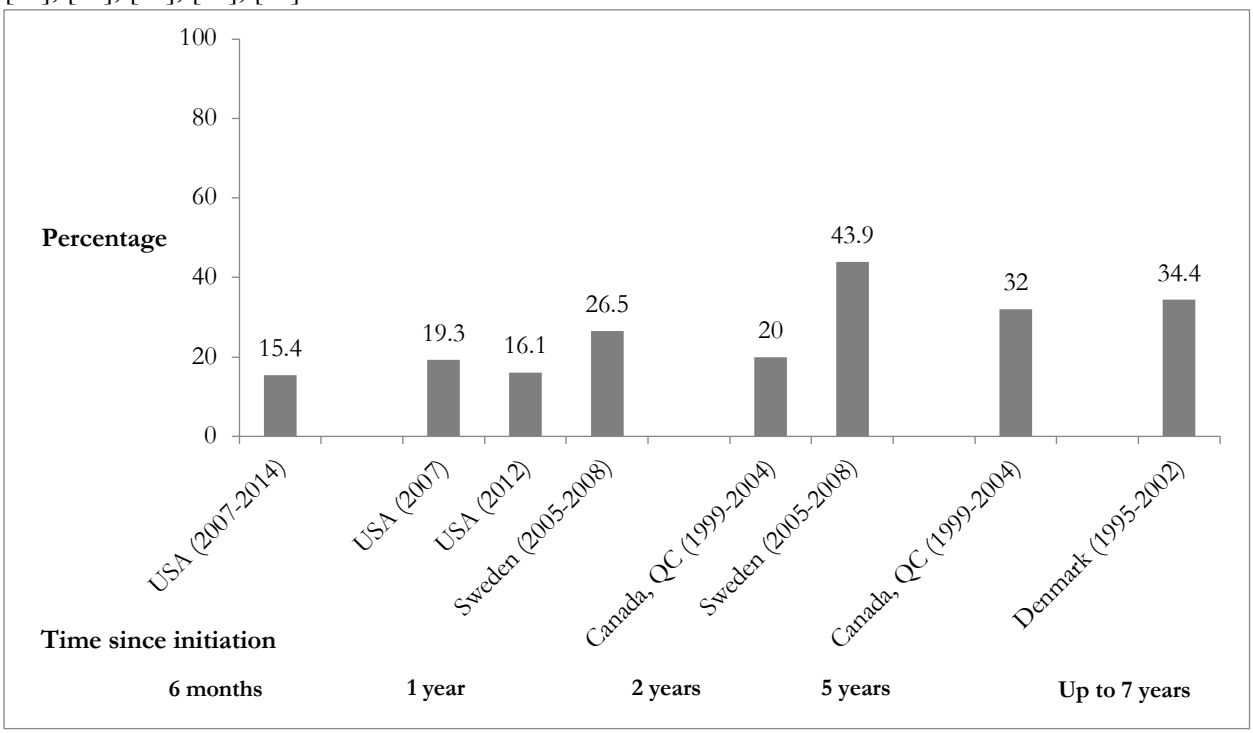
3.4.7. Statin persistence

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.4.7.1. Rates of statin persistence

Non-persistence, defined as the proportion of individuals discontinuing statin treatment at any point in time since initiation (i.e. exceeding a permissible treatment gap as described above) ranged from 15.4% at six months to 43.9% at two years. These rates quantify the proportion of individuals who discontinued treatment within a specific time period since initiation, however, studies did not further examine whether patients re-initiated treatment at any point in time after the index discontinuation. One U.S. study assessed discontinuation rates after one year among elderly MI patients using high-intensity statins and found that discontinuation rates decreased from 19.3% in 2007 to 16.1% in 2012 [34]. In the case of stroke, one Swedish study reported average discontinuation rates of 26.5% within one year and up to 43.9% after two years for the time periods 2005 to 2008 [32]. In contrast, an earlier study examining treatment discontinuation after two years in a general MI study cohort from Quebec, Canada, reported average rates of 20% for women and 27% for men for the period 1999 to 2004 [37]. Furthermore, an earlier longitudinal study from Denmark followed MI patients for up to seven years since discharge and observed an overall discontinuation rate of 34.4% [35]. As the rates are reported across different countries, time periods and population cohorts, it is difficult to discern if rates also vary across similar time periods and countries with similar population groups (**Figure 3.8**).

Figure 3.8 Proportion of statin users discontinuing treatment at different time intervals [32], [34], [35], [37], [47]



3.4.7.2. Determinants of statin persistence

Gender

A negative association between male gender and statin persistence was observed in one study (n=16,433), with male MI patients being at greater risk of discontinuation than female patients (RR 1.14, 95% CI 1.07-1.22) [35]. A second study (n=21,077) did not find a statistically significant association between gender and statin persistence (OR 0.92, 95% CI 0.85-1.01) [32].

Age

The relationship between age and statin (non-)persistence was examined in three studies using different outcome measures (n=58,443). An earlier national-level study from Denmark reported that MI patients aged between 60 to 69 years were at lower risk of discontinuation (RR, 95% CI 0.82-0.94), while individuals who were 80 years old or older had 1.40 times the risk of statin discontinuation within six months since initiation compared to individuals aged 30 to 59 years (RR, 95% CI 1.16-1.68) [35]. In addition, an earlier Canadian study based on similar time periods and with a follow-up period of up to five years assessed the association in 5-year age gaps and stratified results by gender [37]. Similar to the study described above, MI patients aged 80 years or older had a significantly

higher risk of statin discontinuation compared with individuals aged 65 to 69 years, irrespective of gender. Furthermore, both men and women below the age of 45 had an almost two-fold risk of statin discontinuation compared to 65 to 69 year old patients. Although not statistically significant for women, all remaining male age groups were reported to be at higher risk of treatment discontinuation than those aged 65 to 69 years [37]. No statistically significant relationship was found between age group and persistence in the case of stroke, as examined in a longitudinal Swedish study based on a national registry cohort [32]. Please see **Appendix A.9, Table A.13** for a detailed overview of the effect sizes.

Clinical history

Four studies investigated the association between patients' clinical history and statin persistence (n=92,346). For instance, a Canadian study found that male MI patients with dementia, malignancy or a number of hospitalisations in the year prior to the index MI had a higher risk of statin discontinuation, with the latter association also applying to women [37]. Additionally, one Danish study specifically examined statin persistence among patients with both MI and rheumatoid arthritis (RA), and noted that RA patients had a significantly higher likelihood of treatment discontinuation compared to MI-only patients (OR 1.26, 95% CI 1.07-1.48) [38].

In the case of patients with stroke, those with recurrent stroke and lower self-perceived general health were less likely to be persistent with therapy than individuals without recurrent stroke and with good self-perceived health. Patients who used statin treatment before the index stroke onset had a higher likelihood of good persistence with therapy than those who did not use statin therapy prior to the index stroke hospitalisation [32]. Furthermore, one study evaluated the influence of concomitant treatment on non-persistence, and found that MI patients who also used beta-blockers and ACE-inhibitors were at lower risk of non-persistence. However, the association was not found to be statistically significant in the case of loop diuretics and antidiabetic therapies [35]. Please see **Appendix A.9, Table A.13** for a detailed overview of the effect sizes.

Acute care and post-discharge care

Two studies assessed the relevance of acute and aftercare-related factors (n=42,010) and persistence with statin treatment. In the case of acute care, stroke patients hospitalised in stroke unit care were more likely to be persistent with statins [32], and MI patients receiving in-hospital revascularisation procedures or men who had a length of stay of more than

eight days were found to have a lower risk of discontinuing pharmacotherapy in the long-term [37].

When analysing patients' aftercare, stroke patients living in institutions were significantly more likely to remain persistent with treatment compared to those living at home [32]. Additionally, the greater the number of physician visits in the year prior to the index MI, the lower the risk of statin discontinuation, although the association ceased to be statistically significant after more than eleven physician visits. Male MI patients seeing cardiologists had a greater risk of non-persistence with treatment, compared to those seeing family physicians [37]. Please see **Appendix A.9, Table A.13**.

Statin intensity

The relevance of statin intensity to non-persistence with treatment was studied in one large U.S. Medicare cohort consisting of MI patients aged 65 years or older (n=158,795). Compared to low-intensity statins, moderate- and high-intensity statins were associated with a lower risk of statin discontinuation within 6 months since treatment initiation (moderate intensity: RR 0.93, 95% CI 0.89-0.96; high-intensity: RR 0.95, 95% CI 0.91-0.99) [47].

Calendar time effects

Two earlier studies based in Denmark and Canada observed converse time effects on treatment behaviours among MI patients (n=23,708). In Denmark, those hospitalised for an MI between 1999 and 2000 had a greater risk of statin discontinuation than those hospitalised between 1995 and 1996 (RR 1.36, 95% CI 1.23-1.51), although the association was not statistically significant when comparing the time period from 1995-96 to the years 1997-98 and 2001-02 [48]. In contrast, Hudson and colleagues found that men had a lower risk of treatment discontinuation in later years, compared to the year 1999 (2002: HR 0.84, 95% CI 0.75-0.94; 2003: HR 0.74 (0.65-0.84) [37].

3.5. PART B: STUDIES REPORTING RATES AND DETERMINANTS OF ANTIPLATELET THERAPY USE

3.5.1. Overall data characteristics and methods of included studies

Twenty studies using patient-level data were included in the review. The characteristics of the included studies are summarised overall in **Table 3.2** and by outcome measure in **Appendix A.4** and **A.10, Tables A.14-A.17**. Most studies (n=14) were based in Europe, with the remaining studies reporting information on specific US counties (n=6). The median sample size across all studies was 30,053 (interquartile range: 19,941 to 45,438), with three studies capturing information on more than 50,000 individuals. Overall, only three studies examined antiplatelet use in stroke patients. Proportions of antiplatelet therapy use at different treatment stages were reported by all studies. However, only six studies examined determinants of antiplatelet therapy use at a certain treatment stage using regression models. Further details on the characteristics and analytical methods of studies included in the quantitative synthesis are described by outcome measure in **Appendix A.10, Tables A.14-A.17**. Due to the small number and heterogeneity of studies, summaries of results are reported qualitatively and by individual treatment stage only.

Table 3.2 Characteristics of studies included in the systematic review by study quality

		Study quality[39]	
Study characteristics	All studies	Good	Fair
Number of studies	20	15	5
Region			
Europe	14	10	4
North America	6	5	1
Study population			
All adults	19	15	4
Diabetic patients	1	0	1
CVD condition[40]			
MI	18	14	3
Stroke	3	1	2
Sample size			
Median (IQR)	30,053 (19,941, 45,438)	30,986 (25,034, 45,689)	29,325 (14,904, 30,028)
≥ 50,000 participants	3	2	1
10,000 – 49,999 participants	17	13	4
Outcome measure			
Prescription on discharge	10	8	2
Initiation	7	6	1
Adherence	2	1	1
Persistence	4	3	1
Utilisation[41]	2	1	1
Determinants reported			
Yes	6	5	1
Prescription on discharge	3	3	0
Initiation	2	2	0
Adherence	1	1	0
Persistence	2	1	1

[39] No study was classified as of 'poor quality'.
[40] One study reported findings for myocardial infarction and stroke and contributed two cohorts to the data extraction. As a result, the total number of studies reported here is 21 instead of 20.
[41] Summaries of study characteristics and findings are reported in **Appendix A.4** and **A.10**.

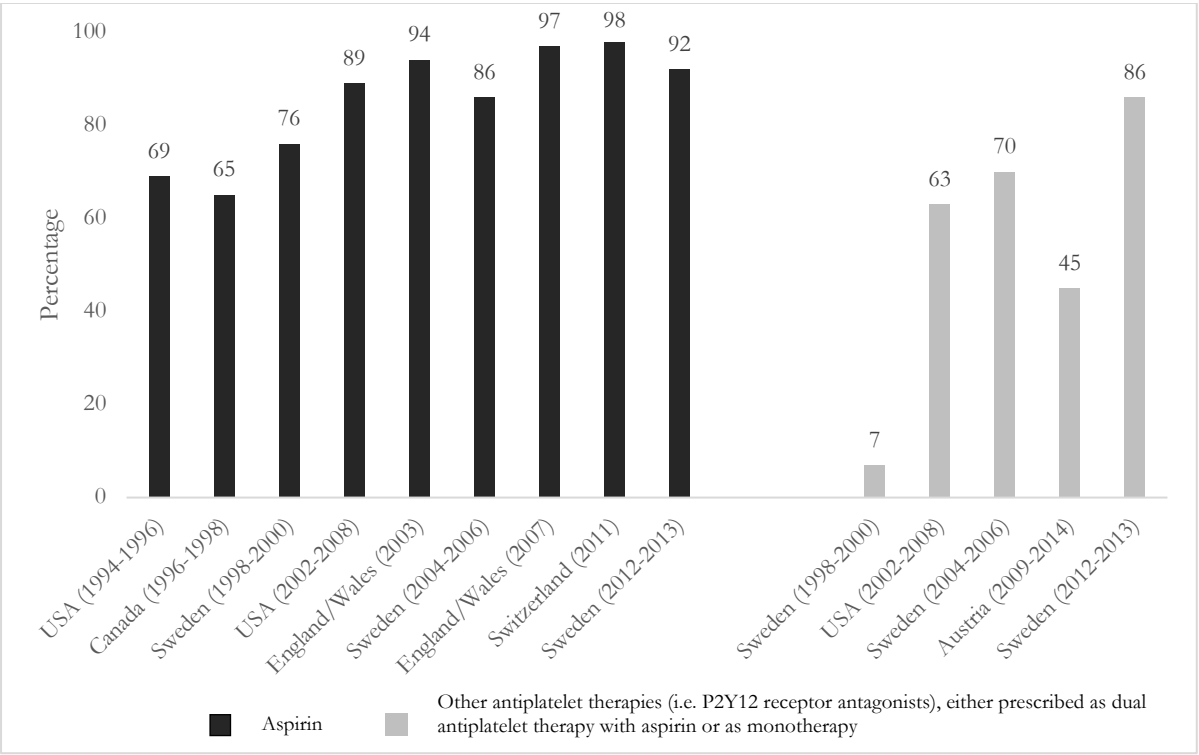
3.5.2. Antiplatelet therapy prescription on discharge

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.5.2.1. Rates of antiplatelet therapy prescription on hospital discharge

The proportion of MI patients receiving aspirin on hospital discharge ranged from 65% to 98% in the period from 1994 to 2014. The rate for other antiplatelet therapies (i.e. P2Y12-receptor antagonists), which were either prescribed as monotherapies or as dual-antiplatelet therapies in addition to aspirin (breakdown of mono- vs. dual therapy not available), ranged from 7% to 86% (**Figure 3.9**). The average aspirin prescription rate has been high since the early 2000s (i.e. 93%), while the prescription rate of other antiplatelets increased over time, with more types of P2Y12-receptor antagonists becoming available (e.g. prasugrel in 2009; ticagrelor in 2011) and clinical guidelines recommending the use of dual antiplatelet therapy in patients with MI over time (e.g. individuals with MI and treated with percutaneous coronary intervention: NICE CG172 and CG167 (2013), SMC Appraisal 317 (2014), SIGN 148 (2016); NICE NG185 (2020); see **Chapter 2**, **Section 2.3**).

Figure 3.9 Proportion of MI patients discharged on antiplatelet therapy (1994-2011) [26]–[29], [49]–[54]



3.5.2.2. Determinants of antiplatelet therapy prescription on discharge

Gender

Two national registry-based studies in Sweden (n=30,077) and Switzerland (n=21,620) examined the relationship between gender and antiplatelet therapy prescription [26], [28]. While the studies did not find a statistically significant association between gender and the likelihood of being prescribed aspirin, women in Sweden were less likely to be prescribed other types of antiplatelet therapies compared to men (OR 0.83, 95% CI 0.78-0.95) (see **Appendix A.11, Table A.19** for a detailed overview of the studies and methods).

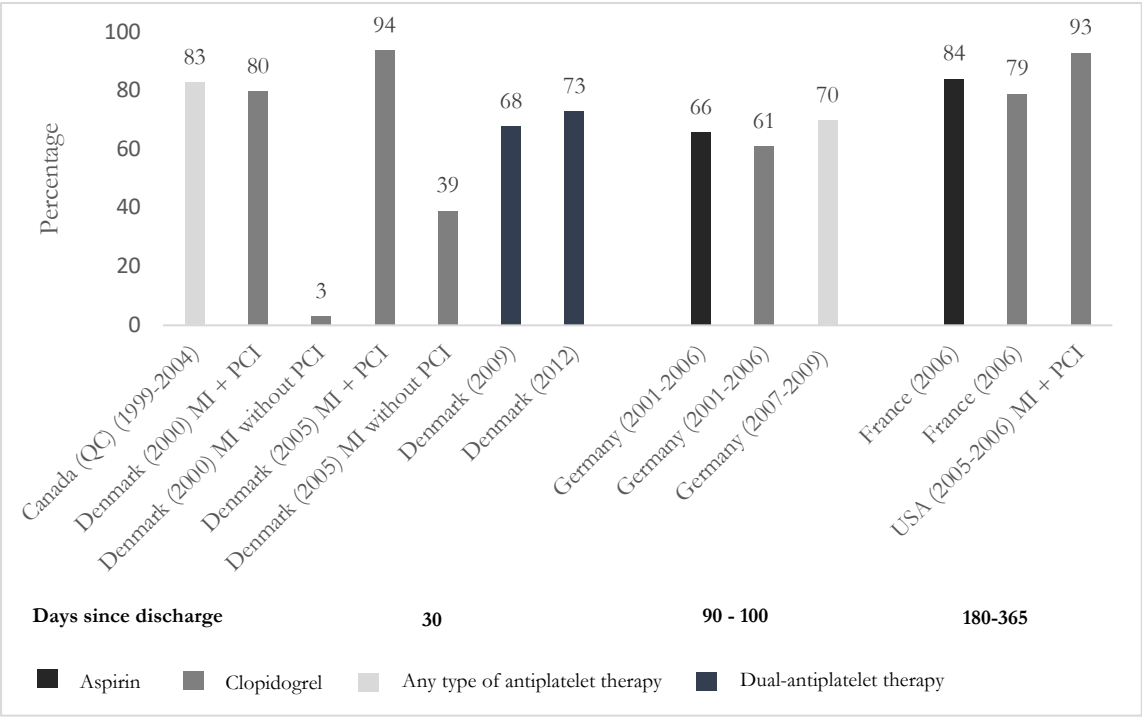
3.5.3. Antiplatelet therapy initiation

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.5.3.1. Rates of antiplatelet therapy initiation

Rates varied by time period, country, type of antiplatelet therapy, the time period measured since index discharge and presence of percutaneous coronary intervention (PCI). Aspirin initiation rates ranged from 66% within 90 days since discharge in 2001-2006 in Germany to an 84% rate within 180 days in France in 2006. Clopidogrel initiation rates varied primarily by presence of PCI treatment, with a higher proportion of individuals treated with PCI receiving the therapy compared to those without PCI. At the same time clopidogrel use increased over time in both patient groups. For example, in Denmark in 2002, 80% of individuals treated with PCI were prescribed clopidogrel versus only 3% in patients without PCI. By 2005, the rates increased to 94% and 39%, respectively. A similar initiation rate among patients with PCI was reported in the US in 2005/06 (i.e. 93%). One Danish national registry-based study (n=28,449) captured the change in dual antiplatelet therapy initiation over time, with the initiation rate increasing from 68% in 2009 to 73% in 2012 (**Figure 3.10**).

Figure 3.10 Proportion of MI patients initiating antiplatelet therapy (2006-2012) [36], [37], [41], [55]–[58]



3.5.3.2. Determinants of antiplatelet therapy initiation

Two studies reported factors associated with the initiation of clopidogrel in MI patients. One study was a Danish retrospective observational cohort study using a national patient register for the period 2002-2005 (n=46,190) assessing initiation within 30 days [58], while the second study was a retrospective analysis of the US MarketScan commercial claims database in 2005/06 (n=10,465) assessing initiation within one year since discharge [57]. No evidence on the associations between patient factors and antiplatelet therapy initiation was available for any other antiplatelet therapy types, such as aspirin.

While the Danish study reported that women without PCI had lower odds of initiating clopidogrel compared to men without PCI (OR 0.86, 95% CI 0.78, 0.95), no statistically significant association was observed in the case of individuals who underwent PCI in the same study, or in the US study that focussed entirely on initiation predictors among patients with PCI. Age below 55 years was associated with greater odds of initiating clopidogrel among patients with PCI in the US study (OR 1.29, 95% CI: not reported), however, this association was not significant in either MI population (i.e., with or without PCI) in Denmark. Presence of specific comorbidities was associated with lower odds of clopidogrel initiation (e.g. cerebral vascular disease, cardiac dysrhythmias, acute renal failure) in both patients with and without PCI in Denmark, while other conditions (not assessed in the previous study), such as atrial fibrillation, hypertension and diabetes, were all associated with higher odds of clopidogrel initiation in the US. Please see **Appendix A.11, Table A.20** for a detailed overview of the determinants and effect sizes by study).

3.5.4. Antiplatelet therapy adherence

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.5.4.1. Rates of antiplatelet therapy adherence

Using administrative data on all hospital discharges in the years 1996-1998 in addition to claims data in Quebec, Canada, one study (n=14,047) reported that the proportion of individuals considered adherent to aspirin (i.e., PDC ≥ 80%) was 71% within one year since treatment initiation among individuals with MI [54]. A second retrospective study using a commercial claims database in the US and only including individuals with MI who also underwent PCI, found that the proportion of patients considered adherent with clopidogrel (i.e., MPR ≥ 80%) within one year since discharge was 67% [57].

3.5.4.2. Determinants of antiplatelet therapy adherence

The US study described above also reported factors associated with patient adherence to clopidogrel among patients who underwent PCI [57]. Patients who did not receive a stent during PCI, those with diabetes, chronic obstructive pulmonary disease (COPD) and prior hospitalisations for any other cause had higher odds of initiating clopidogrel treatment compared to individuals who underwent stenting and those without the presence of the conditions listed prior or previous hospitalisations. Younger individuals below the age of 55 had also higher odds of treatment initiation compared to those aged 55 years or older. Please see **Appendix A.11, Table A.21** for a detailed overview of the determinants and effect sizes). No evidence on the association between patient factors and adherence to antiplatelet therapy was available for any other antiplatelet therapy types, such as aspirin.

3.5.5. Antiplatelet therapy persistence

Please see **Appendix A.4** for data characteristics and analytical methods of studies included in the review.

3.5.5.1. Rates of antiplatelet therapy persistence

Using administrative data on all hospital discharges in the years 1999-2004 in addition to claims data in Quebec, Canada, one study reported antiplatelet therapy discontinuation rates of 22% among women and 25% among men within two years since the index prescription. The rates increased to 36% and 39% among women and men, respectively, in year five since index prescription [37]. Based on national registry-data, the discontinuation rate in Sweden between 2005 to 2008 was estimated at 20.7% within one year and 36.3% within two years since hospital discharge, constituting a higher rate than that reported in Canada [32]. In addition, two studies evaluated discontinuation rates specifically for clopidogrel among MI patients who underwent PCI [57], [58]. One Danish retrospective observational cohort study using a national patient register for the period 2002-2005 (n=46,190) found that 26% of patients had a treatment gap of 30 days or more within nine months since clopidogrel initiation, and could potentially be classified as discontinuers [58]. In addition, a US study using a commercial claims database (n=10,465) reported that patients who had a treatment gap of 30 days or more and thus could be classified as discontinuers, experienced the treatment gap on average within 241 days since initiation [57].

3.5.5.2. Determinants of antiplatelet therapy persistence

One study examined the relevance of patient characteristics to the persistence with antiplatelet therapy following hospital discharge for stroke and identified a number of risk factors [32]. Compared to women, men were less likely to be persistent with treatment (OR 0.92, 95% CI 0.85-0.99). Furthermore, the odds of being persistent increased with age (e.g. individuals aged 75-84 vs. those aged <65: OR 1.18, 95% CI 1.06-1.31). With regard to clinical factors, the presence of atrial fibrillation and low mood, as well as poor self-perceived health, were associated with lower odds of treatment persistence. Please see **Appendix A.11, Table A.22** for a detailed overview of the study characteristics and effect sizes reported in the included study. In addition, one study assessed the association between patient characteristics and discontinuation within one year since the initiation of clopidogrel among MI patients and observed that men had a lower risk of treatment discontinuation than women (HR 0.88, 95% CI 0.78-0.98) [57]. However, no statistically

significant associations were found for age, presence of comorbidities or concomitant use of other drugs such as ACE inhibitors (**Appendix A.11, Table A.22).**

3.6. Discussion

3.6.1. Findings and interpretation of results

This is the first systematic review to investigate both the proportions and determinants of statin and antiplatelet therapy use at every single stage of the treatment pathway (i.e. prescription on discharge, initiation of treatment following discharge, adherence to the daily medical regimen that was prescribed by the treating physician, and the discontinuation of treatment). The review included 47 studies that assessed these outcomes specifically in patients hospitalised for myocardial infarction (MI) and/or stroke and, despite variations in data and methods used, some clear patterns emerged.

Proportions of statin and antiplatelet therapy use for the secondary prevention of myocardial infarction and stroke

Average rates of statin prescription, initiation, adherence and persistence have been increasing over time, particularly in the case of statin prescriptions on discharge among MI patients (average discharge prescription rate in 2007-2015: 87% vs. 44% in 1994-2006). In the case of stroke, the average rate of statin prescriptions on discharge was lower compared to MI (2005-2013: 56%), however, only few studies contributed evidence for this outcome. In comparison, the average rate of aspirin discharge prescriptions among MI patients has been consistently high since the early 2000s, averaging 93%, while the use of other antiplatelet treatments (mono- and dual antiplatelet therapies) has been increasing over time. However, treatment gaps in both statin and antiplatelet treatment use remain present at every stage of the treatment pathway, and this review has highlighted the importance of researching and addressing all stages jointly, rather than independently. For example, the majority of previous systematic reviews examined prescriptions on discharge [1] and adherence to statins [4], [6], [10], as well as interventions to improve treatment adherence (e.g. Rash and colleagues, 2016 [59]), with the aim to raise awareness of specific gaps in cardiovascular disease management that ought to be addressed; however, suboptimal statin initiation rates, as observed in this review, would mitigate any future gains achieved across other treatment stages such as adherence, unless policies and initiatives address all treatment stages together.

Determinants of statin and antiplatelet therapy use for the secondary prevention of myocardial infarction and stroke

In order to inform potential future policies that aim to target the suboptimal medication use described above, this review sought to investigate patient and healthcare provider-related risk factors that are associated with suboptimal statin and antiplatelet use across the treatment pathway. More than 70 individual demographic, socioeconomic, clinical, lifestyle, geographical, and healthcare provider-related factors were analysed in this review, although very few studies provided information on determinants of antiplatelet use. Furthermore, a number of risk factors were observed at multiple stages of the treatment pathway, widening the treatment gap in specific patient populations. For instance, being female was consistently associated with a lower likelihood of statin prescription on discharge and initiation, compared to being male. Similar evidence was also found in the case of aspirin, with women being less likely to be prescribed therapy on discharge than men.

In the case of statin adherence, one study among older people found that White women were relatively more likely to be adherent to statin therapy within 12 months since MI hospital discharge compared to White men. However, Black, Hispanic and Asian women were each somewhat less likely to be adherent to statin therapy than the respective ethnic category of men, suggesting there is some interaction present. A second US study investigated adherence to high-intensity statin therapy amongst older MI patients and found that women were relatively less likely to be adherent to high-intensity therapy within two years since hospital discharge than men. This study adjusted for ethnicity but did not investigate interactions between gender and ethnicity. While different conclusions were reached regarding the relevance of gender to statin adherence, the differences between these studies, particularly with respect to the type of statin therapy analysed (i.e., any statin versus high-intensity statin therapy) and varying adjustments for ethnicity, may explain the contrasting results.

The review showed a reverse association in the case of persistence, with men being at greater risk of statin discontinuation than women. No previous reviews of the associations between gender and statin prescription, initiation and persistence are available to draw conclusions on the consistency of the gender-based treatment gaps evaluated in this review. However, evidence is available in the case of statin adherence, providing insights into a treatment stage for which no conclusive results could be reported in this review. For instance, one meta-analysis of 53 studies, which did not meet the eligibility

criteria for inclusion in this review, quantified gender disparities in adherence to statin therapy and found that compared to men, women had 10% greater odds of non-adherence (OR 1.10, 95% CI 1.07, 1.13), although the significant heterogeneity in the pooled estimates should be taken into consideration [2]. A second meta-analysis of 22 cohort studies found similar results, estimating that women had 7% greater odds of non-adherence than men (OR 1.07, 95% CI 1.04, 1.11) [10].

There was also consistent evidence that age had a U-shaped association with statin discontinuation, with patients aged 69 years or older and those aged below 65 years facing greater risks of statin discontinuation than those aged between 65 to 69 years. In addition, there was some evidence that older patients (i.e. individuals aged 69 years or older, in comparison to patients aged below 69 years) were less likely to receive statin therapy on hospital discharge for stroke. Similar findings were reported in a meta-analysis assessing a different treatment stage, namely adherence to statin treatment, where the oldest (i.e. individuals aged 70 years or older) and the youngest (i.e. individuals aged below 50 years) had lower adherence than middle-aged individuals (50-69 years) [10]. The findings may be partly explained by the fact that there was limited pooled evidence on the efficacy and safety of statin therapy in older people until recently, when a large meta-analysis of randomised trial results (n=186,854), published by the Cholesterol Treatment Trialists' (CTT) Collaboration in 2019, showed that statins produce significant reductions in major vascular events irrespective of age [60].

Moderate evidence suggested that individuals with specific physical comorbidities, such as previous CVD, rheumatoid arthritis and malignancy were at greater risk of suboptimal statin use compared to individuals without these conditions, while the presence of other comorbidities, such as chronic kidney disease[42] and diabetes[43], were not significantly associated with greater risks of non-prescription, non-initiation, non-adherence or poor persistence. However, almost all studies included in the review looked at specific conditions rather than assessing the total number of comorbidities and polypharmacy as a potential risk factor in individuals, which may have provided more conclusive estimates of the relationship between disease burden and suboptimal statin use. Few studies investigated the relationship between psychological comorbidities and

[42] No information was available for the association between the presence of CKD and statin prescription on discharge.

[43] One study reported a negative relationship between the presence of diabetes and medication adherence among MI patients. However, there is consistent evidence that a record of diabetes did not influence statin prescription on discharge, initiation or persistence.

medication use, and three studies did not find any statistically significant associations between depression specifically and suboptimal treatment initiation in MI patients, although one study that investigated the role of mental health conditions other than depression found that MI patients were at greater risk of not initiating statin therapy. In addition, there was moderate evidence presented by one large study of nearly half a million elderly MI patients that patients with depression were not at greater risk of suboptimal adherence to statin therapy than individuals without depression. This finding is contrary to previous systematic reviews that observed a negative association between the presence of depression and adherence to treatments in chronic disease, like heart disease and diabetes, (e.g., Grenard and colleagues, 2011 [61]; Capoccia and colleagues, 2016 [62]). However, it must be noted that the studies included in the above-mentioned reviews encompassed all age groups, which may have influenced the results as prevalence rates of depression vary by age group. According to the U.S. Centers for Disease Control and Prevention, the percentage of adults experiencing depression is highest among those aged 18 to 29 years and 45 to 64 years [63], age groups that were not captured in the study included in the present review. In addition, less than 20% of all studies included in these reviews had a sample size of 10,000 or more individuals, the majority ranging between 100 and 500 patients and even being as small as 43 patients, therefore possibly reporting associations that are not necessarily generalisable to the wider population.

The limited evidence from this review suggests that lower socioeconomic status independently predicted susceptibility to poorer statin initiation, and was associated with better medication adherence if individuals had lower socioeconomic status and were as a result eligible for federal health insurance that covered any prescription medication fees. It must be noted that the studies contributing the evidence were based in the US, and therefore these findings may not be generalisable to national healthcare systems such as the UK, where healthcare coverage and costs do not necessarily constitute an access barrier to care. The observation that individuals from lower socioeconomic backgrounds may have poorer medication adherence if medication cost does constitute an additional factor was observed in one meta-analysis of 67 studies, which showed that the presence of medication co-pay was significantly associated with non-adherence to statin treatment (Rate Ratio (RR) 1.28, 95% CI, 1.09, 1.50) [13]. One meta-analysis studied the effect of socio-economic disadvantage on the discharge prescription of statin and aspirin therapy among patients with acute coronary syndrome, and found that while socioeconomic status

did not affect the prescription of aspirin, the lowest socioeconomic groups were disadvantaged in the case of statin (Prescription Ratio (PR) 0.80, 95% CI 0.62, 0.98) [1].

Whilst the fact that six of the seven included studies in the present review were based on data published prior to 2003 and across heterogenous health systems should be taken into account when interpreting the results, the findings indicate that there may be income- and overall socioeconomic-related gaps specifically in the case of medication prescriptions on discharge, and that further research based on more recent data and multiple treatment stages is needed to investigate the extent socioeconomic status plays a role in the management of CVD. The population cohorts used in previous studies that were reported in this review and in the meta-analyses cited above (i.e., US patients in discrete care or insurance settings) complicate analyses into the role of socioeconomic status as opposed to the role of medication fees in the suboptimal use of treatment. Therefore, using a national setting where all patients are covered by national insurance and do not have to pay any medication fees, such as the Scottish population-wide data used in this thesis (see **Chapter 5** and **Chapter 6**), can offer insights into the role of socioeconomic-related factors other than cost burden in the use of cardioprotective medications.

Lastly, limited evidence from this review suggests that some provider-related characteristics appear to be relevant to the use of statin therapy. For instance, findings from a large US study on patients hospitalised for stroke suggest that hospital characteristics, such as larger hospital size and higher numbers of stroke discharges, were independently associated with greater odds of stroke patients receiving a discharge statin prescription [21]. Counter to expectations, the study also reported that stroke patients discharged from academic hospitals that participated in the Get-With-The-Guidelines (GWTG)-Stroke programme were less likely to implement discharge statin treatment compared to non-academic hospitals in the same programme. However, this finding was not consistent with previous literature and was attributed by the authors to data registry specifics that required further research [21]. Notably, more intensive and specialist provider aftercare was positively associated with patient adherence. For instance, an increase in the number of outpatient visits, and specifically outpatient cardiologist visits, was associated with an increase in adherence to treatment. In addition, patients who were treated by a cardiologist, as opposed to a general physician, and those receiving cardiac rehabilitation, were more likely to be adherent to statin therapy, particularly high-intensity statin treatment, than those without specialist aftercare [34]. In the case of antiplatelet

therapy, none of the studies included in this review investigated the role of provider characteristics in the use of antiplatelet therapy for the secondary prevention of ASCVD.

3.6.2. Limitations

This review is subject to a number of limitations. It was restricted to English language, peer-reviewed research, therefore potentially excluding relevant findings published in other languages or in the non-peer reviewed literature. Furthermore, grey literature may have identified additional studies not reported here, and the review only includes studies published up to June 2018 . While focussing the review on studies of myocardial infarction and stroke provided specific study populations for which clear medication guidelines had been published that recommended the long-term use of both statin and antiplatelet therapy, it led to the exclusion of many publications that assessed the outcomes of interest in other CVD populations which could have provided additional evidence to perform a quantitative synthesis of the determinants of medication use for the secondary prevention of CVD.

Given the considerable heterogeneity between the included studies in terms of outcome measures, methods, data, countries and healthcare settings, formal meta-analyses could not be performed. As a result, it was not possible to make formal inferences about the role of specific risk factors in the use of cardioprotective medication. Qualitative comparisons of relative effects of the determinants of medication use may be confounded by differences between studies. In terms of the study characteristics of the included studies in this review, the majority of studies cover less recent time periods (i.e. 2000 – 2013) and have relatively short follow-up periods, therefore not necessarily reflecting the current treatment situation and generally only reporting information on adherence and discontinuation rates for up to two years since treatment initiation, even though the therapies are indicated for the long-term.

Furthermore, studies that reported evidence of significant determinants, such as gender, did not examine or provide information on the underlying drivers of these treatment gaps (e.g. drivers of gender differences in medication prescriptions and use). Lastly, findings were derived from large observational studies based on administrative registry or claims data that did not capture beliefs or risk perceptions of individuals, which may explain some of the differences in patterns of medication use, as assessed in previous systematic reviews of qualitative studies [7], [8]. Studies were also not able to distinguish whether the initiation and discontinuation of treatment were driven by physicians' or

patients' decision-making, and the limited reporting of adverse events prevents this review from drawing conclusions about the effect of side effects on medication adherence and persistence.

3.6.3. Future research

This review draws attention to the limited number of observational studies examining multivariable predictors of statin and antiplatelet therapy use at multiple stages of the treatment pathway. This thesis (specifically **Chapters 5-7**) builds on the limitations described and research gaps identified in this chapter by conducting analyses of the rates and determinants of both statin and antiplatelet therapy use at three different stages of the treatment pathway, namely initiation after hospitalisation, adherence to and persistence with therapy in a national administrative dataset that covers all residents in Scotland hospitalised for an atherosclerotic cardiovascular disease (ASCVD) since 2009, including MI and stroke. Medication use patterns are assessed over an eight-year time period, going well beyond the time period captured in the studies included in this review, and stratified by gender, age group, CVD type and treatment. Moreover, the research investigates the role of individuals' socioeconomic level, as well as publication of clinical guidelines and availability of new treatments over time in the uptake and continued use of statin and antiplatelet therapy for the secondary prevention of ASCVD.

3.7. Conclusions

The systematic review has shown that rates of prescription, initiation, adherence, and persistence with statin and antiplatelet therapy for the secondary prevention of CVD among myocardial infarction and stroke patients have been increasing over time. However, treatment gaps remain at every stage of the treatment pathway and need to be addressed together rather than independently, in order to reach optimal benefits from the preventative treatments. The review identified multiple patient and provider-related risk factors that are associated with suboptimal medication use at different stages of the treatment pathway. These factors need to be considered in the development of policies that aim to address the treatment gap and improve the management of CVD, specifically gender (association depending on the treatment stage), older age, socio-economic status and specific comorbidities.

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4

National Scottish Health Datasets and Statistical Methods

Summary

In order to investigate the rates and determinants of cardiovascular medication initiation, adherence and persistence, specifically statin and antiplatelet therapy, for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD), this longitudinal open cohort study used anonymised linked NHS Scotland administrative data (General/Acute Inpatient and Day Case, Mental Health Inpatient and Day Case, National Records of Scotland and the Prescribing Information System) for the 167,978 individuals hospitalised for an ASCVD event between 1 October 2009 and 3 July 2017. Rates of statin and antiplatelet therapy initiation, adherence and persistence were calculated overall, and by ASCVD type, discharge calendar year and patients' gender and age group. To study the relevance of patient characteristics and discharge calendar year to the likelihood of initiating statin and antiplatelet therapy, multivariable cross-sectional logistic regression models were used. A Cox proportional hazards model was used to assess the role of patient characteristics, as well as discharge calendar year, in the lack of persistence (i.e. discontinuation) with treatment. Findings are reported for all ASCVD events and, separately, for myocardial infarction, ischaemic stroke, peripheral arterial disease and other atherosclerotic cardiovascular diseases. In addition, a Cox proportional hazards model was used to examine the associations between statin and antiplatelet therapy non-initiation and discontinuation, and subsequent occurrence of fatal and non-fatal ASCVD events.

4.1. Introduction

Even though UK and other international clinical guidelines recommend the use of statins and antiplatelet therapies for the secondary prevention of cardiovascular disease[44], the systematic review in **Chapter 3** has found that their use remains suboptimal. To understand the underlying reasons for this suboptimal use, a number of studies in the review aimed to investigate factors associated with cardioprotective medication use. However, the majority of those studies examined determinants and rates at only one specific treatment stage, such as initiation or adherence, thus not capturing potential treatment gaps across the entire treatment pathway. Furthermore, a large majority of studies estimated rates and determinants for a given calendar year and had no or limited follow-up time, and therefore were not able to record changes in medication use over time or in more recent years. In addition, a number of studies, specifically those using data from North America, performed analyses in specific states or patient populations, and were not able to provide insights into the extent of suboptimal medication use on a national and/or general population level. For a more detailed comparative overview of previous study designs and results, please see **Chapter 3**.

This study sought to address the gaps described above by using Scottish population-wide individual-level patient data with a follow-up time of up to eight years, in order to investigate both the extent and characteristics related to suboptimal statin and antiplatelet use at different stages of the treatment pathway over time. The aims of this study are to (1) estimate the level of statin and antiplatelet use for the secondary prevention of ASCVD over time in Scotland, (2) to identify patient groups that could be targeted to improve medication use, and (3) to analyse the impact of selected national policies on cardioprotective medication use. The first part of this chapter, **Section 4.2**, provides an overview of the study design and data, as well as information on ethical approval and funding. **Section 4.3** describes the selection process of eligible study participants, followed by **Section 4.4**, which outlines the statistical methods used for the analyses presented in **Chapter 5** and **Chapter 6**.

[44] E.g. Scottish guidelines: SIGN 149; English & Welsh guidelines: NICE CG181.

4.2. Study design

4.2.1. Overview

The National Health Service in Scotland (NHS Scotland) provides comprehensive free healthcare to all people living in Scotland. NHS Scotland healthcare providers routinely collect administrative and clinical information locally as part of the care process and to support patient care. The data are then validated by NHS Boards before daily electronic submission to central repositories managed by the Information Services Division (ISD) Scotland, a division of NHS National Services Scotland [1]. After further validation checks by ISD, the data are made available for use other than direct clinical care, such as supporting the NHS in health and care quality improvement, planning and decision-making, as well as research [1], [2]. To ensure data security, the data are stored in ISD's National Safe Haven, a secure environment that can be accessed remotely via a virtual private network. The NHS Scotland health service data are unique in that they contain high quality, linkable information covering the entire Scottish population of over five million people [2], [3]. This facilitates large-scale longitudinal patient-based analyses, thereby allowing in-depth investigations into the level and characteristics related to suboptimal cardiovascular medication use at different treatment stages for the purpose of this Thesis.

The present retrospective open cohort study uses large-scale population-wide individual patient data by linking and anonymising four routine healthcare datasets: (1) General/Acute Inpatient and Day Case (SMR01), (2) Mental Health Inpatient and Day Case (SMR04), (3) National Records of Scotland (NRS deaths), and (4) the Prescribing Information System (PIS). These datasets (further described in **Sections 4.2.2-5**) cover a time period from 1981 onward, with the exception of SMR04, which is complete from 1997 onward, and PIS, which is available from April 2009. Thus, the longitudinal nature of the SMR01 and SMR04 datasets allows for the follow-up of individuals over a time period of up to 40 years and 24 years respectively, providing insight into medical history, while the PIS dataset covers a period of up to 12 years and offers insights into medication uptake and long-term persistence with medical regimens, among other factors. By including all individuals in Scotland who were hospitalised for cardiovascular events in a universal healthcare provider setting, the study is fully representative of Scottish residents receiving CVD healthcare.

4.2.2. The General /Acute and Inpatient Day Case dataset (SMR01)

The NHS Scotland General /Acute and Inpatient Day Case (SMR01) is one of six datasets forming the Scottish Morbidity Database (SMD) and managed by ISD Scotland. The dataset contains episode-level data on inpatient and day case discharges and covers all individuals (residents and non-residents of Scotland) who receive care in non-obstetric, non-psychiatric NHS general acute specialties and hospitals in Scotland. Information has been continuously collected since 1961, and computerised data are available from January 1981 onward, with approximately 1.4 million records added annually [4]. In 1993, the Coppish SMR Project was set up to review and update the existing Scottish Morbidity Record (SMR) schemes to create a comprehensive core dataset and allow for the introduction of ICD-10 [5]. As a result, the Coppish SMR01 replaced the historical SMR01 from 1997 onward, containing some revised data definitions and codes that need to be considered when analysing historical records such as patients' CVD history.

The records provide information on each episode of care, defined as the continuous period of care administered by a particular consultant/in a particular specialty at a single hospital provider, which is initiated by a referral (including e-referral) or admission [6]. Hence, every patient transfer to another specialty or hospital during a continuous inpatient stay (CIS; i.e. an unbroken period of time that a patient spends as an inpatient from admission to discharge) generates a new episode record until the patient is discharged or dies. Each episode contains information on diagnoses using ICD (International Classification of Diseases) codes (including a main diagnosis and up to five other diagnoses or problems dealt with during the episode of health care that affect patient management), and up to four operations or procedures using OPCS (Office of Population, Censuses and Surveys: Classification of Interventions and Procedures) codes.

In addition to the ICD codes, the dataset contains patient identifiable data, such as name, date of birth, Community Health Index (CHI) number, postcode, ethnicity and episode management data. However, for the purpose of this study, ISD Scotland linked and anonymised the data and provided only de-identified patient ID numbers, age in years and ethnicity groups. The data also include a variety of patient and hospital details, such as demographic (e.g. sex), episode management (e.g. dates of admission and discharge, admission type and reason, transfers, specialty), socio-economic (e.g. Scottish Index of Multiple Deprivation, marital status) and geographical information (e.g. NHS Health Board of treatment and patient residence, Scottish Government Urban Rural classification).

Individual hospital records for each patient are linked by ISD Scotland using probability matching methods, thus creating linked patient histories that can be tracked back to 1981. In addition, the CHI number recorded in the SMR01 dataset enables a deterministic data linkage to other indexed datasets [4], of which SMR04 (i.e. mental health inpatient and day case dataset), PIS (i.e. Prescribing Information System) and NRS (i.e. National Records of Scotland) are further described below. Other datasets that can be linked with SMR01 and which were not explored in this analysis include, for example, National datasets on child health, and Scottish Open datasets relating to specific diseases (e.g. SMR06 Cancer Registration and Tumour Enumeration System (SOCRATES)) [3].

4.2.3. The Mental Health Inpatient and Day Case dataset (SMR04)

Like SMR01, the Mental Health Inpatient and Day Case dataset (SMR04) forms part of the Scottish Morbidity Database that is managed by ISD Scotland. It collects all inpatient and day case episode-level data at the point of both admission and discharge, which is generated for anyone (residents and non-residents of Scotland) admitted to and receiving care in hospital mental health specialities and psychiatric hospitals in Scotland (i.e. NHS hospitals and contracted beds in non-NHS institutions). The dataset follows an episode-level recording system identical to that of SMR01, as described in **Section 4.2.1**.

Information has been collected since the 1960s, however, data are available from 1981 onwards and have been routinely collected since 1997, with approximately 21,000 records generated annually [7]. The dataset contains the same range of patient identifiers as SMR01, however, for the purposes of this research, ISD Scotland linked and anonymised the data and provided de-identified patient IDs and age in years. Furthermore, the dataset contains a range of patient characteristics and episode management details in addition to those captured in SMR01, including mental health diagnosis (as classified under ICD-10), previous psychiatric care, types of psychiatric care provided, arrangements for aftercare and whether patients are admitted under Mental Health Legislation. For the purpose of this research, a binary variable was generated to indicate whether a patient had ever been admitted as a day case or inpatient to a mental health specialty or psychiatric hospital at any point in time prior to their index hospitalisation for an ASCVD event.

A deterministic data linkage to other indexed datasets, such as SMR01, is possible through the recording of patients' CHI numbers, with 99% of recent records being CHI complete [7].

4.2.4. The National Records of Scotland (NRS) Death Records

The National Records of Scotland (NRS), previously the General Register Office for Scotland, is responsible for the registration of deaths in Scotland, in addition to births, adoptions, marriages, civil partnerships and divorces. The data are collected weekly and contain information on all deaths occurring in Scotland, adding approximately 55,000 death records annually [8], [9].

The dataset contains individual and death-related information, such as date of death, age and the specific causes of death, i.e. main cause and up to ten secondary causes as classified under ICD-10 [9]. The NRS death records are linked with the NHS Scotland Scottish Morbidity Database, which links the mortality data with the NHS Scotland inpatient and mental health datasets. Linkage of NRS death records with the SMR01 and Prescribing Information Systems dataset (**4.2.5**) allows for the specification of follow-up duration of patients who died at some point in time since hospital discharge in statistical analyses (**4.3.1** and **4.4.2**). Furthermore, information on the main cause of death is used to categorise individuals who have died into two groups: (1) ASCVD-related deaths, i.e. those whose primary cause of death was among the ICD codes listed in **Table 4.1** that were used to identify the ASCVD study population, and (2) other deaths, i.e. individuals whose primary cause of death was any other cause.

4.2.5. The Prescribing Information System dataset (PIS)

The Prescribing Information System (PIS) contains general information on all medicines that were both prescribed and dispensed in the community in Scotland. It does not provide information on medicines that were prescribed but not dispensed. The data are generated by the Practitioner & Counter Fraud Services Division (P&CFS), whose responsibility is to process and price every prescription in Scotland. Also included in the dataset is information on prescriptions written in Scotland that were subsequently dispensed elsewhere in the United Kingdom [10].

This information has been collected monthly since April 1993, adding around 100 million data items per year. However, the availability of CHI data since April 2009 means that linkage to other datasets containing the CHI variable is only possible from that time point onward [10]. The longitudinal nature of the dataset allows for individual follow-up for up to eight years and thereby is suited for an analysis into the uptake of and persistence with medications over time.

The majority of these prescriptions (more than 99% in the case of statin and antiplatelet therapies prescribed to CVD patients) are issued by GPs, with the remainder issued by other authorised prescribers such as nurses and dentists. Prescriptions issued in hospitals and dispensed in the community are also captured in the data, however, prescriptions dispensed within hospitals are not included [10]. Data include information on the patient, prescriber and dispenser, as well as drug information. For instance, patient attributes such as age and ethnic group are recorded, as well as the details relating to the prescribing individual and practice (e.g. age and sex of the GP; list size of GP practice) and to the location where the prescribing or dispensing took place (e.g. geographical location, deprivation quintiles) [11]. The dataset also contains detailed information on prescribed items, such as manufacturer, formulation code and strength, as well as dose instruction details such as timing interval, intake frequency, dose unit and quantity of drug. However, PIS does not provide information on the indication of the prescribed drug (e.g., indications for aspirin use include a number of different, independent conditions, such as CVD, rheumatoid arthritis, colorectal cancer, pain and fever).

All prescriptions are recorded with a British National Formulary (BNF) code, following the classification system developed by NHS England, the British Medical Association and the Royal Pharmaceutical Society. This is available as a pharmaceutical reference book and website, providing details on prescribing and pharmacology for medicines available on the NHS [12]. A hierarchical coding system categorises medications into one of fifteen chapters that relate to a specific system of the body or aspect of medical care. For example, the present study only examined medications listed under BNF Chapter 2, i.e. Cardiovascular System, which is captured in the first two characters of the BNF code. BNF codes are further subdivided into sections and paragraphs that are respectively identified through the first four and the first six characters of the code, with the remaining characters referring to the root drug description that denotes the chemical substance [11]. This study examined cardiovascular medications that are listed under Chapter 2, Sections 9 on Antiplatelet drugs and 12 on Lipid-regulating drugs (statins only) in the BNF. Please see **Appendix B.1** for an overview of the exact BNF codes of all drugs included in this study.

4.2.6. Ethical approval and funding

The research protocol for this study was independently peer reviewed by a senior researcher from the University of Glasgow and received sponsorship approval from

Clinical Trials and Research Governance (CTRG) Oxford (sponsorship PID:13584). The protocol was further reviewed by the Public Benefit and Privacy Panel for Health and Social Care (PBPP) Scotland, who approved the application to access the NHS Scotland data (Ref. 1718-0266). No further ethical approval was required due to the use of retrospective, de-identified data that is controlled by NHS National Services Scotland and only accessible via the National Safe Haven.

The study is funded by the Oxford British Heart Foundation Centre of Research Excellence (BHF CRE) Pump Priming Scheme (grant RE/13/1/30181), the Oxford Medical Research Council Doctoral Training Partnership (Oxford-MRC DTP) studentship, and the Nuffield Department of Population Health studentship. The funders had no role in study design, data collection and analysis.

4.3. Study population

4.3.1. Identification of participants

Eligible individuals were identified from the NHS General/Acute Inpatient and Day Case (SMR01) administrative dataset provided by ISD. The dataset includes 1,271,510 individuals living in Scotland who were hospitalised for diseases of the circulatory system (ICD-10 Chapter IX) or CVD-related procedures and operations (OPCS-4 Chapters K and L) at any point in time since January 1981 and who were still alive and resident in Scotland in April 2009 or onwards and therefore with all relevant information captured in the PIS.

For the purpose of this study, all Scottish residents aged 18 years or older were included if they had a main discharge diagnosis for an ASCVD event (as defined in **Section 4.3.3**), and therefore should have been offered low-density lipoprotein cholesterol (LDL-C)-lowering treatment and antiplatelet therapy according to SIGN's and NICE's clinical guidelines (i.e. SIGN 149 (2017), formerly SIGN 97 (2007); NICE CG181 (2014), formerly CG67 (2008)). All individuals with relevant hospital discharges recorded prior to 1 October 2009 and after 3 July 2017, and without a record of an ASCVD-related hospitalisation between 1 October 2009 and 3 July 2017, were excluded for two reasons. First, data linkage to the Prescribing Information System is only available since 1 April 2009. In order to cover at least six months of medication history prior to an ASCVD event, only the first recorded hospitalisation since 1 October 2009 is included in the analysis. Therefore, the cohort consists of a combination of (1) individuals with first-ever ASCVD-related

hospitalisations captured in the dataset as of 1 October 2009 and (2) individuals with a record of ASCVD-related hospitalisations prior to October 2009, who experienced a subsequent event on or after 1 October 2009. Second, individuals were followed for a maximum of 150 days after hospital discharge to determine whether statin and/or antiplatelet therapy had been initiated; hence 3 July 2017 was selected as the final inclusion date to allow for a follow-up time period of at least 150 days until the end of study on 31 December 2017.

Non-Scottish residents hospitalised for an ASCVD event in Scotland, and those who emigrated or died on or within 150 days after index discharge were excluded. In addition, individuals hospitalised for more than 90 days were excluded, as it was difficult to derive comparable information for this group in view of their discharge status. Specifically, a large proportion of individuals with hospital length of stay of 90 days or more attended rehabilitation services, which are counted as part of a continuous inpatient stay (CIS) record. As a result, the final discharge episode, which is used to derive the final diagnosis and date of discharge, refers to the date the rehabilitation ended in such cases rather than the earlier date at which patients were discharged home, making it difficult to estimate initiation rates of statins and antiplatelet agents in line with the definition outlined in **Section 4.4.1** and given the absence of hospital prescription data. Alternative calculations of initiation were not able to resolve the issue; these are presented in **Appendix B**.**2** including baseline characteristics comparing individuals with a length of stay of less than 90 days to those with 90 days or more.

Lastly, individuals who were dispensed a medication supply covering more than 365 days at any point in time since discharge, which was deemed a data error, or medications in non-pill format (e.g. amount unit reported in ml or mg, or as sprays, puffs, nebules, drops) were excluded to allow for the generation of pill-count based adherence and persistence measures and to remove potentially incorrectly coded pill count fields. Please see **Figure 4.1** for an overview of the study population selection process.

Study population eligibility criteria

Inclusion criteria

- Resident in Scotland between 1 October 2009 and 3 July 2017
- Male or female
- Aged 18 years or above at the time of hospital admission
- Individuals who were admitted and discharged between 1 October 2009 and 3 July 2017 with a record (i.e. main diagnosis) of an ASCVD event (as defined in **Section 4.3.3**)
    - In the case of survival analyses, the time period above is constrained to 1 October 2009 to 31 December 2016 to allow for an additional 12-month period that is used to categorise individuals into one of three statin/antiplatelet therapy use statuses at 12 months since discharge: (1) treatment initiators, (2) non-initiators, (3) discontinuers (methods further described in **Section 4.4.1**).

Exclusion criteria

- Individuals with a main discharge diagnosis for a non-atherosclerotic disease of the cardiovascular system recorded in all of their eligible hospitalisation episodes between 2009 and 2017
- Individuals who were discharged for ASCVD at any time before 1 October 2009 or after 3 July 2017, and did not have a record of an ASCVD-related hospitalisation between 1 October 2009 and 3 July 2017
    - In the case of survival analyses (methods described in **Section 4.4.2**): individuals who were discharged for ASCVD at any time before 1 October 2009 or after 31 December 2016, and did not have a record of an ASCVD-related hospitalisation between 1 October 2009 and 31 December 2016.
- Individuals with ASCVD index admission in the study period but with hospital length of stay > 90 days
- Individuals who died or emigrated within 150 days since index discharge
- All individuals who were prescribed cardiovascular medicines in non-pill format at any point in time since index discharge

- All individuals who were dispensed a medication supply covering more than 365 days at any point in time since index discharge
- Individuals with missing information on sex or deprivation levels.

Figure 4.1 Flowchart of the study population

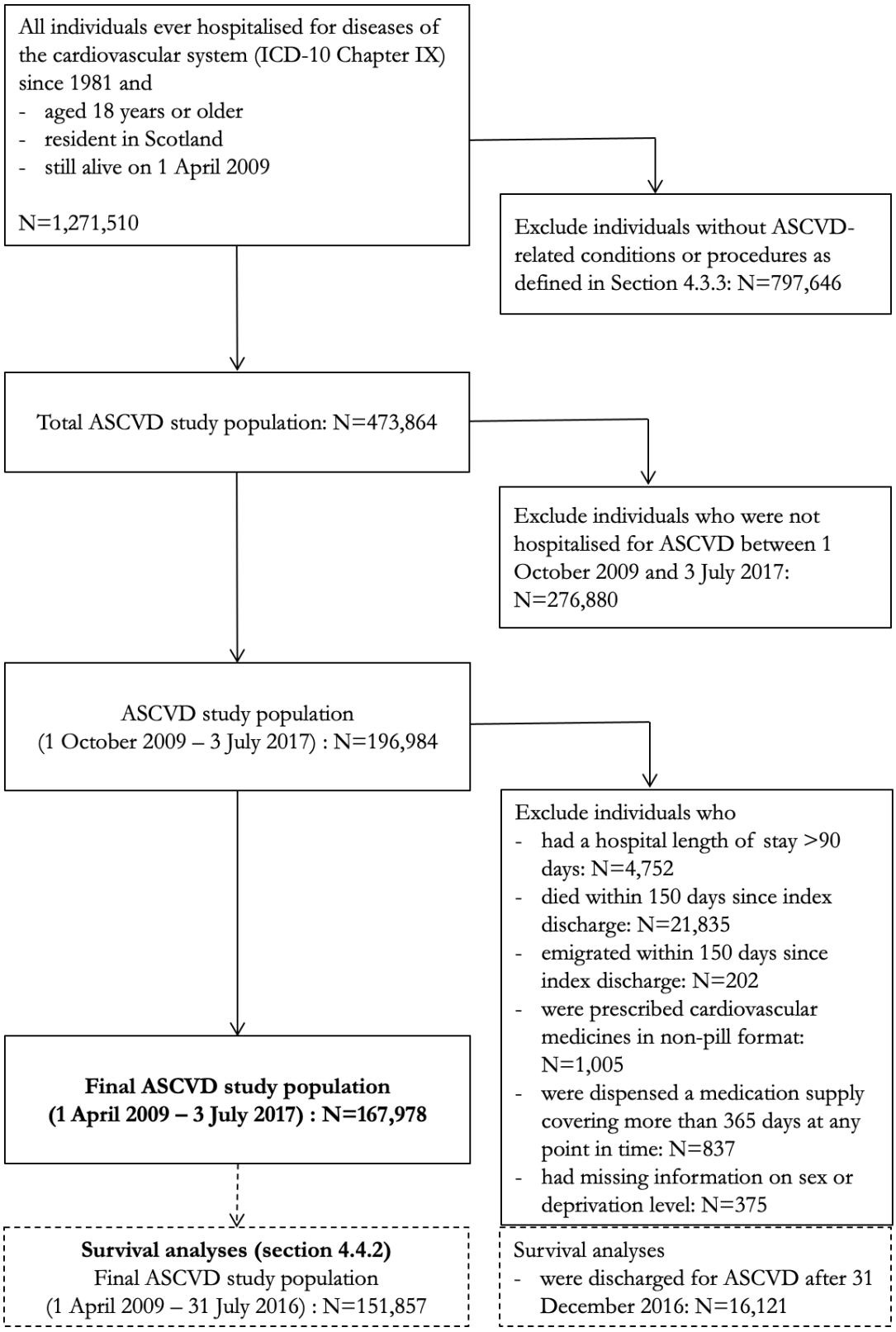
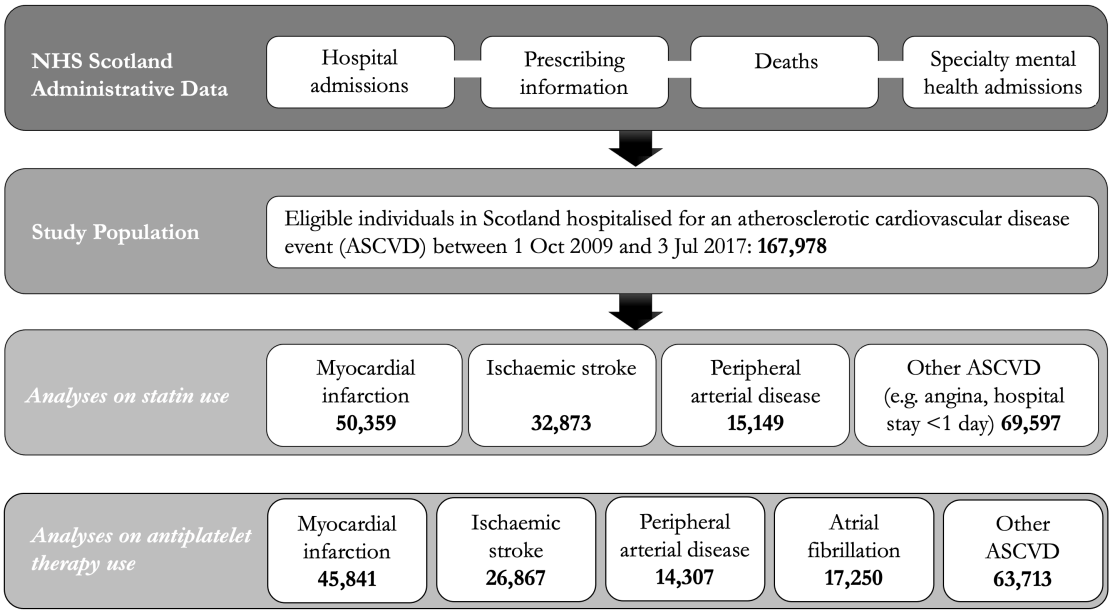


Figure 4.2 Overview of data linkage and study population[1]



[1] The study population consists of individuals discharged for an ASCVD event between 1 October 2009 and 3 July 2017 and only counts the first ASCVD event as of 1 October 2009 per person. The grouping by ASCVD type is based on the condition recorded in the main diagnostic field (or secondary diagnostic field in the case of atrial fibrillation) of the first recorded ASCVD event since 1 October 2009, and therefore there is no overlap between the ASCVD-type groups. For example, individuals discharged with a main diagnosis for myocardial infarction and a secondary diagnosis for stroke were counted in the 'myocardial infarction' group only and not further included in the ischaemic stroke group. Individuals discharged with a secondary diagnosis of atrial fibrillation and main diagnosis of ischaemic stroke were only counted in the atrial fibrillation group and excluded from the stroke group (see **Section 4.3.3**).

4.3.2. Participant follow-up

The study uses retrospective routine data for the time period from 1 October 2009 to 3 July 2017, in order to identify eligible study participants. The end of study is the last date available in the retrospective dataset at the time the data were requested from ISD Scotland, i.e. 31 December 2017. Individuals contributed person-years of outcome data since qualifying discharge from 1 October 2009 until the earliest of their date of death, emigration or the end of study date.

4.3.3. Definition of health conditions

Each discharge episode recorded a main diagnosis (i.e. the main condition treated or investigated) and up to five other diagnoses (this can include other acute events or chronic conditions) using the ICD-9 classification system from 1980 to March 1996 and ICD-10 from April 1996 onward. In addition, each episode can list a main procedure or operation

and up to three other operations, which are recorded using the OPCS-3 classification system from 1977 to 1988 and OPCS-4 from 1989 onward.

The study identified participants with ASCVD-related conditions (based on ICD-10 codes) recorded in the main diagnosis field of the last episode of a continuous inpatient stay (CIS) record, i.e., final discharge diagnosis. Individuals with ASCVD diagnoses recorded in one of the secondary diagnostic fields were excluded, in order to decrease the risk of including conditions that (1) had occurred prior to the index hospital admission and affected patient management and treatment, or (2) were differential diagnoses, or (3) were potentially misdiagnosed on admission, or (4) constituted ASCVD events that randomly occurred during hospitalisation for a non-ASCVD-related condition, and thus may not be communicated to primary care. The aim was to identify a robust and consistent study population that was specifically hospitalised for an ASCVD event and therefore should have been subsequently identified and treated accordingly in primary care, in line with the clinical guidelines for ASCVD.

Health conditions of interest constitute the first recorded atherosclerotic cardiovascular disease (ASCVD) event as of 1 October 2009, further subdivided into myocardial infarction (MI), ischaemic stroke, peripheral arterial disease (PAD), and 'other' ASCVD based on the ICD-10 code listed in the main discharge diagnosis field. For example, individuals discharged with a main diagnosis for myocardial infarction and a secondary diagnosis for stroke were counted in the 'myocardial infarction' group only and not further included in the ischaemic stroke group. As a result, the number of individuals across the four ASCVD groups add up to the total ASCVD population, as depicted in **Figure 4.2.** In the case of analyses on antiplatelet therapy use, a fifth subpopulation group was created consisting of patients with a record of atrial fibrillation (AF; ICD-10 code: I.48) in one of the five secondary diagnostic fields on discharge. This approach was taken because clinical guidelines such as NICE's guideline on *Atrial Fibrillation: Diagnosis and Management* (NG196) recommend anticoagulants, such as warfarin, instead of antiplatelet therapy in the secondary prevention of cardiovascular disease for individuals diagnosed with AF. For example, patients with a main diagnosis of ischaemic stroke and a secondary diagnosis of AF were only counted in the atrial fibrillation group and excluded from the ischaemic stroke group (**Figure 4.2**), in order to prevent an overestimation of the degree of suboptimal antiplatelet therapy use. The selection of ICD-10 codes that relate to these conditions are based on algorithms previously reported in literature [13], [14], and complemented with a list of conditions that was developed in consultation with a clinician

from the University of Oxford[45]. Hence, the study defined ASCVD as the presence of one of the following ICD-10 codes: I20-25, I63-67, I70-71, and I73.9. In the case of myocardial infarction and ischaemic stroke, a minimum hospital length of stay requirement of one day was introduced to exclude potentially incorrectly diagnosed cases of these conditions. Individuals with a discharge diagnosis of MI or stroke and a hospital length of stay of less than one day were classified as 'other' ASCVD. Please see **Table 4.1** for a detailed overview of the health conditions and corresponding ICD-10 codes.

Diagnostic information was further used to indicate whether individuals (1) had been hospitalised for an ASCVD event prior to their index hospitalisation as of October 2009 (using the same ICD-10 codes and ICD-9 code equivalents for ASCVD as above, however, including conditions recorded across all six available diagnostic fields in admission records), (2) had been subsequently hospitalised for an ASCVD-related event after the index hospitalisation (using the same ICD-10 codes as above and recorded in the main diagnosis field on discharge), or (3) had been hospitalised for at least one of seventeen specified comorbidities (using ICD-10 codes recorded across all six available diagnostic fields and across all hospital episodes), as defined by the Charlson Comorbidity Index, within 12 months prior to and including the index discharge (**Table 4.2**) [15]. In addition, information on operation procedures recorded at any point during the index ASCVD hospitalisation were used to identify patients who underwent a revascularisation procedure, specifically percutaneous transluminal balloon angioplasty and insertion of a stent into the coronary artery (i.e. PCI with drug-eluting stent: OPCS-4 code K.75.1-2; PCI with stent: OPCS-4 code K.75.3-9; recorded in any of the four OPCS fields), in order to identify patients eligible for dual-antiplatelet therapy.

[45] Assoc. Prof. David Preiss, Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford.

Table 4.1 Overview of health conditions and associated ICD-10 codes used to identify study participants

ICD-10 codes for acute events recorded in the main diagnosis field on discharge (from 1 October 2009 onwards)				
Total Population	**Populations by ASCVD type**			
Atherosclerotic Cardiovascular Disease (ASCVD)	**Myocardial Infarction (MI)**	**Ischaemic Stroke (IS)**	**Peripheral Arterial Disease (PAD)**	**Other ASCVD**
	Minimum 1 day hospital length of stay			
Coronary artery disease (CAD) **I20.X** Angina pectoris **I21.X** Acute myocardial infarction **I22.X** Subsequent myocardial infarction **I23.X** Certain current complications following MI (within 28 day period) **I24.X** Other acute ischaemic heart disease Chronic ischaemic heart disease **I25.0** Atherosclerotic cardiovascular disease, so described **I25.1** Atherosclerotic heart disease **I25.8** Other forms of chronic ischaemic heart disease **I25.9** Chronic ischaemic heart disease, unspecified **Cerebrovascular disease (CEVD)** **I63.X** Cerebral infarction **I64.X** Stroke, not specified as haemorrhage or infarction **I65.X** Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction **I66.X** Occlusion and stenosis of cerebral	**I21.X** Acute myocardial infarction **I22.X** Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction STEMI **I21.0** ST elevation myocardial infarction (STEMI) of anterior wall **I21.1** STEMI of inferior wall **I21.2** STEMI of other sites **I21.3** STEMI of unspecified site **I22.0** Subsequent STEMI of anterior wall **I22.1** Subsequent STEMI of inferior wall **I22.8** Subsequent STEMI of other sites NSTEMI **I21.4** Non-ST elevation myocardial infarction (NSTEMI) **I21.9** Acute myocardial	**I63.X** Cerebral infarction **I64.X** Stroke, not specified as haemorrhage or infarction	**I71.X** Aortic aneurysm and dissection **I73.9** Peripheral vascular disease, unspecified	**I20.X** Angina pectoris **I23.X** Certain current complications following MI (within 28 day period) **I24.X** Other acute ischaemic heart disease Chronic ischaemic heart disease **I25.0** Atherosclerotic cardiovascular disease, so described **I25.1** Atherosclerotic heart disease **I25.8** Other forms of chronic ischaemic heart disease **I25.9** Chronic ischaemic heart disease, unspecified **I65.X** Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction **I66.X** Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction

ICD-10 codes for acute events recorded in the main diagnosis field on discharge (from 1 October 2009 onwards)				
Total Population	**Populations by ASCVD type**			
Atherosclerotic Cardiovascular Disease (ASCVD)	**Myocardial Infarction (MI)**	**Ischaemic Stroke (IS)**	**Peripheral Arterial Disease (PAD)**	**Other ASCVD**
	Minimum 1 day hospital length of stay			
arteries, not resulting in cerebral infarction **I67.X** Other cerebrovascular diseases **Atherosclerosis** **I70.X** Atherosclerosis **Peripheral arterial disease (PAD)** **I71.X** Aortic aneurysm and dissection **I73.9** Peripheral vascular disease, unspecified **Identification based on secondary diagnostic fields only** **I48.X** Atrial fibrillation	infarction, unspecified **I22.9** Subsequent STEMI of unspecified site			**I67.X** Other cerebrovascular diseases **I70.X** Atherosclerosis **Identification based on secondary diagnostic fields only** **I48.X** Atrial fibrillation

Table 4.2 Overview of conditions and associated ICD-10 codes included in the Charlson Comorbidity Index (CCI) [15]

Condition included in the Charlson Comorbidity Index	ICD-10 code
1. AIDS/HIV	B20.X - B22.X, B24.X
2. Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin	C00.X - C26.X, C30.X - C34.X, C37.X - C41.X, C43. X, C45. X - C58.X, C60. X - C76.X, C81.X - C85.X, C88.X, C90.X - C97.X
3. Cerebrovascular disease	G45.X, G46.X, H34.0, I60.X - I69.X
4. Chronic pulmonary disease	I27.8, I27.9, J40.X - J47.X, J60.X - J67.X, J68.4, J70.1, J70.3
5. Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.X, I50.X, P29.0
6. Dementia	F00.X - F03.X, F05.1, G30.X, G31.1
7. Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
8. Diabetes with chronic complication	E10.2 - E10.5, E10.7, E11.2 - E11.5, E11.7, E12.2 - E12.5, E12.7, E13.2 - E13.5, E13.7, E14.2 - E14.5, E14.7
9. Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.X, G82.X, G83.0 - G83.4, G83.9
10. Metastatic solid tumour	C77.X - C80.X
11. Mild liver disease	B18.X, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.X, K74.X, K76.0, K76.2 - K76.4, K76.8, K76.9, Z94.4
12. Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
13. Myocardial infarction	I21.X, I22.X, I25.2
14. Peptic ulcer disease	K25.X - K28.X
15. Peripheral vascular disease	I70.X x, I71.X, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
16. Renal disease	I12.0, I13.1, N03.2 - N03.7, N05.2 - N05.7, N18.X, N19.X, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2
17. Rheumatic disease	M05.X, M06.X, M31.5, M32.X - M34.X, M35.1, M35.3, M36.0

4.4. Statistical Analysis

4.4.1. Outcome measures

The study estimated the extent of suboptimal cardiovascular medication use for the secondary prevention of ASCVD at two different stages of the treatment pathway: (1) the immediate treatment after discharge and (2) the long-term management of ASCVD. The first examines whether patients initiate treatment prescribed in primary care after hospital discharge for an ASCVD event. The second follows patients over time to assess (a) patients' adherence to and (b) persistence with the pharmacological management of ASCVD. The four outcome measures (i.e., initiation, adherence, persistence and re-initiation) are described in detail below and visualised in **Figure 4.3**.

Two types of treatments for the secondary prevention of ASCVD are assessed, namely the LDL-C-lowering treatment statin (i.e. atorvastatin, fluvastatin sodium, pravastatin sodium, rosuvastatin calcium, simvastatin) and antiplatelet therapies (i.e. aspirin, clopidogrel, ticagrelor, prasugrel, dipyridamole; including mono and dual-antiplatelet therapy combinations of the drugs previously listed). As such, cardiovascular medication use is defined as the use of statin and/or antiplatelet therapy in people who have experienced an ASCVD event and who, according to Scottish (i.e. SIGN) and English/Welsh (i.e. NICE) clinical guideline recommendations (i.e. SIGN 149 (2017), formerly SIGN 97 (2007); NICE CG181 (2014), formerly CG67 (2008)), covering the entire analysed period from 2009 to 2017, should have been offered both statin and antiplatelet treatment long-term to reduce risks of subsequent CVD events. Other cardiovascular pharmacotherapies such as alternative LCL-C-lowering drugs (e.g. ezetimibe or PCSK9 inhibitors) or blood-pressure-lowering medications were not evaluated, because information on these therapies was not available in the dataset.

In addition to examining the use of statins in general, the study assessed the initiation of high-intensity statin therapy compared to low/medium-intensity statins. The grouping of statins into two intensity categories was performed in line with NICE's definition, which is based on the percentage reduction in low-density lipoprotein cholesterol (LDL-C) levels: statins that reduce LDL-C by ≤40% and >40% were categorised as low/medium and high intensity, respectively [16]. Please see **Table 4.3** for a complete list of statins and their respective intensity categories.

Lastly, the study also examined the associations between both statin non-initiation and discontinuation at 12 months since index discharge, and subsequent non-fatal or fatal

ACVD-related events, defined as hospitalisation for a subsequent to index discharge ASCVD event (as defined in **Table 4.1)** or death with ASCVD (as defined in **Table 4.1**) stated as the primary cause of death.

Table 4.3 Definition of high and low/medium statin intensity based on NICE's classification of statin intensity [16]

High-intensity statin	Low-/medium-intensity statin
Atorvastatin 20mg – 80mg	Atorvastatin 10mg
Rosuvastatin 10mg – 40mg	Fluvastatin 20mg – 80mg
Simvastatin 80mg	Pravastatin 10mg – 40mg
	Simvastatin 10mg – 40mg

Immediate management of ASCVD: Initiation of cardiovascular medications

Medication initiation here is defined as individuals being prescribed pharmacotherapy, i.e. statin or antiplatelet therapy, within 90 days from index discharge and dispensed within 60 days from that prescription (please see **Figure 4.3**), covering a time frame post discharge that has been used in previous studies summarised in the systematic review in **Chapter 3**. Non-initiation here refers to individuals who were (a) either not prescribed treatment by their physician within 90 days since discharge or (b) prescribed treatment within 90 days since discharge but did not dispense treatment within 60 days since prescription. The term non-initiation encompasses both failure of physicians to prescribe treatment and failure of patients to dispense treatment.

The NHS Scotland prescribing dataset does not contain information on medications dispensed by hospital staff during the hospitalisation period. Therefore, a time period of 90 days was chosen in consultation with a clinician from the University of Oxford[46] to account for any hospital medications dispensed on hospital discharge (typically <1 month supply) and to allow for sufficient time for a patient to see a community-based prescriber for a new medication prescription or receive a prescription renewal. The number of pills from a previous prescription dispensed prior to the index hospital admission was assessed in order to account for any pills that could have been carried over

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into the time period post-discharge and ensure that the number of remaining pills was less than 90.

In order to allow for the direct comparison of results with those reported in previous literature that used different definitions of initiation (**Chapter 3**), additional analyses are conducted, in which initiation is defined as individuals being both prescribed and dispensed treatment within 30, 60 and 90 days since hospital discharge.

Long-term management of ASCVD: Adherence to cardiovascular medications

Adherence is defined as the degree to which patients follow the agreed recommendations and prescription instructions from a healthcare provider [17]. The patient's refill records are used to indirectly measure adherence as the Proportion of Days Covered (PDC), which is calculated by the ratio of the number of days the patient is covered by the medication in a period to the total number of days in the period that the patient is eligible to have the medication on hand [17]. PDC is calculated as follows:

$$PDC = 100\% \times \frac{Number\ of\ days\ in\ period\ covered\ with\ drug\ prescription}{Number\ of\ days\ in\ period}$$

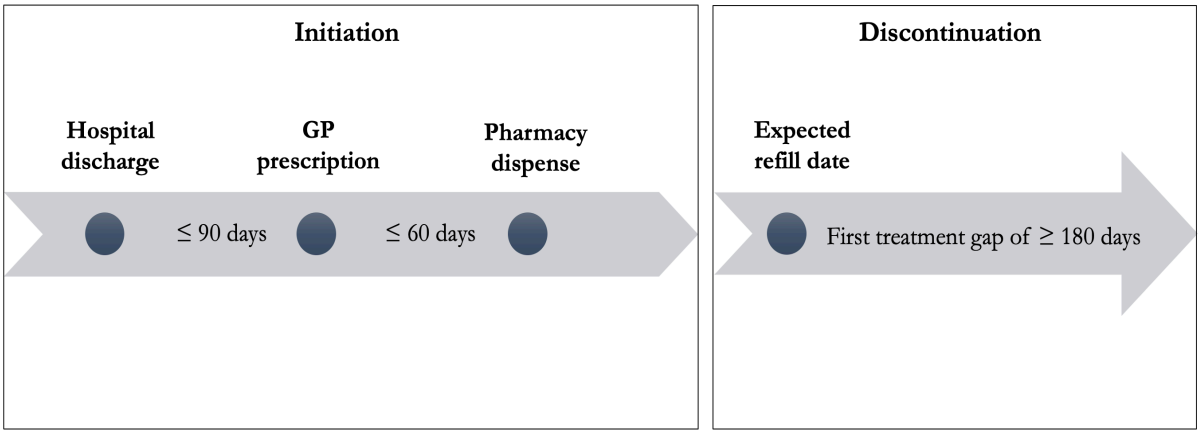
This study uses a commonly employed, arbitrary threshold of ≥ 80% based on Hayne's definition of adherence for the proportion of prescribed doses taken [18], in order to indicate good adherence as both a binary and continuous outcome measure. Adherence is here measured from the first day of treatment initiation until study end, death, emigration or treatment discontinuation (see definition below), depending on which scenario occurred first. In addition, the adherence rate at 12 months since treatment initiation is reported to allow for the direct comparison of results reported in previous literature (**Chapter 3**).

Long-term management of ASCVD: Persistence with cardiovascular medications

Medication persistence refers to the act of continuing treatment for the prescribed duration [19]. It is here defined as the time in days from the start of medication initiation to discontinuation of treatment, where discontinuation is measured as the start of the first continuous medication treatment gap of 180 days or more since initiation (please see **Figure 4.3**). The time frame of 180 days has been previously used in studies estimating persistence with treatment, which are summarised in the systematic review in **Chapter 3**.

In the case of individuals who discontinued treatment, the proportion of individuals who re-initiated treatment at any point in time after their initial treatment gap is calculated. Re-initiation is here defined as a record of having been prescribed and dispensed the previously discontinued therapy at any point in time after the first 180-day treatment gap.

Figure 4.3 Visualisation of the outcome measures *initiation* and *persistence**



*Persistence is measured as the time from initiation to discontinuation of treatment.

4.4.2. Statistical methods

The following statistical methods were used in **Chapter 5** (i.e. the rates and determinants of statin use for the secondary prevention of ASCVD) and **Chapter 6** (i.e. the rates and determinants of antiplatelet therapy use for the secondary prevention of ASCVD). The statistical analyses were performed using Stata SE version 15.

Rates of statin and antiplatelet therapy initiation, adherence and discontinuation

Rates of (1) medication initiation and (2) discontinuation were reported overall and by calendar year, adjusted for patient sex and age group at event date (i.e. 18-49 years, 50-59 years, 60-69 years, 70-79 years, 80-89 years, and 90 years or older). In the case of statin therapy, initiation rates were reported for statins overall and by statin intensity. In order to account for the potential titration of statin therapy within the first 12 months since initiation, statin intensity initiation rates were reported by statin intensity at index initiation and at 12 months since index initiation. In addition, the average duration in days to discontinuation was estimated. Results are reported for all ASCVD events and, separately, for myocardial infarction, ischaemic stroke, peripheral arterial disease and other

atherosclerotic cardiovascular diseases, as well as atrial fibrillation in the case of antiplatelet therapy. Atrial fibrillation patients are more likely to be prescribed anticoagulation instead of antiplatelet therapy and were therefore excluded from the total ASCVD population, as well as each of the four subpopulation groups. Instead, the results for the atrial fibrillation population are reported separately in the appendix. In addition, overall adherence rates while on treatment were reported.

Determinants of statin and antiplatelet therapy initiation and discontinuation, and the association between statin and antiplatelet therapy use and health outcomes

Multivariable cross-sectional logistic regression models were used to study the relevance of patient characteristics and discharge calendar year to the likelihood of initiating statin or antiplatelet therapy (**Model 1a**), and the likelihood of initiating high-intensity statin therapy vs. low/medium-intensity therapy (**Model 1b**). The use of logistic regression analyses, and the resulting exclusion of individuals who died or emigrated within 150 days since discharge, was chosen over survival analyses, such as a Cox proportional hazards model, that would have examined the time from hospital discharge to treatment initiation for the following reasons: (1) many individuals (60%) were effectively on statin and/or antiplatelet therapy at index hospital admission, in addition to many individuals being likely discharged with treatment, and therefore were in effect continuing on treatment rather than de-novo initiating treatment, and (2) while there may have been a number of individuals who died within 150 days since discharge, who would have benefitted from treatment to prevent subsequent fatal vascular events, the cohort would also include many individuals who were more/severely ill and constitute complex patient cases, and therefore physicians may have not prioritised these patients for secondary preventative treatment in the same way as the cohort used in the analyses, which is the assumption when deaths are considered as censoring events in survival analyses.

Secondly, a Cox proportional hazards model was used to assess the role of patient characteristics, as well as discharge calendar year, in the persistence with treatment, censored for death and emigration (**Model 2**). A Schoenfeld residuals test for proportional hazards assumption was performed which showed that the proportional hazards assumptions were met. In addition, a Cox proportional hazards model (**Model 3**) examined the association between statin therapy non-initiation and discontinuation and subsequent risk of a fatal and non-fatal ASCVD event. Based on the results of the

Schoenfeld residuals test for proportional hazards assumption, the model included age group and ASCVD type stratifications to meet the proportional hazards assumptions.

Models 1 and 2 included the following variables of interest: sex (male, female), age group at index event date (≤ 49, 50-59, 60-69, 70-79, 80-89, ≥ 90 years), deprivation quintiles based on the Scottish Index of Multiple Deprivation[47] (where 1 indicates most deprived and 5, least deprived) [21], Charlson Comorbidity Index (measured as the number of comorbidities reported in the 12 months prior to index discharge, where 'no comorbidities' is defined as the absence of 17 (i.e. 16 in the case of MI, stroke and PAD population) specified medical conditions (see **Table 4.2**): no comorbidities, 1, 2, 3, or ≥ 4 comorbidities), inpatient or outpatient admission to a mental health specialty or psychiatric hospital within 12 months prior to index admission (yes, no), history of a previous ASCVD event prior to April 2009 and/or previous cardiovascular medication use in the last 12 months prior to index admission (no history of ASCVD and no prior use of drugs, history of ASCVD and no prior use of drugs, no history of ASCVD and prior use of drugs, history of ASCVD and prior use of drugs), and calendar discharge year group (2009-2011, 2012-214, 2015-2017). In the case of Model 3, which evaluated ASCVD events and deaths in the long-term, the variables listed above were included as covariates when assessing ASCVD risk between individuals who (1) never initiated treatment within 12 months since hospital discharge, (2) those who initiated and subsequently discontinued treatment within 12 months since hospital discharge and (3) those who initiated treatment within 12 months since hospital discharge. The definition of initiation here for all three groups follows the same definition as used prior, i.e., individuals who were prescribed therapy within 90 days since index discharge and dispensed the therapy within 60 days since prescription.

Even though the dataset also contains information on the Scottish Government Urban Rural Classification, this information was not used due to its inability to indicate the distance to health care providers, prescribers and dispensers, as well as its strong correlation with the Scottish Index of Multiple Deprivation (SIMD)[48]. Given that SIMD captures urban-rural classification in addition to seven official domains (i.e., income,

[47] The Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation which ranks the extent to which one of 6,976 small areas in Scotland are deprived across seven domains: income, employment, education, health, access to services, crim and housing. It is an area-based measure of relative deprivation, meaning that not every individual in a highly deprived area will experience high levels of deprivation. Rankings are performed every four years and this thesis uses the SIMD ranking for the year 2009, as was recommended by the Electronic Data Research and Innovation Service (eDRIS) Scotland team in 2018 when the application for the NHS Scotland data was filed. This is because the methodology of the SIMD has changed over time, which prevents a comparison of different versions of the SIMD.

[48] Rural areas in Scotland tended to have lower levels of deprivation.

employment, education, health, access to services, crime and housing), it was selected in the final models. The inclusion of Health Board information to investigate regional differences in medication use was considered. However, Chi-square goodness-of-fit tests showed that the inclusion of this information led to an overfitting and decrease in the goodness-of-fit of the models.

In addition, some available patient information was examined but ultimately excluded from the final models. For instance, the patients' ethnicity group was reported, however, information was missing for 13% of the ASCVD population and there was limited variation, with more than 98% of the study population with available data being categorised as 'white'. Marital status information was not included for the following reasons: (1) more than 45% of data for marital status is missing; (2) some categories are grouped antithetically, e.g. married and separated individuals are grouped together; and (3) marital status is expected to play a role in patients' adherence behaviour over time, but information is only provided on discharge and might change within a follow-up time period of up to eight years.

Lastly, the role of prescriber characteristics in the initiation of and persistence with treatment was not assessed for several reasons, despite data being available for 80% of individuals who initiated either statin or antiplatelet therapy. Firstly, the data does not include records of (a) prescribed medications that were not dispensed and (b) on medications that were not prescribed after consultation with a general practitioner, therefore preventing an analysis into prescriber characteristics associated with patients' non-initiation of medications. Secondly, the dataset does not contain information on whether statins were not initiated or discontinued due to prescribers' recommendations or due to patients' beliefs and attitudes towards treatment. Thirdly, the data does not record whether the prescribing physician had a consultation with the patient or not, making it impossible to assess whether the discontinuation of treatment was discussed between the patient and physician or not.

As a result, the final statistical models can be expressed as follows:

Model 1a – Initiation: logistic regression model

$Drug\ initiation = \gamma Patient\ Characteristics + \beta Discharge\ Year + \epsilon$, where

$Drug\ initiation$ refers to the single dispense of statin and antiplatelet by an individual within a specified time period since index hospital discharge,

$\gamma Patient\ Characteristics$ refers to individuals' demographic, socio-economic and clinical characteristics at index hospital discharge,

$\beta Discharge\ Year$ refers to calendar year discharge group, and

ϵ denotes the error term.

Model 1b – Initiation by statin intensity: logistic regression model

$High\ intensity\ statin\ initiation = \gamma Patient\ Characteristics + \beta Discharge\ Year + \epsilon$, where

$High\ intensity\ statin\ initiation$ refers to the single dispense of high-intensity statin by an individual within a specified time period since index hospital discharge,

$\gamma Patient\ Characteristics$ refers to individuals' demographic, socio-economic and clinical characteristics at index hospital discharge,

$\beta Discharge\ Year$ refers to calendar year discharge group, and

ϵ denotes the error term.

Model 2 – Persistence: Cox proportional hazards model

$h(t) = h_0(t) \times \exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p)$, where

$h(t)$ is the expected hazard of discontinuing treatment at time *t*,

$h_0(t)$ is the baseline hazard, and

the covariates $x_1 \ldots x_p$ refer to patient characteristics (demographic, socio-economic and clinical), and calendar year of discharge group.

Model 3 – Health outcome: Cox proportional hazards survival analysis

$h(t) = h_0(t) \times \exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p)$, where

$h(t)$ is the expected hazard of experiencing a fatal or non-fatal ASCVD-related event at time *t*,

$h_0(t)$ is the baseline hazard, and

the covariates $x_1 \ldots x_p$ refer to patient characteristics that were adjusted for (i.e. demographic, socio-economic and clinical, and calendar year of discharge group).

4.5. Summary

In this chapter, I described the linked National Scottish Health datasets and the design of my study. I provided definitions of health and study outcomes, and described the statistical methods used to investigate the role of patient characteristics in the immediate and continued use of statin and antiplatelet therapy following an ASCVD-related hospitalisation in Scotland. In the next Chapters 5 and 6, I report the results on the level of suboptimal medication use and its association with patient characteristics at different treatment stages, for statin and antiplatelet therapies, respectively.

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5

Rates and determinants of statin use for the secondary prevention of cardiovascular disease

Summary

This chapter uses population-wide individual-level patient data on 167,978 individuals hospitalised for an ASCVD-related event in Scotland in the time period from 1 October 2009 to 3 July 2017, who were followed-up until study end, emigration or death for a period of up to eight years. Out of these individuals, 136,855 (81.5%) initiated statin therapy, while the remainder (19.5%) did not. Of those who initiated statin, 43.4% were using high-intensity statin therapy within 12 months since index prescription, the remainder (56.6%) being prescribed medium- or low-intensity treatment. The initiation rate changed minimally since 2009, and significant age and gender-related treatment gaps were observed throughout the study period, with fewer women and fewer elderly (aged 70 years or older) individuals using statins. Uptake also varied significantly by ASCVD type, from only 75% among patients with peripheral arterial disease (PAD), to 81% in stroke and 88% in myocardial infarction (MI) patients. While on treatment, 90.5% of users were adherent (i.e. a Proportion of Days Covered (PDC) score of 80% or more). However, 24% of statin users discontinued treatment at some point in time, and of those who discontinued, half (50.1%) did so within 1.5 years since initiation, and 80% within 3.5 years. Rates of discontinuation at some point in time varied by ASCVD type, ranging from 22.7% for MI patients, to 25.7% for stroke and 29% for PAD patients. Out of all patients who discontinued treatment, 38% re-initiated statin therapy at some point in time after their initial treatment gap of 180 days. Patient characteristics associated with lower odds of initiating statin and higher risk of discontinuing it if initiated included being female, aged 70 years or older, having three or more comorbidities and experiencing a previous mental health-related admission or day case. Individuals living in the most deprived areas also had lower odds of initiating statin therapy compared to those living in the least deprived areas. Findings from the Cox proportional hazards survival analyses showed that patients who never initiated or discontinued statin therapy were at higher risk of experiencing subsequent fatal and non-fatal ASCVD, irrespective of the type of ASCVD.

5.1. Participant characteristics

Between 1 October 2009 and 3 July 2017, 196,984 individuals were hospitalised for an ASCVD-related event in Scotland, as defined in **Chapter 4, Section 3**. Individuals were excluded if they had a hospital length of stay of more than 90 days (4,752 individuals, 2%), died (21,835 individuals, 11%) or emigrated from Scotland (202 individuals, 0.1%) within 150 days since hospital discharge, had non-pill format prescriptions (1,005 individuals, 0.5%), were prescribed more than 365 pills in a single prescription (837 individuals, 0.4%), or were missing information on sex or deprivation level (375 individuals, 0.2%) (**Chapter 4, Figure 4.1**).

The remaining 167,978 ASCVD patients were followed-up for an average of 4.6 years, and up to 8.2 years, from hospital discharge and until study end, emigration, or death. A large proportion of these individuals (67,114, 40%), had a record of at least one ASCVD-related hospitalisation prior to 1 October 2009, increasing to 50% in the case of patients hospitalised during the study period for peripheral arterial disease (PAD). Average age at hospital discharge was 67.4 years (standard deviation (SD) 12.7 years) and varied by CVD type, ranging from an average of 66 years (SD 14 years) among myocardial infarction (MI) patients to 71 years (SD 13 years) among ischaemic stroke patients (**Table 5.1**).

Of all ASCVD-related hospitalisations, almost two thirds (61%) constituted male patients, with similar rates across CVD types, except for stroke where 52% of patients were men. Of the 87% of all patients for whom ethnicity data were available, the majority of patients were of white ethnic background (98%). More than half of all patients (55.4%) were dispensed statin therapy in the 12 months prior to index admission (i.e., the first recorded ASCVD-related hospital admission in the study period), with rates ranging from 38.3% among MI patients to 69.7% among PAD patients. Most (82%) patients had had one or more hospital discharges for at least one out of 17 specified conditions included in the Charlson Comorbidity Index (CCI) in the 12 months leading up to and including the index discharge (see **Chapter 4** for detailed information on the CCI). In addition to the non-mental health-related conditions included in the CCI, a small proportion of individuals (1.8%) had a record of an inpatient stay or day case attendance in mental health specialities or psychiatric hospitals in Scotland in the 12 months prior to the index admission.

Table 5.1 Baseline characteristics of individuals hospitalised for an ASCVD-related event at index discharge and by CVD type[49]

	Total Atherosclerotic cardiovascular disease (ASCVD)	Myocardial infarction	Ischaemic stroke	Peripheral arterial disease	Other ASCVD
N	167,978	50,359	32,873	15,149	69,597
Age on discharge, years (mean, SD)	67.4 (12.7)	65.9 (13.6)	70.8 (13.4)	68.7 (11.8)	66.6 (11.7)
Female	65,707 (39.1)	17,779 (35.3)	15,851 (48.2)	5,328 (35.2)	26,749 (38.4)
Ethnic group					
White	143,578 (85.4)	43,184 (85.7)	28,069 (85.3)	13,118 (86.6)	59,207 (85.0)
Other	2,373 (1.4)	839 (1.67)	294 (0.9)	62 (0.4)	1,178 (1.7)
Missing	22,027 (13.1)	6,336 (12.6)	4,510 (13.8)	1,969 (13.0)	9,212 (13.3)
SIMD deprivation quintile (2009)[50]					
5 (least deprived)	26,294 (15.7)	7,699 (15.3)	5,223 (15.9)	2,027 (13.4)	11,345 (16.3)
4	30,896 (18.4)	9,243 (18.4)	5,841 (17.8)	2,811 (18.6)	13,001 (18.7)
3	34,330 (20.4)	10,289 (20.4)	6,492 (19.8)	3,226 (21.3)	14,323 (20.6)
2	37,290 (22.2)	11,178 (22.2)	7,343 (22.3)	3,620 (23.9)	15,149 (21.8)
1 (most deprived)	39,168 (23.3)	11,950 (23.7)	7,974 (24.2)	3,465 (22.9)	15,779 (22.7)
Urban/Rural Classification[51]					
Large urban areas	54,126 (32.2)	16,455 (32.7)	11,115 (33.8)	4,198 (27.7)	22,358 (32.1)
Other urban areas	60,563 (36.0)	18,027 (35.8)	11,731 (35.7)	5,808 (38.3)	24,997 (35.9)
Accessible small towns	16,042 (9.6)	4,904 (9.7)	3,126 (9.5)	1,444 (9.5)	6,568 (9.5)
Remote small towns	6,772 (4.0)	2,000 (4.0)	1,282 (3.9)	689 (4.6)	2,801 (4.0)
Accessible rural	19,314 (11.5)	5,804 (11.5)	3,637 (11.1)	1,884 (12.4)	7,989 (11.5)
Remote rural	11,161 (6.7)	3,169 (6.3)	1,982 (6.1)	1,125 (7.4)	4,884 (7.0)
Health Board					
Ayrshire & Arran	13,853 (8.2)	4,403 (8.7)	2,571 (7.8)	1,096 (7.2)	5,783 (8.3)
Borders	4,192 (2.5)	1,290 (2.6)	864 (2.64)	319 (2.1)	1,719 (2.5)
Dumfries & Galloway	5,425 (3.2)	1,542 (3.1)	1,037 (3.2)	586 (3.9)	2,260 (3.3)
Fife	11,358 (6.8)	3,698 (7.3)	2,407 (7.3)	1,507 (10.0)	3,746 (5.4)
Forth Valley	8,884 (5.3)	2,404 (4.8)	1,605 (5.0)	954 (6.3)	3,921 (5.6)
Grampian	16,589 (9.9)	4,786 (9.5)	2,640 (8.0)	2,102 (13.9)	7,061 (10.2)

[49] Numbers are reported as N (%) unless otherwise specified.

[50] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones.

[51] Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.

	Total Atherosclerotic cardiovascular disease (ASCVD)	Myocardial infarction	Ischaemic stroke	Peripheral arterial disease	Other ASCVD
Greater Glasgow and Clyde	36,676 (21.8)	11,113 (22.1)	7.523 (22.9)	2,282 (15.1)	15,758 (22.6)
Highland	11,830 (7.1)	3,276 (6.5)	2,013 (6.2)	1,254 (8.3)	5,287 (7.6)
Lanarkshire	22,332 (13.3)	6,265 (12.4)	4,517 (13.7)	1,854 (12.2)	9,696 (13.9)
Lothian	21,373 (12.7)	7,144 (14.2)	4,662 (14.2)	1,566 (10.3)	8,001 (11.5)
Tayside	13.275 (7.9)	3,848 (7.7)	2,697 (8.2)	1,378 (9.1)	5,352 (7.7)
Other (Orkney, Shetland, Eileanan Siar Western Isles)	2,191 (1.3)	590 (1.2)	337 (1.0)	251 (1.7)	1,013 (1.5)
ASCVD-related hospitalisation prior to 1 October 2009	67,114 (39.9)	15,695 (31.2)	10,751 (32.7)	7,610 (50.2)	33,058 (47.5)
Charlson Comorbidity Index (within 12 months prior and incl. index event)					
0 (no-comorbidities) [52]	30,743 (18.3)	Not applicable	Not applicable	Not applicable	30,743 (44.2)
1	77,182 (45.9)	26,565 (52.8)	18,541 (56.4)	9,501 (62.6)	22,599 (32.4)
2	33,709 (20.1)	14,029 (27.9)	7,624 (23.2)	2,707 (17.9)	9,359 (13.4)
3	14,937 (8.9)	5,501 (10.9)	3,862 (11.8)	1,569 (10.4)	4,009 (5.8)
4 or more comorbidities	11,407 (6.8)	4,264 (8.4)	2,846 (8.7)	1,372 (9.1)	2,926 (4.2)
Mental health inpatient/day case within 12 months prior to index admission	2,994 (1.8)	766 (1.5)	819 (2.5)	202 (1.3)	1,208 (1.7)
At least one statin prescription in last 12 months prior to index admission[53]	93,103 (55.4)	19,268 (38.3)	14,338 (43.6)	10,553 (69.7)	48,979 (70.3)

[52] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

[53] For individuals with index hospitalisations in 2009, information on prior medication use is available from 1 April 2009 and onward, thereby contributing a minimum of 6 months and up to 12 months of medication history. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

5.2. Initiation of statin therapy

5.2.1. Rates of statin initiation

Overall statin initiation rates

Of the 167,978 individuals hospitalised for an ASCVD-related event, 136,855 (81.5%) initiated statin therapy, defined as being prescribed statin therapy within 90 days of the index discharge and subsequently being dispensed the therapy within 60 days since prescription[54]. Among patients hospitalised for MI, ischaemic stroke, PAD and other ASCVDs, the initiation rates were 88%, 81%, 75% and 78%, respectively. Compared to non-initiators, initiators were on average younger (average age 67 years vs. 70 years, $p<0.001$), less likely to be female (36.8% vs. 49.1%, $p<0.001$), less likely to be previous statin users (48.1% vs. 60.6%, $p<0.001$) and were less likely to have had mental health admissions in the 12 months prior to the index event (1.5% vs. 3.1%, $p<0.001$). **Table 5.2** summarises baseline characteristics of statin initiators and non-initiators by CVD type.

The proportion of individuals initiating statin therapy increased marginally over time, from 79.9% among individuals hospitalised for ASCVD between 2009 and 2011, to 81.3% between 2012 to 2014 ($p<0.001$), however, did not significantly increase thereafter (i.e., 81.7% of individuals initiated treatment in the most recent period from 2015 to 2017) (**Table 5.3**). Overall, initiation rates increased across all subgroups, i.e. men ($p<0.001$), women ($p<0.05$), individuals aged between 18 to 69 years ($p<0.001$) and those aged 70 years or older ($p<0.001$). However, initiation rates between subgroups varied substantially. For instance, only 77% of women compared to 84.8% of men initiated statin therapy from 2015 to 2017, with the gender gap fluctuating since 2009 (i.e. 6.8% difference between men and women in 2009/11; 10.2% in 2012/14, and 7.8% in 2015/17). Similar trends were also present when comparing the elderly population aged 70 years or older to those aged 50 to 59 years, where the elderly were less likely to initiate treatment. While initiation rates increased in both age groups over time (except in those aged 90 years or older, where rates decreased in the latest years), the gap between the groups in 2015/2017 ranged from 3.9% (50-59 years vs. 70-79 years) to 12.4% (50-59 years vs. 80-89 years).

[54] The initiation rate varies significantly based on the time interval selected. For instance, only 34.4% of the 167,978 individuals hospitalised for ASCVD were prescribed and dispensed treatment within 30 days since discharge. The proportion increases to 58% and 71.8%, respectively, if using a 60 and 90-day interval, all of which are previously used time intervals in relevant literature, as described in detail in **Chapter 3**.

Table 5.2 Participant characteristics of statin initiators and non-initiators at index admission discharge, total ASCVD and by ASCVD type[55]

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Statin initiation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N (%)	136,855 (81.5)	31,123 (18.5)	44,440 (88.3)	5,919 (11.8)	26,501 (80.6)	6,372 (19.4)	11,364 (75.0)	3,785 (25.0)	54,550 (78.4)	15,047 (21.6)
Age on discharge, years (mean, SD)	66.8 (12.2)	70.0 (14.9)	64.9 (13.1)	73.6 (14.5)	70.1 (12.8)	73.7 (15.4)	68.9 (10.5)	67.9 (14.9)	66.3 (10.9)	67.6 (14.2)
Hospital length of stay, days (mean, SD)	6.8 (12.1)	9.5 (16.1)	6.1 (6.9)	9.8 (12.1)	15.2 (19.6)	21.8 (23.2)	8.3 (12.9)	10.2 (14.6)	2.9 (7.4)	4.0 (10.2)
Female	36.8	49.1	33.6	47.9	46.3	56.3	33.4	40.6	35.6	48.7
Ethnic group										
White	85.3	86.3	85.5	87.6	85.2	86.0	86.6	86.6	84.8	86.0
Other	1.4	1.3	1.7	1.5	0.9	0.8	0.3	0.6	1.7	1.5
Missing	13.3	12.4	12.8	10.9	13.9	13.2	13.1	12.8	13.5	12.5
SIMD quintile (2009)[56]										
5 (least deprived)	15.7	15.5	15.3	15.2	15.8	16.2	13.3	13.8	16.4	15.8
4	18.5	18.1	18.5	17.0	17.8	17.6	18.4	19.1	18.7	18.6
3	20.4	20.6	20.3	21.2	19.8	19.5	21.4	20.9	20.5	20.7
2	22.2	22.3	22.1	22.8	22.2	22.9	24.2	23.1	21.8	21.6
1 (most deprived)	23.3	23.5	23.7	23.8	24.4	23.8	22.8	23.1	22.5	23.3
Urban-Rural Classification[57]										
Large urban areas	31.9	33.3	32.3	35.8	33.7	34.4	27.9	27.1	31.8	33.4
Other urban areas	36.1	35.8	36.0	34.3	35.7	35.5	37.7	40.2	36.1	35.4
Accessible small towns	9.7	9.0	9.8	9.1	9.7	8.8	9.5	9.6	9.6	8.9
Remote small towns	3.9	4.2	3.9	4.5	3.7	4.6	4.8	3.7	4.0	4.1

[55] Tests of significance: t-tests and chi-squared tests were performed to test for statistically significant differences in baseline characteristics between initiators and non-initiators. Results **total ASCVD** population: all characteristics between initiators and non-initiators differed significantly ($p<0.001$), except for SIMD and ethnic groups, where no statistically significant differences were found. **MI**: all characteristics between initiators and non-initiators differed significantly (all $p<0.001$, except urban rural factor $p<0.01$), except for SIMD and ethnic groups, where no stat. significant differences were found. **Stroke**: all characteristics between initiators and non-initiators differed significantly ($p<0.001$), except for SIMD and ethnic groups, where no stat. significant differences were found. **PAD**: all characteristics between initiators and non-initiators differed significantly (all $p<0.001$, except ethnic group $p<0.05$), except for SIMD and CCI, where no stat. significant differences were found. **Other ASCVD**: all characteristics between initiators and non-initiators differed significantly (all $p<0.001$), except for SIMD and ethnic group, where no stat. significant differences were found.

[56] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones.

[57] Scottish Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes' drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Statin initiation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Accessible rural	11.6	11.2	11.7	10.5	11.2	10.5	12.3	12.9	11.5	11.5
Remote rural	6.7	6.4	6.4	5.8	5.6	6.3	7.7	6.6	7.1	6.7
Charlson Comorbidity Index										
0 (no-comorbidities)[58]	18.0	19.3	N/A	N/A	N/A	N/A	N/A	N/A	45.1	40.9
1	47.1	41.4	54.9	36.8	57.8	50.6	62.9	62.2	32.2	33.2
2	20.3	19.2	27.6	29.6	23.0	24.1	17.9	17.8	13.4	13.4
3	8.5	10.5	10.2	18.2	11.3	13.7	10.5	10.0	5.4	6.9
4 or more comorbidities	6.1	9.6	7.3	17.4	7.9	11.7	8.7	9.9	3.8	5.5
Mental health inpatient/day case 12 months prior to index admission	1.5	3.1	1.3	3.5	2.1	4.4	1.1	1.9	1.4	2.9
ASCVD history 12 months prior to index admission[59]										
No ASCVD hospitalisation + no statin use	33.9	41.9	54.1	40.5	45.5	47.8	10.8	48.5	16.6	38.3
ASCVD hospitalisation + no statin use	5.6	25.2	7.1	25.4	8.1	20.5	3.6	29.6	3.5	26.0
No ASCVD hospitalisation + statin use	27.5	12.3	17.1	10.8	23.2	13.3	36.4	9.1	36.1	13.3
ASCVD hospitalisation + statin use	33.1	20.6	21.7	23.3	23.2	18.4	49.2	12.8	43.7	22.4
Time to first primary care level prescription since index discharge, days (mean, SD)[60]	21.4 (19.3)	Not applicable	17.5 (16.8)	Not applicable	18.8 (18.3)	Not applicable	27.6 (21.6)	Not applicable	24.7 (20.2)	Not applicable
Time from prescription to dispense, days (mean, SD)	11.1(13.4)		10.7 (16.9)		12.5 (14.9)		11.1 (13.1)		10.8 (12.9)	

[58] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

[59] For individuals with index hospitalisations in 2009, information on prior medication use is available from 1 April 2009 and onward, thereby contributing a minimum of 6 months and up to 12 months of medication history. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

[60] Please note that this statistic only includes individuals who initiated the prescribed treatment, as the Prescribing Information System (PIS) data do not contain prescribing information for patients who were not dispensed treatment.

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Statin initiation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Statin intensity[61]										
High intensity	40.4		49.4		33.9		31.3		37.3	
Moderate/low intensity	59.6		50.6		66.1		68.7		62.7	

[61] In line with NICE's categorisation of statin intensity, high-intensity statins are defined as statins that reduce LDL-C levels by >40%, while moderate/low-intensity statins reduce LDL-C levels by ≤40% (see **Chapter 4, Table 4.3**).

Table 5.3 Statin initiation rates in the ASCVD study population in Scotland over time and by age and gender (overall and by statin intensity)

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
Statin initiation rates (%) •••	**79.9**	**81.4*** **	**81.7**
Men•••	82.6	84.6***	84.8
Women•	75.8	76.3	77.0**
Individuals aged 18 – 49 years•	76.8	80.2***	78.7
Individuals aged 50 – 59 years•••	84.3	85.9**	86.7
Individuals aged 60 – 69 years•••	84.7	86.4***	86.4
Individuals aged 70 – 79 years•••	81.0	82.2**	82.8
Individuals aged 80 – 89 years•••	71.2	72.1	74.3**
Individuals aged 90 years or older	50.7	52.7	48.4*
Proportion of all statin initiators being dispensed high-intensity statin[62] (%) •••	**33.5**	**39.6*** **	**57.0*** **
Men•••	34.7	41.1***	59.9***
Women•••	31.5	37.2***	52.1***
Individuals aged 18 – 49 years•••	41.5	46.1***	70.5***
Individuals aged 50 – 59 years•••	41.0	46.0***	66.4***
Individuals aged 60 – 69 years•••	36.8	42.3***	60.5***
Individuals aged 70 – 79 years•••	30.7	37.2***	53.0***
Individuals aged 80 – 89 years•••	21.5	30.1***	43.2***
Individuals aged 90 years or older•••	12.3	20.0***	32.5***

See **Appendix C, Tables C1-C4** for initiation rates by ASCVD type over time.
Note: (•) next to patient category denote statistically significant trend across time period from 2009/11 to 2015/17 based on the Cochran-Armitage test for trend, where (•••) p<0.001, (••) p<0.01, (•) p<0.5. Asterisks (*) in the column 2012/2014 and 2015/2017 denote statistically significant changes in the proportion of individuals initiating treatment compared to the previous period (i.e., 2012/14 vs. 2009/11 and 2015/17 vs. 2012/14), where (***) p<0.001, (**) p<0.01, (*) p<0.5.

Initiation rates by statin intensity

Out of all individuals who initiated statin therapy after an ASCVD-related event, 40.4% initiated high-intensity therapy[60], the remainder (59.6%) being prescribed medium or low-intensity statin treatment (**Table 5.2**). Within 12 months since initiation, 5.2% of initiators

[62] Statin intensity at 12 months since index statin prescription is reported to take into account possible titration of treatment. In line with NICE's classification of statin intensity, statins are defined as 'high-intensity' if they reduce LDL-C levels by a minimum of 40%, and 'low/medium-intensity' if LDL-C level reduction is below 40%.

uptitrated to high-intensity statin therapy, while 2.2% downtitrated to low/moderate intensity and 92.6% of individuals remained on the intensity that was first prescribed in a primary care setting after hospital discharge. As a result, 43.4% of statin initiators were using high-intensity statin therapy within 12 months since index prescription and 56.6% were using low/moderate-intensity therapy. High-intensity statin initiation rates for the latest available years (i.e. 2015/17) varied significantly by ASCVD type, ranging from 40% for PAD and 50.9% for stroke, to 72.6% for MI (see **Appendix C, Tables C1-C4** for initiation rates by CVD type over time).

The proportion of statin initiators using high-intensity statins within 12 months since index prescription almost doubled since 2009, increasing from 33.5% for the time period 2009/2011 to 57.0% in 2015/2017 ($p<0.001$) (**Table 5.3**). The sharp increase over time can be observed in all population subgroups, however, similar to statin initiation rates in general, there appear to be significant gender and age gaps in the use of high-intensity statins. Although the aggregate difference between the genders is smaller compared to statin initiation rates in general, more men than women with ASCVD continued to be dispensed high-intensity statins, with the gap having increased over time from 3.2% in 2009/2011 to 7.8% in 2015/2017 ($p<0.001$). Similar trends were observed across the age groups, for example with individuals aged 70 years or older being less likely to be issued high-intensity statins compared to those aged 50 to 59 years, leading to a gap that increased from a 10.3% difference in 2009/2011 to 12.4% in 2015/2017 ($p<0.001$).

Initiation rates by statin type

Changes in the composition of statin types over time were observed. While two-thirds of all statins initiated in 2009/11 were simvastatin, the proportion of simvastatin initiations decreased to 36% in the most recent years while the proportion of individuals initiating atorvastatin more than doubled from 28% to 59% (**Table 5.4**). Initiation rates of other types of statin were low and continued to decrease over time. Information on other types of cholesterol-lowering drugs, such as ezetimibe monotherapy or PCSK9 inhibitors, was not available. However, these drugs constitute an inconsiderable proportion of all lipid-regulating drugs dispensed in Scotland, with their combined use having marginally increased from 0.3% in 2009 to 1% in 2016 of all lipid-lowering medications dispensed in Scotland based on Scottish prescription cost analyses [1].

Table 5.4 Types of statin prescribed and dispensed after index ASCVD hospitalisation by a primary care level prescriber (i.e. percentage of initiators)

Proportion of statin initiators (%)	Index discharge year			
	2009-2011	2012-2014	2015-2017	Overall
Simvastatin	63.9	57.6	35.7	53.5
Atorvastatin	27.8	36.3	59.0	40.0
Rosuvastatin	5.6	3.8	3.4	4.3
Pravastatin	2.3	2.0	1.5	2.0
Fluvastatin	0.12	0.14	0.07	0.15
Simvastatin & Ezetimibe	0.06	0.02	0.01	0.03
Other LDL-C-lowering drugs	Information not available			

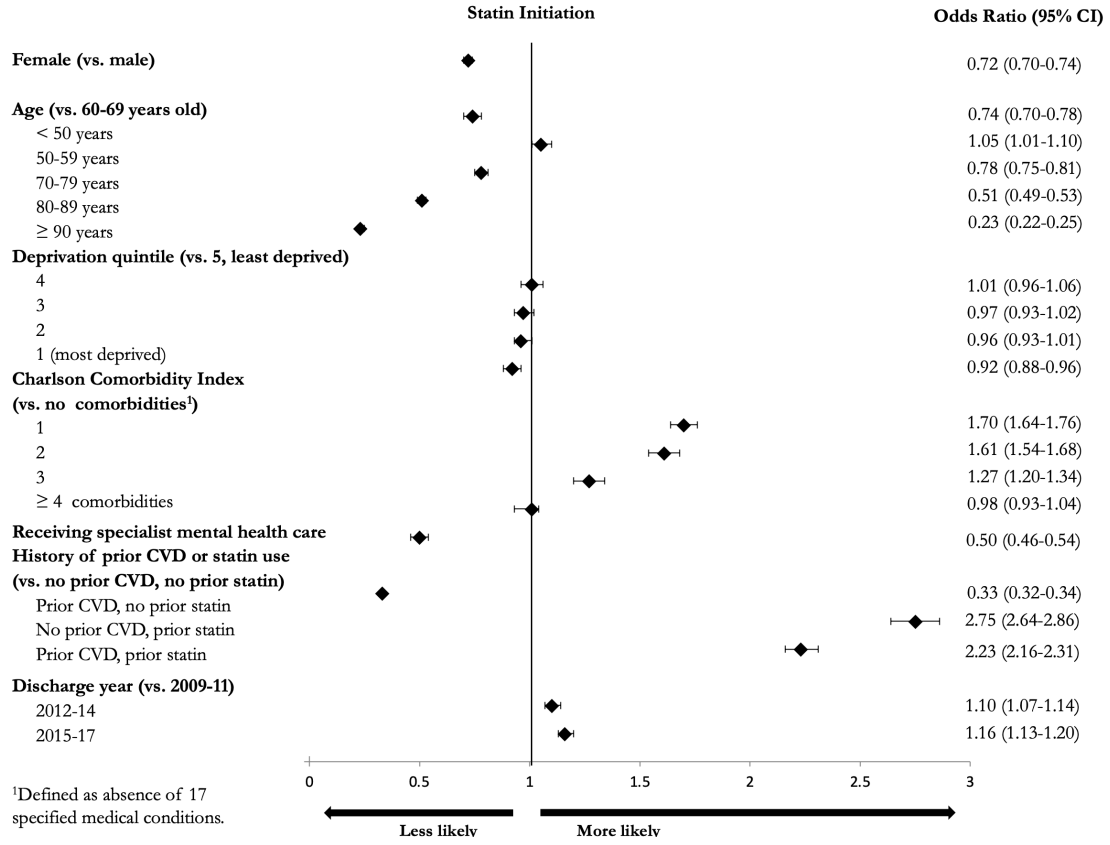
5.2.2. Determinants of statin initiation

Patient characteristics that were significantly associated with statin therapy initiation included age, sex, socioeconomic deprivation, co-presence of medical conditions as defined by the Charlson Comorbidity Index, concomitant mental health conditions, history of CVD and statin therapy use, and the hospital discharge years (**Figure 5.1**). Specifically, compared to individuals aged 60-69 years, those below the age of 50 years and those older than 69 years were significantly less likely to initiate statin treatment, with the likelihood of initiation decreasing as age increased beyond 70 years (<50 years: odds ratio [OR] 0.74, 95% CI 0.70-0.78; 70-79 years: 0.78 [0.75-0.81]; 80-89 years: 0.51 [0.49-0.53]; 90 years or older: 0.23 [0.22-0.25]), indicating a U-shaped association between age and statin initiation. In contrast, patients aged between 50 and 59 years had 5% (95% CI 1.01-1.10) greater odds of initiating statin compared to those aged 60 to 69 years. Overall, women were 28% less likely to initiate statin than men (OR 0.72 [0.70-0.74]), with a gender gap of 9% in the case of peripheral arterial disease, 22% for myocardial infarction and ischaemic stroke, and 33% for other atherosclerotic diseases (see **Appendix C**, **Table C.5** for the association between patient characteristics and statin initiation by ASCVD type). Patients living in the most deprived areas (i.e. SIMD quintile 1) were less likely to initiate statin therapy compared to those in least deprived areas (i.e. SIMD quintile 5) (OR 0.92 [0.88-0.96]). In addition, those with previous hospitalisations at a mental health specialty or psychiatry were only half as likely to initiate statin treatment as those without similar medical histories (OR 0.50 [0.46-0.54]). Compared to patients without prior history of ASCVD and statin therapy, those who used statin prior to the index hospitalisation had significantly greater odds of using treatment after the index event, regardless of having a

history of ASCVD (OR 2.23 [2.16-2.31]) or not (OR 2.75 [2.64-2.86]). Further adjustments for index ASCVD type in the main model did not affect the results (results not shown).

The associations described above were consistent across the four different types of ASCVD (**Appendix C, Table C.5**). In addition, an increase in the number of comorbidities was associated with a decreased likelihood of individuals initiating statin therapy. For example, MI and stroke patients with one additional comorbidity had, respectively, 29% and 22% lower odds of initiating statin compared to individuals with MI or stroke only (MI: OR 0.71 [0.66-0.76]; stroke: OR 0.78 [0.73-0.84]), and MI and stroke patients with three or more comorbidities had 60% and 42% lower odds, respectively (MI: OR 0.40 [0.37-0.44]; stroke: OR 0.58 [0.53-0.64]). Among patients with other ASCVD, those with two or more comorbidities had lower odds of statin initiation than those without any comorbidities (two comorbidities: OR 0.70 [0.64-0.77]; three comorbidities: OR 0.63 [0.57-0.70]; four or more comorbidities: OR 0.53 [0.46-0.61]), while in the case of PAD those with four or more comorbidities (including PAD) had 33% lower odds of initiating therapy than those with PAD only (OR 0.67 [0.58-0.78] (**Appendix C, Table C.5**). Please note that the CCI results presented in **Figure 5.1** are difficult to interpret due to varying implications of 'no comorbidity' across ASCVD types. In the case of total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified CCI conditions. In the case of MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable. Please see **Appendix C.2** for the associations between CCI and statin initiation by ASCVD type.

Figure 5.1 Associations of patient characteristics with statin initiation among individuals with ASCVD (a multivariable logistic regression model)



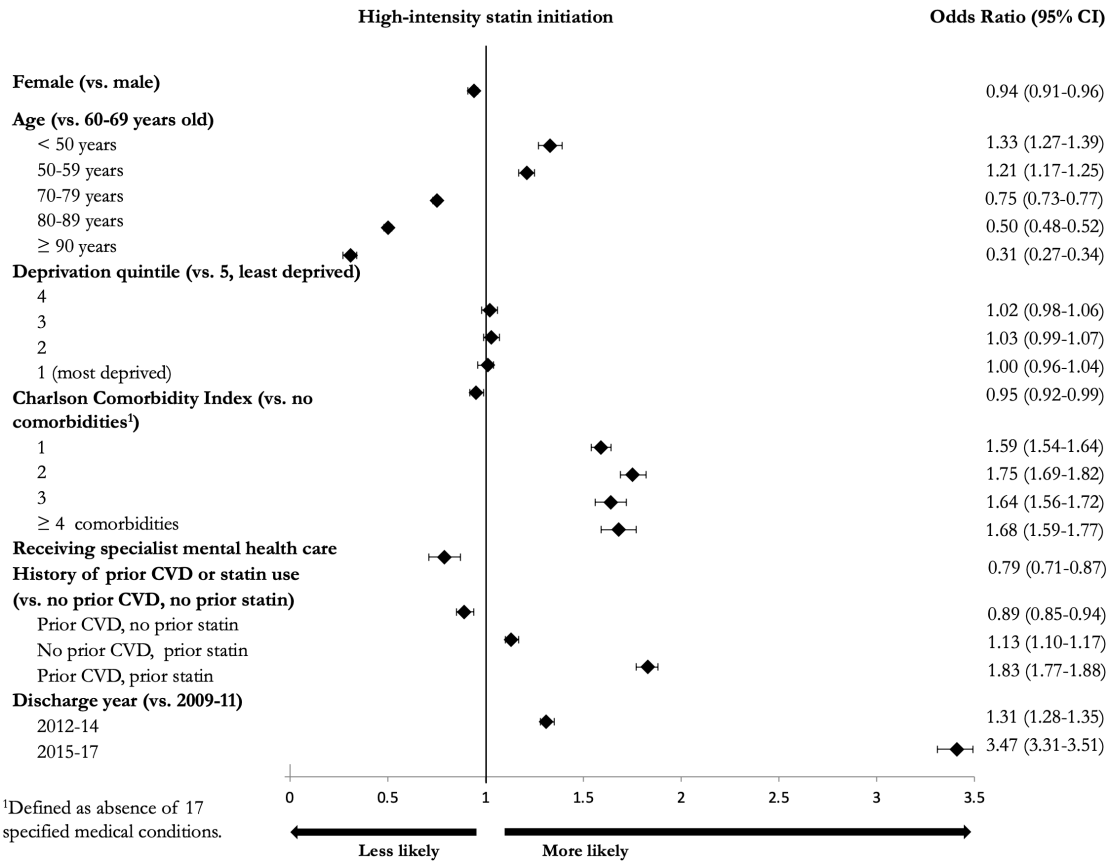
Please note that the CCI results presented in **Figure 5.1** are not easily interpretable due to index MI, stroke and PAD included among the CCI-eligible comorbidities, leaving the remaining index ASCVD conditions in the comparator "no comorbidity" category. Instead, the results are described above and in more detail in **Appendix C.2**, **Table C.5**.

High-intensity statin initiation

Out of 136,855 ASCVD patients initiating statin treatment, 40.4% were using high-intensity statin treatment, with the remainder using low and moderate intensity therapy. Similar to previous findings on the relevance of patient characteristics in the initiation of any statin treatment, women, as well as patients aged 70 years or older, those living in the most deprived areas, those with more than two comorbidities, those with previous mental health-related hospitalisations and those with a history of ASCVD and without any prior use of statin had lower odds of initiating high-intensity statins compared to low/medium intensity therapy (**Figure 5.2**). The odds of initiating high intensity statin increased significantly since 2012, with patients discharged between 2015 and 2017 having almost 3.5 higher odds of initiating high-intensity therapy than those discharged between 2009 and 2011 (2012/14 vs. 2009/10: OR 1.31 [1.28-1.35]; 2015/17 vs. 2009/10: OR 3.47 [3.31-3.51]). Please note that the CCI results presented in **Figure 5.2** are difficult to interpret

due to different definitions of 'no comorbidity' that vary by ASCVD type, as described earlier. Please see **Appendix C.3, Table C.6** for the associations between CCI and high-intensity statin initiation by ASCVD type.

Figure 5.2 Associations of patient characteristics with high-intensity statin initiation (a multivariable logistic regression model)



Please note that the CCI results presented in **Figure 5.2** are not easily interpretable due to index MI, stroke and PAD included among the CCI-eligible comorbidities, leaving the remaining index ASCVD conditions in the comparator "no comorbidity" category. Instead, the results are described above and in more detail in **Appendix C.2**, **Table C.6**.

Statin initiation among individuals with and without a prior history of ASCVD

Please see **Appendix C.4** for a detailed overview of determinants of statin initiation among individuals with and without a prior history of ASCVD.

5.3. Persistence with statin therapy

5.3.1. Statin therapy adherence rates

The average adherence rate among the 136,855 statin therapy initiators, calculated as the proportion of days covered with medication (PDC) from index initiation until end of study date (or date of discontinuation, death or emigration, if any of these events occurred first) was 93.7%. Using a PDC rate of 80% as the threshold for adherence classification (see **Chapter 4, Section 4.1** for further details), the proportion of statin therapy initiators considered to be adherent to treatment was 90.5%. At 12 months since statin initiation, the average adherence rate was 96%, and 94.1% of statin initiators were considered adherent.

5.3.2. Statin discontinuation rates

Out of 136,855 patients with ASCVD who initiated statin therapy after discharge, 32,983 (24.1%) discontinued treatment (i.e. had a treatment gap of 180 days or more since initiation) at some later point in time (**Figure 5.3**). The discontinuation rates varied by type of index ASCVD event, ranging from 22.7% in MI patients, 23.4% in other ASCVD conditions, 25.7% for stroke patients, to 29% in PAD patients. Compared to individuals who did not discontinue statin treatment, those who discontinued were on average older at the time of the index hospital discharge (average age 68.5 years vs. 66.3 years, $p<0.001$) and more likely to be female (41.6 vs. 35.4%, $p<0.001$). The discontinuation group also had a lower proportion of individuals using statins prior to the index admission (57% vs. 61.7%, $p<0.001$), and higher proportion of patients with four or more comorbidities (7.9% vs. 5.6%, $p<0.001$), mental health hospitalisations (2.8% vs. 1.1%, $p<0.001$) and those resident in remote rural areas (7.9% vs. 6.3%, $p<0.001$). Please see **Table 5.5** for an overview of baseline characteristics comparing individuals who discontinued and those who did not discontinue statins across different ASCVD types.

The average time to discontinuation was two years (standard deviation 1.7 years). After taking into account end of follow-up due to deaths, emigration and any subsequent hospitalisations, 50% of individuals who discontinued treatment had done so by 1.5 years since index initiation and 80% by 3.5 years (**Table 5.6**). However, of the 32,983 individuals who discontinued therapy, 12,644 individuals (38%) re-initiated therapy at some point in time after their initial treatment gap of 180 days. On average, individuals re-initiated therapy within 1.1 years since discontinuation.

Figure 5.3 Overview of statin initiation and discontinuation rates in the ASCVD population

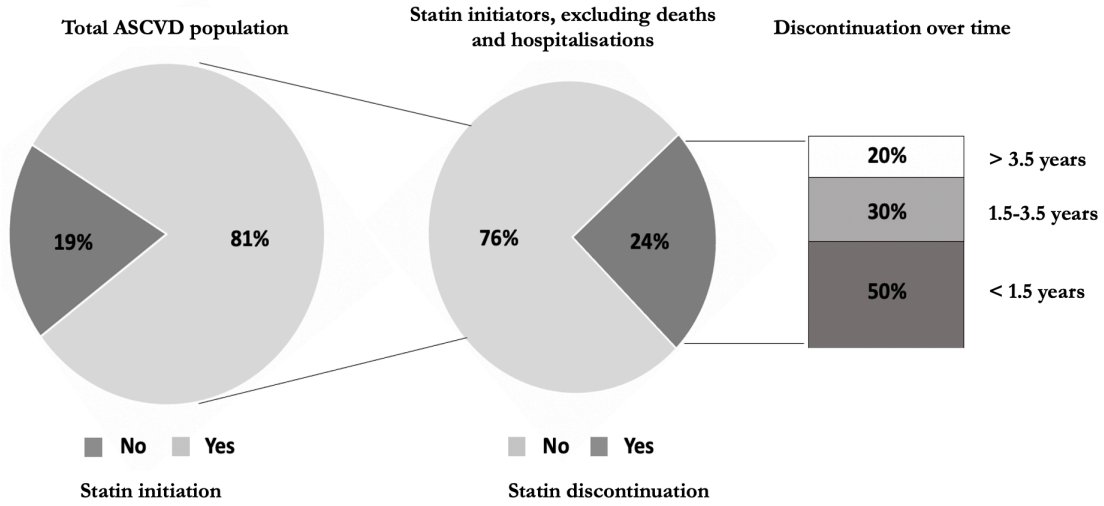


Table 5.5 Characteristics of patients who did and did not discontinue statin therapy, total ASCVD and by ASCVD type[63]

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Statin discontinuation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N (%)	32,983 (24.1)	103,872 (75.9)	10,069 (22.7)	34,371 (77.3)	6,802 (25.7)	19,699 (74.3)	3,343 (29.4)	8,021 (70.6)	12,769 (23.4)	41,781 (76.6)
Age on discharge (mean, SD)	68.5 (13.2)	66.3 (11.8)	67.4 (14.3)	64.2 (12.6)	71.6 (13.8)	69.5 (12.3)	69.8 (11.3)	68.7 (10.2)	67.3 (12.0)	66.1 (10.6)
Deaths during follow-up time	35.4	14.3	32.8	13.1	44.2	10.1	48.7	22.3	29.2	11.6
Age at death (mean, SD)	79.1 (10.4)	77.8 (10.1)	79.5 (10.9)	78.1 (10.6)	81.4 (9.9)	79.9 (9.8)	77.0 (9.6)	76.1 (9.3)	77.7 (10.3)	76.6 (9.8)
Time to death since index discharge (mean, SD)	3.2 years (1.9)	2.8 years (1.8)	3.1 years (1.9)	2.6 years (1.8)	3 years (1.8)	2.6 years (1.7)	3.1 years (1.8)	4.6 years (1.9)	3.4 years (1.9)	3 years (1.9)
Time to discontinuation (mean, SD)	2 years (1.7)	Not applicable	2 years (1.7)	Not applicable	1.9 years (1.7)	Not applicable	2 years (1.7)	Not applicable	2.1 years (1.8)	Not applicable
Female	41.6	35.4	39.7	31.8	50.0	45.0	35.7	32.4	40.2	34.2
Ethnic group										
White	86.2	85.0	86.4	85.3	86.3	84.9	86.4	86.7	86.1	84.4
Other	1.5	1.4	1.9	1.6	0.9	0.9	0.3	0.4	1.8	1.7
Missing	12.3	13.6	11.7	13.1	12.8	14.2	13.3	12.9	12.2	13.8
SIMD quintile (2009)[64]										
5 (least deprived)	15.4	15.8	14.7	15.5	16.5	15.6	12.6	13.5	16.0	16.6
4	19.4	18.1	19.3	18.3	19.7	17.2	19.1	18.1	19.4	18.5
3	21.3	20.1	21.3	20.0	20.9	19.4	23.0	20.8	21.1	20.4
2	22.1	22.2	21.9	22.2	21.5	22.5	23.0	24.6	22.3	21.7
1 (most deprived)	21.8	23.8	22.7	24.0	21.5	25.4	22.2	23.0	21.2	22.9
Urban-Rural Classification[65]										

[63] Tests of significance: t-tests and chi-squared tests were performed to test for statistically significant differences in baseline characteristics between initiators and non-initiators. Results **total ASCVD** population: all characteristics between discontinuation and non-discontinuation differed significantly ($p<0.001$), except for ethnic groups, where no statistically significant differences were found. **MI**: all characteristics between discontinuation and non-discontinuation differed significantly ($p<0.001$), except for ethnic groups, where no statistically significant differences were found. **Stroke**: all characteristics between discontinuation and non-discontinuation differed significantly ($p<0.001$), except for ethnic groups, where no statistically significant differences were found. **PAD**: all characteristics between discontinuation and non-discontinuation differed significantly ($p<0.001$), including SIMD and urban rural factor ($p<0.05$), except for ethnic group and prior ASCVD history, where no statistically significant differences were found. **Other ASCVD**: all characteristics between discontinuation and non-discontinuation differed significantly ($p<0.001$), except for ethnic group, where no statistically significant differences were found.

[64] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones.

[65] Scottish Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes' drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Statin discontinuation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Large urban areas	31.6	32.2	32.1	32.3	33.1	33.9	26.9	28.4	30.5	32.2
Other urban areas	34.4	36.7	33.8	36.6	33.0	36.7	37.5	37.8	34.9	36.4
Accessible small towns	9.7	9.7	9.7	9.9	10.0	9.6	9.0	9.7	9.8	9.5
Remote small towns	4.7	3.8	4.7	3.7	4.5	3.5	5.6	4.5	4.6	3.8
Accessible rural	12.1	11.4	11.9	11.6	12.1	10.9	12.6	12.2	12.1	11.3
Remote rural	7.9	6.3	7.7	5.9	7.3	5.5	8.5	7.4	8.1	6.8
Charlson Comorbidity Index										
0 (no-comorbidities) [66]	17.7	18.0	N/A	N/A	N/A	N/A	N/A	N/A	45.8	44.9
1	44.6	47.9	49.3	56.5	56.2	58.4	59.9	64.1	30.6	32.7
2	20.0	20.4	28.6	27.4	22.6	22.1	17.1	18.2	12.6	13.7
3	9.8	8.1	12.3	9.6	11.8	11.1	12.4	9.7	6.1	5.2
4 or more comorbidities	7.9	5.6	9.8	6.5	9.5	7.4	10.5	8.0	4.8	3.5
Mental health inpatient/day case 12 months prior to index admission	2.8	1.1	2.4	0.9	3.6	1.5	2.0	0.8	2.8	1.0
ASCVD history in the 12 months prior to index admission[67]										
No CVD hospitalisation + no statin	34.6	33.7	51.1	54.9	46.7	45.0	13.0	9.9	20.8	15.4
No CVD hospitalisation + statin use	23.4	28.8	14.1	18.0	19.0	24.8	32.8	37.8	30.6	37.8
CVD hospitalisation + no statin use	8.4	4.6	10.8	6.1	10.6	7.2	6.1	2.6	6.1	2.7
CVD hospitalisation + statin use	33.6	32.9	4.0	21.0	23.8	22.9	48.1	49.7	42.5	44.2

[66] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

[67] For individuals with index hospitalisations in 2009, information on prior medication use is available from 1 April 2009 and onward, thereby contributing a minimum of 6 months and up to 12 months of medication history. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

Table 5.6 Distribution of patients who discontinued statin therapy over time, by time duration since statin initiation

Time since initiation	Individuals discontinuing statin, N (%)	Cumulative percentage
0 to 6 months	7,521 (22.8)	22.8
7 to 12 months	5,112 (15.5)	38.3
13 to 18 months	3,892 (11.8)	50.1
19 to 24 months	3,100 (9.4)	59.5
25 to 30 months	2,606 (7.9)	67.4
31 to 36 months	2,177 (6.6)	74.0
37 to 42 months	1,979 (6.0)	80.0
43 to 48 months	1,517 (4.6)	84.6
49 to 60 months	2,408 (7.3)	91.9
61 to 72 months	1,616 (4.9)	96.8
73 to 84 months	858 (2.6)	99.4
85 to 96 months	198 (0.6)	
Total	**32,983 (100)**	**100**

Note: Individuals who died, emigrated or experienced any subsequent hospitalisation excluded from respective time periods.

5.3.3. Determinants of statin persistence

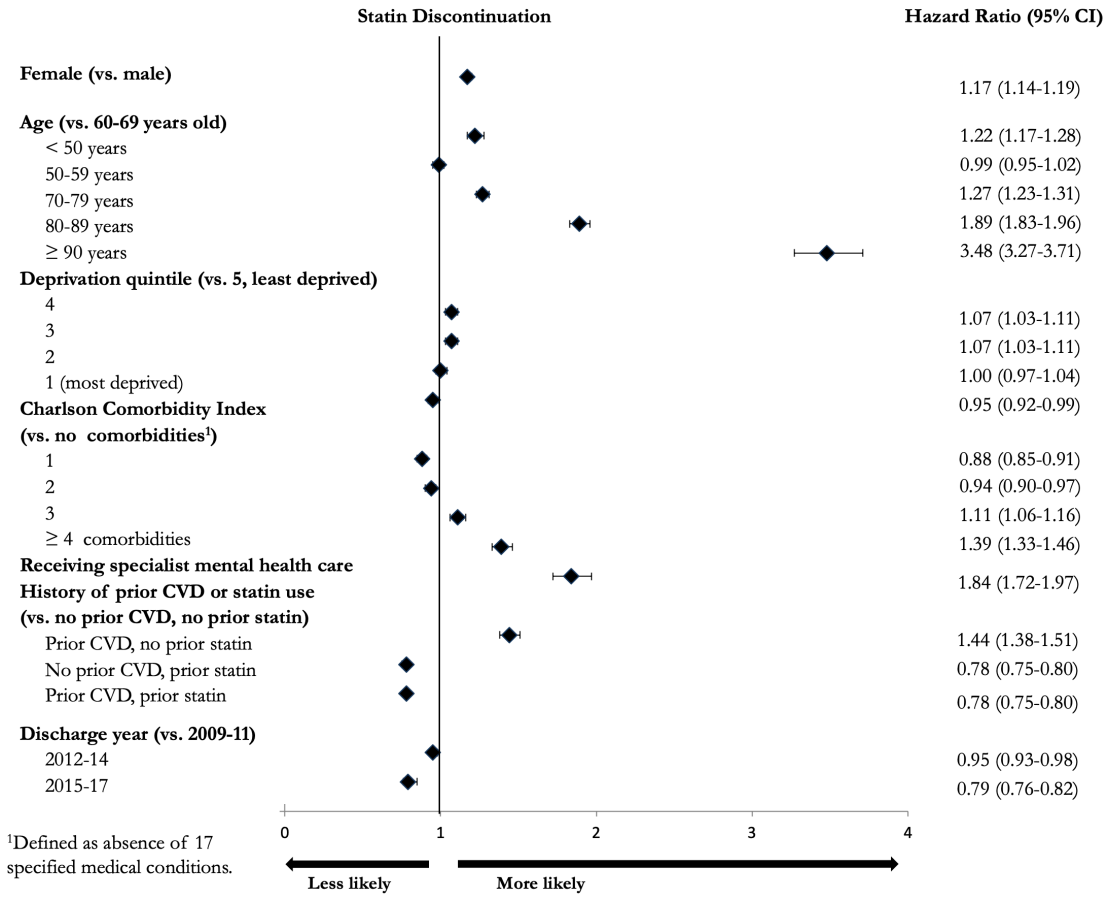
Discontinuation of statin therapy

Patient characteristics associated with discontinuation of statin therapy included gender, age, socioeconomic deprivation, presence of comorbidities, concomitant mental health conditions and history of statin use (**Figure 5.4**). Specifically, women had a 17% higher risk of statin discontinuation than men (hazard ratio [HR] 1.17, 95% CI 1.14-1.19). A U-shaped association with age was observed: compared to individuals aged 60 to 69 years, those below the age of 50 years and those aged 70 years to 79 years had, respectively, 22% (HR 1.22 [1.17-1.28]) and 27% (HR 1.27 [1.23-1.31]) higher risk of discontinuation respectively, with the risk increasing up to 3.5-fold in the case of patients aged 90 years or older (HR 3.48 [3.27-3.71]). Contrary to statin initiation, there was an obverse association between SIMD quintile and treatment discontinuation, with individuals in the most deprived quintile having a slightly lower risk of discontinuation compared to residents in the least deprived quintile (HR 0.95 [0.92-0.99]). Individuals in SIMD quintiles three and four (i.e. those living in medially and relatively less deprived areas) were more likely to discontinue treatment than those resident in the least deprived quintile (3rd and 4th quintile: HR 1.07 [1.03-1.11] for both). Patients with a history of mental health-related

hospitalisations had a 1.8-fold higher risk of discontinuation compared to those without such history (HR 1.84 [1.72-1.97]). Patients with a history of ASCVD and no prior statin use also had a higher discontinuation risk than those without prior ASCVD and no prior statin use (HR 1.44 [1.38-1.51]). Irrespective of previous ASCVD hospitalisations, those who used statins in the 12 months before the index admission had a significantly lower risk of discontinuation (HR 0.78 [0.75-0.80] for both individuals with and without prior ASCVD hospitalisation).

The associations described above were consistent across the four different types of ASCVD (**Appendix C.5, Table C.8**). In addition, an increase in the number of comorbidities was associated with an increased risk of statin discontinuation. MI and stroke patients with one additional comorbidity had about 8% higher discontinuation risk than patients with MI or stroke only (MI: HR 1.08 [1.03-1.13], stroke: HR 1.09 [01.03-1.16]), increasing to approximately 50% higher risk among patients with three or more concomitant conditions (MI: HR 1.50 [1.39-1.61]; stroke: HR 1.47 [1.35-1.60]). PAD patients with three or more comorbidities (including PAD) were at higher risk of discontinuing than patient with PAD only (three comorbidities: HR 1.38 [1.24-1.53]; four or more comorbidities: HR 1.60 [1.1.42-1.79]). Patients with other ASCVD and three or more comorbidities were also at higher risk of discontinuing treatment (three comorbidities: HR 1.15 [1.07-1.24]; four or more comorbidities: HR 1.46 [1.34-1.58]) compared to those without any comorbidities (**Appendix C.5, Table C.8**). Please note that the CCI results presented in **Figure 5.4** are difficult to interpret due to different definitions of 'no comorbidity' that vary by ASCVD type, as described earlier. Please see **Appendix C.5** for the associations between CCI and statin discontinuation by ASCVD type.

Figure 5.4 Associations of patient characteristics with statin discontinuation among individuals with ASCVD (a multivariable Cox proportional hazards model)



Please note that the CCI results presented in **Figure 5.4** are not easily interpretable due to index MI, stroke and PAD included among the CCI-eligible comorbidities, leaving the remaining index ASCVD conditions in the comparator "no comorbidity" category. Instead, the results are described above and in more detail in **Appendix C.5**.

5.4. Suboptimal statin use and subsequent ASCVD risk

Out of 158,507 individuals hospitalised for an ASCVD event between 1 October 2009 and 31 December 2016, 151,857 individuals were still alive 12 months after discharge (see **Chapter 4, Figure 4.1** for identification of participants). Of these, (1) 113,102 individuals (74%) initiated[68] and did not discontinue statin therapy within 12 months since discharge, while (2) 11,304 (7.4%) initiated and subsequently discontinued statin therapy within 12 months since discharge and (3) 27,451 (18%) did not initiate statin within 12 months since discharge (**Table 5.7**). Amongst individuals who initiated statin therapy and remained on

[68] Initiation here follows the same definition as used prior, i.e., individuals who were prescribed therapy within 90 days since index discharge and dispensed the therapy within 60 days since prescription.

statin by 12 months since discharge, 20.3% experienced either a non-fatal or fatal ASCVD-related event during subsequent follow-up. In the case of individuals who discontinued or never initiated therapy, 20.1% and 22.3% of patients, respectively, experienced subsequent ASCVD-related events, with the observed differences between the statin initiator group who remained on statin and statin non-initiator group being significant ($p<0.001$; not accounting for time to event or other characteristics), as well as between the statin non-initiator group and statin discontinuation group ($p<0.001$; not accounting for time to event). No significant differences were observed between statin initiators and statin discontinuers (not accounting for time to event). The characteristics of each patient group and breakdown of adverse events by fatal and non-fatal ASCVD event are reported in **Appendix C.6**, **Table C.9**.

Table 5.7 Proportion of individuals discharged for an ASCVD-related event who experienced subsequent fatal and non-fatal ASCVD-related events during follow up

	Group 1 Initiated statin and remained on statin	**Group 2** Initiated statin and discontinued statin	**Group 3** Non-initiators
Study population	Individuals who initiated[69] statin; and did not discontinue treatment during study follow-up within 12 months since discharge	Individuals who initiated statin; and subsequently discontinued statin within 12 months since discharge	Individuals who did not initiate statin within 12 months since discharge
Total population (N)	113,102	11,304	27,451
Total fatal and non-fatal CVD-related events[70], N (%)	22,934 (20.3)	2,276 (20.1)	6,111 (22.3)

[69] Initiation here for all three groups follows the same definition as used prior, i.e., individuals who were prescribed therapy within 90 days since index discharge and dispensed the therapy within 60 days since prescription.

[70] Please note: the total number of non-fatal and fatal ASCVD-related events only counts one of the two possible events (i.e. subsequent hospitalisation or death) per individual, counting the event that happened first. Counting the first subsequent ASCVD event per person only, regardless of whether individuals experienced more than one subsequent event. ASCVD-related death was defined as an individual's death record listing an ICD-10 code for cardiovascular disease as the primary cause of death, where ASCVD was defined in line with the ICD-10 codes used to define the ASCVD population in this study (see **Chapter 4** Methods for an overview of ICD-10 codes included).

The findings from the adjusted Cox Proportional Hazards survival analyses with age-group and ASCVD type stratification show that statin non-initiators and discontinuers are at higher risk of experiencing a subsequent ASCVD-related event than statin initiators who remained on statin, irrespective of index ASCVD type (**Appendix C.6, Table C.10**). For example, MI patients who never initiated or discontinued statin therapy were, respectively, at 25% and 19% higher risk of experiencing subsequent ASCVD events than those who initiated and did not discontinue therapy. Stroke patients were, respectively, at 17% and 30% higher risk of experiencing events (see **Appendix C.6, Table C.10** for an overview of results by ASCVD type).

5.5. Discussion

5.5.1 Findings and interpretation of results

Overall summary

Based on NHS Scotland national prescribing information for the years 2009 to 2017 for 167,978 individuals hospitalised for an atherosclerotic cardiovascular disease-related event since October 2009, about 80% of patients initiated statin therapy following hospital discharge. Of the patients who initiated statin therapy, 43.4% were prescribed high-intensity therapy within 12 months since index prescription. Almost a quarter of individuals discontinued statin treatment at some point in time, with half of these discontinuations occurring within 1.5 years of initiation. Of the individuals who discontinued statin therapy, only 38% re-initiated therapy at some point in time. Both lower odds of initiation and higher risks of discontinuation were associated with individual-level factors, including older age, being female, having multiple co-morbidities or previous mental health specialty admissions, as well as (in the case of non-initiation) living in deprived areas. The survival analyses have shown that individuals who never initiated or discontinued statin therapy had higher risks of recurring fatal and non-fatal ASCVD-related events compared to individuals who initiated and did not discontinue statin therapy, associations largely consistent with the findings reported by meta-analyses of randomised controlled trials presented in **Chapter 2**.

Determinants of statin initiation and discontinuation

The role of age

This study found that patient's age played a significant role in the initiation and discontinuation of statin therapy, with elderly patients (i.e. individuals aged 70 years or older) being less likely to initiate treatment as well as at a greater risk of discontinuing treatment at some point in time. Six previous studies which estimated the association between age and statin use at different treatment stages have reported similar findings (see **Chapter 3**). For instance, one large stroke registry study covering 173,284 stroke patients from the U.S. reported that as patients' age increased, the likelihood of being prescribed statin therapy decreased [2]. In the case of statin initiation, one study in the U.S. observed that higher age was associated with an increased risk of non-initiation [3]; however, in the case of high-intensity statins, specifically, no relationship was found between age and initiation [4]. The role of age in the long-term management of MI was examined in two studies, showing that patients aged 80 years or older were significantly more likely to discontinue treatment than patients aged in their 60s [5], [6]. In contrast, the opposite relationship was observed in the case of stroke, with stroke patients aged 85 years or older being more likely to be persistent than those below the age of 65 [7].

This age-related treatment gap may be due to misperceptions of adverse effects of statins and uncertainty in statin efficacy amongst both patients and prescribers, as discussed in **Chapter 2**. However, the randomised evidence on statin safety and efficacy, including in older patient groups, is substantial and clear in the case of secondary prevention. For instance, a large meta-analysis of 28 randomised controlled trials compared the effects of statin therapy at different ages and found that statin therapy yields significant reductions in major vascular events irrespective of age and has no adverse effects on non-vascular mortality, cancer death or cancer incidence [8]. Therefore, further attention needs to be paid to the management of older patients.

The role of gender

Gender played a significant role in the initiation and discontinuation of statin therapy, with women being less likely to initiate treatment, while also being at a greater risk of discontinuing treatment at some point in time. Seven studies presented in the systematic review (**Chapter 3**) investigated the association between gender and statin use in MI and stroke patients and highlighted that sex differences in statin treatment continue to persist. Of these, three studies found that women were less likely than men to be prescribed statin

therapy on hospital discharge [2], [9], [10]. Mixed results were reported in the case of the initiation of statin. Similar to the findings in this Chapter, one U.S. study observed that women were less likely to initiate therapy than men [4]. However, a less recent U.S. study reported the opposite association [3], while a large U.S. study of 85,000 elderly MI patients did not find that women were less likely to initiate treatment than men when adjusting for demographic, clinical and other baseline characteristics [11]. None of the studies in the review investigated the role of gender in the persistence with statin therapy, however, two studies examined the relevance of gender in the adherence to statin treatment and found contrasting results, with one U.S. study reporting that females were less likely to be adherent [12], while a second U.S. study observed the opposite relationship [11].

Comparable findings were observed in patients with other cardiovascular diseases in addition to myocardial infarction and stroke, and the differences in these studies arose due to both provider and patient-related factors. For instance, analyses of a U.S. national cohort of 983,476 CVD patients in the Veterans Health Administration care system revealed that women were less likely to receive any statin therapy (or high-intensity statin therapy) than men, highlighting significant facility-level variation [13]. Similar findings were observed using the US nationwide registry of outpatients with or at risk of ASCVD (i.e. the Patient and Provider Assessment of Lipid Management Registry), showing that women were less likely than men to be prescribed any statin therapy or the guideline-recommended intensity [14]. In addition to provider prescribing behaviour, patient-related factors were found to further widen the gender treatment gap. For instance, the study assessed the degree to which patients' trust of physicians and risk perception, as well as statin-reported beliefs, contribute to sex differences, finding that women were less likely than men to believe in the safety and efficacy of statins, while concurrently being more likely to report perceived statin-associated side effects that also led to higher discontinuation risks compared to men. In contrast, men with and without a prior history of statin use were more likely to commence statin therapy [14]. As a result, the treatment gap arises due to a combination of women being less likely to be prescribed statin therapy, while also being more likely to decline and discontinue treatment compared to men. Given the substantial evidence on statin safety and efficacy for the secondary prevention of CVD in women [15], more attention should be paid to the management of female patients and further effort is required to educate and train both providers and patients on the safety and efficacy of statin therapy.

The role of comorbidities

This study showed that individuals with two or more comorbidities had significantly lower odds of initiating statin and were at higher risk of discontinuing therapy compared to individuals without physical comorbidities. Five studies (summarised in **Chapter 3**) estimated the association between concomitant conditions and statin initiation and/or statin persistence among MI patients, however, these studies examined the relevance of specific conditions rather than the total number of co-morbidities reported. For instance, in the case of statin initiation, a U.S. study investigated a range of comorbidities and found that dementia, liver diseases, dialysis (as a proxy for renal disease), heart failure and chronic pulmonary diseases, all of which are captured by the CCI in this chapter, were associated with lower odds of statin initiation [3]. A study in Denmark specifically examined differences between patients with and without rheumatoid arthritis and observed that patients admitted to hospital for an MI event had lower offs of statin initiation and were at greater risk of treatment discontinuation if they also had concomitant rheumatoid arthritis [16]. Furthermore, a Canadian study investigated the association between a range of comorbidities and the long-term use of statin and found that men with dementia and malignancy were at higher risk of statin discontinuation, while no effect was observed in the case of men or women with other CVDs, diabetes, renal disease, COPD, and women with dementia or malignancy [6]. Additionally, one study in Sweden found that among stroke patients, those with worse perceived general health were less likely to be persistent with statin therapy than to those in good self-perceived health [7].

It must be noted that the CCI, which was used in this study to study the presence of specific comorbidities, may have also indirectly captured individuals at risk of polypharmacy as a consequence to the presence of multimorbidities, with polypharmacy having been identified as a factor influencing statin use in previous studies. For example, a U.S. study observed that the total number of medications used by a patient was negatively associated with the initiation of high-intensity statin compared to moderate/low intensity therapy amongst both younger patients aged 19 to 64 and elderly individuals aged 65 or older [4] (summarised in **Chapter 3**). Specifically, individuals with 5 to 9 medications and those using 10 or more different medications were significantly less likely to initiate high-intensity therapy compared to patients using less than five treatments [4].

Independently of physical comorbidities, it is noteworthy that a history of hospital admission for psychiatric and specialist mental care was associated with 50% lower odds of initiation and 84% higher risks of discontinuation of statin therapy in this study

compared to individuals without such history. Another study summarised in the review presented a significant association between mental disorders other than depression and statin initiation and observed that individuals with mental disorders were less likely to initiate treatment, although the effect was not mirrored in the case of statin discontinuation [3]. However, studies summarised in the systematic literature review (**Chapter 3**), which looked specifically at the potential effects of depression on the initiation and adherence to statin therapy, found no significant association between depression and statin initiation and adherence [3], [4], [12]. These differences may be explained by the fact that the research presented in this chapter only investigated more severe cases of mental health conditions resulting in a hospital episode, and was not able to capture less severe mental health history that was treated at the primary care level, such as anxiety or more moderate stages of depression. Further research is required to examine the association between gradients of mental health conditions and statin use.

The role of socioeconomic status

This study found that patients living in the most deprived areas were less likely to initiate statin therapy than those living in the least deprived areas, a finding that is consistent with the results observed in a Canadian study [17] (see **Chapter 3** for further detail). The findings presented in this chapter do not provide any indications of actual prescription rates across socioeconomic groups in Scotland, however, reasons for suboptimal statin use may be driven by both provider and patient-related factors. For instance, a meta-analysis of seven studies including 41,462 individuals with acute coronary syndrome found that individuals or neighbourhoods in the lowest socioeconomic status (SES) group were less likely to be prescribed statin therapy, compared to those in the highest SES groups [18]. Therefore, provider training and targeted patient education in specific areas may further improve the uptake of statin therapy. However, the findings from this study suggest that sex and age play a more important role in statin use than socioeconomic status.

Long-term associations between suboptimal statin use and health outcomes

Findings from the Cox proportional hazards survival analyses have shown that patients who never initiated or discontinued statin therapy were at significantly higher risk of experiencing subsequent fatal and non-fatal ASCVD events compared to individuals who initiated and did not discontinue their statin treatment, irrespective of the type of ASCVD the patient was originally hospitalised for. These results are largely consistent with evidence from randomised controlled trials that were analysed in a large meta-analysis by the

Cholesterol Treatment Triallists' (CTT) Collaboration (presented in **Chapter 2**), which have shown that statins yield a proportional reduction in coronary heart disease deaths by 20% per 1 mmol/l reduction in LDL-C. Non-fatal myocardial infarctions and ischaemic vascular events were proportionally reduced by 27% and 21%, respectively, per 1 mmol/l reduction in LDL-C. With 20% of ASCVD patients not initiating treatment, in addition to individuals discontinuing treatment over time, about 25% of patient-years were not covered by statin therapy after an event. About a quarter of events in those patient years (i.e. 6% of all major ASCVD events in the entire ASCVD population) might have been prevented if moderate-intensity statins had been used throughout, and up to 40% of these events (i.e. 10% of all major ASCVD events in the entire ASCVD population) could have been avoided if optimal high-intensity statin therapy was used across this population.

5.5.2 Limitations

Limitations of observational data

Our data only included prescribing information for individuals who were both prescribed and dispensed treatment. As a result, it is not possible to determine if patients (a) were never prescribed treatment or (b) whether they received a prescription which was ultimately not dispensed for any reason, and therefore the magnitude of these potential problems cannot be quantified. Consequently, the analysis could not distinguish between treatment gaps that arose due to suboptimal prescribing and those due to suboptimal patient initiation. For instance, the rate of statin prescriptions may have been increasing over the years, however, the data only capture the overall proportion of individuals who ultimately dispensed statin therapy. Additionally, due to missing observations and information not available on whether prescribers advised patients to discontinue therapy or not, it was not possible to reach firm conclusions as to whether prescriber characteristics, such as age and gender, played a role in the long-term management of ASCVD.

Furthermore, the data only include information on prescriptions issued in primary care. Consequently, overall prescription rates and types of statin and statin intensity used during the ASCVD-related hospitalisation and prescribed in hospital at discharge could not be evaluated. This prevents any investigation into the rates and determinants of statin prescriptions in secondary care, the continuity of care and possible communication gaps between secondary and primary care providers. However, this does not represent a major

deficiency, as statins issued during a hospitalisation would typically only last a few weeks, requiring patients to continue treatment in primary care.

Patient characteristics are derived from hospital records, which do not capture patient's full medical history and diagnoses existing only in primary care records. Hence, the CCI only covers conditions for which the patient had been hospitalised 12 months prior to the index ASCVD event and may underestimate the actual proportion of individuals with physical co-morbidities. This also applies to patient's prior history of mental health conditions, which are based on day cases and inpatient admissions to mental health specialities and psychiatric hospitals only and therefore the analyses could not explore the role of different gradients of mental health conditions in the initiation of and persistence with statin therapy. In addition, our prescribing data only included information on statin and antiplatelet therapy. Hence, the presence of comorbidities, such as diabetes, cannot be accurately estimated through prescription records, nor can the total number of medications taken by a patient be derived to estimate any associations between polypharmacy and suboptimal statin use.

Lastly, a number of patient characteristics that may be relevant to the likelihood of using statin therapy, such as patient's ethnicity and marital status, could not be robustly studied due to large numbers of missing observations. The data also do not provide insights into clinicians' and patients' beliefs, preferences or risk perceptions of statin therapy. Despite these limitations, the dataset has major strengths in that it captures the entire national population of Scotland and the care received under a single provider, including every individual ever hospitalised for an ASCVD-related event from April 2009 onwards, allowing for a longitudinal follow-up of up to eight years, and is therefore highly representative.

5.5.3 Conclusions

Overall, 81% of ASCVD patients initiated statin therapy from 2009 to 2017 in Scotland, with rates varying between 80% to 88% across ASCVD types and increasing only marginally over time. Almost a quarter of initiators discontinued statin therapy at some point in time, with rates of discontinuation being significantly higher in the PAD population. Patient factors associated with lower statin initiation likelihood included being female, aged below 50 or above 70 years, having two or more comorbidities, having experienced specialty mental health hospital admissions, not taking statins previously and being resident in the most deprived areas. Except for socioeconomic deprivation, the same

factors were also associated with a higher risk of statin discontinuation. Lastly, the proportion of high-intensity statin initiators increased significantly over time, however, overall use remains suboptimal with only 58% of patients initiating high-intensity therapy in the latest available years. Predictors that played a role in decreasing the likelihood of high-intensity statin initiation were identical to the predictors associated with lower likelihood of statin initiation in general. Individuals who never initiated or discontinued statin therapy had a relatively higher risk of experiencing subsequent fatal and non-fatal ASCVD events. Despite the availability of substantial evidence on the safety and efficacy of statin treatment, significant variations between patient groups continue to persist, which need to be addressed by clinicians and policy-makers.

5.6. Summary

This chapter has provided novel evidence on patient characteristics associated with the initiation and discontinuation of statin therapy among individuals hospitalised with ASCVD using Scotland population-wide individual-level patient data and identified patient groups that could be targeted to improve medication use. In the next chapter, I present the analyses of the initiation of and persistence with antiplatelet therapies for the secondary prevention of cardiovascular disease.

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6

Rates and determinants of antiplatelet therapy use for the secondary prevention of cardiovascular disease

Summary

This chapter uses population-wide individual-level patient data on 167,978 individuals hospitalised for an ASCVD-related event in Scotland in the time period from 1 October 2009 to 3 July 2017, who were followed-up until study end, emigration or death for a period of up to eight years. Out of all individuals without a record of atrial fibrillation on discharge (N=150,728), 126,338 (83.8%) initiated antiplatelet therapy (APT), while the remainder (16.2%) did not. The initiation rates among patients hospitalised for MI, ischaemic stroke, PAD and other ASCVDs were 93.7%, 83%, 68% and 80.6%, respectively. Some gender- and age-related treatment gaps were observed. Among individuals who underwent percutaneous coronary intervention, 96.8% initiated APT, however, only 68.4% of patients who underwent PCI in 2015/17 received guideline-recommended dual-antiplatelet therapy (DAPT), the remainder being prescribed monotherapy. Meanwhile, 71.9% of MI initiators used DAPT, while, in line with clinical guideline recommendations, almost all stroke and PAD patients used monotherapy. While on treatment, 92.4% of users were adherent (i.e., a proportion of days covered (PDC) score of 80% or more) throughout the study period. However, 22.4% of APT users discontinued treatment at some point in time and, of those who discontinued, half (51%) discontinued within 1.5 years since initiation, and 79% within 3.5 years. Discontinuation rates varied by ASCVD type, ranging from 18.7% for MI patients, 23.9% for other ASCVD conditions and 24% for ischaemic stroke, to 27.7% in PAD patients. Out of all patients who discontinued treatment, 37% re-initiated some type of antiplatelet therapy at some point in time after their initial 180-day treatment gap. Patient characteristics associated with the non-initiation and discontinuation of APT included being female, elderly individuals aged 70 years or older, individuals aged 49 years or younger, those with two or more comorbidities (depending on ASCVD type) and individuals with a previous mental health-related admission or day case record. Residents living in the most deprived areas also had lower odds of initiating APT compared to individuals living in the least deprived areas. Individuals who never initiated or discontinued were at higher risk of experiencing subsequent fatal and non-fatal ASCVD events.

Summary of participant characteristics

The study population used to assess the rates and determinants of antiplatelet therapy use for the secondary prevention of cardiovascular disease in this chapter is the same ASCVD population that was analysed in **Chapter 5** with regard to the rates and determinants of statin use. The identification of the ASCVD study population is described in **Chapter 4**, and the participant baseline characteristics are described in detail in **Chapter 5 Section 1** and **Table 5.1**. In summary, 167,978 ASCVD patients were identified and followed from their first ASCVD-related hospital discharge as of 1 October 2009 until the date of study end (i.e. 31 December 2017), emigration or death (depending on which occurred first) for an average of 4.6 years, and up to 8.2 years. As described in the methods (**Chapter 4**), the patients were further categorised into five ASCVD types based on the primary ICD-10 diagnosis[71] recorded on discharge, namely (1) myocardial infarction (N=45,841), (2) ischaemic stroke (N=26,867), (3) peripheral arterial disease (N=14,307), (4) atrial fibrillation (N=17,250), and (5) other ASCVD, such as angina (N=63,713). Atrial fibrillation patients are more likely to be prescribed anticoagulation therapy instead of antiplatelet therapy (in accordance with clinical guidelines) and were therefore excluded from the total ASCVD population, as well as from each of the four subpopulation groups; results for ASCVD patients with concurrent atrial fibrillation are reported separately in **Appendix D, D.1**. Results are also reported for ASCVD patients who underwent a percutaneous coronary revascularisation procedure (PCI) with and without stent during the index hospitalisation (N=19,177) (see **Chapter 4** for a detailed overview of the ICD-10-based classification of ASCVD types). The Antiplatelet therapies analysed in this chapter include all guideline-recommended treatments for the secondary prevention of ASCVD post-acute stage, i.e. aspirin, clopidogrel, ticagrelor prasugrel and dipyridamole (i.e. mono and dual-antiplatelet therapy combinations of these drugs, as defined under BNF chapter 2, Section 9). Hence, other antiplatelet therapies that are only used during hospitalisation were excluded (e.g. Glycoprotein IIb/IIIa during PCI).

[71] In the case of atrial fibrillation (AF), diagnosis was based on a record of AF in the primary or any of the five secondary ICD-10 diagnostic fields on discharge.

6.1. Initiation of antiplatelet therapy

6.1.1. Rates of antiplatelet therapy initiation

Overall antiplatelet therapy initiation rates

Of the 150,728 individuals hospitalised for an ASCVD event (after excluding atrial fibrillation[72], see also **Chapter 4**, **Section 4.3.3**), 126,338 (83.8%) initiated antiplatelet therapy (APT), i.e. were prescribed any type of antiplatelet therapy within 90 days of the index discharge and subsequently dispensed the therapy within 60 days since prescription[73]. The initiation rates among patients hospitalised for MI, ischaemic stroke, PAD and other ASCVDs were 93.7%, 83%, 68% and 80.6%, respectively. In addition, 96.8% of the 19,711 individuals who underwent percutaneous coronary intervention during the index hospitalisation period initiated APT. Compared to all individuals with ASCVD who did not initiate ATP, initiators were on average younger (average age 66.3 years vs. 67.5 years, $p<0.001$); less likely to be female (37.4% vs. 45.3%, $p<0.001$) or to have had mental health hospital admissions in the 12 months prior to the index event (1.6% vs. 3%, $p<0.001$); and were more likely to be previous antiplatelet therapy users (53.9% vs. 38%, $p<0.001$); Please see **Table 6.1** for a comparison of baseline characteristics of antiplatelet therapy initiators and non-initiators by ASCVD type.

The proportion of individuals initiating antiplatelet therapy marginally increased from 82.1% among individuals hospitalised for ASCVD between 2009 and 2011, to 84.3% for the years 2012 to 2014 and 85.3% for the most recent years, i.e. 2015 to 2017 ($p<0.001$) (**Table 6.2**). Initiation rates increased across all subgroups[74], albeit some differences between subgroups persisted. For instance, 82.8% of women compared to 86.9% of men initiated antiplatelet therapy from 2015 to 2017, with differences fluctuating minimally since 2009. Similar trends were also present in comparison between age groups. For example, 82.3% of individuals aged 18-49 years and 81.3% of patients aged 80 years or older initiated APT compared to 87.7% of all individuals aged 60 to 69 years in 2015/17. Similar results were observed across different ASCVD types (**Appendix D.2**).

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[72] Atrial fibrillation (AF) patients are more likely to be prescribed anticoagulation therapy instead of APT and were therefore excluded from the total ASCVD population, as well as each of the four subpopulation groups. The results for the atrial fibrillation population are reported separately in **Appendix D.1.**

[73] The initiation rate varies significantly based on the time interval selected. For instance, only 46% of the 150,728 individuals hospitalised for ASCVD (excluding AF) were prescribed and dispensed treatment within 30 days since discharge. The proportion increases to 69% and 74%, respectively, if using a 60 and 90-day interval, all of which are previously used time intervals in relevant literature, as described in **Chapter 3**.

[74] Men ($p<0.001$), women ($p<0.001$), individuals aged between 18 to 49 years ($p<0.001$), 50 to 59 years ($p<0.001$), 60 to 69 ($p<0.001$), 70 to 79 ($p<0.001$), 80 to 89 ($p<0.001$), 90 years or older (not significant).

Table 6.1 Participant characteristics of antiplatelet therapy initiators and non-initiators at index admission discharge, total ASCVD[75] and by ASCVD type[76]

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Antiplatelet therapy initiation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N (%)	126,338 (83.8)	24,390 (16.2)	42,943 (93.7)	2,898 (6.3)	22,303 (83.0)	4,564 (17.0)	9,729 (68.0)	4,578 (32.0)	51,363 (80.6)	12,350 (19.4)
Age on discharge, in years (mean, SD)	66.3 (12.4)	67.5 (14.2)	64.6 (13.3)	70.4 (14.8)	68.9 (13.4)	71.8 (16.1)	68.6 (10.9)	67.6 (13.4)	66.1 (11.1)	65.5 (13.7)
Hospital length of stay, in days (mean, SD)	6.3 (11.4)	9.1 (16.0)	6.0 (6.9)	10.3 (12.1)	14.3 (18.9)	21.4 (23.1)	8.1 (13.1)	9.2 (13.4)	2..7 (7.1)	3.8 (10.0)
Female	37.4	45.3	34.2	42.5	46.6	51.8	35.0	35.7	36.6	47.1
Ethnic group										
White	85.0	85.3	85.3	85.7	84.7	85.7	86.7	86.2	84.6	84.8
Other	1.5	1.3	1.7	2.1	1.0	0.9	0.4	0.5	1.8	1.6
Missing	13.5	13.3	13.0	12.3	14.3	13.4	12.9	13.3	13.6	13.6
SIMD quintile (2009)[77]										
5 (least deprived)	15.4	15.4	15.2	13.8	14.9	15.6	12.9	14.1	16.1	16.1
4	18.3	17.8	18.5	15.7	17.6	16.4	18.2	19.2	18.6	18.3
3	20.5	20.3	20.5	20.3	19.8	19.7	21.1	20.7	20.7	20.3
2	22.3	22.2	22.1	22.1	22.5	22.7	24.5	22.9	21.8	21.8
1 (most deprived)	23.6	24.3	23.7	28.1	25.2	25.6	23.3	23.1	22.7	23.4
Urban-Rural Classification[78]										
Large urban areas	31.5	34.9	32.0	39.9	32.7	37.1	27.3	29.6	31.4	34.9

[75] The total ASCVD population and four subpopulation groups exclude individuals with a record of atrial fibrillation (AF) recorded in any of the available diagnostic fields during the index hospitalisation, as AF patients are more likely to be prescribed anticoagulation therapy (see Chapter 2). Participant characteristics of individuals with AF are summarised in Appendix D.1.

[76] Tests of significance: t-tests and chi-squared tests were performed to test for statistically significant differences in baseline characteristics between initiators and non-initiators. Results **total ASCVD** population: all characteristics between initiators and non-initiators differed significantly ($p<0.001$), in addition to SIMD ($p<0.05$). **MI**: all characteristics between initiators and non-initiators differed significantly ($p<0.001$), except for ethnic group where no statistically significant differences were found. **Stroke**: all characteristics between initiators and non-initiators differed significantly ($p<0.001$), except for ethnic group where no statistically significant differences were found. **PAD**: characteristics between initiators and non-initiators differed significantly for ASCVD history, CCI, prior APT use, ($p<0.001$), as well as urban rural factor, prior mental health hospitalisation ($p<0.01$) and SIMD ($p<0.05$), whereas no statistically significant differences were found for sex and ethnic group. **Other ASCVD**: all characteristics between initiators and non-initiators differed significantly ($p<0.001$), except for SIMD and history of ASCVD where no statistically significant differences were found.

[77] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones based on 2009 data. The SIMD was also published in 2012 and 2016, with limited changes in groupings in later years, and the 2009 classification was applied to patients' residence location at the time of ASCVD-related index discharge.

[78] Scottish Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes' drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Antiplatelet therapy initiation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Other urban areas	36.5	35.2	36.1	34.1	36.5	35.1	38.5	38.1	36.5	34.4
Accessible small towns	9.7	8.8	9.9	8.3	9.7	8.1	9.6	9.4	9.5	8.9
Remote small towns	4.1	3.9	4.0	3.8	3.9	4.2	4.9	3.7	4.1	3.9
Accessible rural	11.6	10.9	11.7	9.0	11.1	9.9	12.2	12.7	11.6	11.0
Remote rural	6.7	6.3	6.4	4.9	6.1	5.6	7.6	6.4	7.0	6.8
Charlson Comorbidity Index										
0 (no-comorbidities)[79]	18.7	22.1	N/A	N/A	N/A	N/A	N/A	N/A	45.9	43.6
1	47.2	43.5	55.2	39.7	58.7	54.6	64.7	62.7	32.2	33.2
2	20.0	16.9	27.5	27.6	22.7	22.6	17.6	16.6	13.0	12.4
3	8.2	9.3	9.9	16.5	10.9	12.7	9.7	10.2	5.2	5.9
4 or more comorbidities	6.0	8.2	7.4	16.2	7.8	10.1	8.0	10.4	3.7	4.8
Mental health inpatient/day case in the 12 months prior to index admission	1.6	3.0	1.3	4.0	2.2	4.6	1.1	1.8	1.5	2.7
History of ASCVD and antiplatelet therapy (APT) use 12 months prior to index admission[80]										
No ASCVD hospitalisation + no APT use	39.6	41.0	61.5	43.3	54.2	48.1	15.9	40.3	19.5	38.2
ASCVD hospitalisation + no APT use	6.5	21.0	8.0	16.1	8.5	16.8	5.6	26.3	4.4	21.7
No ASCVD hospitalisation + APT use	22.6	15.6	10.3	11.9	16.2	14.6	32.7	13.6	33.9	17.6
ASCVD hospitalisation + APT use	31.3	22.4	20.2	28.6	21.2	20.5	45.9	19.8	42.2	22.5

[79] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions within 12 months prior to and including the index admission. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

[80] For individuals with index hospitalisations between October 2009 and March 2010, information on prior medication use is available for the 6 to 11 months prior to index admission. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Antiplatelet therapy initiation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Time to first primary care level prescription since index discharge, in days (mean, SD)[81]	18.2 (17.8)	Not applicable	14.1 (13.7)	Not applicable	16.0 (16.5)	Not applicable	25.9 (22.0)	Not applicable	21.2 (19.5)	Not applicable
Time from prescription to dispense, in days (mean, SD)	11.5 (13.4)		11.1 (13.0)		12.7 (14.8)		11.5 (13.4)		11.2 (13.0)	

[81] Please note that this statistic only includes individuals who initiated the prescribed treatment, as the Prescribing Information System (PIS) data do not contain prescribing information for patients who were not dispensed treatment.

Table 6.2 Antiplatelet therapy (APT) initiation rates in the ASCVD study population (excluding atrial fibrillation patients) in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
APT initiation rates (%)•••	**82.1**	**84.3**	**85.3**
Men•••	83.6	86.4***	86.9
Women•••	79.7	80.9**	82.8***
Individuals aged 18 – 49 years•••	78.4	82.5***	82.3
Individuals aged 50 – 59 years•••	84.4	86.8***	87.8*
Individuals aged 60 – 69 years•••	84.9	86.9***	87.7
Individuals aged 70 – 79 years•••	82.1	83.8***	85.1**
Individuals aged 80 – 89 years•••	77.3	79.1**	81.3**
Individuals aged 90 years or older	73.3	75.7	74.8

See **Appendix D.2, Tables D2-D7** for initiation rates by ASCVD type over time.
Note: (•) next to patient category denote statistically significant trend across time period from 2009/11 to 2015/17 based on the Cochran-Armitage test for trend, where (•••) p<0.001, (••) p<0.01, (•) p<0.5. Asterisks (*) in the column 2012/2014 and 2015/2017 denote statistically significant changes in the proportion of individuals initiating treatment compared to the previous period (i.e., 2012/14 vs. 2009/11 and 2015/17 vs. 2012/14), where (***) p<0.001, (**) p<0.01, (*) p<0.5.

Initiation rates by antiplatelet therapy type

Despite the overall antiplatelet therapy (APT) initiation rate remaining reasonably constant throughout the study period, there were notable changes in the composition of antiplatelet therapy types. Overall, 68.1% of APT initiators used one of the five monotherapies available, while 31.9% used one of the four dual antiplatelet therapies that combine aspirin with an additional antiplatelet treatment (DAPT) (**Table 6.3**). However, the rates and respective changes over time varied significantly by ASCVD type (**Appendix D.3**). For example, NICE clinical guideline NG185 (2020; as well as former guidelines CG172 (2013) and CG172 (2013)) recommend DAPT in individuals who underwent PCI for at least 12 months since discharge, yet, only 65.4% of APT initiators who underwent PCI with a drug-eluting stent (DES), 69.8% of initiators with PCI and non-DES stent, and 70.1% of initiators with PCI without stent initiated DAPT in 2015/17, the remainder using antiplatelet monotherapy. DAPT initiation rates in these three groups have increased significantly since 2009/11: by 8.9% in PCI + DES (p<0.001), by 20.9% in PCI + non-DES (p<0.001), and by 24.2% in PCI without stent (p<0.001).

In the case of myocardial infarction (MI) without PCI, the guidelines have in the past recommended aspirin monotherapy or alternatively clopidogrel monotherapy, which ought to be continued indefinitely (NICE CG181 (2014), CG67 (2008); SMC Sign 149

(2017), SIGN 97 (2007)), while the most recent NICE guideline NG185 (2020) also recommends DAPT for 12 months in MI patients. In 2015/17, 71.9% of MI initiators without PCI used DAPT treatment instead of monotherapy, and DAPT initiations have increased by 18.6% since 2009/11 ($p<0.001$), showing that patients were treated more intensively than the guidelines recommended at the time. The most common DAPT combination in 2015/17 was aspirin and ticagrelor (41.9%), followed by aspirin and clopidogrel (28.9%). Only 12.8% and 8.9% of patients used aspirin and clopidogrel monotherapy, respectively.

For stroke patients, the guidelines recommend APT monotherapy, in particular clopidogrel, or the DAPT aspirin + dipyridamole (NICE CG181 (2014), CG67 (2008); SMC Sign 149 (2017), SIGN 97 (2007)). In line with the recommendations, 97.6% of stroke initiators received monotherapy (92.4% were prescribed clopidogrel, 5.1% were prescribed aspirin), while 2.4% were prescribed DAPT, of which the majority (2.1%) was for aspirin and clopidogrel combination therapy. A significant decrease in DAPT prescription was observed between the periods 2009/11 and 2012/14: while 30.6% of stroke initiators discharged in 2009/11 used DAPT, only 3% of those discharged in 2012/14 did ($p<0.001$). The monotherapy initiation rate among PAD patients increased marginally from 94.1% in 2009/11 to 95.7% in 2012/14 ($p<0.01$) and remained constant since, which is in line with clinical guidelines (NICE TA210 (2010)), which recommend clopidogrel monotherapy or alternatively aspirin and dipyridamole combination therapy. In 2015/17, 95.8% of PAD initiators were using monotherapy, the majority being prescribed aspirin (69.8%), followed by clopidogrel (25.5%), and DAPT aspirin + clopidogrel (3.8%). For a detailed overview of the types of antiplatelet therapies used by ASCVD type, see **Appendix D.3**.

Table 6.3 Types of Antiplatelet therapy prescribed and dispensed after index ASCVD hospitalisation (excluding individuals with atrial fibrillation) by a primary care level prescriber (i.e. percentage of initiators)

Proportion of Antiplatelet therapy initiators (%)	Index discharge year			
	2009-2011	2012-2014	2015-2017	Overall
Monotherapy•••	**69.3**	**69.4**	**64.9*** **	**68.1**
Aspirin•••	46.6	36.5***	28.3***	37.5
Clopidogrel•••	20.5	31.0***	33.4***	28.2
Ticagrelor•••	0.0	1.7***	3.0***	1.5
Dipyridamole•••	2.0	0.1***	0.1	0.8
Prasugrel••	0.1	0.2*	0.2	0.2
Dual Antiplatelet Therapy (DAPT)•••	**30.7**	**30.6**	**35.1*** **	**31.9**
Aspirin + Clopidogrel•••	24.7	23.0***	16.4***	21.7
Aspirin + Ticagrelor•••	0.0	7.1***	18.0***	7.8
Aspirin + Dipyridamole•••	5.8	0.3***	0.1***	2.0
Aspirin + Prasugrel•••	0.1	0.2**	0.6***	0.3

See **Appendix D.3, Tables D8-D10** for initiation rates by ASCVD type over time.
Note: (•) denotes a statistically significant trend across time period from 2009/11 to 2015/17 based on the Cochran-Armitage test for trend, where (•••) p<0.001, (••) p<0.01, (•) p<0.5. Asterisks (*) in the column 2012/2014 and 2015/2017 denote statistically significant changes in the proportion of individuals initiating treatment compared to the previous period (i.e., 2012/14 vs. 2009/11 and 2015/17 vs. 2012/14), where (***) p<0.001, (**) p<0.01, (*) p<0.5.

6.1.2. Determinants of antiplatelet therapy initiation

Patient characteristics that were significantly associated with antiplatelet therapy initiation among patients discharged with ASCVD (excluding atrial fibrillation) included age, sex, socioeconomic deprivation, co-presence of medical conditions as defined by the Charlson Comorbidity Index, concomitant mental health conditions, prior history of ASCVD and prior antiplatelet therapy use, and the hospital discharge year (**Figure 6.1**). Specifically, compared to individuals aged 60-69 years, those below the age of 50 years and those older than 69 years were significantly less likely to initiate antiplatelet therapy treatment, with the likelihood of initiation decreasing as age increased beyond 70 years (<50 years: odds ratio [OR] 0.74, 95% CI 0.70-0.78; 70-79 years: 0.79 [0.76-0.83]; 80-89 years: 0.61 [0.59-0.64]; 90 years or older: 0.49 [0.45-0.54]). Overall, women had 22% lower odds of initiating

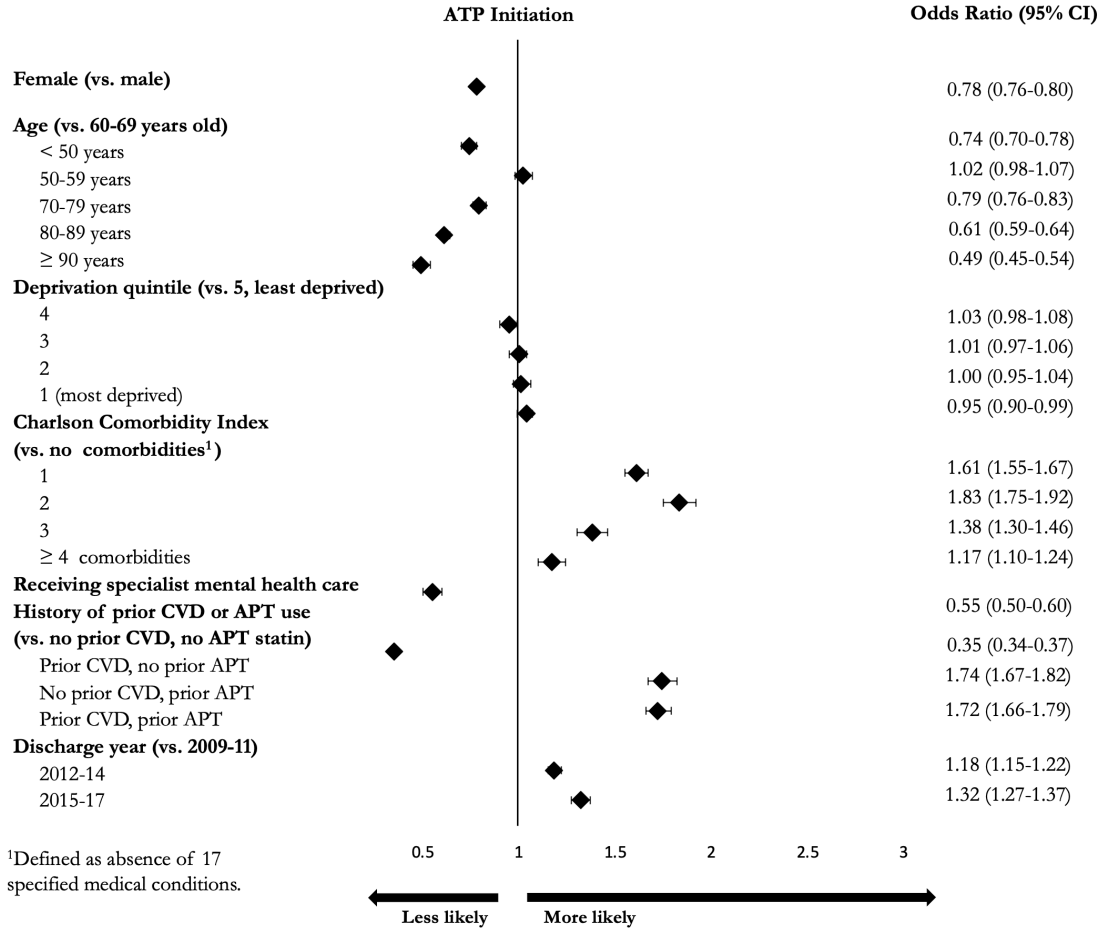
antiplatelet therapy than men (OR 0.78 [0.76-0.80]). Patients living in the most deprived areas (i.e. SIMD quintile 1) had 5% lower odds of initiating antiplatelet therapy compared to those in least deprived areas (i.e. SIMD quintile 5) (OR 0.95 [0.90-0.99]) when other factors were adjusted for.

In addition, those with previous hospitalisations at a mental health specialty or psychiatry had 45% lower odds of initiating antiplatelet therapy treatment compared to those without (OR 0.55 [0.50-0.60]). Relative to patients without prior history of ASCVD and not using antiplatelet therapy, those who used antiplatelet therapies prior to the index hospitalisation had significantly greater odds of using antiplatelet treatment after the index event, regardless of having a history of ASCVD (with ASCVD history OR 1.72 [1.66-1.79]) and without ASCVD history (OR 1.74 [1.67-1.82]). Lastly, patients discharged in later years had greater odds of initiating treatment compared to those discharged between 2009 and 2011 (2012-2014: OR 1.18 [1.15-1.22]; 2015-2017: OR 1.32 [1.27-1.37]). Further adjustments for index ASCVD admission type in the main model did not affect these findings (results not shown).

These associations were consistent across the ischaemic stroke, PAD and other ASCVD study populations (**Appendix D.4**, **Table D.11**). In addition, an increase in the number of comorbidities was associated with a decreased likelihood of individuals initiating APT. Please note that the CCI results presented in **Figure 6.1** are not easily interpretable due to index MI, stroke and PAD included among the CCI-eligible comorbidities, leaving the remaining index ASCVD conditions in the comparator "no comorbidity" category. Instead, the results are described below and in more detail in **Appendix D.4**. For example. MI patients with one or more comorbidities in addition to MI were less likely to initiate treatment than those with MI only (two comorbidities (including MI) vs. MI only: OR 0.83 [0.75-0.891]; three comorbidities: OR 0.58 [0.51-0.65]; four or more comorbidities: OR 0.49 [0.44-0.56]). Stroke patients with three or more concomitant conditions (including stroke) were less likely to initiate treatment than those with stroke only, with the likelihood decreasing with the number of comorbidities (e.g. three comorbidities: OR 0.85 [0.76-0.94]; four or more comorbidities: OR 0.79 [0.70-0.88]). Similarly, patients discharged with any other ASCVD and two or more comorbidities were less likely to initiate treatment compared to those without any comorbidities as defined by the CCI. PAD patients with three comorbidities and those with four or more comorbidities had lower odds of initiating treatment than PAD patients

with PAD only. The associations of patient characteristics with APT by ASCVD type are reported in **Appendix D.4.**

Figure 6.1 Associations of patient characteristics with antiplatelet therapy initiation among individuals with ASCVD (excluding atrial fibrillation) (a multivariable logistic regression model)



* Please note that the CCI results presented in **Figure 6.1** are not easily interpretable due to index MI, stroke and PAD included among the CCI-eligible comorbidities, leaving the remaining index ASCVD conditions in the comparator "no comorbidity" category. Instead, the results are described above and in more detail in **Appendix D.7**.

Results for the study populations (1) MI with PCI and (2) MI without PCI differed from those reported above. In the case of patients with MI with PCI, only few patient characteristics were significantly associated with APT initiation, which include the presence of comorbidities, history of ASCVD and APT use, and calendar year (**Appendix D.4**, **Table D.12**). For instance, patients with four or more comorbidities (including MI) had 40% lower odds of initiating APT (OR 0.60 [0.36-0.99]) than those with MI and no further comorbidities; those with prior ASCVD were less likely to initiate therapy than those

without, regardless of previous APT use (ASCVD, no prior APT use: OR 0.53 [0.36-0.80]; ASCVD and prior APT use: OR 0.66 [0.48-0.92]); and those discharged in 2012/14 had 39% greater odds of initiating APT than those discharged in 2009/11 (OR 1.39 [1.05-1.85]). No statistically significant association between sex, age, socioeconomic deprivation, previous specialty mental health hospitalisation and APT use were observed.

In the case of MI patients who did not undergo PCI, characteristics that were significantly associated with APT initiation include age, socioeconomic deprivation, presence of comorbidities, history of specialty mental care, history of prior ASCVD and APT use and calendar year (**Appendix D.4**, **Table D.12**). For instance, compared to individuals aged 60 to 69, those aged below 50 years and above 70 years were less likely to initiate treatment (e.g. individuals aged <50 years: OR 0.84 [0.72-0.99]; individuals aged 70-79 years: OR 0.66 [0.58-0.75]). Individuals residing in the most deprived areas in Scotland had 21% lower odds of initiating APT compared to those residing in the least deprived areas (OR 0.79 [0.69-0.91]). Patients with two or more comorbidities in addition to MI were also less likely to initiate therapy (2 comorbidities: OR 0.83 [0.75-0.91; four or more comorbidities: OR 0.50 [0.44-0.57]), while those with prior history of specialty mental health care had 62% lower odds of initiating APT than those without (OR 0.38 [0.31-0.48]).

In addition, an analysis into the association between patient characteristics and initiation of DAPT versus antiplatelet monotherapy among individuals who underwent PCI regardless of ASCVD type showed that age, socioeconomic status, presence of comorbidities, history of ASCVD and APT use and calendar year played an important role in this relationship. For example, patients aged 49 years or younger had 22% greater odds of initiating DAPT than those aged 60 to 69 years (OR 1.22 [1.07-1.38]), while older patients aged 70 to 79 years had 17% lower odds of initiating DAPT than the same comparator age group (OR 0.83 [0.75-0.91]). Individuals living in the most deprived areas had 18% lower odds of initiating DAPT compared to those residing in the least deprived areas (OR 0.82 [0.73-0.92]). Patients with one or more comorbidities were significantly more likely to receive DAPT compared to those without concomitant conditions (e.g., 1 comorbidity: OR 1.71 [1.56-1.87]). Meanwhile, individuals with prior ASCVD, regardless of prior APT use, and those without a history of ASCVD and prior APT use had lower odds of initiating DAPT than patients without a history of ASCVD and without prior APT use. Lastly, patients discharged in more recent years had greater odds of initiating DAPT

than those discharged in 2009/11 (2012/14: OR 1.33 [1.22-1.45]; 2015/17: OR 1.63 [1.49-1.78]) (**Appendix D.4 Table D.13**).

APT initiation among individuals with and without a prior history of ASCVD

Please see **Appendix D.5** for a detailed summary of determinants of APT initiation among individuals with and without a prior history of ASCVD.

6.2. Persistence with antiplatelet therapy

6.2.1. Antiplatelet therapy adherence rates

The average adherence rate among the 126,338 APT initiators, calculated as the proportion of days covered with medication (PDC) while on treatment (i.e. from index initiation until end of study date, or date of discontinuation, death or emigration, if any of these events occurred first) was 94.9%. Using a PDC rate of 80% as the threshold for adherence classification (see **Chapter 4, Section 4.4.1** for further details), the proportion of APT initiators considered to be adherent to treatment was 92.4%. At 12 months since APT initiation, the average adherence rate was 96.9%, and 95% of APT initiators were considered adherent.

6.2.2. Antiplatelet therapy discontinuation rates

Out of 126,338 patients with ASCVD who initiated antiplatelet therapy after discharge, 28,343 (22.4%) discontinued treatment (i.e. had a treatment gap of 180 days or more since initiation) at some later point in time (**Figure 6.2**). The discontinuation rates varied by type of index ASCVD event, ranging from 18.7% for MI patients, 23.9% for other ASCVD conditions and 24% for ischaemic stroke, to 27.7% in PAD patients. Compared to individuals who did not discontinue antiplatelet therapy treatment, those who discontinued were on average older at the time of the index hospital discharge (average age 67.7 years vs. 65.8 years, $p<0.001$) and more likely to be female (40.9% vs. 36.4%, $p<0.001$). The discontinuation group also had a higher proportion of patients with three and four or more comorbidities (16% vs. 13.7%, $p<0.01$), mental health hospitalisations (2.7% vs. 1.2%, $p<0.001$) and were more likely to be resident in remote rural areas (7.6% vs. 6.4%, $p<0.01$); the discontinuation group also had a lower proportion of individuals living in other urban areas (34.5% vs. 37.1%, $p<0.001$). Please see **Table 6.4** for an overview of baseline characteristics comparing individuals who discontinued and those who did not discontinue

antiplatelet therapies across different ASCVD types. The average time to discontinuation was 2 years (SD 1.7 years). After accounting for deaths, emigration and any subsequent hospitalisations, 51% of individuals who discontinued treatment had done so by 1.5 years since index initiation and 79% by 3.5 years (**Table 6.5**). Of the 28,343 individuals who discontinued antiplatelet therapy, 10,517 (37%) re-initiated some type of antiplatelet therapy at some point in time after their initial 180-day treatment gap. On average, individuals re-initiated therapy within 1.1 years since discontinuation. The discontinuation rates and respective baseline characteristics for patients with atrial fibrillation are reported in **Appendix D.6**.

Table 6.4 Participant characteristics among patients with ASCVD (excluding atrial fibrillation) who discontinued or did not discontinue antiplatelet therapy, by index ASCVD type[82]

	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Antiplatelet therapy discontinuation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N (%)	28,343 (22.4)	97,995 (77.6)	8,039 (18.7)	34,904 (81.3)	5,355 (24.0)	16,948 (76.0)	2,690 (27.7)	7,039 (72.3)	12,259 (23.9)	39,104 (76.1)
Age on discharge, in years (mean, SD)	67.7 (12.9)	65.8 (12.2)	67.2 (14.2)	64.0 (13.0)	70.1 (13.8)	68.6 (13.2)	69.2 (11.7)	68.4 (10.5)	66.7 (11.8)	65.8 (10.9)
Female	40.9	36.4	38.6	33.1	48.0	46.2	35.7	34.8	40.4	35.4
Ethnic group										
White	86.4	84.6	87.0	84.9	86.1	84.2	87.7	86.3	85.8	84.2
Other	1.7	1.5	1.9	1.6	1.1	0.9	0.3	0.4	2.1	1.8
Missing	11.9	13.9	11.1	13.4	12.8	14.8	12.0	13.3	12.2	14.0
SIMD quintile (2009)[83]										
5 (least deprived)	15.4	15.3	14.8	15.3	15.8	14.7	12.8	12.9	16.2	16.1
4	18.5	18.3	18.3	18.5	18.0	17.4	17.5	18.5	19.0	18.5
3	21.2	20.3	20.9	20.4	19.9	19.8	22.6	20.5	21.7	20.4
2	22.2	22.3	22.4	22.1	22.7	22.4	23.2	25.0	21.5	21.9
1 (most deprived)	22.7	23.8	23.6	23.8	23.6	25.7	23.9	23.1	21.6	23.1
Urban-Rural Classification[84]										
Large urban areas	32.5	31.3	34.1	31.6	33.8	32.4	26.1	27.7	32.2	31.1
Other urban areas	34.5	37.1	33.8	36.7	33.8	37.4	39.8	38.1	34.0	37.2

[82] Tests of significance: t-tests and chi-squared tests were performed to test for statistically significant differences in baseline characteristics between initiators and non-initiators. Results **total ASCVD** population: all characteristics between discontinuation and non-discontinuation differed significantly ($p<0.001$), except for ethnic groups, where no statistically significant differences were found. **MI**: all characteristics between discontinuation and non-discontinuation differed significantly (all $p<0.001$), except for ethnic groups and SIMD, where no statistically significant differences were found. **Stroke**: all characteristics between discontinuation and non-discontinuation differed significantly ($p<0.001$), in addition to sex ($p<0.05$), except for ethnic groups, where no statistically significant differences were found. **PAD**: all characteristics between discontinuation and non-discontinuation differed significantly (all $p<0.001$), including urban rural factor ($p<0.05$), except for sex, ethnic group, SIMD and prior ASCVD history, where no statistically significant differences were found. **Other ASCVD**: all characteristics between discontinuation and non-discontinuation differed significantly (all $p<0.001$), except for ethnic group, where no statistically significant differences were found.

[83] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones based on 2009 data. The SIMD was also published in 2012 and 2016, with limited changes in groupings in later years, and the 2009 classification was applied to patients' residence location at the time of ASCVD-related index discharge.

[84] Scottish Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes' drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.

Antiplatelet therapy discontinuation	Total Atherosclerotic cardiovascular disease		Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Accessible small towns	9.3	9.8	9.3	10.0	9.2	9.6	9.1	9.8	9.2	9.6
Remote small towns	4.5	3.9	4.5	3.8	4.2	3.9	5.3	4.7	4.5	4.0
Accessible rural	11.6	11.5	11.1	11.8	11.7	10.9	11.2	12.5	11.9	11.5
Remote rural	7.6	6.4	7.2	6.2	6.4	6.0	8.5	7.3	8.2	6.6
Charlson Comorbidity Index										
0 (no-comorbidities) [85]	20.4	18.2	N/A	N/A	N/A	N/A	N/A	N/A	47.1	45.5
1	44.2	48.1	48.2	56.8	58.3	58.8	64.5	64.7	30.9	32.5
2	19.5	20.2	28.8	27.2	21.9	22.9	17.0	17.9	12.8	13.1
3	8.8	8.0	12.5	9.3	11.2	10.8	9.9	9.7	5.1	5.2
4 or more comorbidities	7.2	5.7	10.6	6.7	8.6	7.5	8.6	7.7	4.0	3.6
Mental health inpatient/day case 12 months prior to index admission	2.7	1.2	2.6	1.1	3.5	1.8	1.8	0.9	2.6	1.2
History of ASCVD and antiplatelet therapy use 12 months prior to index admission[86]										
No ASCVD hospitalisation + no antiplatelet therapy	35.3	37.4	52.3	57.0	49.7	49.9	18.4	14.1	21.6	18.5
ASCVD hospitalisation + no antiplatelet therapy use	8.7	7.3	11.8	16.6	17.0	21.6	7.1	6.9	6.5	6.3
No ASCVD hospitalisation + antiplatelet therapy use	22.9	26.1	11.7	7.8	9.8	9.0	31.8	33.8	30.8	35.2
ASCVD hospitalisation + antiplatelet therapy use	33.1	29.2	24.2	18.6	23.5	19.5	42.7	45.2	41.1	40.0
Time to discontinuation, in years (mean, SD)	2.0 (1.7)	Not applicable	2.1 (1.7)	Not applicable	1.8 (1.7)	Not applicable	1.9 (1.8)	Not applicable	2.0 (1.8)	Not applicable

[85] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

[86] For individuals with index hospitalisations between October 2009 and March 2010, information on prior medication use is available for the 6 to 11 months prior to index admission. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

Figure 6.2 Overview of antiplatelet therapy initiation and discontinuation rates in the ASCVD population (after excluding patients with atrial fibrillation)

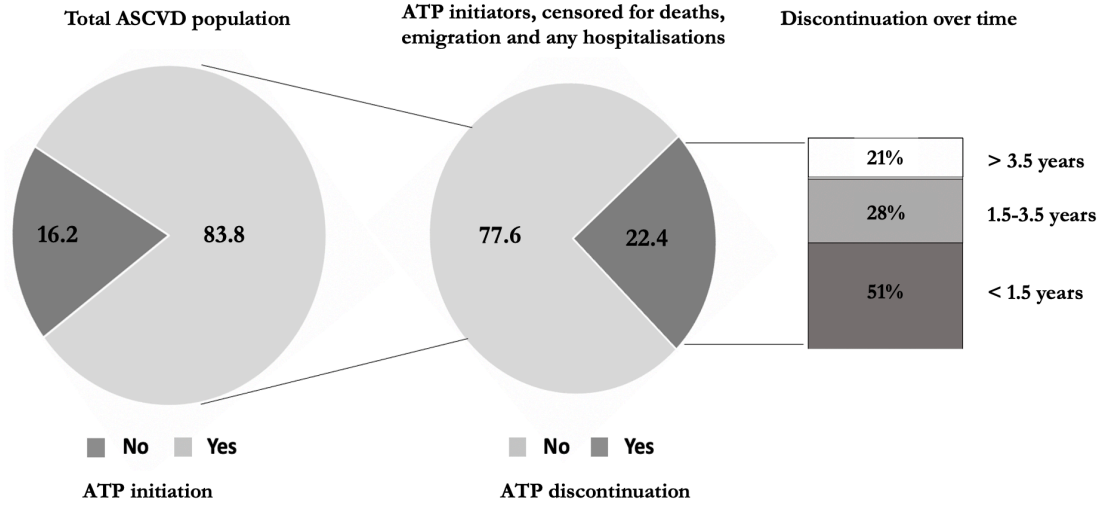


Table 6.5 Distribution of ASCVD patients (after excluding patients with atrial fibrillation) who discontinued antiplatelet therapy over time, by time duration since antiplatelet therapy initiation

Time since initiation	Individuals discontinuing antiplatelet therapy, N (%)	Cumulative percentage
0 to 6 months	6,744 (23.9)	23.9
7 to 12 months	4,251 (15.0)	39.0
13 to 18 months	3,401 (12.0)	51.1
19 to 24 months	2,551 (9.0)	59.9
25 to 30 months	2,267 (8.0)	67.5
31 to 36 months	1,984 (7.0)	74.2
37 to 42 months	1,701 (6.0)	80.0
43 to 48 months	1,417 (5.0)	85.0
49 to 60 months	1,984 (7.0)	92.2
61 to 72 months	1,417 (5.0)	97.0
73 to 84 months	850 (3.0)	99.5
85 to 96 months	141 (0.5)	100
Total	**28,343 (100)**	**100**

Note: Individuals who died, emigrated or experienced any subsequent hospitalisation excluded from respective time periods.

6.2.3. Determinants of antiplatelet therapy persistence

Discontinuation of antiplatelet therapy

Patient characteristics associated with discontinuation of antiplatelet therapy included sex, age, presence of comorbidities, concomitant mental health conditions and prior history of antiplatelet therapy use (**Figure 6.3**). Specifically, women had a 11% higher risk of discontinuation than men (Hazard Ratio [HR] 1.11, 95% CI 1.08-1.13). A U-shaped association was observed by age. Compared to individuals aged 60 to 69 years, those aged 50-59 had a lower risk of discontinuation (HR 0.92 [0.88-0.95]). All remaining age groups were at higher risk of discontinuation and the risk significantly increased with age, with a 13% higher risk among those aged below 50 years (HR 1.13 [1.08-1.18]), a 32% higher risk among individuals aged 70-79 (HR 1.32 [1.27-1.36]), a 68% higher risk among individuals aged 80-89 years (HR 1.68 [1.61-1.74]), and the risk increasing up to 2.2-fold in the case of patients aged 90 years or older (HR 2.17 [2.02-2.34). Unlike the association observed for the initiation of antiplatelet therapy, there was no statistically significant relationship between socioeconomic status and the risk of discontinuing antiplatelet therapy.

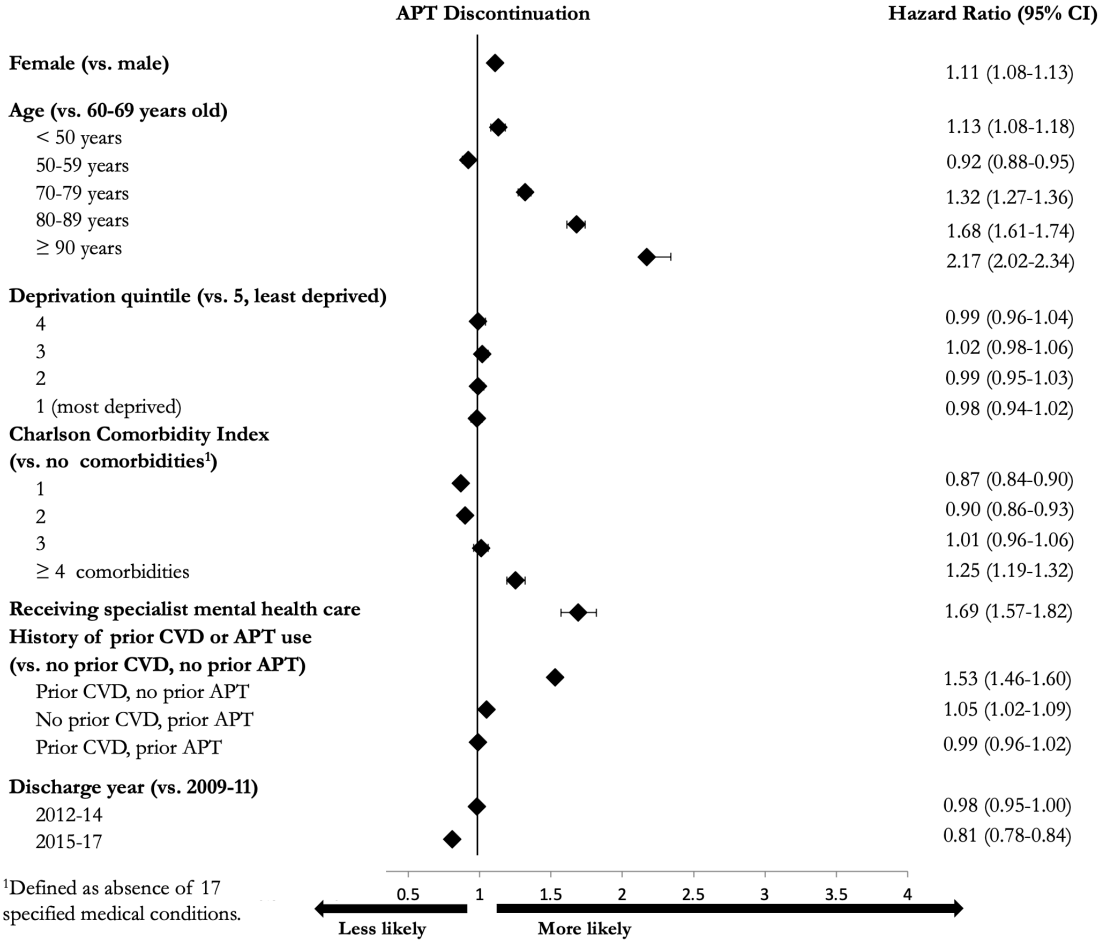
Patients with a history of mental health-related hospitalisations had 1.7-fold increased risk of discontinuation compared to those without such a medical history (HR 1.69 [1.57-1.82]). Furthermore, compared to individuals without a prior history of ASCVD and no previous antiplatelet therapy use, those without an ASCVD history and with previous antiplatelet treatment were at higher risk of treatment discontinuation (HR 1.05 [1.02-1.09]), as were individuals with a prior history of ASCVD who did not use antiplatelet therapy in the 12 months prior to index hospitalisation (HR 1.53 [1.46-1.60]). Individuals discharged in more recent years had a lower risk of treatment discontinuation than those discharged in 2009/11 (2015-2017: HR 0.81 [0.78-0.84]).

The associations were consistent across ASCVD types, except for the following differences (see **Appendix D.7** for a complete overview of results). Patients hospitalised for stroke and other ASCVD, who lived in the most deprived areas in Scotland, had a relatively lower risk of treatment discontinuation than those residing in the least deprived areas (stroke: HR 0.87 [0.80-0.95]; other ASCVD: HR 0.94 [0.90-0.98]). MI and stroke patients with a prior history of ASCVD with and without prior APT use, as well as those without a prior history of ASCVD and with prior APT use, were at relatively greater risk of discontinuation than individuals without a prior history of ASCVD and without APT use (e.g. MI: prior ASCVD without prior APT: HR 1.69 [1.57-1.83]; prior ASCVD and

prior APT: HR 1.14 [1.07-1.21]; no prior ASCVD and prior APT: HR 1.12 [1.04-1.21]). Patients with PAD and other ASCVD were at relatively lower risk of treatment discontinuation if they used APT previously, compared to individuals who did not use APT before being hospitalised for ASCVD (e.g. PAD: no prior ASCVD and prior APT: HR 0.75 [0.67-0.84]; prior ASCVD and prior APT: HR 0.66 [0.59-0.73]).

In addition, a significant relationship between the presence and number of comorbidities and treatment discontinuation was observed across all ASCVD types. In the case of MI, patients with comorbidities in addition to MI had a greater risk of discontinuing APT compared to patients with MI only, with the relative risk increasing as the number of comorbidities increases (e.g. one extra comorbidity: HR 1.11 [1.05-1.17]; three or more extra comorbidities: HR 1.66 [1.54-2.04]). In the case of PAD and stroke, the association was significant if individuals had three or more comorbidities compared to those with PAD or stroke only (e.g. stroke: three or more comorbidities: HR 1.29 [1.16-1.42]). Patients with other ASCVD and four or more comorbidities were also at relatively greater risk of treatment discontinuation compared to those without any concomitant conditions (HR 1.24 [1.13-1.36], however, those with one comorbidity had a slightly lower risk of discontinuation than those without comorbidities (HR 0.94 [0.90-0.98]). Please note that the CCI results presented in **Figure 6.3** are not easily interpretable due to index MI, stroke and PAD included among the CCI-eligible comorbidities, leaving the remaining index ASCVD conditions in the comparator "no comorbidity" category. Please see **Appendix D.7** for the associations between CCI and statin discontinuation by ASCVD type.

Figure 6.3 Associations of patient characteristics with antiplatelet therapy discontinuation among individuals with ASCVD (a multivariable Cox proportional hazards model)



* Please note that the CCI results presented in **Figure 6.3** are not easily interpretable due to index MI, stroke and PAD included among the CCI-eligible comorbidities, leaving the remaining index ASCVD conditions in the comparator "no comorbidity" category. Instead, the results are described above and in more detail in **Appendix D.7**.

6.3. Suboptimal antiplatelet therapy use and subsequent ASCVD risk

Out of 158,507 individuals hospitalised for an ASCVD event between 1 October 2009 and 31 December 2016, 151,857 individuals were still alive 12 months after discharge and 137,013 of them did not have a record of atrial fibrillation on discharge (see **Chapter 4, Section 4.3.3** for identification of participants). Of the latter, (1) 105,407 individuals (77%)

initiated[87] antiplatelet therapy and remained on treatment within 12 months since discharge, while (2) 9,800 (7%) initiated and subsequently discontinued antiplatelet therapy within 12 months since discharge and (3) 21,806 (16%) did not initiate antiplatelet therapy within 12 months since discharge (**Table 6.6**). Amongst individuals who initiated and remained on antiplatelet therapy, 20.4% experienced either a non-fatal or fatal ASCVD-related event during study follow-up. In the case of individuals who discontinued or never initiated therapy, 17.7% and 20.9% of patients, respectively, experienced subsequent ASCVD-related events, with the observed differences between the APT initiator group who remained on treatment and the APT initiator group who discontinued APT being significant ($p<0.001$; not accounting for time to event or other characteristics). No significant differences were observed between APT initiators and APT non-initiators (not accounting for time to event). The characteristics of each patient group and breakdown of ASCVD events experienced are presented in **Appendix D.8**, **Table D.17**).

Table 6.6 Proportion of individuals discharged for an ASCVD-related event who experienced subsequent fatal and non-fatal ASCVD-related events during follow up

	Group 1 Initiated APT and remained on APT	**Group 2** Initiated APT and discontinued APT	**Group 3** Non-initiators
Study population	Individuals who initiated[88] and did not discontinue antiplatelet therapy within 12 months since discharge	Individuals who initiated and subsequently discontinued antiplatelet therapy within 12 months since discharge	Individuals who did not initiate antiplatelet therapy within 12 months since discharge
Total population (N)	105,407	9,800	21,806
Individuals experiencing fatal and non-fatal ASCVD-related events[89], N (%)	21,524 (20.4)	1,734 (17.7)	4,559 (20.9)

[87] Initiation here follows the same definition as used prior, i.e., individuals who were prescribed therapy within 90 days since index discharge and dispensed the therapy within 60 days since prescription.

[88] Initiation here for all three groups follows the same definition as used prior, i.e., individuals who were prescribed therapy within 90 days since index discharge and dispensed the therapy within 60 days since prescription.

[89] Please note: The total number of non-fatal and fatal ASCVD-related events only counts one of the two possible events (i.e. subsequent hospitalisation or death) per individuals, counting the event that happened first. Counting the first subsequent ASCVD event per person only, regardless of whether individuals experienced more than one subsequent event. ASCVD-related death was defined as an individual's death record listing an ICD-10 code for cardiovascular disease as the primary cause of death, where ASCVD was

The findings from the adjusted Cox proportional hazards survival analyses, stratified by age-group and ASCVD type, suggest that, APT non-initiators are at higher risk of experiencing a subsequent ASCVD-related event than APT initiators in the case of MI and stroke (**Appendix D.7, Table D.18**). For example, MI and stroke patients who did not initiate APT each had an 11% higher risk of experiencing subsequent ASCVD event compared to those who initiated APT. No statistically significant findings were observed for MI, stroke and PAD patients who discontinued APT, and PAD patients who never initiated APT. However, patients with other ASCVD, who did not initiate and those who discontinued APT were associated with lower risks of subsequent ASCVD events than APT initiators who remained on treatment (see **Appendix D.7, Table D.18** for an overview of results by ASCVD type).

6.4. Discussion

6.4.1 Findings and interpretation of results

Overall summary

Using NHS Scotland national prescribing information for the years 2009 to 2017 for 150,728 individuals hospitalised for an ASCVD event (and without record of atrial fibrillation at discharge) since October 2009 showed that approximately 84% of patients initiated antiplatelet therapy (APT) following hospital discharge. While initiation rates were high among MI patients (93.7%) and those treated with PCI (97.2%) in the most recent years 2015/17, only 68% of PAD patients initiated APT. Comparatively low APT initiation rates among PAD patients were previously observed in other large observational studies (e.g. Rammos et al., 2021 [1]) that have highlighted low awareness of the PAD diagnosis in the primary care setting [1]. Initiation rates in the ischaemic stroke (83%) and other ASCVD populations (80.6%) also highlighted scope for further improvements in CVD management. Lower odds of initiation were associated with individual-level factors, including older age (70+ years), younger age (<50 years), being female, having multiple comorbidities, history of mental health admissions and higher socioeconomic deprivation, and the findings were consistent across ASCVD types, with the exception of patients with

defined in line with the ICD-10 codes used to define the ASCVD population in this study (see **Chapter 4** Methods for an overview of ICD-10 codes included).

MI who underwent PCI, where only few characteristics played a significant role in APT initiation, as nearly every individuals treated with PCI initiated APT.

Furthermore, despite clinical guidelines recommending dual-antiplatelet therapy (DAPT) for the first 12 months in patients treated with PCI since 2013, only 65.4% of initiators treated with PCI with drug-eluting stents (DES), 69.8% of initiators treated with PCI with non-drug eluting stents, and 70.1% of those treated with PCI without stent used DAPT in 2015/17, the remainder still being prescribed monotherapy. DAPT has been consistently shown to reduce major adverse cardiovascular events (MACE) in patients undergoing PCI with DES, but at the expense of an increased risk of major bleeding [2]. Shorter durations of DAPT (3-6 months) were previously reported to reduce the rates of bleeding [3], while longer durations (18-48 months) yielded higher reduction in MACE but at a higher risk of major bleeding, highlighting the trade-off between efficacy (i.e. risk reduction of recurrent CVD events) and safety (i.e. major bleedings) [2]. While further research is required to identify which patients based on individual ischaemic and bleeding risk could benefit from shorter DAPT use, overall, the incidence of major bleeding is relatively low [4], [5] and DAPT is still recommended in patients treated with PCI (e.g. NICE NG185 (2020)), thereby highlighting significant treatment gaps in the current study population. In addition, this study has shown that the odds of DAPT initiation were lower for patients of older age, higher socioeconomic deprivation, and with prior history of ASCVD and APT use, i.e., factors that besides older age are not related to safety of DAPT use.

It must be emphasised that while on treatment, the vast majority (92.4%) of users were adherent (i.e. a PDC score of 80% or more). However, almost a quarter of patients (22.4%) discontinued antiplatelet therapy treatment at some point in time, with 51% of discontinuations recorded within 1.5 years since initiation. For example, despite clinical guidelines recommending the indefinite use of APT in MI patients, 18.7% of these patients discontinued therapy. Of all the individuals who discontinued treatment, 37% re-initiated some type of antiplatelet therapy at some point in time after their initial 180-day treatment gap. Independent baseline predictors of discontinuation included older age (70+ years), younger age (<50 years), being female, having multiple co-morbidities and previous mental health specialty admissions, and were fairly consistent across ASCVD types. Whilst it is likely that some of these individuals discontinued treatment in response to side effects such as dyspepsia and bleeding, as has been reported in previous literature (e.g. an observational prospective cohort study of patients with acute coronary syndrome showed that 10.4% of

individuals who discontinued DAPT with ticagrelor experienced bleeding events compared to 2.7% of individuals who did not discontinue [6]), major bleeding events are relatively rare (e.g. based on six randomised controlled trials summarised in meta-analysis of aspirin treatment for the primary prevention of CVD events, between 0.01% and 0.004% of patients treated with aspirin were found to experience major bleeding [7]; and would not explain the comparatively high number of discontinuations. Lastly, MI and stroke patients who never initiated APT were at 11% higher risk of experiencing subsequent ASCVD events compared to individuals who initiated APT.

Determinants of antiplatelet therapy initiation and discontinuation

The role of age

This study found a significant U-shaped relationship between age and the initiation and discontinuation of antiplatelet therapies, with younger individuals below 50 years and elderly individuals aged 70 years or older being less likely to initiate treatment, while concurrently having higher risks of treatment discontinuation. Three previous studies assessed the above relationship at different treatment stages and reported differing results. Similar to the results presented in this analysis, a nationwide cohort study from Finland found that individuals aged 66 years and older, who were hospitalised for an acute coronary syndrome (ACS) event, were less likely to initiate oral antiplatelets within seven days since discharge compared to patients aged 65 years or younger, with the likelihood of initiation decreasing with age. Elderly individuals aged 75 years or older were also at greater risk of discontinuing treatment within 12 months compared to patients below 65 years of age [8]. In contrast, a retrospective cohort study using data from The Health Improvement Network (THIN), a database containing approximately 4 million individuals registered with participating primary care practices in the UK, did not observe any significant associations between age and the discontinuation of aspirin monotherapy or dual antiplatelet therapy, contrary to the findings in this study. Instead, an obverse relationship was found in the case of clopidogrel monotherapy, with individuals aged 60 years or older having a decreased risk of treatment discontinuation compared to those aged 50 to 59 years [9].

Previous studies have demonstrated a positive association between older age and haemorrhagic risk, which increases exponentially from the seventh decade and was further associated with increased mortality [10], [11]. This bleeding risk could be related to the intrinsic characteristics of the elderly population, such as presence of comorbidities, complex coronary disease, physical disabilities and frailty [12]. Therefore, it is possible that

a trade-off between efficacy and safety has been considered by the prescribing physicians in this study, reflected in the relatively lower initiation and persistence rates. However, this study has shown that individuals below the age of 50 also have a higher risk of non-initiation and discontinuation of treatment compared to individuals aged 60 to 69 years and thereby further clinician and patient education on the safety and efficacy of antiplatelet therapy may be advantageous, particularly in light of clinical guidelines recommending the indefinite use of APT for MI patients and its potential in reducing recurrent vascular events in individuals at high risk of CVD.

The role of gender

This study observed a significant association between gender and the initiation and discontinuation of antiplatelet therapy, with women being less likely to initiate treatment and concurrently being at higher risk of treatment discontinuation[90]. Six studies (partly presented in **Chapter 3**) reported similar findings at different treatment stages. For instance, compared to men, women hospitalised for MI were less likely to be prescribed aspirin at discharge in Sweden and Switzerland [13]–[15]. Comparable observations were made at the treatment initiation stage. For instance, a nationwide cohort study from Finland found that women hospitalised for an acute coronary syndrome (ACS) event were less likely to initiate antiplatelet therapy within seven days since discharge than men [8], while an observational study using claims data on individuals hospitalised with acute coronary syndrome (ACS) in Tianjin, China, has shown that even within 30 days of discharge, women were significantly less likely to initiate treatment than men [16]. In addition, the latter study noted worse antiplatelet treatment persistence in women, which has also been reported in a retrospective UK cohort study among individuals hospitalised for an acute coronary event [9], as well as in this study. Consequently, the suboptimal antiplatelet therapy use at every treatment stage continues to widen the gender treatment gap.

A large meta-analysis of randomised controlled trials examining the use of aspirin for the secondary prevention of CVD published by the Antithrombotic Trialists' (ATT) Collaboration found no convincing evidence of gender differences in the effects of aspirin compared to placebo for the secondary prevention of CVD. In fact, the relative risk reduction of serious vascular events during follow-up with aspirin was reported to be 19%

[90] The associations were significant for all ASCVD types except for MI with PCI, MI without PCI and PAD in the case of APT initiation, and all ASCVD types except for PAD and stroke in the case of APT discontinuation.

for both genders, while similarly increasing the risk of bleeding in women and in men, showing that women derive significant benefits from antiplatelet therapy [4], [17]. A large meta-analysis documented that clopidogrel vs. placebo in addition to aspirin therapy was associated with more frequent major bleedings in the long-term in both genders, although the odds of major bleeding were higher in women (OR 1.43, 95% CI 1.15-1.79 vs. men: OR 1.22, 95% CI 1.05-1.42) [18]. While this higher risk could have partly explained a lower initiation of DAPT in women, this study has shown that gender was not significantly associated with the likelihood of initiating DAPT. In addition, previous large meta-analyses of randomised controlled trials such as those published by the Antithrombotic Trialists' (ATT) Collaboration have noted that the benefits of APT substantially exceed the risks of major gastrointestinal or other extracranial bleeds in the secondary prevention of CVD, with the increase of these events being an order of magnitude smaller than the gains [4]. Closer attention should be paid to the management of female patients with CVD, and further training and education on the safety and efficacy of antiplatelet therapy among both providers and patients will be required to further narrow the gap.

The role of comorbidities

This study showed that the presence of comorbidities in ASCVD patients was associated with both lower odds of antiplatelet therapy initiation and higher risks of treatment discontinuation. Similar to these findings, a nationwide cohort study in Finland examined the role of comorbidities in oral antiplatelet initiation and found that ACS patients with three or more comorbidities were less likely to initiate antiplatelet therapy compared to individuals without any comorbidities, as defined by the Charlson Comorbidity Index [8]. Patients with multiple comorbidities were also at higher risk of discontinuing treatment [8], [19]. In addition to physical comorbidities, this study also investigated the role of mental health-related hospitalisations and found a significant association between patients with a history of mental health admissions and lower odds of treatment initiation, as well as higher risks of treatment discontinuation. The studies summarised in the systematic literature review (**Chapter 3**) did not evaluate the role of mental health conditions and therefore no comparisons could be drawn. There may be an association between certain comorbidities and bleeding risk that could explain the lower utilisation rates in patients with physical comorbidities. For example, a meta-analysis of randomised controlled trials investigated potential risk factors of major bleeding events and found that chronic obstructive pulmonary disease (COPD) and diabetes may constitute probable risk factors

[20]. However, current risk factors assessed in validated bleeding risk assessments such as the PRECISE-DAPT[91] (Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) do not include comorbidities[92] [23]. Furthermore, this study has shown that in addition to physical comorbidities, a history of specialty mental health admissions played a key role in APT initiation and discontinuation. Further research is required on the possible associations between physical comorbidities and bleeding risk and to expand on currently available risk assessment tools. In addition, further training and education on the safety and efficacy of antiplatelet therapy in patients with concomitant physical or mental health conditions among both providers and patients may yield improvements in the current comorbidity-related treatment gap.

Long-term associations between suboptimal antiplatelet therapy use and health outcomes

Findings from the Cox proportional hazards survival analyses have shown that MI and stroke patients who never initiated APT were at significantly higher risk of experiencing subsequent fatal and non-fatal ASCVD events compared to individuals who initiated and did not discontinue their treatment. The results are consistent with evidence from randomised controlled trials summarised in **Chapter 2**, which have shown that antiplatelet therapies like aspirin and clopidogrel yield a relative risk reduction of 30% in myocardial infarctions, 20% in strokes and 30% in other vascular events. Patients with other ASCVD, such as angina and those with a hospital length of stay of less than one day, who did not initiate and those who discontinued APT were associated with lower risks of subsequent ASCVD events. This may be due to diagnostic uncertainties in this patient group, where patients, upon re-evaluation by a general practitioner, may have been deemed to have an uncertain CVD diagnosis and leading to physicians actively changing or stopping the medical regimen accordingly. There may also be a potential for implicit treatment selection based on risk, for example, those initiated on treatment may have been perceived as a substantially higher risk group than those who were not treated. This unexpected observation underlines the importance of randomised evidence in reliably informing health

[91] PRECISE-DAPT has been validated in eight multicentre randomised trials [21], [22]. It is a simple 5-item risk score including information on age, creatinine clearance, haemoglobin, white-blood-cell count and previous spontaneous bleeding [23].

[92] A number of validated risks for the risk assessment of 1-year risk of major bleeding in people taking anticoagulation for atrial fibrillation (e.g. HAS-BLED) for example include hypertension, renal disease, liver disease and stroke history in their score calculation. However, this is not the case in scores developed for antiplatelet therapy use [24].

policy. Overall, with 16% of ASCVD patients not initiating treatment, in addition to individuals discontinuing treatment over time, about 20% of patient-years were not covered by antiplatelet therapy after an event. About 25% of events in those patient years (i.e. 5% of all major ASCVD events in the entire ASCVD population) might have been prevented if antiplatelet therapy had been used. The potential benefits would have come at the cost of some additional bleeding events.

6.4.2 Limitations

Limitations of observational data

This study should be interpreted in the context of the following limitations, which have been described in detail in **Chapter 5.5.2**. The data only included prescribing information for individuals who were both prescribed and dispensed treatment. As a result, it is not possible to determine if patients (a) were never prescribed antiplatelet treatment or (b) whether they received a prescription which was ultimately not dispensed for any reason, and therefore the magnitude of these potential problems cannot be quantified. Consequently, the analysis could not distinguish between treatment gaps that arose due to suboptimal prescribing and those due to suboptimal patient initiation. Furthermore, the data only include information on prescriptions issued in primary care. Consequently, overall prescription rates and types of antiplatelet therapies used during the ASCVD-related hospitalisation and prescribed in hospital at discharge could not be evaluated.

Patient characteristics were derived from hospital records, which do not capture patient's full medical history and diagnoses documented in primary care records. As the data only included information on antiplatelet therapies and statin, comorbidities such as diabetes could not be derived from the prescription records. The use of antiplatelet therapy can also increase the risks of major gastrointestinal (GI) and extracranial bleeds, however, efforts in primary care to reduce bleeding risks, such as the prescription of proton pump inhibitors for the prevention of aspirin-induced ulcers, for example, were not captured due to the reasons described above, and prevented the creation of bleeding risk scores. As a result, it is possible that some individuals discontinued APT due to side effects such as bleeds (or perceived risk of bleeding), which were not analysed. However, it must be pointed out that both randomized controlled trials and observational studies have reported low incidences of major bleeding due to antiplatelet use, concluding that the benefits of APT substantially exceed the risks in the secondary prevention of CVD [4], [5]

Lastly, a number of patient characteristics that may be relevant to the likelihood of using antiplatelet therapy, such as patients' ethnicity and marital status, could not be robustly studied due to large numbers of missing observations. The data also do not provide insights into clinicians' and patients' beliefs, preferences or risk perceptions of antiplatelet therapy. Despite these limitations, the dataset has major strengths in that it captures the entire national population of Scotland and their healthcare under a single provider, including every individual ever hospitalised for an ASCVD-related event from April 2009 onwards, allowing for a longitudinal follow-up of up to eight years.

6.4.3 Conclusions

Overall, 84% of patients in Scotland admitted to hospital with ASCVD in the period 2009 to 2017 (excluding patients with atrial fibrillation) initiated antiplatelet therapy (APT) , with rates varying across ASCVD types and procedures (e.g. 66% in PAD vs. 97% in patients treated with PCI), and changing only marginally over time. Only 68% of individuals treated with PCI, who initiated treatment, used dual-antiplatelet therapy (DAPT) as recommended in clinical guidelines. The vast majority (92%) of patients were adherent (i.e. a PDC score of 80% or more), however, almost a quarter of initiators (22%) discontinued antiplatelet therapy at some point in time, with rates of discontinuation being significantly higher in the PAD population. Patient factors that were associated with both lower likelihood of antiplatelet therapy initiation and higher risk of treatment discontinuation included being female, those aged below 50 or above 70 years, patients with multimorbidities and specialty mental health admissions. Socioeconomic deprivation was also associated with lower odds of treatment initiation. MI and stroke patients who never initiated APT were at higher risk of experiencing subsequent fatal and non-fatal ASCVD events. Despite the available evidence that the efficacy of APT outweighs the risks of side effects such as bleeding events in the secondary prevention of ASCVD, significant variations between patient groups continue to persist, which need to be investigated by clinicians and policy-makers.

6.5. Summary

This chapter provided novel evidence on the scope of antiplatelet therapy use and patient characteristics associated with the initiation and discontinuation of therapy among individuals hospitalised with ASCVD using Scotland population-wide individual-level patient data and identified patient groups that could be targeted to improve medication use. In the next chapter, I present analyses that investigate the effect of national-level

policies and market forces, specifically the introduction of clinical guidelines for the secondary prevention of ASCVD and the market entry of generic statins, on the initiation of statin therapy for the secondary prevention of ASCVD.

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7

Impact of selected policies on the initiation of statin therapy

Summary

This chapter uses population-wide individual-level patient data on 136,855 individuals hospitalised for an ASCVD-related event in Scotland in the time period from 1 October 2009 to 3 July 2017, who were prescribed statin therapy within 90 days since discharge and dispensed the treatment within 60 days since prescription (i.e., defined as statin initiators). The study assesses the effect of two national policies on the initiation of different statin types and intensities using retrospective individual-level interrupted time series (ITS) analyses. The policies include (1) the UK market entry of generic atorvastatin on 8 May 2012 and (2) the introduction of NICE clinical guideline CG181 on 18 July 2014 recommending the use of high-intensity statin, particularly atorvastatin 80mg/day, for the secondary prevention of CVD. The market entry of generic atorvastatin had a significant positive effect on high-intensity statin prescription trends, which were further accelerated with the introduction of NICE clinical guideline CG181. The narrowing price gap between simvastatin and atorvastatin as a result of the generic availability of the latter led to a significant increase in the uptake of the more potent atorvastatin, even before the publication of the NICE guideline in 2014 that specifically recommended the use of high-intensity statin therapy. The relative cost-effectiveness of different statin types appeared to be a key influencing factor in prescribing decisions. If there are significant price differences between statins, decision-makers tend to opt for a statin with lower acquisition cost, as the additional cost of a more expensive potent statin type may not be outweighed by its additional marginal benefits. However, when prices converge as a result of the availability of generic statins and with time, the marginal clinical benefits of higher-intensity statins outweigh their minimally higher costs relative to statins with lower costs and benefits, leading to a significant increase in the use of more potent statin types.

7.1. Introduction

7.1.1. Background

Statins are the most prescribed drugs for the secondary prevention of CVD due to their efficacy and safety in reducing the risk of cardiovascular events and ability to improve survival (**Chapter 2**). There are five types of statins available in the UK to date, launched as branded versions in the market between 1988 and 1997 (see **Figure 7.1**). However, the dose-based potency between statin types differs significantly (**Table 7.1**). Out of five statin types, only atorvastatin and rosuvastatin have the potency to reduce LDL-C levels by at least 50%, with this threshold being achievable using a smaller dose of rosuvastatin 40mg, compared to the 80mg-dose atorvastatin [1]. Clinical trials have shown that a larger reduction in LDL-C levels is directly associated with larger proportional reductions in risks of cardiovascular events [2], therefore clinicians are encouraged to treat patients with a history of CVD with high-intensity therapy, defined as those reducing LDL-C level by a minimum of 40% in the UK (and a minimum of 50% in the US) (**Chapter 2, Table 2.3**) [3], [4]. In July 2014, the National Institute for Health and Care Excellence (NICE) published the clinical guideline CG181 recommending the use of high-intensity statin treatment, specifically atorvastatin 80mg, for the secondary prevention of CVD [5].

When statins entered the UK market in the late 1980s, they quickly began to dominate the lipid-lowering market, accounting for more than 90% of the overall expenditure on lipid-lowering drugs in 2004 [6]. A combination of (1) increased statin use and (2) the use of more expensive branded agents led to a significant cost burden to the UK's National Health System (NHS), with lipid-lowering drugs constituting the largest annual drug cost at £738 million in the UK in 2004, of which Scotland's statin expenditure amounted close to £90 million [6]–[9]. With the introduction of generic statins[93], the quantity of statins prescribed began to increase while spending on statins started to fall. In England the number of statin prescriptions increased by 46% in the period from 2008 to 2018, while the costs of dispensing those items fell by 79% over the ten-year period [10]. Similarly, in Scotland the statin prescription rate increased by 412% in the 14-year period from 2001 to 2015, while overall costs decreased by 50% in the same time period [9]. The large extent to which the price of statins decreased and the rate of prescriptions increased

[93] Simvastatin moved off-patent in 2003; pravastatin in 2004; atorvastatin in 2012; fluvastatin 20mg and 40mg in 2013, 80mg in 2015; rosuvastatin in 2017.

was influenced by a combination of supply- and demand-side measures further discussed below.

Supply-side measures influencing the price of statins

The (1) increasing availability of generic substitutes between 2003 to 2012 and (2) the large number of competing generic manufacturers led to a significant drop in the price of statins to as low as 3% of the pre-patent loss originator prices, such as in the case of simvastatin [11], [12]. The price reduction induced by these supply-side measures was further enhanced by government policies in the UK, such as the introduction of the 'M' (manufacturer) and 'W' (wholesaler) scheme in April 2005 [9]. The scheme promoted transparency in the prices of generic drugs, including any rebates, leading to an average decrease of 32% in prices of generics by April 2006 [13]–[15]. An overview of the changes in price of branded and generic statin types over time is presented in **Table 7.1**.

Demand-side measures influencing the volume of statins prescribed

There is no direct relationship between the price of medications and the volume of medications prescribed in the UK, as patients are not paying for the treatment and are not necessarily aware of the changes in prices[94]. Instead, there is an indirect effect of price on volume due to national or regional demand-side measures on the part of the government or NHS Health Boards that regulate and influence medication uptake. These measures include the introduction of prescribing guidelines, further education of physicians, availability of regional formularies and reimbursement of medications, monitoring of prescribing patterns, setting efficiency and quality targets, as well as financial incentives [17].

These initiatives, particularly the publication of prescribing guidelines and physician education, are important, because pharmacists in the UK are not allowed to dispense an identical lower-cost generic version of a drug if a physician prescribes an expensive originator drug. In the case of statins, national clinical guidelines were introduced in 2007 in Scotland (SIGN 97) and 2008 in England (NICE CG67) promoting the prescribing of statins with low acquisition costs as a first line treatment, specifically simvastatin 40mg [18], [19]. As a result of local initiatives by NHS Boards to encourage

[94] The four National Health Service Systems (NHS) in the UK provides universal healthcare. In Wales (since 2007) and Scotland (since 2011), residents are entitled to free medications on prescription following the abolition of NHS prescription charges. In England, patients continue to pay a prescription fee of £9.35 per item (2021 fee), however, many individuals like those aged 60 or over and individuals on income support are eligible for an exemption of prescription fees [16].

generic prescribing, generic simvastatin accounted for 59% of all statins prescribed in 2011/12 in Scotland [20]. In contrast, the guidelines only recommended atorvastatin (at the time still on patent) in the case that other statins were not effective. As a result, spending per head of population on atorvastatin increased until 2007/08, before levelling off when the guidelines were introduced [20]. In addition, prescribing based on International Non-proprietary Names or 'generic name' (i.e. INN prescribing) was promoted in medical schools and practice settings through educational initiatives and IT support systems to push for the use of lower-cost drug alternatives [13], [21]. INN-based prescribing rates were 99.1% for simvastatin and 99.7% for atorvastatin and pravastatin in 2015 [22].

Demand-side measures influencing the potency of statins prescribed

In addition to the regulation of prescription drug volume, policies and initiatives were introduced to improve the quality of prescribing. For instance, the Quality and Outcome Framework (QOF) was introduced in 2004 in the UK to link financial incentives with quality targets, such as the prescription of statins for individuals with a specific LDL-C level, to further improve the management of CVD and other conditions. Furthermore, in 2007/08, clinical guidelines for the secondary prevention of CVD (i.e., SIGN 67, NICE CG67) were introduced to promote the use of higher dose statins, such as medium-intensity statin therapy (i.e., simvastatin 40mg/day) as opposed to low-intensity therapy, following the publication of results from the Heart Protection Study [18]. In contrast, less potent statins such as pravastatin and fluvastatin were no longer recommended by Health Boards in Scotland despite their low price.

The guidelines were updated in 2014 when NICE published CG181 recommending the use of high-intensity statin therapy (particularly atorvastatin 80mg/day) as opposed to medium-intensity therapy for the secondary prevention of CVD [5]. A similar guideline was published in Scotland in 2017 (SIGN 149) [23]. An overview of both national supply- and demand-side measures and their influence on statin use is presented in **Figure 7.1**.

Figure 7.1 Timeline of national supply- and demand-side measures influencing the price, volume and potency of statin prescriptions in the UK from 1987 to 2017

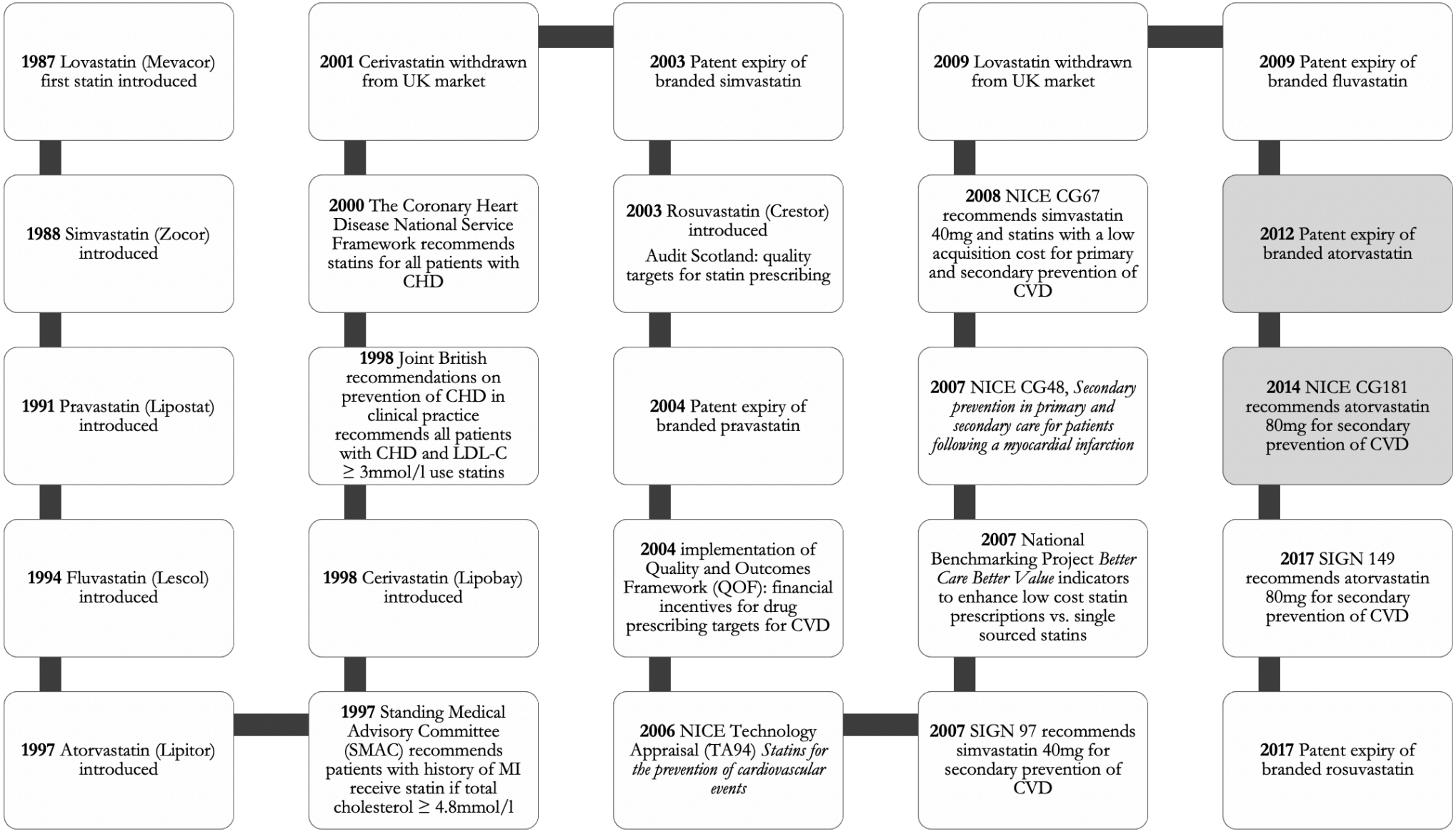

Table 7.1 Cost (in £) of branded and generic statins in Scotland between 2009 to 2017, by statin dose and reduction in LDL-C cholesterol [24]

	Statin therapy cost in £ per 28 days for branded statin (and generic version)							
	Reduction in LDL-C level	**Low-intensity statin**		**Medium-intensity statin**		**High-intensity statin**		
		21-24%	**27-29%**	**31-33%**	**37-38%**	**42-45%**	**48-49%**	**53-55%**
			10mg/day	**20 mg/day**	**40mg/day**	**80mg/day**		
	2009		30.28 (0.96)	50.92 (1.24)	50.63 (2.24)	50.89 (6.22)		
Simvastatin	2011		29.46 (1.59)	50.06 (1.80)	51.23 (2.34)	59.73 (4.31)		
Zocor (generic)	2013		32.37 (1.45)	50.86 (1.65)	55.37 (2.01)	61.46 (3.01)		
	2015		33.36 (1.41)	50.93 (1.59)	51.53 (1.96)	60.25 (2.94)		
	2017		34.45 (1.44)	54.44 (1.61)	54.79 (2.00)	55.89 (3.01)		
					10mg/day	**20mg/day**	**40mg/day**	**80mg/day**
	2009				21.86	30.95	32.14	32.09
Atorvastatin	2011				20.50	32.08	30.77	35.69
Lipitor (generic)	2013				17.34 (3.77)	35.45 (6.11)	42.19 (6.65)	47.40 (10.66)
	2015				18.19 (2.18)	40.89 (2.82)	43.36 (3.15)	46.69 (5.60)
	2017				19.48 (1.95)	41.17 (2.33)	44.15 (2.59)	47.58 (4.30)
					5mg/day	**10mg/day**	**20mg/day**	**40mg/day**
	2009				19.32	20.15	29.75	36.59
Rosuvastatin	2011				27.62	28.09	33.67	41.16
Crestor (generic)	2013				29.76	30.39	44.20	51.46
	2015				30.20	31.32	44.97	52.39
	2017				29.81	30.80	44.12	51.52
		20mg/day	**40mg/day**					
	2009	40.61(5.27)	40.06 (7.62)					
Pravastatin	2011	43.77(4.03)	42.30 (5.04)					
Lipostat (generic)	2013	45.11(2.71)	41.67 (3.37)					
	2015	45.76(2.66)	45.52 (3.32)					
	2017	52.09(2.72)	78.03 (3.36)					
		20mg/day	**40mg/day**	**80mg/day**				
	2009	25.27	28.18	30.18				
Fluvastatin	2011	25.38	22.96	29.74				
Luscol (generic)	2013	36.35(5.33)	26.05 (6.03)	30.73 (NA)				
	2015	35.34(5.46)	30.52 (5.90)	31.73 (NA)				
	2017	34.83(5.24)	38.15 (6.01)	34.48 (NA)				

The balance between statin potency and cost of statins

Health systems need to identify the right balance between the effectiveness and the cost of drugs prescribed. Therefore, the question arises as to what extent the type of statins prescribed are driven by (a) changes in price as a result of supply side measures and (b) demand-side initiatives that promote higher potency of statins for the secondary prevention of CVD. Three studies ascertained the effects of supply and/or demand-side activities on the efficient prescribing of lipid-lowering agents in the UK.

For instance, Chapman and colleagues examined changes in use patterns of statins in England to study the impact of decreasing acquisition costs of statin on prescribing in England for the time period 1998 to 2015 [6]. Using interrupted time series analyses based on primary care utilisation data from the Health and Social Care Information Centre database, the study found that in cases of significant price differences between statins, acquisition costs appear to be the key factor influencing statin use; however, if costs of statins are similar, potency becomes the key factor, suggesting that cost-effectiveness and possibly budget impact of therapies play an important role in prescribing decisions.

Leporowski and colleagues assessed the utilisation of and expenditure on key lipid-lowering agents between 2001 and 2015 in Scotland, alongside supply and demand side initiatives. Using the prescription costs analysis (PCA) database compiled by the Information Services Division (ISD) Scotland, the descriptive analysis highlighted that generic availability coupled with demand-side measures, such as educational initiatives and clinical guidelines recommending the use of generic and more potent statins, resulted in positive shifts in statin prescribing behaviours that improved the quality and efficiency of prescribing, while concurrently easing financial pressures on the NHS [9].

Helali and Mclay also conducted a drug utilisation study, which examined prescribing trends of statin in Scotland for the period 2005 to 2010, using descriptive analyses of an observational cross-sectional retrospective cohort of approximately 200 primary care practices in Scotland. The study found that 63%, 27%, 5%, 4% and 1% patients were prescribed simvastatin, atorvastatin, pravastatin, rosuvastatin and fluvastatin, respectively, in the given time period [11].

Limitations of previous research on the influence of supply and demand side measures on statin use

The maximum time period covered by the studies described above was up to 2015, therefore not capturing or assessing the impact on prescribing patterns of the introduction of NICE's clinical guideline CG181 in 2014. In fact, Chapman and colleagues only assessed the role of price changes on the prescribing of statins [6], while Leporowski and colleagues

focussed primarily on the effect of the supply- and demand-side measures on national drug expenditure [9]. Furthermore, two of the three studies only provided descriptive statistics of the data and did not quantify the effect of the association between specific supply- and demand-side measures and statin use [9], [11]. Except for one study (i.e., Helali et al. 2013 [11]), the former analyses were conducted at a population-level and did not take into account changes in prescribing patterns due to changes in patient characteristics over time. Therefore, none of the studies to date ascertained the difference in effects between supply and demand-side activities using individual patient-level data, nor how changes in price of generic atorvastatin and the introduction of NICE clinical guidelines CG181 influenced changes in the use of different statin types as well as doses in later years.

7.1.2. Aims of the research

This is the first research to use administrative NHS patient-level data and to consider a time period that extends beyond 2015, allowing for a comparison of the individual and combined effects of (a) price changes and (b) public policy on the type of statin potency used for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in Scotland for the time period of October 2009 to July 2017.

The aims are twofold: firstly, to analyse the effect of a key supply-side measure, namely the sharp drop in price of atorvastatin in May 2012 following the market entry of its generic version on clinicians' prescribing behaviours, specifically, how it affected the trends in initiations of (1) relatively more potent atorvastatin, compared to (2) other relatively less potent and lower-cost generic statins (e.g. simvastatin, pravastatin, fluvastatin) and (3) relatively more potent and more expensive branded rosuvastatin. Secondly, to investigate changes in statin prescribing patterns segmented by potency following the introduction of a demand-side measure, namely the publication of NICE clinical guideline CG181 in July 2014, which recommended the use of high-intensity statin (i.e. atorvastatin 80mg/day) for the secondary prevention of CVD.

7.2. Methods

7.2.1. Design and interventions

Investigation of the historic impact of two non-experimental national policies on the initiation of statin therapy among individuals with ASCVD in Scotland using retrospective individual-level NHS Scotland administrative data, namely (1) the UK market entry of generic atorvastatin on 8 May 2012 and (2) the introduction of NICE clinical guideline CG181.

7.2.2. Participants

Anonymised linked NHS Scotland administrative data (General/Acute Inpatient and Day Case, Mental Health Inpatient and Day Case, National Records of Scotland and the Prescribing Information System) were used to define the study population. A detailed description of the data and identification process of study participants is provided in **Chapter 4**. The study population included the 136,855 individuals hospitalised for an atherosclerotic CVD event between 1 October 2009 and 4 July 2017, who initiated[95] statin therapy following hospital discharge.

7.2.3. Exposure

Individuals in these analyses were exposed to the introduction of (1) generic atorvastatin in May 2012 and (2) the publication of NICE clinical guideline CG181 in July 2014, and therefore constituted the intervention group (**Table 7.2**). As the policies were introduced on a national level and also at the same time in England and Wales, no concurrent counterfactual group, i.e. a comparable control group that was not exposed to the policies in the same time period, was available to assess in this scenario.

It must be noted that the scope of the second exposure (i.e., NICE's clinical guideline publication) may be restricted. NICE is a non-departmental public body of the Department of Health in England, which publishes guidelines on the use of health technologies in England and Wales. In Scotland, the role of improving patient care through evidence-based guidelines falls into the realm of the Scottish Intercollegiate Network (SIGN), which is part of the Evidence Directorate of Healthcare improvement Scotland (see **Chapter 2, Section 2.3** for further detail). However, it was not until June 2017 that

[95] Initiation is defined as individuals being prescribed statin within 90 days from index discharge and dispensed within 60 days from that prescription This also includes individuals who used statin therapy prior to being hospitalised for an ASCVD event and who re-initiated/continued statin therapy after the index ASCVD-related hospitalisation.

SIGN updated its guidelines (SIGN 149) in line with those published by NICE in 2014, recommending the use of high-intensity statin for the secondary prevention of CVD. As the study data only include individuals hospitalised in Scotland until 4 July 2017, there are not enough data to assess the direct impact of the SIGN guideline on the use of high-intensity statins from June 2017 onwards. Instead, the publication of NICE guidelines was used as an alternative exposure, as it captured recommendations based on the latest findings from clinical trials at that time, which would have also been available to the medical community in Scotland.

Table 7.2 Definition of intervention groups by policy

	Market entry of generic atorvastatin	**Introduction of NICE clinical guideline CG181**
Intervention implementation	8 May 2012	18 July 2014
Pre-intervention time period[1]	1 October 2009 – 7 May 2012	1 October 2009 – 17 July 2014
Post-intervention time period[2]	8 May 2012 – 4 July 2017	18 July 2014 – 4 July 2017
Intervention group	All individuals hospitalised for ASCVD in Scotland, who initiated statin therapy	All individuals hospitalised for ASCVD in Scotland, who initiated statin therapy
Counterfactual group	Not applicable	Not applicable

[1]Pre-intervention time period is defined as the period from the first available time point in the data (i.e.,1 October 2009) to the day before the policy was introduced. [2]Post-intervention time period is defined as the period from the first day the policy was introduced to the last available time point in the data, i.e., 4 July 2017.

7.2.4. Outcome measures

In the first policy analysis assessing the market entry of generic atorvastatin, the primary outcome was measured as the monthly proportion of individuals who were prescribed atorvastatin (both brand and generic versions[96]) compared to individuals who received prescriptions for other statin types, such as simvastatin, rosuvastatin, pravastatin and fluvastatin. In the second policy analysis examining the publication of NICE clinical guideline CG181, the outcome of interest was measured as the monthly proportion of individuals who were prescribed high-intensity statin compared to individuals with prescriptions for low or medium-intensity statins. The categorisation of statin intensity was based on NICE's definition that is contingent on the percentage reduction in low-density lipoprotein cholesterol (LDL-C) levels. Statins that reduce LDL-C by ≤40% were classified as low/medium intensity, while those reducing LDL-C by more than 40% were classed as high intensity therapy (see **Table 7.1** for an overview of the classification by statin type and dose). The same classification was also endorsed in Scotland and has remained unchanged. It must be noted that the second policy analysis focuses on the first statin intensity prescribed in a primary care setting, therefore not considering the intensity prescribed by hospital staff on discharge nor dose titrations[97] over time.

7.2.5. Statistical analysis

Ordinary Least Squares (OLS)-based interrupted time series regressions with Newey-West standard errors were performed to study the effect of (1) the market entry of generic atorvastatin on the proportion (in %) of individuals being prescribed atorvastatin each month, and separately conducted for each of the other four statin types, and (2) the introduction of NICE clinical guideline CG181 on the proportion (in %) of individuals being prescribed high-intensity statin therapy each month. The analyses involve a before-after comparison within the same population of proportions of atorvastatin (and other statin type) initiators and, separately, high-intensity statin initiators, thereby limiting potential confounding due to between-group differences[98].

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[96] The prescribing data does not contain information on whether the prescribed/dispensed treatment was a brand or generic statin.

[97] It must be noted that the rate of up-titrations from low/medium-intensity to high-intensity statin within 12 months since index statin initiation was relatively low (i.e., 5.2% of all individuals who initiated statin therapy in 2009-2017).

[98] Confounding is further limited by the fact that the study data includes all individuals in Scotland ever hospitalised for an ASCVD event and meeting eligibility criteria listed in **Chapter 4**. Whilst the composition of the different ASCVD types may differ over time, it is unlikely to change significantly over the 8-year period.

The data are collapsed into the proportion of individuals being prescribed a specific group of statins at each time point, namely every month since the start of study period, amounting to 93 months in total. Using the respective monthly proportions as described above, linear regressions were run on the 93 monthly observations. A time lag was introduced into both regressions to account for autocorrelation.

In the case of the second policy analysis examining the publication of NICE clinical guideline CG181, the model was run with two points of interruption, namely (a) the market entry of generic atorvastatin in May 2012 and (b) the introduction of the NICE guideline in July 2014, in order to take into account a potentially earlier increase in uptake of high-intensity statins. In addition, and in order to compare the two models and quantify the initiation trend over time when including and excluding the introduction of the clinical guideline, a second model was run that only includes one point of interruption, i.e. the May 2012 market entry of generic atorvastatin that led to lower acquisition costs of high-intensity statin therapy. Lastly, a third model was run with the two interruptions (as described in model 1) that stratified high-intensity atorvastatin into its three different doses, namely 20mg/day, 40mg/day and 80mg/day, as well as the remaining statin types into high-intensity or low/medium intensity, to assess whether the guideline achieved an increased uptake in its recommendation of atorvastatin 80mg for the secondary prevention of CVD. The models can be written out as follows:

(1) Market entry of generic atorvastatin in May 2012

Model 2.1 Single group analysis with one policy interruption

$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \epsilon_t$, where

Y_t refers to the proportion of individuals being prescribed a particular statin type versus other statin types measured at month *t*,

T_t is the month since the start of the study,

X_t is a dummy variable representing the intervention, i.e. period May 2012 to July 2017,

$X_t T_t$ is an interaction term,

β_0 represents the intercept (i.e. starting level) of the outcome variable,

β_1 is the slope of the outcome variable until the introduction of generic atorvastatin,

β_2 represents the change in the level of the outcome that occurs in the period immediately following the market entry of generic atorvastatin,

β_3 represents the difference between pre- and post-intervention slopes of the outcome, and

ϵ_t denotes the error term.

(2) Introduction of NICE clinical guideline CG181 in July 2014

Model 2.2 Single group analysis with two policy interruptions

$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \beta_4 Z_t + \beta_5 Z_t T_t + \epsilon_t$, where

Y_t refers to the proportion of individuals being prescribed high-intensity statin therapy versus low or medium-intensity therapy measured at month *t*,

T_t is the month since the start of the study,

X_t is a dummy variable representing the first intervention period, i.e. market entry of generic atorvastatin period May 2012 to July 2014 to July 2017,

$X_t T_t$ is an interaction term,

Z_t is a dummy variable representing the second intervention period, i.e. the period following the publication of NICE clinical guideline from July 2014 to July 2017,

$Z_t T_t$ is an interaction term,

β_0 represents the intercept (i.e. starting level) of the outcome variable,

β_1 is the slope of the outcome variable until the introduction of generic atorvastatin,

β_2 represents the change in the level of the outcome that occurs in the period immediately following the market entry of generic atorvastatin,

β_3 represents the difference between the first pre- and post-intervention slopes of the outcome,

β_4 represents the change in the level of the outcome that occurs in the period immediately following the publication of the clinical guideline,

β_5 represents the difference between the second pre- and post-intervention slopes of the outcome, and

ϵ_t denotes the error term.

7.2.6. Sensitivity Analyses

The ITS regression models do not take into account patient characteristics and assume that populations remain unchanged throughout the study period. Therefore, sensitivity analyses were performed using logistic regression models that adjusted for patient characteristics on discharge, including age, sex, socio-economic deprivation level, clinical characteristics (Charlson Comorbidity Index and previous specialty mental health hospitalisation within 12 months prior to index hospital admission; history of prior ASCVD hospitalisation and use of statin therapy), as well as time as a key exposure variable. These patient characteristics of interest are described in further detail in **Chapter 4**. The outcome measures remained the same as described in **Section 7.2.4**. The models are defined as follows:

(1) Market entry of generic atorvastatin in May 2012

$Drug\ initiation_{it} = \beta_0 + \beta_1 T + \beta_2 I + \beta_3 IT + \beta_4 X_{it} + \epsilon_{it}$, where

$Drug\ initiation_{it}$ refers to the single dispense of statin (i.e., one statin type vs. another statin) by an individual (i) within a specified time period (t) since index hospital discharge,

T refers to continuous time in months, with time being equal to zero at the point of intervention,

I refers to the binary variable indicating whether the period is pre or post the market entry of generic atorvastatin (i.e. intervention = 1 if post market entry/ = 0 if pre market entry),

IT refers to the interaction between intervention and time,

X_{it} refers to other explanatory variables, i.e., individuals' characteristics, and

ϵ_{it} denotes the error term.

(2) Introduction of NICE clinical guideline CG181 in July 2014

$Drug\ initiation_{it} = \beta_0 + \beta_1 T + \beta_2 I_1 + \beta_3 I_1 T + \beta_4 I_2 + \beta_5 I_2 T + \beta_6 X_{it} + \epsilon_{it}$

$Drug\ initiation_{it}$ refers to the first dispensed statin (i.e., high-intensity vs. low/medium-intensity statin) by an individual (i) within a specified time period (t) since index hospital discharge,

T refers to continuous time in months, with time being equal to zero at the point of intervention,

I_1 refers to the binary variable indicating whether the period is pre or post the market entry of generic atorvastatin,

I_1T refers to the interaction between intervention and time,

I_2 refers to the binary variable indicating whether the period is pre or post the market entry of generic atorvastatin,

I_2T refers to the interaction between intervention and time,

X_{it} refers to other explanatory variables, i.e., individuals' characteristics, and

ϵ_{it} denotes the error term.

7.3. Results

7.3.1. Participant characteristics

Statin type use before and after the market entry of generic atorvastatin in May 2012

Overall, 136,855 individuals were both prescribed and dispensed statin therapy following an ASCVD-related hospital discharge between 1 October 2009 and 4 July 2017. Of these statin initiators, 40% were prescribed atorvastatin as opposed to one of the other four statin types (i.e. simvastatin, rosuvastatin, pravastatin or fluvastatin), with the average monthly atorvastatin initiation rates increasing from 28.1% (range 22.3%-47.9%) in the time period prior to the launch of generic atorvastatin in May 2012 to 47.3% (24.3%-73.2%) after May 2012 (**Appendix E, Table E.1**). The participant characteristics at baseline are described in detail in **Appendix E, Table E.1**).

High- versus low-/medium-intensity statin use before and after the introduction of NICE clinical guideline CG181 in July 2014

Out of the 136,855 individuals who initiated statin therapy for the secondary prevention of ASCVD in the period of 1 October 2009 to 4 July 2017, high-intensity statins were prescribed to 54,932 individuals (40%). The monthly proportion of high-intensity statin initiations ranged from 24.8% to 56.2% prior to the policy introduction, and increased to 38.9%-70.4% in the time period after the guideline publication (**Appendix E, Table E.2**). The participant characteristics at baseline are described in detail in **Appendix E, E.2**).

7.3.2. Effects of the market entry of generic atorvastatin on statin type use

The linearity of pre- and post- statin initiation trends over time were confirmed through visualisation (see **Figures 7.2 to 7.5**). Both the results of the visual inspection (**Figures 7.2 to 7.5**) and the ITS analyses (**Table 7.3**) indicated a significant positive effect of generic atorvastatin entering the UK market in May 2012 on the proportion of individuals being prescribed atorvastatin instead of other statin types, specifically simvastatin.

In October 2009, 32.4% of individuals hospitalised for an ASCVD-related event initiated atorvastatin, while the remainder initiated simvastatin (58.7%), rosuvastatin (6.31%) or pravastatin (2.4%). During the time period from October 2009 to May 2012, the proportion of individuals initiating atorvastatin therapy prior to the launch of its generic version decreased every month by 0.35% ($p<0.001$, 95% CI: -0.45%, -0.25%). After the generic market entry in May 2012, the proportion of individuals who initiated atorvastatin therapy in the first month since the launch increased significantly by an average of 5.6% compared to the months prior ($p<0.001$, 95% CI: 3.32%, 7.84%). This positive step change was followed by a significant monthly increase in the proportion of atorvastatin initiators at a rate of 0.68% ($p<0.001$, 95% CI: 0.64%, 0.71%).

Prior to May 2012, the proportion of simvastatin users increased monthly at a rate of 0.43% ($p<0.001$, 95% CI: 0.34%, 0.52%). However, in May 2012 a significant decrease of an average of 5.23% compared to prior months was observed in the proportion of patients being prescribed and subsequently dispensed simvastatin ($p<0.001$, 95% CI: -7.4%, -3.04%). Thereafter, the proportion of individuals initiating simvastatin decreased monthly at a rate of 0.66% ($p<0.001$, 95% CI: -0.69%, -0.62%).

In the case of rosuvastatin, a monthly decrease of 0.07% in the proportion of individuals initiating this type of statin was observed prior to May 2012 ($p<0.001$, 95% CI: -0.09%, -0.04%). However, no significant changes were observed in the proportion of individuals being prescribed this statin type in May 2012, or in later time periods. There were no changes in the proportion of individuals initiating pravastatin before or shortly after the launch of generic atorvastatin, nor in the long-term initiation trend, mainly due to small number of individuals using this therapy, leading to less robust monthly initiation rates. Lastly, no trends could be reported for the initiation of fluvastatin due to the very small number of individuals initiating this therapy. Please see **Table 7.3** for an overview of the ITS analyses results.

Table 7.3 Results of ITS analyses of the impact of introducing generic atorvastatin in the market in Scotland on the proportion of statin type prescriptions

	Atorvastatin (Coeff., 95% CI)	**Simvastatin** (Coeff., 95% CI)	**Rosuvastatin** (Coeff., 95% CI)	**Pravastatin** (Coeff., 95% CI)
Intercept	32.41 (30.72, 33.94) **	58.73 (57.32, 60.11) **	6.31 (5.86, 6.75) **	2.40 (2.00, 2.70) **
Monthly change prior to atorvastatin market entry	-0.35 (-0.45, -0.25) **	0.43 (0.34, 0.52) **	-0.07 (-0.09, -0.04) **	-0.01 (-0.02, -0.003)
Step change following market entry	5.58 (3.32, 7.84) **	-5.23 (-7.42, -3.07) **	-0.39 (-0.82, 0.44)	0.04 (-0.31, 0.40)
Post-intervention linear trend following atorvastatin market entry	0.68 (0.64, 0.71) **	-0.66 (-0.69, -0.62) **	-0.01 (-0.01, 0.00)	-0.01 (-0.02, 0.01)

**p<0.001; Coeff.: Coefficient; CI: Confidence Interval.; ITS: Interrupted Time Series analysis

Figure 7.2 Proportion of monthly statin initiators (%) using atorvastatin over time, with generic atorvastatin entering the market in May 2012

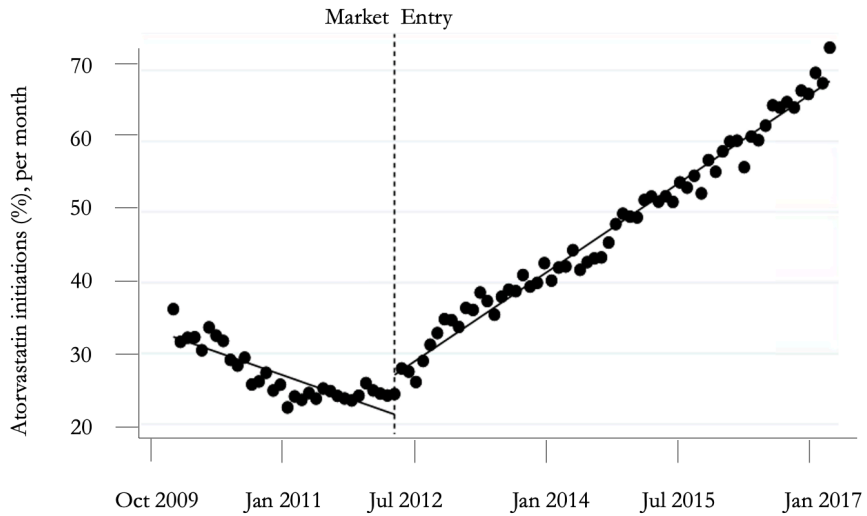


Figure 7.3 Proportion of monthly statin initiators (%) using simvastatin over time, with generic atorvastatin entering the market in May 2012

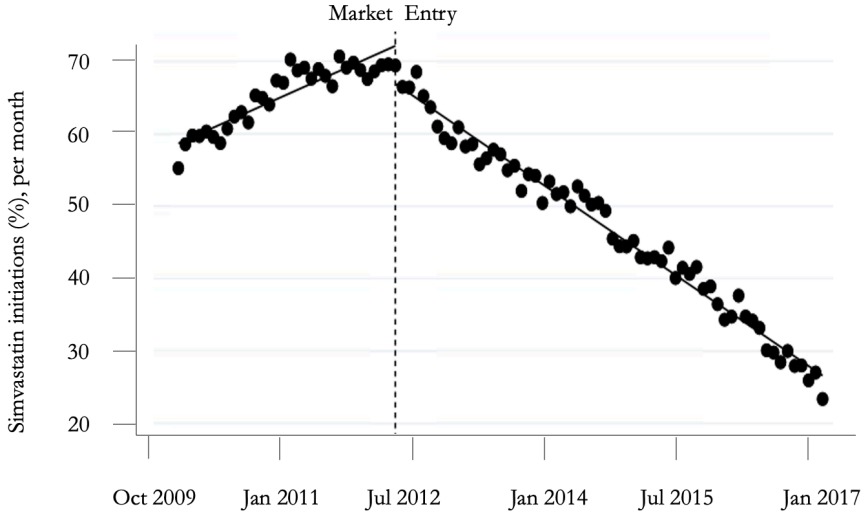


Figure 7.4 Proportion of monthly statin initiators (%) using rosuvastatin over time, with generic atorvastatin entering the market in May 2012

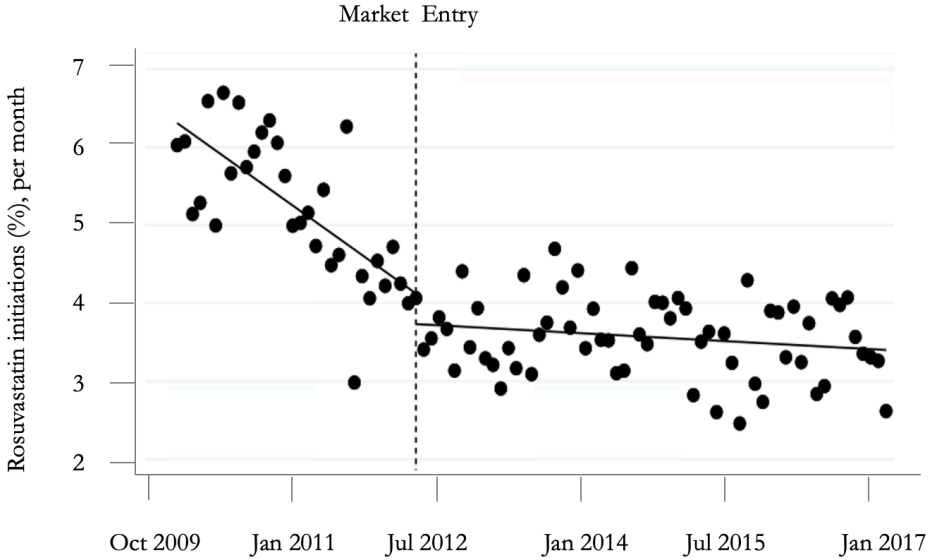
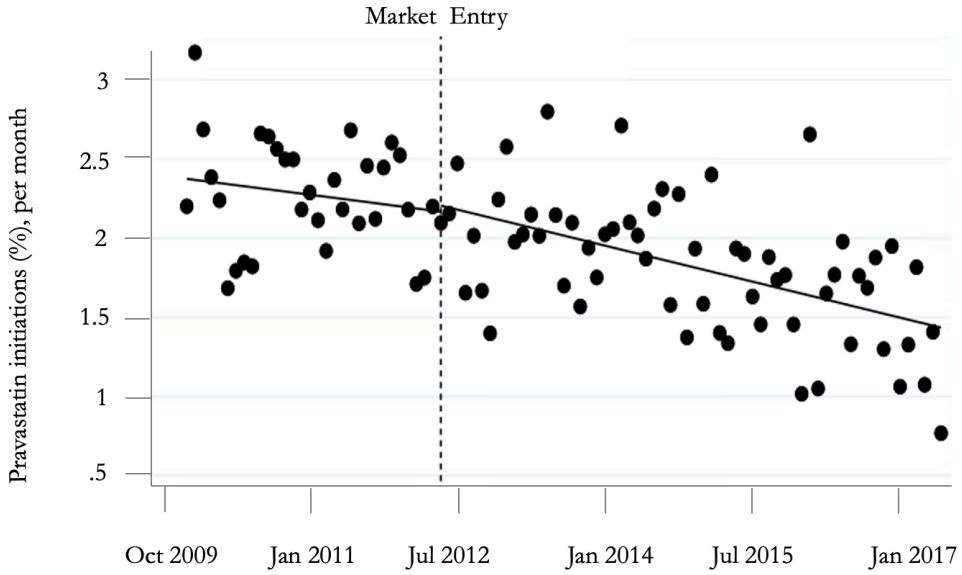


Figure 7.5 Proportion of monthly statin initiators (%) using pravastatin over time, with generic atorvastatin entering the market in May 2012



Sensitivity analysis

The logistic regression results are consistent with the findings from the ITS analyses, showing a positive effect of the market entry of generic atorvastatin on the increased likelihood of individuals initiating atorvastatin instead of other statin types, following adjustment for individual patient characteristics (see **Appendix E, Table E.3** for a detailed overview of results).

7.3.3. Effects of the market entry of generic atorvastatin and the publication of NICE clinical guideline CG181 on statin intensity at initiation

Both the results of the visual inspection (**Figure 7.6**) and the ITS analyses (**Table 7.4**) indicate a significant positive effect of generic atorvastatin entering the UK market in May 2012 on the proportion of individuals being prescribed and dispensed high-intensity statin instead of low or medium-intensity therapies. Furthermore, the introduction of NICE clinical guideline CG181 recommending the use of high-intensity statin for the secondary prevention of CVD in England appears to have further accelerated this positive trend, even though no direct increase was recorded in the month the guidelines became public.

In October 2009, 35.9% of individuals hospitalised for an ASCVD-related event were prescribed and subsequently initiated high-intensity statin following discharge, while the majority (64.1%) initiated statin therapy with a low or medium-intensity statin. During the time period from October 2009 to May 2012, the proportion of individuals initiating high-intensity therapy decreased every month by 0.42% ($p<0.001$, 95% CI: -0.52%, -0.31%). When generic atorvastatin entered the market, there was a positive step change in May 2012 with the proportion of individuals initiating high-intensity therapy having increased by an average of 4.7% compared to the months prior ($p<0.001$, 95% CI: 3.32%, 7.3%). Thereafter, the proportion of high-intensity statin initiations increased monthly at a rate of 0.62% ($p<0.001$, 95% CI: 0.52%, 0.71%).

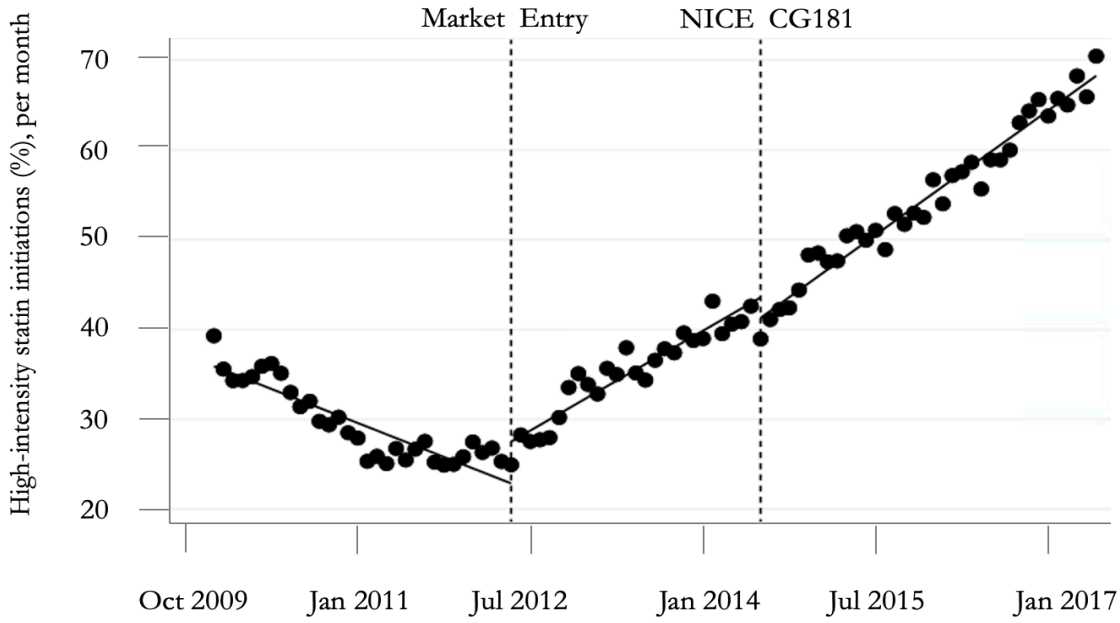
Once the NICE guidelines CG181 were published in England in July 2014, the proportion of high-intensity statin initiations further increased monthly at a rate of 0.78% ($p<0.05$, 95% CI: 0.71%, 0.83%). The small, yet significant acceleration in monthly high-intensity statin initiations following the guideline publication is further highlighted when comparing the results of the first model with two interruptions (**Figure 7.6**) to a second model that only plots one interruption, namely the market entry of generic atorvastatin (**Appendix E, E.5**).

Table 7.4 Results of ITS analyses of the impact of the market entry of generic atorvastatin and the introduction of NICE clinical guideline CG181 on the proportion of high-intensity statin prescriptions

	Proportion of high-intensity statin initiations (Coeff, 95% CI)
Intercept	35.9 (34.2, 37.5) **
Monthly change prior to market entry of generic atorvastatin	-0.42 (-0.52, -0.31) **
Step change following market entry of generic atorvastatin	4.7 (3.2, 7.3) **
Post-intervention linear trend following market entry of generic atorvastatin	0.62 (0.52, 0.71) **
Step change following NICE guideline CG181 introduction	-2.3 (-3.9, -0.6) *
Post-intervention linear trend following NICE guideline CG181 introduction compared to the period May 2012 to June 2014	0.78 (0.71, 0.83) *

*p<0.05; **p<0.001; Coeff.: Coefficient; CI: Confidence Interval.

Figure 7.6 Proportion of monthly statin initiators (%) using high-intensity statin over time, with generic atorvastatin entering the market in May 2012 and NICE clinical guideline CG181 being introduced in July 2014



Sensitivity analysis

The logistic regression results are consistent with the findings from the ITS analyses, showing a positive effect of both the market entry of generic atorvastatin and publication of NICE guidelines CG181 on the increased likelihood of individuals initiating high-intensity statin therapy instead of low/medium-intensity therapy, following adjustment for individual patient characteristics (see **Appendix E, E.4** for a detailed overview of results).

7.3.4. Effects of NICE introduction of clinical guideline CG181 on the type of high-intensity statin used

The previous analyses (**Section 7.3.3**) showed an increase in the overall trend of high-intensity statin initiation, however, it also important to consider the trends across different types of high-intensity therapies, as some high-intensity statins reduce LDL-C levels to a greater extent than others, as presented in **Table 7.1**. While atorvastatin 20mg is classified as a high-intensity statin in the UK based on LDL-C reductions of approximately 40%, the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines define it as a moderate intensity statin based on LDL-C reductions below their high intensity threshold of 50% [4]. As a result, only atorvastatin 40mg-80mg and rosuvastatin 20mg-40mg are classed as high-intensity statins according to ACC/AHA based on their propensity to reduce LDL-C levels by a minimum of 50%.

As depicted in **Table 7.5**, the overall proportion of individuals initiating atorvastatin 20mg in Scotland doubled from 3.8% in the period 2009 – 2011 to 7.5% in the years 2015 to 2017, compared to the proportion of individuals initiating any of the other low, moderate or high-intensity statin therapies. Similarly, the proportion of individuals initiating atorvastatin 40mg and 80mg more than doubled during the same time period from 21.5% to 47.9%. Out of all the individuals who ever initiated atorvastatin, the majority initiated 80mg, followed by 40mg across all three time periods. In contrast, the proportion of individuals initiating other high-intensity treatments (i.e. simvastatin 80mg or rosuvastatin 10mg-40mg) or low/moderate intensity statins, decreased respectively from 5.4% and 69.3% in 2009/11 to 2.1% and 42.4% in 2015/17.

Table 7.5 Proportion of individuals (%) initiating different statin intensities, by calendar year group

N (%), Column percentages presented	2009-2011	2012-2014	2015-2017
High-intensity statins	**13,894 (30.7)**	**18,582 (35.8)**	**22,456 (57.6)**
Atorvastatin 20mg	1,702 (3.8)	2,947 (5.7)	2,934 (7.5)
Atorvastatin 40mg	3,951 (8.7)	6,255 (12.1)	7,887 (20.2)
Atorvastatin 80mg	5,777 (12.8)	7,896 (15.2)	10,804 (27.7)
Other high-intensity statins (*Simvastatin 80mg; Rosuvastatin 10mg–40mg)*	2,464 (5.4)	1,484 (2.9)	831 (2.1)
Low/medium-intensity statins	**31,394 (69.3)**	**33,302 (64.2)**	**16,549 (42.4)**

The introduction of generic atorvastatin in 2012 and the NICE clinical guideline CG181 specifically recommending atorvastatin 80mg in 2014 had different effects on the different high-intensity statin types, as shown in **Table 7.6** and **Figure 7.7**. Initially, atorvastatin 80mg was initiated by 17% of all statin initiators in October 2009, however, the proportion of initiators significantly decreased every month by 0.3% until April 2012 ($p<0.001$, 95% CI: 0.25%, 0.33%). As soon as the generic version became available, a significant increase of 3.8% ($p<0.001$, 95% CI: 1.8%, 5.8%) in the proportion of individuals initiating this treatment can be observed in May 2012. Afterwards, the trend in monthly atorvastatin 80mg initiations continued to increase significantly at a rate of 0.3% ($p<0.001$, 95% CI: 0.26%, 0.33%) from June 2012 to June 2014, relative to the pre-market entry trend. This trend increase was further accelerated once NICE published CG181 in July 2014, which specifically recommended the use of atorvastatin 80mg, increasing the monthly trend by an additional 0.15% relative to 2-year trend prior ($p<0.001$, 95% CI: 0.4%, 0.5%).

No significant step change in initiations was observed for atorvastatin 40mg initiations in May 2012. However, from May 2012 onwards there was a significant increase in the monthly trend of atorvastatin 40mg initiations of 0.3% relative to the pre-intervention period ($p<0.001$, 95% CI: 0.2%, 0.3%), which continued at similar rates after the publication of the guideline. Lastly, 3.8% of all statin initiators were dispensed branded atorvastatin 20mg between 2009 and 2011. Once the generic version became available in May 2012, there was a positive step-change increase of 1% in the proportion of any atorvastatin 20mg initiations ($p<0.05$, 95% CI: 0.2%, 1.8%), followed by only a minor increase in the monthly initiation trend of 0.03% relative to the pre-intervention trend ($p<0.001$, 95% CI: 0.01%, 0.05%).

In the case of other high-intensity statins (i.e. simvastatin 80mg and rosuvastatin 10-40mg), the proportion of individuals initiating these therapies was already decreasing monthly by 0.1% even before cheaper generic high-intensity atorvastatin therapies became available in 2012 (p<0.001, 95% CI: -0.1%, -0.05%). Once generic atorvastatin was launched in May 2012, initiations decreased by 0.6% in the same month (p<0.05, 95% CI: -1.1%, -0.1%), followed by a minor decrease of 0.03% in the monthly initiation trend, relative to the pre-intervention period (p<0.001, 95% CI: -0.04%, -0.01%).

Conversely, at the beginning of the study period the majority of statin initiators (64%) were dispensed low or medium intensity statins, with the proportion increasing every month by 0.4% until April 2012 (p<0.001, 95% CI: 0.3%, 0.5%). However, the launch of generic atorvastatin led to a significant drop of 4.7% in the same month (p<0.001, 95% CI: -7.3%, -2%), followed by a significant decrease in the monthly initiation trend of 0.6% relative to the pre-intervention period (p<0.001, 95% CI: -0.7%, -0.5%), to a point where at the end of the study period the proportion of low and moderate intensity users in June 2017 was lower than the overall proportion of individuals initiating high-intensity therapy and specifically atorvastatin 80mg (**Figure 7.7**).

Figure 7.7 Proportion of monthly statin initiators (%) using different statin types and intensities over time, with generic atorvastatin entering the market in May 2012 and NICE clinical guideline CG181 being introduced in July 2014

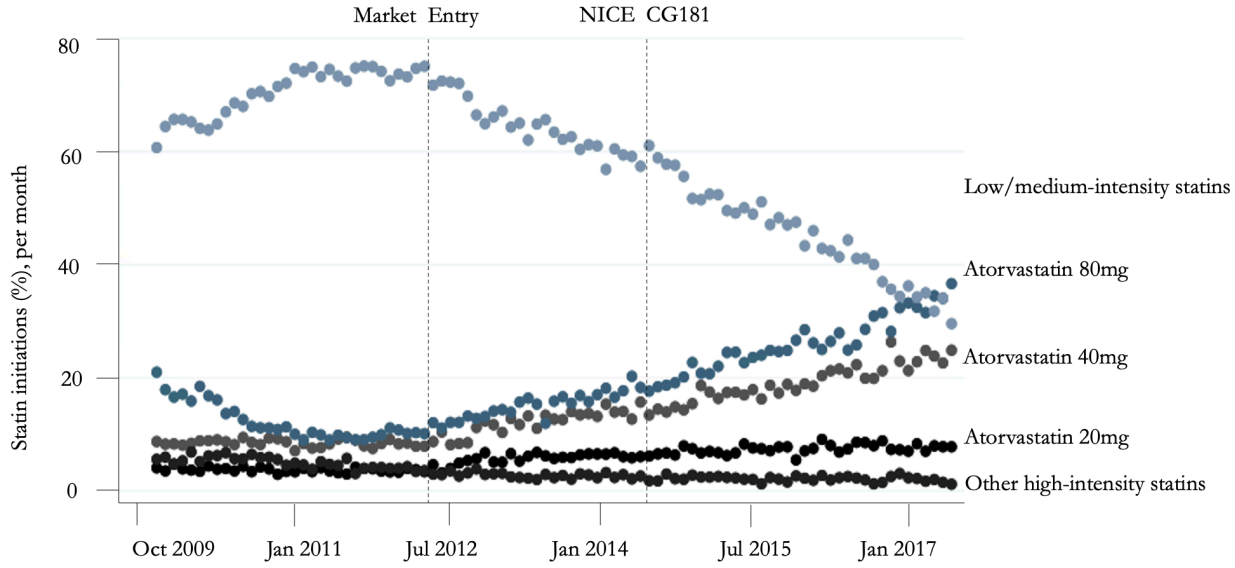


Table 7.6 Results of ITS analyses of the impact of the market entry of generic atorvastatin and the introduction of NICE clinical guideline CG181 on the proportion of different statin type and intensity prescriptions

	Atorvastatin 20mg/day (Coeff., 95% CI)	**Atorvastatin 40mg/day** (Coeff., 95% CI)	**Atorvastatin 80mg/day** (Coeff., 95% CI)	**Other high-intensity statins** (Coeff., 95% CI)	**Low/medium intensity statins** (Coeff., 95% CI)
Intercept	3.9 (3.7, 4.1) **	8.6 (8.2, 8.9) **	17.1 (15.4, 18.8) **	6.2 (6.7, 6.8) **	64.1 (62.5, 65.7) **
Monthly change prior to market entry of generic atorvastatin	-.01 (-0.03, 0.0)	-0.01 (-0.02, 0.01)	-0.3 (-0.4, -0.2) **	-0.1 (-0.1, -0.05) **	0.4 (0.3, 0.5) **
Step change following market entry of generic atorvastatin	0.9 (0.2, 1.8) *	0.5 (-0.6, 1.5)	3.8 (1.8, 5.8) **	-0.6 (-1.1, -0.1) *	-4.7 (-7.3, -2.0) *
Post-intervention linear trend market entry of generic atorvastatin	0.1 (0.05, 0.14) **	0.3 (0.2, 0.3) **	0.3 (0.26, 0.33) **	-0.03 (-0.04, -0.01) *	-0.6 (-0.7, -0.5) **
Step change following NICE guideline introduction	-0.2 (-0.9, 0.5)	-1.3 (-2.4, -0.2) *	-0.8 (-1.8, 0.3)	-0.02 (-0.4, 0.3)	2.3 (0.6, 3.9) *
Post-intervention linear trend NICE guideline introduction compared to the period May 2012 to June 2014	0.03 (0.01, 0.05) **	0.3 (0.25, 0.33)**	0.45 (0.4, 0.5) **	-0.01 (-0.02, 0.0)	-0.77 (-0.8, -0.71) *

* p<0.05; **p<0.001; Coeff.: Coefficient; CI: Confidence Interval

7.4. Discussion

7.4.1. Findings and interpretation of results

Trends in the use of different statin types before the market entry of generic atorvastatin in May 2012

The findings from this study build on the trends reported in earlier research and fill the prescription information gap for the time period from 2009 onwards. The results showed that in the period 2009 until April 2012, the majority (64%) of patients hospitalised for an ASCVD-related event in Scotland subsequently initiated low/medium-intensity simvastatin, followed by 28% initiating branded atorvastatin (in the order of highest to lowest relative proportions: 80mg, followed by 40mg and 20mg, **Figure 7.7**), 5.5% on rosuvastatin, 2.3% on pravastatin and 0.2% on fluvastatin (**Table 7.3**), driven by factors such as cost, potency and availability of robust clinical trial data that are explained in more detail in the section to follow. The findings are consistent with the utilisation rates by statin type reported by Helali and Mclay for the period 2005 to 2010 (**Section 7.1.1**) [11].

The market entry of generic simvastatin in 2003 in the UK reduced the overall cost of simvastatin 20mg and 40mg 20-fold and eightfold, respectively, as well as the cost relative to atorvastatin (£3.89 compared to £18.03 for atorvastatin 10mg and £24.74 for atorvastatin 20mg) [6], [7], [25]. Despite the significant cost reduction, the proportion of individuals being prescribed simvastatin was only marginally higher than those being prescribed branded atorvastatin in 2004 in England (40% vs. 45%) [7]. Based on findings from controlled dosing studies showing that simvastatin 40mg and atorvastatin 10mg-20mg, were equally effective, NICE published the guideline CG67 in 2008 recommending the use of statins with a low acquisition cost, specifically simvastatin 40mg[99] [19], [27], [28]. By 2011, simvastatin captured 66% of the statin market share [6].

These prescribing trends were in line with those reported for Scotland for the time period 2005 to 2010, with 63% of all statin prescriptions issued for branded and generic simvastatin, followed by 27% for branded atorvastatin, 5% for generic and branded pravastatin, 4% for branded rosuvastatin and 1% for branded fluvastatin [11]. Although

[99] There were only limited long-term and safety data available for simvastatin 80mg, which achieves similar LDL-C reductions to atorvastatin 20mg, and findings from a large randomised trial (SEARCH) in 2010 reported increased risks of myopathy, showing that intensive LDL-C lowering could also be achieved safely with other therapies [26].

generic pravastatin and fluvastatin became available, respectively, in 2004 and 2009, their lower potency (maximum LDL-C reduction <33%) while being priced closely to more potent and safe generic simvastatin, explains their overall low uptake [6], [29].

Branded rosuvastatin (Crestor) was approved in the US in 2003 and to date remains the most potent statin on a dose-by-dose basis, with the ability to reduce LDL-C levels by more than 50% at a dose as low as 20mg. However, the underprescription of this statin in this time period can be explained by the limited data on long-term safety at that time and its sole indication for use in primary hypercholesterolaemia in the UK [30], as well as its high cost (£38.2 compared to £5 for generic simvastatin 40mg in England in 2006) [6]. Therefore, GPs would have been inclined to limit prescription of this drug primarily to patients who did not tolerate well other statin options [11].

Effects of the market entry of generic atorvastatin in May 2012 on the type of statin and intensity used for the secondary prevention of ASCVD

Once generic atorvastatin entered the UK market in May 2012, there was a significant increase in the proportion of atorvastatin initiations of 5.6% in the same month, followed by a significant increase of 0.68% in the monthly initiation trend relative to the pre-intervention period (see **Table 7.3** and **Figure 7.2**). Specifically, the time series analyses stratified by different atorvastatin intensities showed a significant increase in the proportion of individuals initiating atorvastatin 80mg and 20mg in the month the generic became available compared to the months prior (80mg: 3.8%; 20mg: 0.9%). This was followed by a significant increase in the monthly initiation trend for all three high-intensity atorvastatin therapies, ranging from 0.1% for 20mg to 0.3% for 80mg and 40mg to, relative to the pre-intervention time period (see **Table 7.6** and **Figure 7.7**). These findings are consistent with the observations made by Chapman and colleagues, who performed a similar ITS analysis of the effect of the market entry of generic atorvastatin on the use of different statin types and intensities in England, examining the period from 2008 to 2014 [6].

These positive trends were driven by the rapid decrease in acquisition cost for generic atorvastatin, drastically narrowing the price gap between atorvastatin and simvastatin, and the findings are in line with the descriptive observations reported by Leporowski and colleagues for the period 2012 to 2015 in Scotland [9]. For example, the price gap between more potent atorvastatin 80mg/day and generic simvastatin 40mg/day decreased from £29.85 in 2009/10 to £8.65 in 2012/13 (£1.76 for atorvastatin 20mg/day), while increasing the relative cost of the branded and more potent rosuvastatin therapy by

almost 5-fold for 40mg/day in 2012/13. Concurrently, the greater efficacy of atorvastatin in reducing LDL-C levels at lower doses compared with simvastatin likely further prompted the increased prescription and initiation of atorvastatin.

With regard to the effect of generic atorvastatin entering the UK market on the use of simvastatin, a significant drop of 5.2% in simvastatin initiations was observed in the same month generic atorvastatin became available, followed by a significant decrease in the monthly trend of simvastatin initiations of 0.66% relative to the pre-intervention period (see **Table 7.3**). However, despite (a) the decrease in acquisition cost of generic atorvastatin to £6.22 for 20mg/day in 2012/13 narrowing the price gap with generic simvastatin (£2.94 for 40mg/day), (b) the greater efficacy of atorvastatin compared to simvastatin, and (c) the significant decrease in trend of simvastatin initiations as a result of points a and b, overall the majority, i.e.. 64% of all statin initiators in the years 2012 to 2014, were still treated with low/medium-intensity therapy, primarily simvastatin (see **Table 7.5** and **Figure 7.7**).

Effects of the publication of NICE clinical guideline CG181 in July 2014 on the use of high-intensity statin therapy for the secondary prevention of ASCVD

Building on the steady increase in the use of high-intensity therapy as a result of the market entry of lower cost generic atorvastatin in 2012 and the increasing amount of clinical evidence supporting the safe and efficacious use of high-intensity statins (e.g. based on findings from the Cholesterol Treatment Trialists' (CTT) Collaboration in 2010 [2]), NICE published its clinical guideline CG181 in July 2014, specifically recommending the use of high-intensity therapy atorvastatin 80mg for the secondary prevention of ASCVD [5]. This study observed an acceleration in the uptake of high-intensity therapy (specifically atorvastatin 80mg) associated with the guideline publication, although, the additional increase appeared relatively inconsequential compared to the increase in initiations as a result of the market entry of generic atorvastatin in 2012 that resulted in the availability of lower cost high-intensity statin therapy. A significantly higher increase in the trend of atorvastatin 80mg initiations was observed compared to atorvastatin 40mg and 20mg, suggesting an overall intensification across atorvastatin dosing after the guideline publication. No significant changes in the level or trend of other high-intensity statins were observed after the guideline publication (see **Table 7.6**).

As a result, the proportion of individuals initiating high-intensity therapy and those initiating low/medium-intensity therapy converged in the period from 2014 to 2017, and the overall proportion of individuals initiating high-intensity therapy after an ASCVD-

related event increased from an average of 31% in 2009/11 to 36% in 2012/14 to 58% in 2015/17 (see **Table 7.5**). Although the dataset used in this study ends in early July 2017, the increasing trends in the use of high-intensity statin therapy are expected to continue to grow and further research is required to understand the impact of the generic market entry of rosuvastatin in July 2017 on the prescription of different high-intensity statins.

7.4.2. Limitations

As previously discussed in detail in **Chapter 5**, **Section 5.5.2**, the data only contains information on prescriptions for individuals who were both prescribed and dispensed treatment. Therefore, the current analyses could only explore the effects of interventions on trends in statin initiations, not trends in overall prescriptions. For instance, the monthly rate of high-intensity statin prescriptions may have been increasing at a faster or lower rate than high-intensity initiations, however, the data only capture the overall proportion of individuals who ultimately dispensed statins and their associated rates over time. It must also be noted that the analyses focus on the first statin intensity prescribed in a primary care setting, therefore not considering the intensity prescribed by hospital staff on discharge nor dose titrations over time.

Furthermore, prescribing information is only available from April 2009 onwards, therefore not capturing trends in statin initiations prior to this time period. As a result, it was not possible to examine the initiation trends of different statins prior to and immediately after (1) the market entry of branded rosuvastatin and (2) the patent expiry of branded simvastatin in 2003, which may have visualised the onset of the gradual decline of atorvastatin that was captured in time period 2009 to 2012, as well as further insights on the association between price and clinical effectiveness and statin initiation patterns.

With regard to the methods used, the ITS model estimates do not control for patient characteristics and assume that these characteristics remain unchanged throughout the study period [31]. Therefore, changes in the population base, which may have explained changes in the outcome, i.e. the initiation of specific statin types or the initiation of high-intensity therapy, were not accounted for. However, sensitivity analyses using logistic regression models adjusted for patient features were performed and indicated consistent findings to those produced using ITS-based regressions. The limited role of patient characteristics can be explained by the fact that the target population consisted of all individuals in Scotland hospitalised for an atherosclerotic cardiovascular event, and thus all patients included in the analyses are expected to be on statin therapy, regardless of their

characteristics. Moreover, there is minimal personalisation regarding the choice of statin type and prescription decisions regarding statin type are based on the patient's LDL-C levels, therefore limiting the risks of potential confounding. Also, the interpretation of the ITS results is compatible with sequences of events, but the method does not establish causality.

Lastly, the findings on the effects of the introduction of NICE clinical guideline CG181 should be interpreted with caution and, overall, not overestimated. As previously emphasised in **Section 7.2.3**, NICE publishes clinical guidelines for England and Wales, while in Scotland the development and publication of clinical guidelines falls into the realm of SIGN. SIGN did not publicly recommend high-intensity statin therapy for the secondary prevention of CVD until June 2017. As the study data only include individuals hospitalised in Scotland until 4 July 2017, there are not enough data to assess the direct impact of the SIGN guideline on the use of high-intensity statins. Instead, the publication of NICE guidelines was used as an alternative exposure, as it captured recommendations based on the latest findings from clinical trials at that time, which would have also been available to the medical community in Scotland. Furthermore, NICE publications may be used by health professionals in Scotland as sources of evidence when considering clinical issues (see **Chapter 2**, **Section 2.3**).

7.4.3. Conclusions

The increasing supply of generic statins in the time period from 2003 to 2012 has led to significant cost savings for the NHS. Coupled with demand-side measures that are initiated on a national or local level, such as educational initiatives and clinical guidelines that advocate the use of higher-intensity statin therapy, the efficiency of statin prescribing for the secondary prevention of ASCVD has improved significantly over the time period from 2009 to 2017 in Scotland. Specifically, the market entry of generic atorvastatin in May 2012 has had a significant positive effect on high-intensity statin prescription trends, which were further accelerated with the introduction of NICE clinical guideline CG181 in July 2014 that recommended the use of atorvastatin 80mg/day for the secondary prevention of CVD. The notion of relative cost-effectiveness of different statin types remains a key influencing factor in prescribing decisions. If there are significant price differences between statins, decision-makers may opt for a statin with lower acquisition cost, as the additional cost of a more expensive potent statin type may not be outweighed by its additional marginal benefits. However, when prices converge over time, the marginal

clinical benefits of higher-intensity statins outweigh their minimally higher costs relative to a statin with lower cost and benefit.

7.5. Summary

This chapter provided novel evidence on the effects of the UK market entry of generic atorvastatin in May 2012 and the introduction of NICE clinical guideline CG181 recommending the use of high-intensity statin therapy in July 2014 on the initiation of both different statin types and statin intensities, using Scotland population-wide individual-level patient data. In the next chapter, I present a summary of findings from Chapter 3 to Chapter 7 and discuss these in the context of policy development for the secondary prevention of ASCVD.

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8

Discussion

8.1. Findings and interpretation

8.1.1. Rates of statin and antiplatelet therapy use for the secondary prevention of CVD

Summary of results

At the outset of this thesis, I summarised estimates of statin and antiplatelet therapy usage rates at different treatment stages for the secondary prevention of CVD from previous large studies of myocardial infarction and ischaemic stroke data, and presented evidence of gradually increasing, yet suboptimal medication use at almost every stage[100] of the treatment pathway for both statin and antiplatelet therapy (**Chapter 3**). Most previous studies reported rates of medication use for a specific stage in the treatment pathway (i.e. prescription on discharge, initiation, adherence or persistence) and no studies analysed treatment gaps across more than two stages. Furthermore, the observational cohort studies had an average follow-up time of three years, with the majority of studies reporting rates in a given year, at a specific stage and for a certain country, thereby limiting the ability to generalise results and insights into the full extent of suboptimal use across the entire treatment pathway and over time.

In order to address these evidence gaps, I used national hospitalisation and prescription information data on all individuals in Scotland ever hospitalised for a cardiovascular event since 2009 with a follow-up time of up to eight years (as described in **Chapter 4**), and examined the initiation, adherence and persistence rates by ASCVD type. About 82% and 84% of individuals hospitalised for a vascular event subsequently initiated statin and antiplatelet therapy, respectively, with rates varying significantly by ASCVD type (e.g. statin: 75% of PAD patients initiated therapy vs. 88% of MI patients; antiplatelet therapy: 68% of PAD patients vs. 94% of MI patients). Although more than 90% of individuals who initiated statin and/or antiplatelet therapy were adherent[101] while on medication, one quarter of individuals eventually discontinued treatment, with 50% of individuals ceasing statin and/or antiplatelet therapy within 1.5 years, and 80% within 3.5 years, despite clinical guidelines recommending lifelong treatment. Out of the individuals

[100] Suboptimal medication use was reported at every stage of the treatment pathway for both statin and antiplatelet therapy, except in the case of prescriptions of antiplatelet therapy on discharge, where almost 100% of patients received antiplatelet therapy on discharge.

[101] I.e., the patient used the treatment as instructed by their physician in terms of dose and frequency for at least 80% of the specified time period.

who discontinued treatment, 38% and 37% of individuals re-initiated, respectively, some type of statin or antiplatelet therapy at some point in time after their initial treatment gap of 180 days. (**Chapters 5-6**). The initiation rates for both therapies hardly increased since 2009/11 (approximately 1.5% absolute increase in initiations over an eight-year period), and the use of high-intensity statin within 12 months since index statin prescription was observed for only 57% of all statin initiations between 2015 and 2017, even though NICE's clinical guideline (CG181) has been recommending high-intensity treatment for the secondary prevention of CVD since 2014. Importantly, significant age and gender gaps in CVD management continue to persist, with fewer women and elderly aged 70 years or over initiating treatment (in 2015/17 the age gap between 50-59 years vs. 80-89 years was 16% for statins and 13% for antiplatelet agents; the gender gap was 8% for statins and 5% for antiplatelet agents).

Comparison with other studies

Findings from my systematic literature review and the present analyses using NHS Scotland data confirmed that there remain significant treatment gaps in the use of statin and antiplatelet therapy for the secondary prevention of CVD at every stage of the treatment pathway. The results from the Scottish data analyses are comparable with findings in previous literature summarised in **Chapter 3**, when comparing across similar time periods and, where possible, with healthcare systems with universal healthcare coverage. As the systematic review captures earlier time periods than those covered in the Scottish data (i.e. pre-2009), comparisons need to be drawn for individual studies with the latest available years, rather than using the average medication use rates calculated for each treatment stage in the review. In the case of statin initiation, the 180-day post discharge initiation rates (2009-11) reported in Scotland are slightly lower than those found in France in 2006 (81% vs. 85.4%) [1]. Adherence rates at 12 months since discharge were higher in the Scottish population than for example in Norway during the same time period (2009-2013), i.e. 93% vs. 83.6% [2]. This could be because previous studies conflated adherence and persistence by evaluating the proportion of days patients were covered with medication from the day of treatment initiation until the study end, whereas this study excluded individuals in the analysis once they discontinued treatment, which allowed for an assessment into the degree patients adhere to the medical regimen instructed by their physicians up until discontinuation. Similarly, methodological differences affect the direct comparison of statin discontinuation rates, which were significantly lower in Scotland in 2009/11 than those reported in Sweden in 2005/8 (i.e. 12 months: 10.5% vs. 26.5%; 24

months: 15% vs. 43.9%) [3]. For example, the Swedish study evaluated the total number of individuals not using treatment regardless of whether individuals initiated treatment in the first place or not, thereby inflating the rate because it simultaneously captured parts of the non-initiation rate in Sweden.

More pronounced differences were observed for antiplatelet therapy use. For example, 21% of patients initiated antiplatelet therapy within 30 days since discharge in Scotland in 2012 compared to 73% of patients in Denmark in the same year [4]. However, these differences likely arise due to arbitrary selections of time intervals. Specifically, the average time to be prescribed and dispensed treatment in Scotland was 32 days, therefore many later initiators were excluded at the 30-day threshold. Instead, a longer interval was more appropriate in the case of Scotland, and initiation rates increased to 80.8% when extending the period to 150 days since discharge, which is similar to the rate reported in Denmark at 30 days. Discontinuation rates at one and two years since initiation were lower in Scotland in 2009/11 than Sweden in 2005/8 (12 months: 9.8% vs. 20.7%; 24 months: 15.3% vs. 36.3%) which may in part be explained by the same methodological differences described earlier [3].

8.1.2. Determinants of statin and antiplatelet use for the secondary prevention of CVD

Summary of results

This thesis identified patient phenotypes that were consistently associated with higher risks of suboptimal statin and antiplatelet therapy use across two stages of the treatment pathway, namely treatment initiation and discontinuation (**Chapters 5-6**). Specifically, women, individuals who were younger than 50 years and those aged 70 years or more (compared to individuals aged 60 to 69 years), individuals with multiple physical morbidities, individuals with a previous record of receiving specialist mental health care, patients residing in the most deprived areas (compared to those living in the least deprived areas)[102], and patients hospitalised in the earlier time period in study (i.e. before 2015) had lower odds of treatment initiation, while concurrently having higher risk of treatment discontinuation. For example, compared to men, women had on average 28% and 20% lower odds of initiating statin or antiplatelet treatment, respectively, and 17% and 8% higher risks of discontinuing statin and antiplatelet therapy during the study period.

[102] In the case of statin therapy initiation only.

Amongst all individuals who initiated statin treatment, the same characteristics described above were also associated with lower odds of initiating high-intensity statin therapy compared to medium or low-intensity statins, even in the later time periods (i.e. 2015 to 2017), despite clinical guidelines recommending high-intensity statin treatment for the secondary prevention of CVD since 2014 (NICE CG181) (**Chapter 5**). In addition to patient-related factors, this thesis showed that the intensity of statins prescribed was significantly associated with market supply forces, such as the market entry of lower cost generic atorvastatin in 2012, and further accelerated via health care system demand-side measures, such as clinical guidelines and educational initiatives advocating for the use of higher intensity statin treatment (**Chapter 7**). The overall prescribing budget and the notion of relative cost-effectiveness of different statin types are likely key influencing factors in prescribing decisions. If there are significant price differences between statins, decision-makers tend to opt for a statin with lower acquisition cost, as the additional cost of a more expensive potent statin is not outweighed by its additional marginal benefits. However, when prices converge as a result of the availability of generic statins and with time, the additional clinical benefits with higher-intensity statins outweigh their minimally higher costs relative to statins with lower costs and benefits, leading to a significant increase in the use of more potent statin doses and types.

Comparison with other studies

The results presented above are partly reflected in the findings of the systematic review (**Chapter 3, Section 3.4.3**), and complete information gaps on the role of certain determinants at specific treatment stages that had not been previously studied, particularly in the case of antiplatelet therapy. For instance, the suboptimal pharmacological treatment and management of women with ASCVD was observed across a number of studies [5]–[9], with the exception that the review found two studies recording relatively higher risks of statin discontinuation amongst men than women [3], [10]. While the literature review pointed towards a U-shaped association between age and statin use, this thesis provides strong evidence for the presence of such an association at every stage of the treatment pathway for both statin and antiplatelet therapy. A number of previous studies summarised in the systematic review also investigated the role of specific comorbidities, such as diabetes, or number of comorbidities measured via the Charlson Comorbidity Index, and found no significant or conflicting associations with statin use (**Appendix A.9**). This thesis further adds to the literature by reporting a negative association between the presence and number of concomitant conditions and statin use. It is noteworthy that of the few studies

that investigated the effects of mental health-related comorbidities, specifically depression, none observed a significant impact on statin initiation or adherence [9], [11], [12]; in contrast, this thesis found clear evidence that individuals with previous mental health specialty admissions were at significantly higher risk of suboptimal treatment than those without. However, the possibility that these differences in findings could be explained by differences in the severity of cases captured requires further investigation. For instance, patients with severe depression are more likely to be treated at a specialist mental health clinic or a hospital, while mild to moderate depression is likely to be treated in primary or community care. Lastly, both the thesis review and the results of my analyses using Scottish routine healthcare data identified an association between socio-economic status and statin initiation, with individuals in the lowest socioeconomic group having lower odds of treatment initiation than those in the highest socioeconomic group. This is one of a few select studies [13]–[15] showing that this relationship also exists in healthcare systems outside of North America that have universal healthcare coverage and absence of prescription costs, or low-income prescription charge exemptions like England, implying that factors other than out-of-pocket payments constitute barriers to care.

8.1.3. Contribution and strengths of thesis

As shown in **Chapter 3**, previous literature analysed the rates and determinants of cardioprotective medication use at one or maximum two treatment stages, providing only limited and fragmented insights into the burden of and reasons for suboptimal statin and antiplatelet therapy use for the secondary prevention of CVD. However, for the purposes of healthcare policy making, planning and commissioning, a complete overview and more detailed understanding of the rates and determinants of suboptimal medication use at every stage of the treatment pathway, evaluated in a single comprehensive dataset, such as provided in this thesis, is valuable. Furthermore, most studies used a conflated outcome measure that combined adherence and persistence, leading to findings of artificially low adherence rates, which consequently called for further research and investment into possibly inappropriate interventions to address the seemingly poor adherence rates, such as electronic reminders [16]. In addition, few studies had sufficiently long follow-up times to capture changes in treatment use over time and were not able to assess the role of market and system factors in the use of cardioprotective treatment that go beyond patient and provider characteristics.

These evidence gaps were addressed in this thesis using detailed and high-quality national administrative data on all 167,978 individuals hospitalised for an atherosclerotic

cardiovascular event[103] in Scotland since April 2009, following patients for a time period of up to eight years. The NHS Scotland health service data are unique in that they contain high quality, linkable information covering the entire Scottish population, who are eligible for the same level of treatment in Scotland's universal free healthcare system. By including all individuals in Scotland who were hospitalised for cardiovascular events in a universal healthcare provider setting, the study is fully representative of Scottish residents treated for ASCVD.

The results provide novel estimates of the degree of suboptimal statin and antiplatelet therapy use by ASCVD type at three different treatment stages, (i.e. initiation, adherence and persistence), highlighting that interventions addressing initiation and persistence, rather than adherence, as well as focusing attention on individual ASCVD types such as PAD and ischaemic stroke, would yield the most significant gains for patients and the healthcare system. It is also the most comprehensive study internationally, and enabled robust estimation of patient- and policy maker-related predictors of suboptimal cardioprotective medication use. The study identified population groups with higher likelihood of non-initiation and discontinuation, and thus at higher risk of subsequent CVD events. These groups could be targeted in future trials of interventions to improve cardioprotective medication use at specific stages of the treatment pathway. Though there are limits to the international transferability of results, the key findings on the specific treatment stages and CVD types that present opportunities for improvement, as well as patient phenotypes at risk of suboptimal medication use and thus recurrent vascular events, should be more widely relevant.

8.2. Implications of results

8.2.1. Overview

Despite the availability of efficacious, safe and cost-effective medications for the prevention of vascular events, the findings of the systematic review and data analysis point to ongoing and significant treatment gaps in the secondary prevention of CVD, a condition that remains the leading cause of morbidity and mortality worldwide, as described in **Chapter 2**. These findings suggest a need for further investment in programmes designed to improve statin and antiplatelet therapy use, and likely other cardioprotective therapies, that go beyond the mere publication of clinical guideline recommendations, in order to

[103] As defined in **Chapter 4, Section 4.3.3**.

curtail preventable and recurrent CVD-related hospitalisations and deaths that constitute a significant cost burden to the healthcare system. The detailed results highlighting treatment stages of concern, and identifying patient-types at higher risk of poor CVD management, should also provide valuable information to governments, healthcare commissioners, hospitals and primary care practices, as well as the pharmaceutical and medical technology industry, making investment and prioritisation decisions.

8.2.2. Policy prioritisations

Interventions targeting the initiation and discontinuation of medication use

The findings derived from the detailed breakdown and quantification of statin and antiplatelet therapy use at three key treatment stages managed in primary care highlight the need for further research and investment in interventions that (1) increase the rate of cardioprotective medication initiation after hospital discharge and (2) decrease treatment discontinuation rates. While there is some room to further improve adherence rates, gains at this treatment stage are minimal and will not yield gains as significant as those derived from understanding and addressing why individuals do not initiate, or pre-maturely stop, beneficial and safe long-term treatments. For instance, with 20% of CVD patients not initiating statins, in addition to 25% of initiators discontinuing statins over time, about 25% of patient-years were not covered by cardioprotective therapy after an event. About a quarter of events in those patient years, or 6% of all major CVD events in the entire CVD population, might have been prevented if statins had been used, and up to 40% of these events could have been avoided if optimal high-intensity statin therapy were used across this population. Even more events could have been prevented if taking into account suboptimal use of antiplatelet therapies, as well as potentially other effective therapies such as blood-pressure-lowering medications (e.g. ACE inhibitors and beta blockers). Furthermore, deploying interventions that improve adherence without concurrently tackling the issue of treatment discontinuation would undermine any investments, as individuals with high adherence are still at risk of discontinuing treatment at some point in time. **Chapters 5** and **6** provide a detailed overview of patient phenotypes at higher risk of suboptimal initiation and persistence, and can inform future trials on interventions as well as future policies targeting these patient categories.

Management of peripheral arterial disease, ischaemic stroke and other high-risk patients

The findings of this thesis have shown that there is considerable variability in statin and antiplatelet therapy initiation and discontinuation rates by ASCVD type. Despite the presence of clear clinical guidelines for the secondary prevention of ASCVD in Scotland, England and Wales (see **Chapter 2**), the treatment rates for peripheral arterial disease (PAD) and ischaemic stroke are significantly lower than those observed for myocardial infarction (MI). Therefore, provider training and targeted patient education with a focus on PAD and stroke may further improve the use of cardioprotective medications in these patient populations, specifically amongst patients identified in **Chapter 5** and **6**, and would narrow the gap with cardiovascular disease types where guideline recommendations are being followed more rigorously or where there appear to be clearer net benefits.

The thesis also identified patients at higher risk of suboptimal statin and antiplatelet therapy use within each of the CVD types, showing that women, elderly patients, and those with physical and mental health comorbidities were particularly affected. These findings are concerning, as especially the elderly and those with comorbidities face an even higher absolute risk of experiencing vascular events than younger patients with fewer concomitant conditions. Provider training and targeted patient education may be of further benefit.

Uptake of high-intensity statin therapy

In addition to the suboptimal initiation of statin therapy among CVD patients in general, there is also suboptimal uptake of more effective high-intensity statin therapies, despite NICE and SMC clinical guidelines (CG181 and SIGN 149) recommending high-intensity statins for the secondary prevention of CVD since 2014 and 2017, respectively. Even though initiation rates of high-intensity statins have doubled since 2009/11, fewer than 60% of all statin initiators in 2015/17 ended up using high-intensity treatment in Scotland. This thesis has identified patient groups that are less likely to initiate such therapies and which could be targeted in future patient education initiatives and patient consultations, specifically women, individuals aged 70 years or older, individuals resident in the most deprived areas, patients receiving specialist mental health care, and those with a history of ASCVD and without any prior use of statin (**Chapter 5**). Going beyond patient factors, findings from this thesis have shown that the overall prescription budgets and relative cost-effectiveness of different statin doses and types are likely the key influencing factors in prescribing decisions (**Chapter 7**). Costs of high-intensity therapy have continued to decrease following the market entry of generic atorvastatin in 2012 and rosuvastatin in

2016, and statin prices should therefore play a reduced role in future decision-making. This financial incentive should be coupled with further physician training to achieve optimised high-intensity statin usage rates.

Uptake of dual-antiplatelet therapy after revascularisation and myocardial infarction

Even though 97% of ASCVD patients[104] who underwent percutaneous transluminal balloon angioplasty (i.e. percutaneous coronary intervention, PCI) initiated antiplatelet therapy, only 65% of all initiators who were treated with PCI and drug-eluting stent (DES), 69.8% of initiators with PCI and a non-DES stent, and 70.1% of initiators with PCI without stent used dual-antiplatelet therapy (DAPT), which is recommended for up to 12 months since hospital discharge by NICE and SMC clinical guidelines (NG185 and SIGN 148) (**Chapter 6**). This thesis has shown that particularly individuals aged 70 years or older and women[105] had significantly lower odds of initiating DAPT, and should therefore be targeted in future patient consultations. In the case of myocardial infarction patients, in whom DAPT has only been officially recommended since 2020 (NG185), 72% of patients without PCI had initiated DAPT in 2015/17, showing that patients were treated more intensively than the guidelines recommended at the time. Women, individuals aged below 60 years and those aged 70 years or older had significantly lower odds of DAPT initiation. Therefore, provider training and targeted patient education may be of further benefit.

8.3. Limitations

8.3.1. Independent prescribing information and serum blood levels not included

In this thesis, I estimated the degree and determinants of suboptimal statin and antiplatelet therapy use, and its effects on ASCVD-related hospitalisations and deaths, using routine administrative healthcare data. While the data offer insights into the proportion of patients taking up prescribed medications, it does not include information on patients who were offered medication during consultations but refused the recommended treatment before it could be prescribed. As a result, an analysis into the proportion of patients having been offered treatment by a physician, in order to assess whether current gaps in treatment

[104] ASCVD here excludes atrial fibrillation.
[105] The association between being female and lower odds of DATP initiation was significant at a 10% significance level.

initiation are driven by the patient or provider side, or both, was not feasible. Furthermore, clinician characteristics, such as age, gender and experience, and their association with suboptimal medication use could not be assessed due to large numbers of missing observations and the lack of information as to whether and when patients had clinician consultations to discuss their medical regimen. Consequently, this thesis provides an unbalanced overview of the potential reasons for suboptimal use, focussing primarily on the role of patients. Moreover, information on initial prescriptions in secondary care – for example at the point of discharge following hospitalisation for a cardiovascular event – was not available, therefore preventing an evaluation across the complete treatment pathway for CVD.

It should be noted that dispensed medications serve as a proxy for medication use and may not necessarily reflect the actual patients' drug usage. While this thesis provides an overview of the current state of medication use in Scotland, it does not provide estimates of actual treatment success such as changes in cholesterol over time, due to absence of information on LDL-cholesterol levels. Such information would have enabled further research into whether the current management of CVD is sufficient or whether more aggressive lipid-lowering is required to effectively prevent recurrent CVD.

8.3.2. Limits of patient information

Although the thesis provides novel and robust insights into the types of patients who are at higher risk of suboptimal use and should be targeted in future patient management, it does not explain the underlying reasons for these relationships, for instance, doctor's and patient's risk perceptions. Preferences and beliefs towards statin and antiplatelet therapy are not captured in the data, which may explain suboptimal medication use independent of other characteristics, such as age and gender. A number of patient characteristics that may be relevant to the likelihood of using cardioprotective medications, such as patients' ethnicity and marital status, could not be robustly studied due to large numbers of missing observations. Additionally, information on access barriers to treatment is not available. For example, distance to pharmacies, particularly in rural areas, may play a role in optimal medication use.

Moreover, patient information is mainly derived from hospital records, and primary-care diagnoses are not included. As a result, the current estimation of the relationship between comorbidities and medication use is based on conditions that are recorded in secondary care and so are likely to be more severe. Furthermore, due to the unavailability of information on medications other than statin and antiplatelet therapy,

comorbidities such as diabetes could not be derived from the prescription records. Therefore, the actual proportion of individuals with comorbidities is likely to be higher than estimated here. This further complicates examinations of potential gradients within comorbidities, particularly in the case of mental health where the majority of patients are treated within primary and community care [17]. Even though this thesis has shown that individuals with previous admissions to mental health specialties were at significantly higher risk of suboptimal medication use, no associations were observed for depression in previous literature (**Chapter 3**), suggesting that the severity of comorbidities may also constitute a factor in addition to the type and number of comorbidities.

8.3.3. Limitations of observational data

The research presented in this thesis was based on analysis of retrospective observational data, allowing for robust estimates of suboptimal medication use and its association with patient phenotypes. However, limitations of the observational data were made apparent when attempting to quantify the effects of suboptimal medication use on the incidence of subsequent cardiovascular events, using a Cox proportional hazards survival analysis **Chapter 5** and **6**). Whilst the survival analysis yielded statistically significant results that were consistent with previous findings from randomised controlled trials, inferences of treatment effectiveness are difficult due to risks of bias (e.g. treatment may have been selectively prescribed to individuals perceived at higher risk by physicians) and presence of unobserved confounders that are likely relevant to ASCVD risk. Robust evidence of the efficacy of statin and antiplatelet therapy, and the degree to which these medications can prevent fatal and non-fatal cardiovascular events is available from a large number of randomised controlled trials and meta-analyses thereof, such as those published by the Cholesterol Treatment Trialists' (CTT) and the Antithrombotic Treatment Trialists' (ATT) Collaboration presented in **Chapter 2**. As a result, the effects of suboptimal medication use on subsequent vascular events in Scotland can be indirectly estimated using average efficacy information reported in high-quality meta-analyses, as reported in **Chapters 5** and **6**.

8.3.4. Generalisability of results

The research, based on national routine administrative healthcare data, included all individuals resident in Scotland aged 18 years or older, who have been hospitalised for a CVD-related event (as specified in **Chapter 4**) at any point in time between April 2009 and July 2017. As such, the data are representative of CVD management in Scotland for

the specified time period, in a healthcare system that has universal healthcare coverage and free at point of use (i.e. without direct patient costs such as prescription charges or other co-payments). However, healthcare systems differ in a number of important aspects which may influence the estimated degree and relationship between patient characteristics and cardioprotective medication use, including the financing and structure of healthcare delivery, different rates of technology adoption and implementation of treatment guidelines, different treatment patterns and clinical guideline recommendations, and, in the case of pharmaceuticals, substantial global variations in prices. Furthermore, the underrepresentation of ethnic groups in the Scottish population and unreliable recording of ethnicity in hospital records both prevented me from drawing conclusions on the importance of ethnicity.

Although attention needs to be paid to differences in guidelines at certain points in time, as well as the role of patient costs that may constitute additional access barriers not captured in this analysis and which are prevalent in other healthcare systems (e.g. United States), there are reasons to think that the associations reported in this thesis may be similar in spite of these differences. Clinical guidelines for the secondary prevention of CVD have been fairly consistent across different jurisdictions due to the vast amount of high-quality evidence available and exchange of information and research on an international level, and thus we may expect to observe similar patterns of healthcare utilisation associated with the secondary prevention of CVD. This hypothesis is consistent with the results of the systematic literature review presented in **Chapter 3**, in which similar associations and treatment gaps were observed in North America and Europe.

Lastly, the overlap between treatment gaps of multiple treatments for the prevention of ASCVD, and whether medication underuse of concomitant statin and antiplatelet therapy was concentrated in the same individuals as identified at risk of suboptimal statin use, and separately, antiplatelet therapy use, was not assessed. However, the communalities in the identified patient characteristics that were associated with higher risks of suboptimal use of both statin and antiplatelet therapy, were suggestive of concentrated treatment gaps.

8.4. Future research

Estimations of the rates and determinants of statin and antiplatelet therapy prescriptions

While this thesis is able to examine the trends in medication initiation and long-term use over time, it cannot differentiate between treatment gaps that arose due to suboptimal clinician prescribing and those due to suboptimal patient initiation, as prescribing information data is only available for individuals who were both prescribed and dispensed treatment. Consequently, it was not possible to assess the level of absolute prescription rates over time and the extent to which suboptimal use is driven by physicians rather than patients. Furthermore, due to missing observations and information not available on whether prescribers advised patients to discontinue therapy or not, it was not possible to reach firm conclusions as to whether prescriber characteristics, such as age and gender, as well continuity of care (i.e. whether having the same physician throughout the years) and practice characteristics played a role in the long-term management of ASCVD. Such research would provide more balanced insights into policy decision-making, as the majority of previous literature has focussed on identifying patient-related factors associated with suboptimal medication use, not able to fully quantify the influence of important clinician-related factors.

Reasons for suboptimal medication use

The results presented in this thesis provide the most comprehensive overview of predictors of suboptimal medication use by treatment stage and ASCVD type to date. Whilst this information is valuable in informing policy and clinical decision-making and future trials on interventions, the underlying reasons for the suboptimal use remain unknown (e.g. why are women and elderly patients at higher risk of non-initiation and discontinuation of treatment, despite clinical guidelines recommending the use of statin and antiplatelet therapies for both populations?). Therefore, qualitative research should be conducted to further inform the design of interventions aimed at optimising medication use.

The impact of out-of-pocket expenditure on the uptake and long-term use of medications

Whilst the thesis was able to show an association between lower socioeconomic level and suboptimal medication use, the large number of missing observations on patients'

exemption status from prescription charges prevented an interrupted time series analysis that could have provided estimates of the role of financial barriers to patients (i.e. medication prescription charges) on the uptake of efficacious and safe treatments. The abolition of prescription charges in Scotland in 2011, which has been controversial due to limited evidence of its impact on access to care and patient outcomes, would have otherwise constituted a favourable setting for a natural experiment analysis. If a study were able to conduct such research in a different healthcare setting with similar opportunities for a natural experiment analysis, this will help investigate the role of patient cost barriers in the suboptimal use of cardioprotective medications. This information could inform policy-makers, such as those in England, whether to reduce or abolish prescription charges in return for optimised patient outcomes and lower healthcare costs due to improved disease prevention.

Interventions for the improvement of medication initiation and discontinuation

The findings of this thesis have highlighted that treatment initiation and persistence constitute the key treatment stages at which future interventions could potentially yield major improvements in medication use and consequently a further reduction in preventable hospitalisations and deaths. However, due to the use of conflated measures of medication adherence, which led to an artificially low adherence rate, the majority of previous literature sought to investigate interventions that improve adherence, such as electronic reminders, while research into interventions that target the uptake and persistence with medications were largely neglected. Such research has a large potential to support implementations of cost-effective interventions that could improve the management of ASCVD.

LDL-cholesterol level achievements in practice

This thesis has quantified the proportion of individuals initiating and using statin therapy in the long-term, in line with clinical guideline recommendations. However, it was not able to assess, if patients attain the LDL-cholesterol levels recommended in national clinical guidelines and whether more aggressive and complimentary pharmacotherapy, as well as lifestyle modifications, would be necessary to effectively prevent adverse vascular events. As the NHS Scotland administrative data on medication prescriptions and hospitalisation rates can be linked with primary care data, future research could delve into examining to what extent the current CVD management achieves optimal LDL-cholesterol levels.

8.5. Conclusions

In this thesis, I demonstrated that despite the availability of efficacious, safe and cost-effective medications for the secondary prevention of ASCVD, statin and antiplatelet therapy use remains suboptimal at every stage of the treatment pathway, specifically in the case of medication initiation and persistence, with significant variations observed between CVD types and patient groups. Key patient groups associated with suboptimal medication use included women, elderly individuals aged 70 years or older, patients with physical comorbidities and specialty mental health hospitalisations, as well as those resident in areas with higher deprivation levels. In addition, high-intensity statin therapy remains under-utilised, even with rates having increased significantly over time. Overall prescribing budgets and relative cost-effectiveness of statins were suggested to be influencing factors in policy makers' prescribing recommendations in the presence of significant price differences between statins, with higher intensity statins favoured when price differences converged over time.

The results of this thesis provide novel estimates of the degree and determinants of suboptimal statin and antiplatelet therapy use by ASCVD type and treatment stage, and is the most comprehensive study to date, offering a level of detail not previously available. Although there are limits to the international transferability of results, findings on treatment stages and ASCVD types that present major opportunities for improvements in patient outcomes, as well as patient phenotypes at risk of suboptimal medication use and thus recurrent vascular events, should be informative in other healthcare settings.

The detailed understanding of the treatment stages and ASCVD types of concern, as well as patients at higher risk of poor CVD management, should be useful to governments, healthcare commissioners, hospitals and primary care practices, as well as the pharmaceutical and medical technology industry, in making investment and prioritisation decisions. In addition, the results underline calls for greater investments in interventions designed to improve medication initiation and persistence, particularly for ischaemic stroke and peripheral arterial disease patients, in order to curtail the rising costs due to hospitalisation for preventable adverse vascular events.

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Appendices

A

Systematic Literature Review

A.1 Overview of scoping review

A.1.1 Methods

A scoping review was conducted to identify research gaps in published systematic reviews of studies examining the association between specific factors and statin and/or aspirin use for the secondary prevention of CVD. The NICE Evidence and Prospero databases were searched for relevant publications published or registered up to 10 April 2018. In addition, basic search was performed using Google Scholar (first five pages; hits ordered by most cited) to complement the NICE database search.

A.1.2 Electronic search strategy

The following search terms were used in a title and subject header field search

1. Systematic review
2. Meta-analysis
3. Statin*
4. (Lipid adj3 lower*)
5. (Cholesterol adj3 lower*)
6. Antiplatelet*
7. Aspirin*
8. Prescription* or prescribe* or prescribing
9. Initiation
10. Adher* or MEDICATION ADHERENCE/ or exp Patient Compliance/ or GUIDELINE ADHERENCE/ or "TREATMENT ADHERENCE AND COMPLIANCE"/
11. Non-adher* or nonadher*
12. Complian*or comply or complies or complied
13. Noncomplian* or non-complian*
14. Discontinuation* or discontinue*
15. Persistence or persist or persists or persisted or persisting
16. Use* or usage
17. Utili?ation
18. Cardiovascular disease*.mp.
19. Cardiovascular diseases/ or exp heart diseases/ or exp myocardial ischemia/ or exp vascular diseases/ or exp cerebrovascular disorders/
20. 1-2/OR
21. 3-7/OR
22. 8-17/OR
23. 18-19/OR
24. (20) AND (21) AND (22) AND (23)
25. Limit (24) to (human and English)

A.1.3 Results

Fifteen systematic reviews were identified, which examined the association between specific factors and statin and antiplatelet use for the primary and secondary prevention of CVD. An overview of the systematic reviews by medication type and treatment stage is presented in **Tables A.1-A.4**.

Search results using NICE Evidence database:

1. Statin prescriptions
    - 1 out of 105 systematic reviews identified.
2. Statin adherence
    - 13 out of 306 systematic reviews identified.
3. Aspirin prescriptions
    - 1 out of 69 systematic reviews identified.
4. Aspirin adherence
    - 3 out of 84 systematic reviews identified.

Table A.1 List of systematic reviews of statin prescriptions

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(1) 2017 Hyun et al.	The effect of socioeconomic disadvantage on prescription of guideline-recommended medications for patients with acute coronary syndrome: systematic review and meta-analysis.	Database: • Medline • EMBASE • Global Health Time period: 1946-2016	• 7 • Observational studies • 1992-2009	• Patients with ACS, stratified by patient's SES • Studies reported rate or odds of any of the prescription of guideline-recommended ACS medications at hospital discharge.	• No language or date restrictions.	• SES (i.e. employment, occupation, income and education).	• Considerable heterogeneity between studies (although risk of bias low). • Relatively old studies included. • Only studied SES and excluded all other possible determinants.	• Prescription ratio (PR) between the lowest and highest SES groups. • Lower SES associated with lower statin prescription.

Table A.2 List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(1) 2017 Deshpande et al.	A systematic review to assess adherence and persistence with statins.	Database: • Medline • EMBASE • Medline In-process & Daily Update • CENTRAL • DARE • Health Technology Database • CDSR Time period: 2005-2016	• 151 • Any design • 2005-2016	• Studies of any design reporting on patient adherence or persistence (or equivalent) with any statin therapy in adults with hypercholesterolemia were included • Publically available data	• N/a.	• N/a.	• Does not examine determinants of adherence. • Focus on patients with hypercholesterolemia only. • Found that 98.8% of the studies did not report valid or reliable methods to measure treatment adherence or persistence.	• Conference abstracts from four major cardiovascular disease conferences were screened as well (European Atherosclerosis Society Congress; European Society of Cardiology Congress; American College of Cardiology Annual Scientific Session; and American Heart Association Annual Scientific Sessions, for the years 2013–2016)
(2) 2017 Ofori-Asenso et al. Study still in progress	Patterns and predictors of adherence to statin therapy among older patients: a systematic review	• Medline • CINAHL • PsycINFO • Database of Abstracts of Reviews of Effects (DARE) • NHSEED • Cochrane Central Register of Controlled Trials	• N/a. • Observational (prospective and retrospective) studies and RCTs • N/a.	• Elderly patients (65+) • No restriction on country • Observational studies and RCTs that evaluated statin adherence/persistence as an outcome • Adherence/ persistence assessed via objective measure (e.g. pill count, medication refill data etc.) or cross-sectional via a validated self-reported instrument	• Studies conducted solely among participants within in-patient settings • Studies in which medications are administered by a carer or healthcare personnel	• N/a.	• Excludes patients below the age of 65	

Table A.2 (continued) List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(3) 2017 Vadhariya et al.	A Review of Patient Related Barriers to Statin Adherence.	Database: • PubMed Time period: Not stated.	• Not stated. • Not stated. • Not stated	• N/a.	• N/a.	• Socio-demographic factors • Factors relating to patient perceptions • Adverse events of the medication • Other disease conditions the patients suffered from. • High co-payment/Costs	• Very limited search only including the terms 'statin' and 'adherence' • Low quality review.	
(4) 2016 Xu et al.	Adherence, compliance, and persistence with lipid-lowering therapies: A systematic review	N/a.	• N/a. • U.S. studies that enrolled adults on lipid-lowering therapies • 2004 - 2016	• US studies that enrolled adults on LLT published since 2004 • Primary data on adherence, such as MPR, PDC, time to discontinuation, percentage discontinued etc. • Any LLT for primary or secondary prevention. LLTs included statins, ezetimibe, fibrates, niacin, or resins (generic or branded, combination therapies also included)	N/a.	N/a.	• Includes U.S. studies only	

Table A.2 (continued) List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(4) 2015 Logue et al.	Systematic review of studies exploring reasons for statin non-adherence and randomised controlled trials of interventions to improve adherence to statin therapy	• EMBASE • Medline • Cochrane Register of Controlled trials	• 9 • Qualitative studies • 1996 onwards	• Limited to human, English language and 1996 onwards • Qualitative studies	• N/a.	Adherence improved when • patients knew about the importance of the medication and how to use it • had better mental skills and overcame physical limitation and mental obstacles • More money • More information and feedback from provider • Patient education • Satisfaction with current therapy • Believe in treatment necessity		
(6) 2014 Murphy et al.	Cardiovascular medication utilization and adherence among adults living in rural and urban areas: a systematic review and meta-analysis.	Database: • Medline • PubMed • EMBASE • Intl. Pharmac. Abstracts • CINAHL • Web of Science	• 51 • Observational studies and controlled clinical trials	• Adults with established cardiovascular disease (atrial fibrillation, hypertension, heart failure, coronary artery disease) or diabetes, and reported cardiovascular medication use or adherence patterns for patients living in rural versus urban communities.	• No language, study design or date restrictions were applied.		• Focus on urban-rural factor only. • Does not include major CVD such as MI or stroke.	• Use and adherence did not differ between urban versus rural patients.

Table A.2 (continued) List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(7) 2014 Kelly et al.	Knowledge, attitudes and beliefs of patients and carers regarding medication adherence: a review of qualitative literature.	Database: • CINAHL • EMBASE • PubMed • Web of Knowledge Time period: Inception-2013	• 34 • Qualitative studies	• Original research in the English language • Qualitative articles including interviews or focus groups with patients or carers regarding medication adherence • Participants of any age	• Reviews, meta-analyses, editorials, commentary or conference abstracts • Use of questionnaires to elicit patient or carer views • Quantitative studies on medication adherence	• There were eight analytical themes identified regarding the knowledge of patients and carers concerning medication adherence.	• A number of studies were carried out in specific populations such as heart failure, HIV and transplant patients, the results may not be applicable to the general population.	Eight analytical themes were identified: (i) beliefs and experiences of medicines, (ii) family support and culture, (iii) role of and relationship with health-care practitioners, (iv) factors related to the disease, (v) self-regulation, (vi) communication, (vii) cost and (viii) access.
(8) 2013 Lewey et al.	Gender and racial disparities in adherence to statin therapy: a meta-analysis.	Database: • Medline • EMBASE • ClinicalTrials.gov • Cochrane Database of Systematic Reviews Time period: Inception-2010	• 53	• Studies reporting on adherence to statins by men and women or patients of white and non-white race were included.	• Studies that did not (1) present quantitative measures of adherence; (2) present original data; (3) evaluate gender, race, or ethnicity as a predictor of adherence; or (4) evaluate statin use.	• Gender • Ethnicity	• Focus on gender and ethnicity only.	• Among patients prescribed statins, women and non-white patients are at increased risk for nonadherence.

Table A.2 (continued) List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(9) 2013 Chowdhury et al.	Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences	Database: • Medline • Web of Science • EMBASE • Cochrane Time period: 1960-2012	• 44 • Prospective epidemiological studies (cohort, nested case-control, or clinical trial)	• Prospective study • Adult population (18 years or older) • Study reported risk estimates of cardiovascular medication adherence with any CVD (i.e. any fatal or non-fatal CHD, stroke or sudden cardiac death) and/or all-cause mortality outcomes.	• No language restrictions.	• Age • Gender • Comorbidity • Polypharmacy	• Excludes retrospective studies. • Most included studies used indirect methods to assess adherence. • Scope for analysis according to prevention type was restricted.	• 15 studies on statin adherence were included.
(10) 2012 Lemstra et al.	Proportion and Risk Indicators of Nonadherence to Statin Therapy: A Meta-analysis	• PubMed • PsycINFO • (CINAHL) • Cochrane Central • DARE • NHSEED • Health Technology Assessment Database (HTAD) • EMBASE	• 67 studies • Observational cohort studies and RCTs • Database inception to June 2011	• Published article that determined the proportion of adherence to statin therapy during a defined period • Observational cohort study (prospective or retrospective) or randomized controlled trial (RCT) • Use of a validated tool for measurement of adherence to statins • Published in English	• Opinion papers, letters to the editor, case reports, or case studies • Studies with fewer than 50 participants	• After meta-analysis, only 6 variables were associated with nonadherence to statin medications: (1) primary prevention (2) new statin users (3) Co-payment (4) lower income status (5) Fewer than 2 lipid tests performed (6) not having hypertension		• Significant differences in the proportion of patients adhering in RCTs vs. obs. studies (90.3% vs. 43%)

Table A.2 (continued) List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(11) 2012 Naderi et al.	Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients	Database: • PubMed Time period: 1998-2010* (*Time of publication only; hence data is from 2009 or older).	• 20	• Studies that measured adherence to drugs for the prevention of coronary heart disease in patients with and without a diagnosis of coronary heart disease. • Drug classes included aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, thiazide diuretics, and statins. • Studies had to measure adherence using pharmacy prescription refill data and report the number of patients obtaining drugs for at least 75% of days over a defined period of time. • Studies were also required to report the method of payment for medication (self-payment, state payment, or assisted payment). • USA, Canada, AUS, Europe		• Meta-regression was used to examine effects of age and patient medication-related out-of-pocket payments, and neither factor was found to be statistically associated with adherence.	• Limited search strategy	• 11 studies on statin adherence were included. • CHD comprised: myocardial infarction, ischaemic heart disease, angina, percutaneous coronary intervention, or coronary artery bypass grafting. • No difference in adherence level observed between individuals using statins for the primary and those using statins for the secondary CVD prevention.

Table A.2 (continued) List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(12) 2010 Mann et al.	Predictors of non-adherence to statins: A systematic review and meta-analysis	• Medline • EMBASE • Psychinfo • Cochrane Central register of Controlled Trials • Database of Abstracts of Reviews of Effects • National Health Service Economic and Evaluation Database • Health Technology Assessment database	• 22 • Cohort studies • All studies from inception to February 2009	• Prospective or retrospective observational cohort studies • Full text in English • Included: community dwelling, adult patients 18 years of age and older • Description of study design available • Analysis reported on at least 2 predictors of adherence in a multivariable analysis with relative risks and variance	• Studies of fewer than 50 participants	Predictors of nonadherence: • Youngest (<50) and oldest (>70) had lower adherence than middle-aged • Women and those with lower incomes Predictors of adherence • History of CVD • Diagnosis of hypertension and diabetes	• Studies published after 2009 are not included • Narrowed study question to statin adherence studies with validated measurements of adherence to identify a homogenous group of studies, however, it did not eliminate significant heterogeneity between studies.	• Only 1 article used validated self-report scale • No articles using either electronic medication monitoring or pill counts; hence, only studies using pharmacy and insurance database refill rates were included for meta-analysis • No relevant articles were found from prior to 1998

Table A.2 (continued) List of systematic reviews of statin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(13) 2007 Cramer et al.	The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review.	Database: • Medline • Embase Time period: 2000-2005	• 139 • 2000-2005	• English papers • Studies investigating patient compliance/ persistence with cardiovascular or antidiabetic medication • Provided a numeric measure of compliance or persistence with an adequate description of the methodology used. • Patients with CVD or diabetes.	• Trials of clinical efficacy were not included unless they specifically investigated compliance. • Clinical trials.	• N/a.	• Limited time frame (i.e. 2000-2005). • Studied adherence rates only, not determinants.	• Different medicines possession ratios (MPRs) for antihypertensive and lipid-lowering medications.

Table A.3 List of systematic reviews of aspirin prescription

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(1) 2017 Hyun et al.	The effect of socioeconomic disadvantage on prescription of guideline-recommended medications for patients with acute coronary syndrome: systematic review and meta-analysis.	Database: • Medline • EMBASE • Global Health Time period: 1946-2016	• 7 • Observational studies • 1992-2009	• Patients with ACS, stratified by patient's SES • Studies reported rate or odds of any of the prescription of guideline-recommended ACS medications at hospital discharge.	• No language or date restrictions.	• SES (i.e. employment, occupation, income and education).	• Considerable heterogeneity between studies (although risk of bias low). • Relatively old studies included. • Only studied SES and excluded all other possible determinants.	• Prescription ratio (PR) between the lowest and highest SES groups. • Lower SES associated with lower statin prescription.

Table A.4 List of systematic reviews of aspirin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(1) 2014 Czarny et al.	Adherence to dual-antiplatelet therapy after coronary stenting: a systematic review	Database: • PubMed • CINAHL • EMBASE • Web of Knowledge Time period: Inception-2012	• 34 • Observational studies • 2002- 2012	• Patients receiving at least one drug-eluting stent (DES) replacement and reported adherence to aspirin, ticlopidine, clopidogrel, or prasugel at 1,6, or 12 months post-procedure. • Adherence defined as use of a medication during the prescribed period.	• Studies that selected patients based on adherence-related factors (e.g. stent thrombosis) or reported on patients not filing prescriptions. • Clinical trials, meta-analyses and reviews.	• Bleeding • Lower educational level • Immigrant status • Lack of education regarding DAPT	• Focus on treatment after coronary stenting only. • Significant heterogeneity between studies. • Did not account for the reason for DATP discontinuation.	• Includes both adherence rates and determinants of adherence.
(2) 2013 Chowdhury et al.	Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences	Database: • Medline • Web of Science • EMBASE • Cochrane Time period: 1960-2012	• 44 • Prospective epidemiological studies (cohort, nested case-control, or clinical trial)	• Prospective study • Adult population (18 years or older) • Study reported risk estimates of cardiovascular medication adherence with any CVD (i.e. any fatal or non-fatal CHD, stroke or sudden cardiac death) and/or all-cause mortality outcomes.	• No language restrictions.	• Age • Gender • Comorbidity • Polypharmacy	• Excludes retrospective studies. • Most included studies used indirect methods to assess adherence. • Scope for analysis according to prevention type was restricted.	• Only 2 studies on aspirin adherence were included.

Table A.4 (continued) List of systematic reviews of aspirin adherence (in chronological order)

Year/author(s)	Title	Databases	Number, type and time period of studies	Inclusion criteria	Exclusion criteria	Predictors identified in systematic review	Limitations/gaps	Notes
(3) 2012 Naderi et al.	Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients	Database: • PubMed Time period: 1998-2010* (*Time of publication only; hence data is from 2009 or older).	• 20	• Studies that measured adherence to drugs for the prevention of coronary heart disease in patients with and without a diagnosis of coronary heart disease. • Drug classes included aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, thiazide diuretics, and statins. • Studies had to measure adherence using pharmacy prescription refill data and report the number of patients obtaining drugs for at least 75% of days over a defined period of time. • Studies were also required to report the method of payment for medication (self-payment, state payment, or assisted payment). • USA, Canada, AUS, Europe		• Meta-regression was used to examine effects of age and patient medication-related out-of-pocket payments, and neither factor was found to be statistically associated with adherence.	• Limited search strategy	• Only 2 studies on aspirin adherence. • CHD comprised: myocardial infarction, ischaemic heart disease, angina, percutaneous coronary intervention, or coronary artery bypass grafting. • Adherence to preventive treatment is poor and little related to class of drug, suggesting that side effects are not the main cause.

A.2 Electronic search strategy

Medline, Embase, Web of Science, CINAHL, Scopus, Global Health and PsychInfo will be searched from inception.

Search terms using Ovid SP

1. (Lipid adj3 lower*).mp.
2. (Cholesterol adj3 lower*).mp.
3. Hydroxymethylglutaryl-CoA Reductase Inhibitor*.mp. or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
4. (HMG CoA reductase inhibitor* or HMG-CoA reductase inhibitor*).mp.
5. Statin*.mp.
6. (Atorvastatin or Lipitor or Torvast).mp.
7. (Cerivastatin or Lipobay or Baycol).mp.
8. (Fluvastatin or Lescol).mp.
9. (Lovastatin or Mevacor or Altoprev or Altocor).mp.
10. (Mevastatin).mp.
11. (Pitavastatin or Livalo or Pitava).mp.
12. (Pravastatin or Pravachol or Selektine or Lipostat).mp.
13. (Rosuvastatin or Crestor).mp.
14. (Simvastatin or Zocor or Lipex).mp.
15. Aspirin.mp. or clopidogrel.mp or dipyrudamole.mp or ticagrelor.mp or prasurel.mp

16. Prescription* or prescribe* or prescribing.mp.
17. Adher*.mp. or MEDICATION ADHERENCE/ or exp Patient Compliance/ or GUIDELINE ADHERENCE/ or "TREATMENT ADHERENCE AND COMPLIANCE"/
18. Non-adher* or nonadher*.mp.
19. Complian*or comply or complies or complied.mp.
20. Noncomplian* or non-complian*.mp.
21. Nonfilling or non-filling.mp.
22. Discontinuation* or discontinue*.mp.
23. Continuation* or continue*.mp.
24. Concordance.mp.
25. Persistence or persist or persists or persisted or persisting.mp.
26. Usage.mp.
27. Utili?ation.mp.
28. Uptake.mp.
29. Initiation.mp.
30. Refill.mp.
31. Switch*.mp.
32. Reinitiat* or re-initiat*.mp.
33. Stop*.mp.
34. Treatment refusal.mp.

35. Socioeconomic.mp. or exp Social Class/ or exp SOCIOECONOMIC FACTORS/
36. Socio-economic.mp.
37. SES.mp.
38. Depriv*.mp.
39. Education.mp.
40. Educational status.mp.
41. Income.mp. or exp INCOME/
42. Unemployment.mp.
43. Occupation*.mp.

SES

44. Lifestyle or Life Style.mp.
45. Behavior* or Behaviour*.mp.
46. Exercise.mp.
47. Sedentary Lifestyle
48. Physical activity.mp.
49. Sport*.mp.
50. Diet.mp.
51. Nutrition.mp.
52. Television or TV.mp.
53. Sleep.mp.

Health behaviour

54. Cardiovascular disease*.mp.
55. Cardiovascular diseases/ or exp heart diseases/ or exp myocardial ischemia/ or exp vascular diseases/ or exp cerebrovascular disorders/

CVD

56. (Rat* or mouse or mice or hamster* or animal or dog* or cat* or bovine or sheep or primate* or rabbit* or swine or minipig* or pig* or guinea pig* or mammal*).mp.

57. 1-15/OR
58. 16-53/OR
59. 54-55/OR
60. (57) AND (58) AND (59)
61. 60 not 56
62. Limit 61 to (human and English)

Notes

.mp.: searches a word in the MeSH subject heading field, title field, abstract or name of substance field.

The search included any cardiovascular disease to capture publications that may report results for myocardial infarction and ischaemic stroke in the full-text.

A.3 Data extraction form

1. General Information

1.1. Date form completed (*dd/mm/yyyy*)	
1.2. Name of reviewer extracting data	

2. Study Details

2.1. Study ID (ID number followed by surname of first author and year first full report of study was published, e.g. 01 Smith 2001)	
2.2. Title	
2.3. Author (first name initial, last name)	
2.4. Author contact details	
2.5. Year published	
2.6. Funding	☐ Commercial ☐ Non-commercial ☐ Charity ☐ Unfunded ☐ Not specified
2.7. Notes	

3. Eligibility

Study characteristics (eligibility criteria)	Review inclusion criteria	Location in text (page/fig./table)
3.1. Language of study (i.e. English)	☐ English ☐ Other (exclude study)	
3.2. Publication type (i.e. full text; exclude editorials, abstracts and poster presentations)	☐ Full text publication/report ☐ Other (exclude study)	
3.3. Type of study (i.e. any quantitative study type except for randomised controlled trials)	☐ Observational study ☐ Randomised controlled trial (RCT) (exclude study) ☐ Qualitative study (exclude study) ☐ Other type of study (exclude study)	
3.4. Sample size (i.e. number of individuals with a history of myocardial infarction (MI) and/or stroke is greater than 10,000 individuals)	Sample size of individuals with MI and stroke combined or MI or stroke separately reported ☐ ≥ 10,000 individuals ☐ < 10,000 individuals (exclude study)	

3.5.	Population description (i.e. individuals aged 18 years old or older)	Does the study data include children and adolescents under the age of 18 years? ☐ No ☐ Yes (exclude study)	
3.6.	Conditions/diseases (i.e. secondary prevention of MI and/or stroke with separately reported results for each condition; excluding other conditions such as TIA and angina)	Secondary prevention of ☐ Myocardial infarction (MI) only ☐ Stroke only ☐ MI and stroke combined ☐ MI and stroke separately reported ☐ None of the conditions listed above (exclude study)	
3.7.	Interventions (i.e. statins and/or aspirin with separately reported results for each intervention)	Interventions include ☐ Statins ☐ Dual therapy including statins (*) ☐ Aspirin ☐ None of the interventions listed above (exclude study) (*) If dual therapy, please specify below: Click here to enter text.	
3.8.	Types of primary outcome measures (i.e. any measure of statin and/or aspirin prescription, initiation, utilisation, persistence, adherence/compliance rates separately reported for each intervention)	Any measure of statin and/or aspirin _____ ☐ Prescription rates ☐ Initiation rates ☐ Utilisation rates ☐ Persistence rates ☐ Adherence/compliance rates ☐ None of the outcomes measured above (Please go to Question 3.9)	
3.9.	Types of secondary outcome measures (if available, factors (i.e. barriers and facilitators) that are associated with statin and/or aspirin prescribing, initiation, use, persistence, adherence/compliance)	The study reports factors that are associated with statin and/or aspirin use ☐ Yes ☐ No (If answered 'None' for question 3.8, exclude study)	
3.10.	Decision (with reasons for exclusion)	☐ Include study ☐ Exclude study If exclude, please list reasons below: Click here to enter text.	
3.11.	Notes		

4. Population and setting

		Description as stated in publication	Location in text (page/fig./table)
4.1.	Population description (from which study participants are drawn)		
4.2.	Data source (e.g. government administrative data,		

	public insurance admin. data, private insurance admin. data, hospital admin. data, pharmacy claims admin. data, registry data, prospective study data)		
4.3.	Specification of data source(s) (e.g. name of register/database)		
4.4.	Level of location setting	☐ National ☐ Sub-national	
4.5.	Location (country, state, city)		
4.6.	Setting	☐ Primary care ☐ Secondary care ☐ Tertiary care ☐ Supported living ☐ Mixed setting ☐ Unclear ☐ Other, please specify: Click here to enter text.	
4.7.	Specification of population (based on condition, ethnicity, age, gender) (e.g. diabetes population; elderly)	☐ Yes ☐ No If yes, please specify ethnic group(s) below: Click here to enter text.	
4.8.	Notes		

5. Methods

	Description as stated in publication	Location in text (page/fig./table)
5.1. Aim of study (does the analysis of the prevalence and predictors of statin and aspirin use constitute the primary or secondary aim of the study?)	☐ Primary ☐ Secondary ☐ Unclear	
5.2. Design	Observational study ☐ Longitudinal study ☐ Cross-sectional study ☐ Case-control study ☐ Other, please specify: Click here to enter text.	
5.3. Sampling technique		
5.4. Study start date		
5.5. Study end date		
5.6. Length of patient follow up in study (in months)		
5.7. Notes		

6. Participants

	Description as stated in publication	Location in text (page/fig./table)
6.1. Sample size (i.e. number of individuals with MI or stroke)	Total number of individuals with a history of MI: Click here to enter text. Total number of individuals with a history of stroke: Click here to enter text. Total number of individuals with a history of MI and stroke combined: Click here to enter text. Overall sample size of the study (e.g. including other conditions, interventions and subpopulations): Click here to enter text.	
6.2. Type of condition assessment	☐ Clinician-recorded diagnosis ☐ Self-reported diagnosis ☐ Unclear ☐ Other, please specify: Click here to enter text.	
6.3. Age (mean age, standard deviation and range)	Mean age: Click here to enter text. Standard deviation: Click here to enter text. Age range: Click here to enter text.	
6.4. Gender (% female)		
6.5. Ethnic groups (% of individuals in each group)		
6.6. Socio-demographic information (e.g. % of individuals in each level of SES, education)		
6.7. Other participant characteristics (e.g. LDL Cholesterol level)		
6.8. Any subgroups established	☐ Yes ☐ No If yes, please specify: Click here to enter text.	
6.9. Notes		

7. Outcome measures

Primary outcome: **Prevalence rate of medication**	Description as stated in publication	Location in text (page/fig./table)
7.1. Outcome(s) measured	☐ Prescription of therapies at hospital discharge ☐ Prescription of therapies through primary care channels ☐ Initiation of therapies ☐ Utilisation of therapies ☐ Persistence with therapies ☐ Adherence to/compliance with therapies ☐ Other, please specify: Click here to enter text.	

7.2. Outcome definition(s)	List the definitions for each of the corresponding outcomes above: Click here to enter text.	
7.3. Adherence threshold, if applicable (e.g. 80%)		
7.4. Outcome measures	Direct measures ☐ Serum drug levels ☐ Other, please specify: Click here to enter text. Indirect Measures *Measures involving secondary database analysis* ☐ Electronic prescription service ☐ Pharmacy dispensing/refill/claims data ☐ Insurance claims ☐ Other, please specify: Click here to enter text. *Electronic Medication Packaging (EMP) devices* ☐ Medication Event Monitoring System (MEMS) ☐ Other, please specify: Click here to enter text. *Clinician assessment* ☐ Pill counts ☐ Other, please specify: Click here to enter text. *Self-reported* ☐ Self-reported with further clinician assessment ☐ Self-reported without further assessment	
7.5. Metrics and survey instruments	Prescription of therapies ☐ Percentage ☐ Other, please specify: Click here to enter text. Initiation of therapies ☐ Percentage ☐ Other, please specify: Click here to enter text. Utilisation of therapies ☐ Percentage ☐ Other, please specify: Click here to enter text. Persistence with therapies ☐ Time to discontinuation ☐ Percentage of individuals discontinuing with a specified permissible gap period. Please specify length of permissible gap period: Click here to enter text. ☐ Other, please specify: Click here to enter text. Adherence to/compliance with therapies ☐ Medication Possessions Ratio (MPR) ☐ Proportion of doses taken (PDT)	

	☐ Proportion of days covered (PDC) ☐ Morisky Medication Adherence Scale (MMAS) ☐ Medication Adherence Questionnaire (MAQ) ☐ Other validated questionnaire or scale, please specify: Click here to enter text. ☐ Other, please specify: Click here to enter text.	
7.6. Time points measured	☐ Single time point only ☐ Baseline ☐ Follow-up	
7.7. If follow-up: interval of time points measured	☐ Daily ☐ Weekly ☐ Monthly ☐ Quarterly ☐ Biannual ☐ Annual ☐ Biennial ☐ Other, please specify: Click here to enter text.	
7.8. Time from CVD event to first measure (in days)	Click here to enter text.	
7.9. Notes		
Secondary outcome: **Predictors**	Description as stated in publication	Location in text (page/fig./table)
7.10. Does the study report predictors (i.e. factors, barriers, facilitators) associated with statin and aspirin prescribing or use? (Including initiation, utilisation, persistence, adherence/compliance)	☐ Yes ☐ No If no, please proceed to section 8.	
7.11. Outcome	☐ Prescription of therapies at hospital discharge ☐ Prescription of therapies through primary care channels ☐ Initiation of therapies ☐ Use of therapies ☐ Persistence with therapies ☐ Adherence to/compliance with therapies ☐ Other, please specify: Click here to enter text.	
7.12. List of factors	Please list all factors potentially associated with statin and aspirin use that were evaluated in the study: Click here to enter text.	
7.13. Definition, details and measure of factor(s) (where necessary, e.g. insurance status)		

7.14.	Type of measure (e.g. OR/RR)		
7.15.	Statistical method used (e.g. multivariate regression)		
7.16.	Time points measured	☐ Single time point only ☐ Baseline ☐ Follow-up	
7.17.	If follow-up: interval of time points measured	☐ Daily ☐ Weekly ☐ Monthly ☐ Quarterly ☐ Biannual ☐ Annual ☐ Biennial ☐ Other, please specify: Click here to enter text.	
7.18.	Time from CVD event to first measure (in days)	Click here to enter text.	
7.19.	Notes		

8. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required

Primary outcome: **Prevalence rate of medication**		Description as stated in publication	Location in text (page/fig./table)
8.1.	Outcome	☐ Prescription of therapies at hospital discharge ☐ Prescription of therapies through primary care channels ☐ Initiation of therapies ☐ Utilisation of therapies ☐ Persistence with therapies ☐ Adherence to/compliance with therapies ☐ Other, please specify: Click here to enter text.	
8.2.	Subgroup (if any, e.g. age specific prevalence reporting)		
8.3.	Results (unadjusted)		
8.4.	Were outcomes adjusted?	☐ Yes ☐ No Please list the adjustors below: Click here to enter text.	
8.5.	Level of adjustment	Number of adjusting variables in the model: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4	

	☐ > 4	
8.6. Types of adjusting variables included in the statistical model	☐ Demographic factors ☐ Socio-economic factors ☐ Lifestyle factors ☐ Co-morbidities ☐ Anthropometric measures ☐ Other, please specify: Click here to enter text.	
8.7. Results (adjusted)		
8.8. Response/non-response rate		
8.9. How were missing data addressed?		
8.10. Are the results standardised for target population?	☐ Yes ☐ No ☐ Unclear ☐ Not stated	
8.11. Notes		

Secondary outcome: **Predictors**	Description as stated in publication	Location in text (page/fig./table)
8.12. Factor		
8.13. Subgroup (if any, e.g. age specific prevalence reporting)		
8.14. Outcome	☐ Prescription of therapies at hospital discharge ☐ Prescription of therapies through primary care channels ☐ Initiation of therapies ☐ Utilisation of therapies ☐ Persistence with therapies ☐ Adherence to/compliance with therapies ☐ Other, please specify: Click here to enter text.	
8.15. Results (unadjusted) (include standard error, 95% Confidence Interval, *p*-value)		
8.16. Were outcomes adjusted?	☐ Yes ☐ No Please list the adjustors below: Click here to enter text.	
8.17. Level of adjustment	Number of adjusting variables: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ > 4	

8.18. Types of adjusting variables included in the statistical model	☐ Demographic factors ☐ Socio-economic factors ☐ Lifestyle factors ☐ Co-morbidities ☐ Anthropometric measures ☐ Other, please specify: Click here to enter text.	
8.19. Results (adjusted) (include standard error, 95% Confidence Interval, *p*-value)		
8.20. Significant factors (in addition to section 8.19, please list all significant factors to facilitate the extraction of information into a summary table)	Please list all factors that were found to be associated with the outcome: Click here to enter text.	
8.21. Non-significant factors (in addition to section 8.19, please list all non-significant factors to facilitate the extraction of information into a summary table)	Please list all factors that were found not to be associated with the outcome: Click here to enter text.	
8.22. Response/non-response rate		
8.23. How were missing data addressed?		
8.24. Notes		

9. Strengths and limitations

Strengths and limitations reported by study author(s)	Description as stated in publication	Location in text (page/fig./table)
9.1. Notes		

10. Conclusions and other information

Conclusions and other information reported by study author(s)	Description as stated in publication	Location in text (page/fig./table)
10.1. Notes		

11. Risk of bias and quality assessment

Note: The following is a reduced version of Down and Black's 27-item checklist for the assessment of the methodological quality of observational studies of health care interventions.

Item	Criteria	Answer
Reporting		
11.1.	Are the characteristics of the patients included in the study clearly described?	☐ Yes = 1 ☐ No = 0

	In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	
11.2.	Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.	☐ Yes = 2 ☐ Partially = 1 ☐ No = 0
11.3.	Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the interquartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	☐ Yes = 1 ☐ No = 0
11.4.	Have the characteristics of patients lost to follow-up been described? This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.	☐ Yes = 1 ☐ No = 0
External validity		
11.5.	Were the subjects in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	☐ Yes = 1 ☐ No = 0 ☐ Unable to determine = 0
11.6.	Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	☐ Yes = 1 ☐ No = 0 ☐ Unable to determine = 0
Internal validity		
11.7.	Were the main outcome measures used accurate (valid and reliable)? For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	☐ Yes = 1 ☐ No = 0 ☐ Unable to determine = 0
11.8.	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? In non-randomized studies if the effect of the main confounders was not investigated or confounding was	☐ Yes = 1 ☐ No = 0 ☐ Unable to determine = 0

	demonstrated but no adjustment was made in the final analyses the question should be answered as no.	
11.9.	Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	☐ Yes = 1 ☐ No = 0 ☐ Unable to determine = 0

A.4 Data characteristics and analytical methods of studies included in the systematic review

A.4.1 Statin prescription on discharge

Study characteristics

Fifteen retrospective cross-sectional and cohort studies reported rates of statin prescriptions on hospital discharge, of which seven also reported determinants. Twelve studies were judged to have a good quality assessment score between 7 and 9, and three studies had a fair score between 4 and 6. The median sample size across all studies was 33,421 (interquartile range: 21,077 to 61,238). Most studies were based on individuals in Europe (n=11), with the remainder based on residents in North America (n=4) or Asia (n=1), and looked at entire national populations (European studies only), or general, mostly representative, populations. Trends in statin prescribing over time were captured in some studies, and combined information is available for a time period from 1994 to 2014.

Studies measured rates as the proportion of individuals with MI (n=12) or stroke (n=3) receiving statin on discharge from hospital. The prescription rates were reported as crude estimates, with some studies also reporting age-, year-, MI type-, hospital procedure- or department-specific rates. A few studies specifically examined STEMI (n=3) or NSTEMI (n=1) patients only, or stroke patients with LDL-C levels of > 100mg/dL (n=2). See **Appendix A.5 Table A.5** for a detailed overview of characteristics by study.

Quantitative analysis

Fourteen studies were included in the quantitative review of prescription rates, with one study (Redfors et al., 2015) being excluded due to the use of the same dataset and overlapping time period as another study, only providing information on a single state as opposed to the entire country.

Furthermore, seven studies investigated determinants associated with statin prescriptions on discharge, using regression-modelling techniques and adjusting for some confounders. Three out of the seven studies qualified for a quantitative synthesis assessing the association between gender and statin prescribing (Ovbiagele et al., 2010; Redfors et al., 2015; Radovanovic et al., 2012). One of the seven studies reporting information on gender was excluded due to overlapping datasets and time periods (Lawesson et al., 2012). However, the meta-analysis revealed pooled estimates with high heterogeneity (I2=84.5%) (**Appendix A.8, Figure A.2**), therefore only the qualitative synthesis is reported. See **Appendix A.9 Table A.10** for a detailed overview of all risk factors and effect sizes reported in studies.

A.4.2 Statin initiation

Study characteristics

Fifteen retrospective cross-sectional and cohort studies reported rates of statin initiation after index MI (n=14) or stroke (n=1) hospitalisation, of which six also reported determinants. Ten studies were judged to have a good quality assessment score between 7 and 9, and five studies had a fair score between 4 and 6. The median sample size across all studies was 45,188 (interquartile range: 22,608 to 85,017), including entire national populations, generally sampled but representative, or elderly populations only (n=6) from North America (n=9) and Europe (n=6). Trends in statin initiation over time were captured in some studies, with information available for a time period from 1992 to 2014.

Initiation was defined as filling a prescription, receiving a refund or purchasing a statin within a specific time period since index hospital discharge, with time periods ranging from 30 days (n=7), to 90 (n=2), 120-180 (n=4), or 365 days (n=1), or not defined (n=1). Initiation rates were generally reported as crude estimates (n=10), or specifically for age, gender, ethnicity, disease group and/or discharge year (n=4); only one study provided rates adjusted for age and sex and clustered by hospital and discharging physician. One study examined initiation of high-intensity statins only. See **Appendix A.5 Table A.6** for a detailed overview of characteristics by study.

Quantitative analysis

Thirteen studies were included in the quantitative summary of initiation rates. One study was excluded because of identical datasets and time periods (Fang et al., 2014), while a second study was excluded due to rates being reported by income quintile only (Hanley et al., 2011).

Five studies investigated determinants associated with statin initiation after hospital discharge, using regression-modelling techniques and adjusting for some confounders. Three studies investigated the association between gender, ethnicity and statin initiation, however, different outcome measures were used and therefore the studies were qualitatively summarised. The remaining studies were analysed qualitatively as they did not investigate the same predictors. See **Appendix A.9 Table A.11** for a detailed overview of all risk factors and effect sizes reported in studies

A.4.3 Statin adherence

Study characteristics

Seven retrospective cohort studies reported statin adherence rates since initiation (n=5), prescription on hospital discharge (n=1) or re-initiation after statin discontinuation (n=1) amongst MI (n=6) and stroke (n=1) patients, of which four also reported determinants associated with good adherence. Four studies were judged to have a good quality assessment score between 7 and 9, and three studies had a fair score between 4 and 6. The median adherence-specific sample size across all studies was 38,223 (interquartile range: 15,137 to 52,185), including entire national populations, generally sampled but representative, or elderly populations only (n=4) from North America (n=4) and Europe (i.e. Scandinavia) (n=3) over a time period form 1995 to 2014.

Adherence was defined as the extent to which patients followed their statin regimen during the prescription period and calculated as the Proportion of Days Covered (PDC) (n=5) or the availability of pills to patients/statin use at a specific time (n=2). Studies that calculated PDC used a binary adherence outcome, where being adherent was defined as a patient being covered with prescription supply for more than 80% of time. All studies assessed adherence at 12 months, with one following individuals for 12-18 months (Halvorsen et al., 2016), one study also reporting rates from 6 months up to 2 years (for high-intensity statin therapy only) (Colantonio et al., 2017), and a third one also reporting adherence after three and five years (Gislason et al., 2006). One study assessed adherence to high-intensity statins only (Colantonio et al., 2017), and one study investigated adherence after re-initiaton of statin since its first discontinuation, with discontinuation defined as a treatment gap of 90 days or more (Booth et al., 2017). Adherence rates were generally reported as crude estimates (n=5) or specifically for age-group and discharge year (Colantonio et al., 2017), statin intensity and history of statin use (Booth et al., 2017); only one study provided rates adjusted for age and sex and clustered by hospital and discharging physician. See **Appendix A.5 Table A.7** for a detailed overview of characteristics by study.

Quantitative analysis

Five studies were included in the quantitative summary of adherence rates. Two studies were excluded due to the use of overlapping datasets and time periods (Booth et al, 2017; Fang et al., 2014), recording either identical results or only evaluating adherence after re-initiation of statin therapy since discontinuation.

In addition, four studies investigated determinants associated with good adherence, using regression-modelling techniques and adjusting for some confounders. Due to the heterogeneity in regression methods and not enough similar determinants being assessed, none of the studies were included in the quantitative summary of adherence predictors. See **Appendix A.9 Table A.12** for a detailed overview of all risk factors and effect sizes reported in studies

A.4.4 Statin persistence

Study characteristics

Six retrospective cohort studies reported statin therapy persistence rates since index initiation, of which four and an additional study also reported determinants associated the discontinuation of treatment amongst individuals with a history of MI (n=5) or stroke (n=1). Three studies were judged to have a good quality assessment score between 7 and 9, and three studies had a fair score between 4 and 6. The median sample size across all studies was 34,319 (interquartile range: 20,800 to 52,099), including entire national populations or general population samples (n=4), or elderly populations only (n=2) from North America (n=3) and Europe (i.e. Scandinavia) (n=3) over a time period from 1995 to 2014.

Five studies measured persistence as the time from medication initiation to discontinuation of treatment, where discontinuation was defined as an individual exceeding a permissible treatment gap during the follow-up period (e.g. patient is not dispensed refill medication for a minimum 90 days in a row, indicating temporary or permanent discontinuation of treatment). The length of treatment gaps varied by study, from using gaps of 60 days or more (n=3) to 90 days or more (n=2). One study defined persistent users as patients who purchased the drug at least once during each 4-month interval. Persistence was assessed at time intervals ranging from a minimum of six months up to five years, with one study examining rates throughout the overall study time period without interval specification.

The included studies calculated the percentage of individuals out of all statin initiators who discontinued treatment, with initiation defined as the index uptake of treatment within 30 to 180 days since hospital discharge; one study did not specify the time interval for initiation. Discontinuation rates were estimated as crude rates (n=4), or reported specifically by age group and discharge year for high-intensity statins only (n=1) (Colantonio et al., 2017). Rates were also reported by gender (n=1) (Hudson et al., 2007), as well as by statin intensity and history of statin use (n=1) (Booth et al., 2017). One study did not report rates, as the primary objective of the study was to assess adherence, however, it did report determinants of statin persistence. See **Appendix A.5 Table A.8** for a detailed overview of characteristics by study.

Quantitative analysis

All studies that reported persistence rates (n=5) were included in the quantitative summary and rates were stratified by time interval. Studies that reported rates at more than one time interval were included in the analyses of each time interval group. If two or more studies used the same dataset with an overlapping time period for the same time interval, then the study with less information (i.e. shorter and less recent time periods) was excluded (n=1, i.e. Colantonio et al., 2017); however, despite exclusion from one time interval group, the study contributed information to a different interval group.

In addition, five studies examined predictors of persistence using survival analysis modelling adjusted for some key confounders such as age and sex. Even though more than two studies investigated similar predictors (e.g. gender), studies used different outcome measures (e.g. HR vs. RR), reference groups and different definitions of persistence (e.g. discontinuation of treatment vs. good persistence defined as utilisation at a given time). Consequently, the information was summarised qualitatively, not quantitatively. See **Appendix A.9 Table A.13** for a detailed overview of all risk factors and effect sizes reported in studies

A.4.5 Antiplatelet therapy prescription on discharge

Study characteristics

Ten retrospective cross-sectional and cohort studies reported rates of antiplatelet therapy prescription on discharge among individuals hospitalised for myocardial infarction, of which three also reported determinants. Eight studies were judged to have a good quality assessment score between 7 and 9, and two studies had a fair score between 4 and 6. The median sample size was 31,908 (interquartile range: 28,999 to 50,846). The majority of studies were based in Europe (n=6), with the remainder in the US (n=4). Trends in antiplatelet prescriptions on discharge were captured in some studies and overall information is available for a time period from 1987 to 2014. The prescription rate was calculated as the proportion of individuals hospitalised for MI who received antiplatelet therapy on hospital discharge. Prescription rates were reported as crude estimates, with some studies reporting rates across time periods, age groups, gender, MI type and hospital procedure (see **Appendix A.10, Table A.14** for a detailed overview of study characteristics and prescription rates).

Quantitative analysis

Eight studies were included in the review of prescription rates. One study (Redfors et al., 2015) was excluded due to use of county-specific data which was part of a national registry dataset used to report prescription rates in another study for the same time period. A second study (Basra et al., 2018) only reported the breakdown of different types of antiplatelet therapies prescribed on discharge among individuals who received antiplatelet therapy on discharge. Therefore, the actual prescription rate on discharge could not be deduced. In addition, two studies examined determinants associated with antiplatelet therapy prescriptions on hospital discharge using logistic regression models and adjusting for some confounders (**Appendix A.11, Table A.19**). One study (Redfors et al., 2015) was excluded for the same reason as described above.

A.4.6 Antiplatelet therapy initiation

Study characteristics

Seven retrospective cohort studies reported initiation rates of antiplatelet therapy among individuals hospitalised for MI. Six studies were judged to have a good quality assessment score between 7 and 9, and one study had a fair score between 4 and 6. The median sample size was 30,028 (interquartile range: 21,228 to 39,961). Four studies reported initiation rates in three European countries (i.e. Germany, France and Denmark), spanning the time period from 2006 to 2012, with time trends captured in one study (Green et al., 2016); the remaining studies were based on data from the USA and Canada. The initiation rate was defined as the proportion of individuals being dispensed antiplatelet therapy within 30, 90, 100 or 180 days since discharge, with one study calculating the initiation rate as the proportion of individuals filling a prescription within 180 days

prior to the index admission and within 30 days since index discharge, and another within 12 months since index charge. The studies reported crude estimates of the initiation rates, however, none of the studies investigated determinants of antiplatelet therapy initiation (see **Appendix A.10 Table A.15** for a detailed overview of study characteristics and initiation rates).

Quantitative analysis

Seven studies were included in the review of initiation rates and grouped by time within which initiation must have occurred (e.g. prescription within 30, 90, 180 days since discharge). In addition, two studies examined determinants associated with antiplatelet therapy initiation using logistic regression models and adjusting for some confounders (**Appendix A.11, Table A.20**).

A.4.7 Antiplatelet therapy adherence

Study characteristics

Two retrospective observational cohort studies reported adherence rates for antiplatelet therapy use among MI patients based in the USA (2005-2006) and Canada (1996-1998). The US study (n=10,057) was judged to have a good quality assessment score of 7 and the Canadian study (n=14,057) had a fair score of 6. The latter estimated adherence as the proportion of days covered (PDC), while the US study used the medicines possession ratio (MPR); both used a threshold of 80% for the PDC and MPR to classify individuals as adherent, and reported crude rates. The US study also reported determinants of ATP adherence (see **Appendix A.10 Table A.16** for a detailed overview of study characteristics and adherence rates).

Quantitative analysis

No pooling or quantitative analysis was performed due variations in the definition of persistence measures. One study (Zhu et al., 2011) also reported determinants associated with non-adherence to antiplatelet therapy (**Appendix A.11, Table A.21**).

A.4.8 Antiplatelet therapy persistence

Study characteristics

Four retrospective observational cohort studies based in Sweden (2005-2008), Denmark (2002-2005), the US (2005-2006) and Quebec, Canada (1999-2004), reported rates of persistence with antiplatelet therapy. Three studies were judged to have a good quality assessment score between 7 and 8, and one study had a fair score of 5. The median sample size was 24,820 (interquartile range: 13,794 to 37,598). Persistence was defined differently across each of the four studies. Two studies used a treatment gap of 30 days to indicate discontinuation (Sorenson et al., 2021, and Zhu et al., 2011), although one calculated the proportion of discontinuers while the other quantified that time in days until discontinuation. The third study measured discontinuation, defined as the failure to

renew a medication for more than 60 days after continuous exposure since the initial prescription (Hudson et al., 2007). The fourth study (Glader et al., 2010) evaluated persistence, which was defined as individuals purchasing drugs at least once during each 4-month interval after hospital discharge; all studies reported crude rates. Please see **Appendix A.10 Table A.17** for a detailed overview of study characteristics and rates of persistence.

Quantitative analysis

No pooling or quantitative analysis was performed due to the use of different adherence measures in each study. Two studies also reported determinants associated with either treatment discontinuation or treatment persistence (**Appendix A.11, Table A.22**).

A.5 Characteristics of studies included in the systematic review of statin therapy use

The following **Tables A.5-A.9** provide an overview of the characteristics and findings of studies reporting rates of statin therapy use at different stages of the treatment pathway.

Table A.5 Characteristics of studies included in the systematic review of statin prescriptions on hospital discharge

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Prescriptions on discharge (%)	Rate adjustment	Determinants	QA score
Erne et al. (2015)	Switzerland/ AMIS Plus nationwide prospective ACS registry	2002-2014	MI	33,421	Proportion of individuals (%) who received statin on hospital discharge	90.1% for outpatient-onset AMI and 80.1% for inpatient onset AMI	Crude rates reported by AMI-onset location	Yes	9
Glader et al. (2010)	Sweden/ National RIKS-Stroke registry	2005-2008	Stroke	21,077		34.5%	No	No	5
Gottwick et al. (2001)	Germany/ MITRA-1 and MIR prospective multicentre observational studies	1994-1999	MI	19,337		38.2% for hospitals with cardiology departments and 30.8% without cardiology departments.	Crude rates reported by hospital department type	No	8
Halvorsen et al. (2016)	Norway/ National registries	2009-2013	MI	42,707		89.5%	Crude rates	No	6
Jernberg et al. (2011)	Sweden /National RIKS-HIA ACS registry	1996-2007	MI (STEMI only)	61,238		1997: 23% 2007: 83%	Crude rates	No	9
Jortweit et al. (2017)	Norway/ National Norwegian MI registry	2015	MI	12,612		91% (ranging between 57% to 97% across all hospitals)	Crude rates	No	5

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Prescriptions on discharge (%)	Rate adjustment	Determinants	QA score
Lawesson et al. (2011)	Sweden/ National SWEDE-Heart registry	P1: 1998-2000 P2: 2004-2006	MI (STEMI only)	30,077	Proportion of individuals (%) who received statin on hospital discharge	P1: men: 44%, women: 38.1% P2: men: 85.2, women: 73.8	Crude rates by gender and time period	Yes	9
Li et al. (2016)	China/ China National Stroke Registry (CNSR)	2007-2008 Phase 1 2012-2013 Phase 2	Stroke (for individuals with LDL > 100 mg/dL)	12,173 P1 19,604 P2 Total: 31,777		P1: 42.6% P2: 66.3%	Crude rates	Yes	7
O'Brien et al. (2012)	USA/ ARIC: retrospective surveillance study of hospitalized CHD; North Caroline, Mississippi, Minnesota, Maryland	1987-2008	MI	15,732	Medication receipt during hospitalisation or at discharge	1997-2001: 40% 2002-2008: 72.2%	Crude rates by time period Age standardised to the 2000 United States census age distribution.	No	8
Ovbiagele et al. (2010)	USA/GWTG-Stroke	2005-2007	Stroke	173,284	Proportion of individuals (%) who received statin on hospital discharge	79.2%	Crude rates	Yes	7
McNamara et al. (2013)	MINAP/NICOR, SWEDEHEART/ RIKS-HIA, and ACTION	2007-2010	MI (NSTEMI only)	England/ Wales: 137,009 Sweden: 45,069		England/Wales: 91.5% Sweden: 81.1% USA: 84.5%	Crude rates	No	7

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Prescriptions on discharge (%)	Rate adjustment	Determinants	QA score
	Registry-GWTG/NCDR national registries			USA: 147,438					
Radanovic et al. (2012)	Switzerland/ AMIS Plus nationwide prospective ACS registry	1997-2011	MI (STEMI only)	21,620		Since 2008: 95% in men, 89% in women	Crude rates reported by gender	Yes	9
Redfors et al. (2015)	Sweden/ 1 county, SWEDE-HEART	1995-2014	MI	48,118		Men: 62% Women: 52% (Overall: 57.3%)	Crude rates reported by gender	Yes	9
Somma et al. (2012)	USA/ GWTG–CAD national registry	2006-2010	MI	72,352		90.2	Crude rates	Yes	9
Stenestrand et al. (2001)	Sweden/ RIKS-HIA national registry	1995-1998	MI	19,599		28%	Crude rate	No	8

Table A.6 Characteristics of studies included in the systematic review of statin initiation since index hospital discharge

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Statin initiators (%)	Rate adjustment	Determinants	QA score
Austin et al. (2008)	Canada (ON)/Elderly 65+ years, Ontario Myocardial Infarction Database	1992-2005	MI	132,778	Statin prescription fill within 90 days since discharge	1992: 4.2% 2005: 79.2%	Crude rates	No	7
Colantonio et al. (2017)	USA/ Elderly 65+ years	2007-2012	MI	495,073	High intensity statin fill within 30 days since discharge	(11.7%)	Crude rates	No	5
Fang et al. (2014)	USA/ Elderly 65+ years, Medicare Chronic Condition Data Warehouse (CCW)	2007-2009	MI	85,017	Filled a prescription within 30 days since discharge	61%	Crude rates	No	5
Gasse et al. (2008)	Denmark/ 3 counties, national hospital discharge registiries	1997-2003	MI	11,927	Filling at least one prescription within 180 days since discharge	45.8 % (1997: ~18% 2003: ~70%)	Crude rates	Yes	8

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Statin initiators (%)	Rate adjustment	Determinants	QA score
Gislason et al. (2006)	Denmark/ National Hospital Registry	1995-2002	MI	48,412	First prescription claim dispensed within 180 days from discharge	Overall: 33.5% 1995: 11.7% 2002: 63%	Crude rates	No	8
Hanley et al. (2011)	Canada (BC)/population-based cohort using state-wide administrative data	1999-2006	MI	28,216	Filling at least one prescription 120 days post discharge	Men Q1: 64.4% Q2: 62% Q3: 68.2% Q4: 74.9% Q5: 78.8% Women Q1: 57.1% Q2: 57.2% Q3: 57.8 Q4: 62% Q5: 69.9%	Gender and income quintile specific rates	Yes	6
Hoer et al. (2013)	Germany / one big statutory health insurance (SHI) fund with 7M beneficiaries	2006-2009	MI	45,188	At least one prescription documented within 12 months since index event	Total: 65.3% NSTEMI/UA: 61.3% STEMI: 76.8%	Crude rates	No	8

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Statin initiators (%)	Rate adjustment	Determinants	QA score
Hudson et al. (2007)	Canada (QC)/ Quebec provincial discharge summary database	1999-2004	MI	34,735	Rate of prescriptions within 30 days after discharge	1999-2004: 58.3% 2003-2004: 72%	Crude rates	No	8
Lauffenburger et al. (2014)	USA/ Elderly 65+ years, (CMS) and Medicare Chronic Condition Data Warehouse (CCW) enrolment summary	2007-2009	MI	85,017	Filling a prescription within 30 days post discharge.	61.3%	Crude rates	Yes	8
Lindhardsen et al. (2012)	Denmark / Danish National Patient Register	2002-2009	MI	66,107	At least one redeemed prescription within 30 days after discharge	Rheumatoid Arthritis (RA): 57.3% Non-RA: 68 %	Crude rates	Yes	7
Margulis et al. (2011)	Canada (BC)/ province-funded British Columbia Medical	1997-2004	MI	25,848	Filling a prescription within 30 days after discharge	38.6% Results section vs. Table 2 adjusted	Adjusted rates: age, sex, clustered by (1) hospitals, (2) discharging physician (3)	No	7

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Statin initiators (%)	Rate adjustment	Determinants	QA score
	Services Plan (96% of all BC residents)					rates which differ significantly			
Rosenson et al. (2017)	USA/Representative and Elderly 65+ years, Medicare Chronic Condition Data Warehouse (CCW)	2011-2014	MI	15,278	Filling a high-intensity statin prescription within 30 days after discharge	(2011 MarketScan: 33.5% Medicare: 24.8% 2014 MarketScan: 71.7% Medicare: 57.5%)	Crude rates	Yes	6
Setoguchi et al. (2007)	USA/ Elderly 65+ years, New Jersey Medicare and Pharmaceutical Assistance for the Aged and Disabled and the Pennsylvania Medicare and Pharmaceutical Assistance Contract for	1995-2004	MI	19,368	Filling a prescription within 90 days after discharge	Overall: 34% 1995:11% 2004: 61%	Crude rates	Yes	5

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Statin initiators (%)	Rate adjustment	Determinants	QA score
	the Elderly programs								
Tuppin et al. (2010)	France/ SNIIRAM i.e. general health insurance covering 70% of population.	2006	MI	14,007	Received refunds (insurance) for drugs within 6 months after discharge	85.4%	Crude rates	No	7
Wettermark et al. (2008)	Sweden/ 2 counties, national Hospital Discharge Register	1997-2006	Stroke	12,362	Purchase of medicines in 2005-2006	2005-2006: 40%	Crude rates	No	7

Table A.7 Characteristics of studies included in the systematic review of statin adherence

Study	Country/ Data Source	Time period	CVD Condition	N	Adherence measure	Adherence definition	Follow-up in months	Adherent (%)	Determinants	QA score
Aarnio et al. (2014)	Finland/National population register	2000-2004	Stroke	13,840	PDC since initiation	≥ 80%	12	64.3%	No	7
Booth et al. (2017)	USA/ Elderly 65+ years, Medicare beneficiaries.	2007-2012	MI	13,132	PDC since re-initiation	≥ 80%	6 months since reinitiation	48.8%	Yes	7
Colantonio et al. (2017)	USA / Elderly 65+ years, Medicare beneficiaries.	2007-2012	MI	45,876	PDC since initiation	≥ 80%	2007 6, 12, 18, 24 2012 6, 12, 18, 24	(High intensity statins only: 53.5% 43.2% 38.8% 35.2% 62.7% 54.4% 50.0% 46.9%)	Yes	5
Fang et al. (2014)	USA/ Elderly 65+ years, Medicare Chronic Condition Data Warehouse (CCW)	2007-2009	MI	52,185	PDC since initiation	≥ 80%	12	Median: 66.0%	Yes	5

Study	Country/ Data Source	Time period	CVD Condition	N	Adherence measure	Adherence definition	Follow-up in months	Adherent (%)	Determinants	QA score
Gislason et al. (2006)	Denmark/ National Hospital Registry	1995-2002	MI	16,433	Availability of tablets since initiation.	NA	1 year 3 years 5 years	85%, 80%, 82%	No	8
Halvorsen et al. (2016)	Norway / Norwegian national registries	2009-2013	MI	38,223	Difficult to tell – Days on treatment Since prescription on discharge.	NA	Up to 24 but statistics reported for: 12-18	83.6%	No	6
Lauffenburger et al. (2014)	USA/ Elderly 65+ years, Medicaid Services (CMS) Medicare Chronic Condition Data Warehouse (CCW) enrolment summary	2007-2009	MI	52,185	PDC since initiation	≥ 80%	12	66.0%	Yes	8

Table A.8 Characteristics of studies included in the systematic review of statin therapy persistence

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/Definition	Follow-up in months	Discontinuation (%)	Determinants	QA score
Booth et al. (2017)	USA/ Elderly 65+ years, Medicare beneficiaries.	2007-2014	MI	158,795	60-day continuous period without statin supply since initiation.	182 days	6 months: 15.4 discontinued	Yes	7
Colantonio et al. (2017)	USA / Elderly 65+ years, Medicare beneficiaries.	2007-2012	MI	57,888	No statin available in the last 60 days of each follow-up period.	2007 6, 12, 18, 24 2012 6, 12, 18, 24 months	2007 14.7, 19.3, 20.5, 23% 2012 12, 16.1, 18.6, 19.2%	No	5
Gislason et al. (2006)	Denmark/ National Hospital Registry	1995-2002	MI	16,433	Break of at least 90 days since initiation.	Up to 5 years	Overall time period: 34.4%	Yes	8
Glader et al. (2010)	Sweden/ National stroke register RIKS-Stroke	2005-2008	Stroke	7,275	Persistence: Drug purchase at least once during each 4-month interval after hospital discharge.	Up to 2 years	73.6% (i.e. 26.5% discontinued) at 12 months; 56.1% (i.e. 43.9% discontinued) at 24 months.	Yes	5

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/Definition	Follow-up in months	Discontinuation (%)	Determinants	QA score
Hudson et al. (2007)	Canada (QC)/ Quebec provincial discharge summary database	1999-2004	MI	34,735	Failure to renew medication for more than 60 days initiation.	Up to 5 years	At 2 years women: 20%; men: 27% At 5 years women: 32%; men: 37%	Yes: reported separately for men and women	6
Lindhardsen et al. (2012)	Denmark / National patient registers	2002-2009	MI	33,903	First treatment gap of 90 days or more since drug initiation.	Full time period	Not reported	Yes	7

Table A.9 Characteristics of studies included in the systematic review of statin utilisation

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Statin utilisation (%)	Rate adjustment	Determinants	QA score
Danese et al. (2018)	UK / Clinical Practice Research Datalink (CPRD)	2013-2013	MI	35,012	Lipid modifying therapy (LMT)distribution in selected sub-groups of very high-risk patients; utilisation in a given calendar year regardless of when the event occurred	Out of those who initiated/were using statins: High intensity statins: 34% Moderate intensity statins: 59% Low intensity statins, Ezetimibe, other LMT: 7%:	Crude rates	No	6
Huang et al. (2016)	USA/ 14 geographical areas, HealthCore Integrated Research Database	2006-2014	Stroke	58,411	Identified first statin claim	HI statin: 3.6% LMI: 23.3% No statin: 73%	Crude rates reported specifically for intensity.	No	7
Koopman et al. (2016)	Netherlands/ Dutch	1997 and 2007	MI	110,770	Drug use	1997: 33% 2007: 47%	Year-specific rates reported.	No	6

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Statin utilisation (%)	Rate adjustment	Determinants	QA score
	national hospital discharge register								
Savoie et al. (2002)	Canada (BC)/ population-wide PharmaNet database	1996-1997	MI	30,763	Prescriptions for statins	Age standardized population prescription rates for statins: 2.40 per 100	Age standardized population prescription rates per 100 for statins	No	6
Wettermark et al. (2008)	Sweden/ 2 counties, national Hospital Discharge Register	1997-2006	Stroke	12,362	Purchase of medicines	2005-2006: 40% Looking at rates in 2005-2006, including all stroke discharges prior to that.	Crude rates (also gender and age group and year of discharge specific rates reported)	No	7

A.6 Rates of statin and antiplatelet therapy utilisation

A.6.1 Statin utilisation

Data characteristics and analytical methods of included studies

Study characteristics

Five retrospective cross-sectional and cohort studies reported statin utilisation rates amongst individuals with MI (n=3) and stroke (n=2), of which none investigated potential determinants. Two studies were judged to have a good quality assessment score between 7 and 9, and three studies had a fair score between 4 and 6. The median sample size across all studies was 35,012 (interquartile range: 30,763 to 58,411), including entire national populations or generally sampled but representative populations from North America (n=2) and Europe (n=3) over a time period from 1996 to 2014.

Definitions of utilisation varied by study and included the overall purchase, prescriptions or prescription fill rates in a specific year or over a calendar time period. Two studies looked specifically at the distribution of different statin intensities, calculating the proportion of individuals on high, medium and low-intensity statins among MI and stroke patients. Utilisation rates (i.e. proportion of individuals using statins) were generally reported as crude estimates, except for one study that calculated age-standardised population rates (Savoie et al., 2002). Please see **Appendix A.5 Table A.9** for a detailed overview of study characteristics and utilisation rates).

Quantitative analysis

Due to the heterogeneity in the calculation of utilisation rates and absence of determinants, no studies were summarised quantitatively.

Rates of statin utilisation

Three cross-sectional and two longitudinal studies reported statin utilisation rates for MI and stroke patients in a given calendar year (i.e. not year since a CVD event). Two studies focused specifically on the variation in utilisation rates across different statin intensity groups. A cross-sectional study examining lipid-modifying therapy distribution in MI patients in a general, representative UK population in 2013 found that among statin initiators the majority of MI patients (59%) were using moderate intensity statins, with the remainder using high (34%) or low-intensity statins, Ezetimibe and other lipid-modifying therapies (7%) (Danese et al., 2018).

In the case of general statin use, an earlier cross-sectional study based in Sweden reported that approximately 40% of patients discharged for stroke between 1997 and 2006 (and still alive in 2006) purchased statins in 2005 to 2006. (Wettermark et al., 2008). Furthermore, a U.S. study reported that the majority of stroke patients (73%) were not using any statin treatment in the period 2006 to 2014 (Huang et al., 2016). In addition, Koopman and colleagues assessed the change in statin utilisation over time and found that drug use (i.e. in a given calendar year; not within a specific time period since discharge) among MI patients in the Netherlands increased from 33% in 1997 to 47% a decade later (Koopman et al., 2016).

A.6.2 Antiplatelet therapy utilisation

Data characteristics and analytical methods of included studies

Two retrospective cohort studies examined antiplatelet therapy use in a given year or at any point since index discharge for MI and/or stroke. One study was based on county data of 12,362 individuals previously hospitalised for stroke in Sweden, while the second study focussed on German and Austrian residents with diabetes and concomitant records of previous MI or stroke hospitalisations, as reported in national diabetes registries (n=29,325). One study was judged to have a good quality assessment score of 7, and one study had a fair score of 6. The studies reported crude estimates of the utilisation rates, and neither study evaluated determinants of antiplatelet therapy use (see **Appendix A.10 Table A.18** for a detailed overview of study characteristics and utilisation rates).

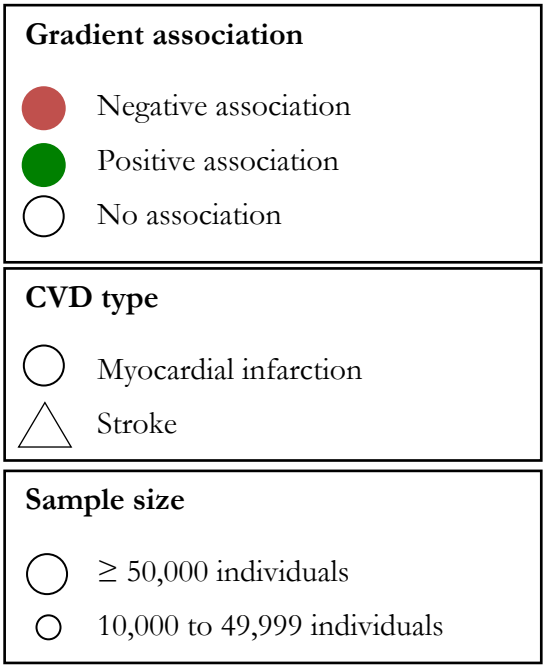
Rates of antiplatelet therapy utilisation

In a cohort of stroke patients in Sweden the utilisation rate of aspirin and clopidogrel, respectively, was 59% and 7% in 2005 to 2006. Among diabetic patients in Germany and Austria (2006-2015), who also had a record of stroke, the utilisation rate of antiplatelet therapy in general was estimated to be 32%. This rate was significantly lower than the rate reported amongst diabetic patients with concomitant myocardial infarction (i.e. 51%).

A.7 Visualisation of determinants

The following **Figure A.1** is an extension of **Figure 3.3** reported in **Chapter 3**, and visualises the association between patient and provider-related characteristics, as well as other factors (e.g. time effects), and statin use at different treatment stages on a more granular level. For example, factors such as previous CVD, comorbidities and medication use are further divided into the respective types of conditions and drugs, and additional risk factors are reported (e.g. geographical location).

Key to **Figure A.1**[106]



[106] Outcomes from studies that performed separate regression analyses for multiple datasets or different population groups were treated as different cohorts.

Figure A.1 Overview of factors associated with statin use at different stages of the treatment pathway

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Demographic				
Women (vs. men)	▲ ● ●	● ● ● ●	● ●	● ▲
Older age groups, i.e., 69 years or older (vs. < 69 years)/increasing age in years	▲	● ○ ○	○	● ● ●
Younger age groups, i.e., 64 years or younger (vs. > 65 years)				● ● ●
Black/African American ethnicity/race (reference: White)		● ● ○	● ●	
Asian ethnicity/race (reference: White)[107]		●	○ ○	
Other ethnicity/race (reference: White)[108]	▲	○ ○ ○	● ●	
Socioeconomic status				
Lower (household) income/ low income/ low-income subsidy/Medicare Part D/Dual Medicare and Medicaid coverage[109]		● ● ○	●	
Clinical history				
STEMI (vs. NSTEMI)	●			

[107] Initiation: statistically significant for female Asians only.
[108] 'Other' is here defined as any ethnic group except for 'White'.
[109] The results refer specifically to US patients with dual Medicare and Medicaid coverage with lower socioeconomic status, however, are as a result covered by federal health insurance and therefore do not have to pay any prescription medication-related charges.

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Recurrent MI (vs. no prior MI)			●	
Recurrent stroke (vs. no prior stroke)				▲
History of CHD (vs. no history)		● ○	●	
History of CAD/MI (vs. no history)	▲			
History of/current atrial fibrillation (AF) (vs. no history/no current AF)	▲	●		
(Congestive) Heart Failure (vs. no CHF)		● ○ ○	○	○ ○
Cardiac dysrhythmias (vs. no dysrhythmias)				○ ○
History of Carotid Stenosis (vs. no history)	▲			
History of hypertension (vs. no history)	▲	●		○ ○
History of dyslipidaemia (vs. no history)	▲			
History of stroke/cerebrovascular diseases (vs. no history)	▲	● ○ ○	●	○ ○
TIA (vs. stroke)	▲			
History of PVD/PAD (vs. no history)	▲	○ ○ ○		
Diabetes (vs. no diabetes)	△	○ ○ ○	●	○ ○
Liver diseases (vs. no liver disease)		●		
Chronic kidney disease/renal disease (vs. no CKD/renal disease)		○ ○ ○	○	○ ○
Dialysis (no dialysis)		●		
Chronic pulmonary diseases (vs. no CPD)		●		
COPD (vs. no COPD)				○ ○

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Cancer/malignancy (vs. no cancer)		●	◯	● ◯
Dementia (vs. no dementia)		● ◯ ◯		● ◯
Rheumatoid arthritis (vs. no RA)		●		●
Depression (vs. no depression)		◯ ◯	◯	
Mental health problems (other than depression)/Low mood (vs. no mental health problems)		●		△
Charlson Comorbidity Index (reference: zero)		◯ ◯	●	
Previous hospitalisations (any) (vs. no prior hospitalisations)		◯ ◯	●	● ●
Operations/Procedures				
Prosthetic heart valve (vs. no prosthetic heart valve)	▲			
In-hospital revascularisation procedures/angiography or stent during index hospitalisation (vs. no coronary procedure)		●	◯	● ●
Cardiac surgery (during index hospitalisation) (vs. no cardiac surgery)		◯		
Medication use				
Previous lipid-lowering medication use (vs. no prior use)	▲			▲
Increase in number of medications taken/polypharmacy		● ●	●	
Use of non-statin lipid-lowering therapy (vs. statin therapy)		◯ ◯		

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Beta-Blocker (vs. no beta blocker use)				●
ACE-inhibitor (vs. no ACE inhibitor use)				●
Loop diuretics (vs. no loop diuretics use)				○
Antidiabetics (vs. no antidiabetics use)				○
New high-intensity statin users (vs. prior high-intensity statin use)			●	
Moderate intensity (vs. low)			○	●
High intensity (vs. low)			●	●
Up-titration (vs. index dose)			○	
Down-titration (vs. index dose)			●	
Change in statin type (vs. index statin type)			●	
Acute care				
Inpatient-onset AMI (reference: outpatient-onset AMI)	●			
Larger hospital size (e.g. increase in number of hospital beds)	▲			
Acute cardiologist care (vs. no receipt of acute cardiologist care)		● ○	●	
Stroke unit care (vs. care in other unit)				▲
Acute care: Internist (vs. other clinician type)				○
Hospital type: academic (vs. non-academic)	▲			
Hospitals with higher numbers of stroke discharges	▲			
Longer length of hospitalisation		●		● ○

Factor	Treatment stage			
	Prescription on discharge (Yes)	**Initiation** (Yes)	**Adherence** (Good adherence)	**Persistence** (No discontinuation)
Aftercare/Post-hospitalisation				
Post-MI Cardiac rehabilitation (vs. no rehabilitation)			●	
Cardiologist (vs. physician care)				● ○
Outpatient visits (per 5 visits)			●	△
Outpatient cardiologist visits (reference: 0)			●	
Medical coverage gap (vs. no coverage gap)			●	
Institutional living (vs. living at home)				▲
Poor self-perceived health (vs. good)				▲
Lifestyle/Behaviour				
Smoking (yes)	▲			
Alcohol abuse (yes)		●		
Time effects				
Later calendar years	▲	●		● ● ○
Geographical				
Rural residence (vs. urban)			●	
U.S. Midwest vs. West U.S. South vs. West	▲			
Other				
Publication of SPARCL trial results (vs. period prior to publication)	△			

A.8 Quantitative and qualitative pooling of determinants

Figures A.2-A.4 visualise the pooling of results for the determinants of statin prescription on discharge and statin initiation, based on the availability of at least three studies reporting the relevant predictor.

Figure A.2 The relationship between gender (i.e. female vs male) and statin prescription on MI discharge, random effects meta-analysis

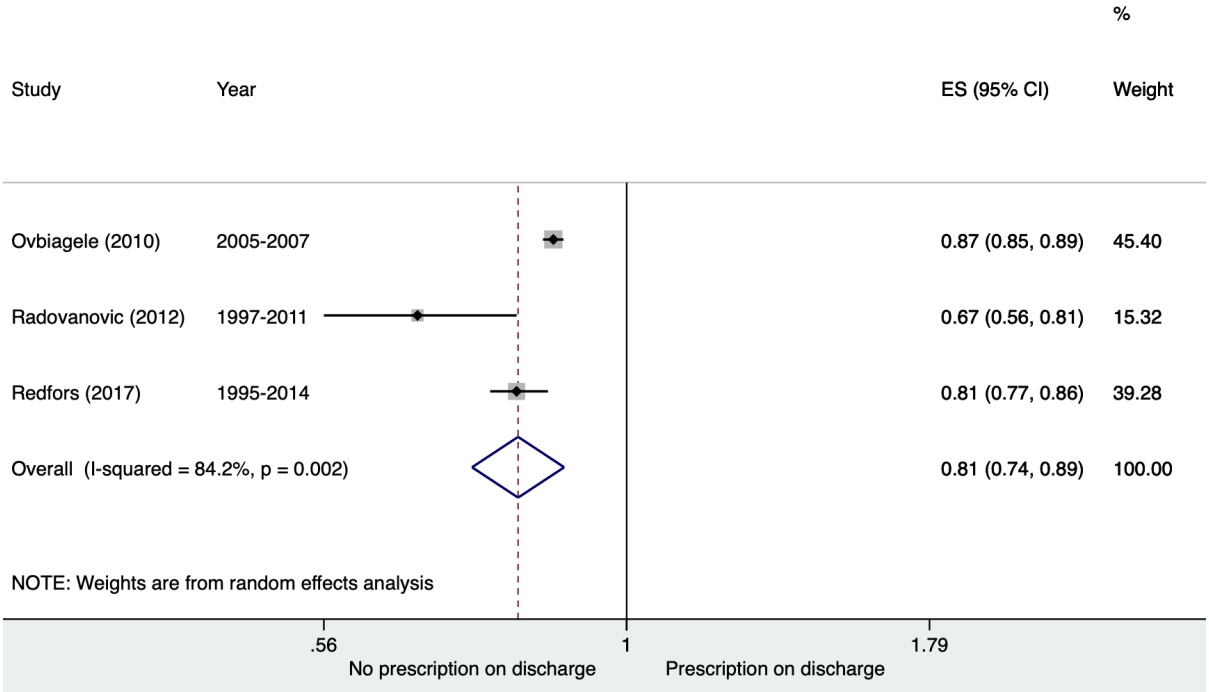


Figure A.3 Association between gender (i.e. being male) and statin initiation after hospital discharge for MI

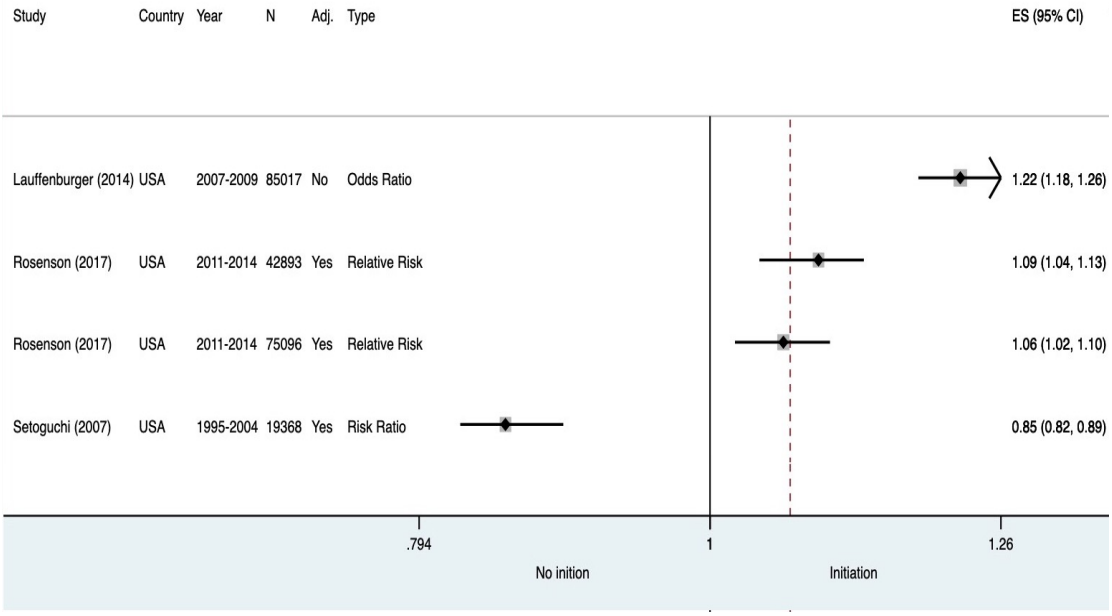
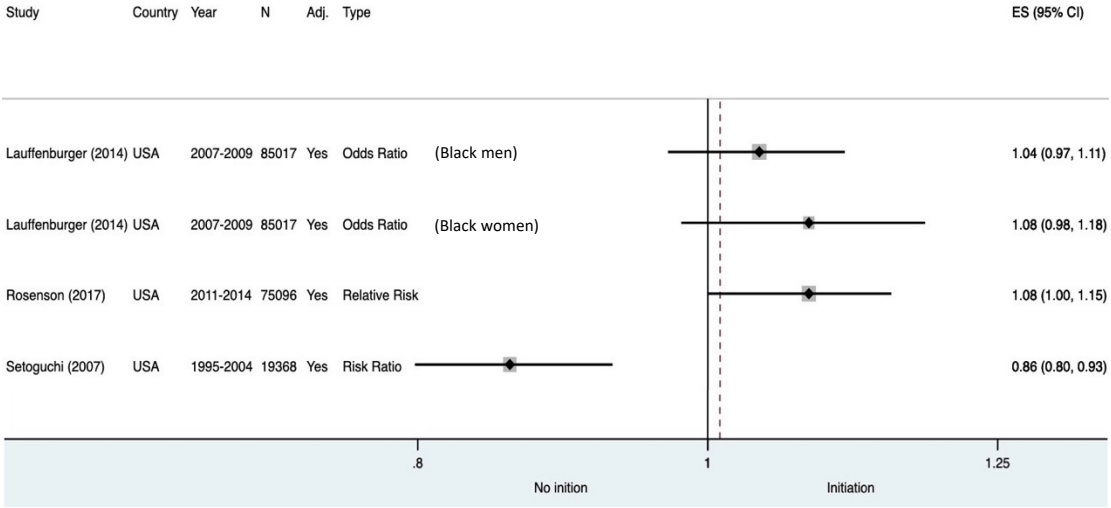


Figure A.4 Association between race/ethnicity (i.e. Black/African-Americans compared to White Americans) and statin initiation after hospital discharge for MI



A.9 Determinants of statin therapy use reported in the included studies

The following **Tables A.10-A.13** provide an overview of the characteristics and findings of studies reporting determinants of statin therapy use at different stages of the treatment pathway.

Table A.10 Study characteristics and determinants of statin prescriptions on discharge investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with prescribing**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with prescribing**	**Covariates included in model**
Erne et al. (2015)	Switzerland (2002-2014)	MI	Inpatient-onset AMI (reference: outpatient-onset AMI)	0.51 (0.41-0.63)	Na	Age, gender
Lawesson et al. (2011)	Sweden (1998-2006)	MI (STEMI)	Gender (Female)	1998-2000 1.16 (1.06-1.27) 2004-2006 0.76 (0.73-0.78)	Na	Age, smoking, previous MI, PCI, CABG, stroke, hypertension, DM, COPD, HF, CKD, PAD, dementia, cancer within 3 years, therapies on arrival, interventional hospital and year of inclusion
Li et al. (2016)	China (2007-2013)	Stroke	Time effects: 2012/13 (reference: 2007/08) (i.e. improvement in adherence to performance measures in acute ischaemic stroke care)	2.72 (2.02-3.65)	Na	Patient characteristics: Age, race, sex, insurance schemes, previous stroke/TIA, DM, hypertension, dyslipidemia, CHD/previous MI, AF, ever smoking, stroke severity; hospital characteristics: geographic region, teaching status, number of hospital beds, and annual stroke discharges
Ovbiagele et al. (2010)	USA (2005-2007)	Stroke	Age (per 10 years)	0.93 (0.91-0.94)	History of diabetes; dissemination of SPARCL trial results; Region (Northeast vs.	Covariates explored in analysis
			Race (white vs. other)	0.87 (0.82-0.92)		
			Female (vs. male)	0.86 (0.85-0.88)		
			TIA vs. Ischaemic stroke	0.64 (0.62-0.66)		
			History of stroke	0.86 (0.84-0.88)		

Study	Country/ Time period	CVD condition	Factors associated with prescribing	Effect size (Odds Ratio, 95% CI)	Factors not associated with prescribing	Covariates included in model
			History of CAD/MI	0.95 (0.92-0.97)	West); No. of stroke discharges (101-300 vs. 301+)	
			History of carotid stenosis	1.10 (1.04-1.16)		
			History of hypertension	1.05 (1.02-1.07)		
			History of PVD	0.90 (0.86-0.95)		
			History of smoking	1.23 (1.20-1.27)		
			History of dyslipidaemia	1.99 (1.92-2.06)		
			Taking cholesterol reducer at admission	8.47 (7.86-9.12)		
			History of or current AF	0.70 (0.68-0.72)		
			Prosthetic heart valve	0.79 (0.73-0.85)		
			No. of hospital beds (per 100-unit change)	1.03 (1.004-1.06)		
			Hospital type (academic vs. non-academic)	0.74 (0.67-0.83)		
			Region Midwest vs. West South vs. West	 0.71 (0.58-0.86) 0.66 (0.56-0.78)		

Study	**Country/ Time period**	**CVD condition**	**Factors associated with prescribing**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with prescribing**	**Covariates included in model**
			No. of annual stroke discharges (0-100 vs. 301+)	0.67 (0.57-0.78)		
Radovanovic et al. (2012)	Switzerland (1997-2011)	MI	Women (vs. men)	0.67 (0.56-0.81)	Na	Age, Killip classes>2, risk factors (smoking, dyslipidemia, hypertension, diabetes) and comorbidities (Charlson weighted index ≥2) and admission year.
Redfors et al. (2015)	Sweden (1 county)/ 1995-2014	MI	Women (vs. men)	0.81 (0.77-0.86)	Na	Age, smoking habits, hypertension, diabetes, hyperlipidemia, previous MI, previous cardiac surgery, previous PCI, STEMI, and calendar year.
Somma et al. (2012)	USA (2006-2010)	MI	STEMI (vs. NSTEMI)	1.71 (1.56-1.86)		Age, sex, race, medical history of COPD or asthma, DM, hyperlipidemia, hypertension, PVD, stroke or TIA, HF, renal insufficiency, smoking, geographic region of the United States, teaching hospital, number of hospital beds

Table A.11 Study characteristics and determinants of statin initiation investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with initiation**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with initiation**	**Covariates included in model**
Hanley et al. (2011)	Canada (BC) (1999-2006)	MI	Income quintile by gender Men (reference: Q1, lowest income) Women (reference: Q1, lowest income)	Men Q2: 0.96 (0.87-1.07) Q3: 1.15 (1.03-1.28) Q4: 1.45 (1.30-1.62) Q5: 1.71 (1.53-1.90) Women Q2: 0.94 (0.83-1.06) Q3: 0.98 (0.86-1.11) Q4: 1.07 (0.93-1.23) Q5: 1.32 (1.12-1.54)	Na	Age group, urban residence, general health status
Lauffenburger et al. (2014)	USA (2007-2009)	MI	Race/ethnicity and gender (reference: white men)	Asian women: 1.20 (1.02-1.41)	Other race/ethnicity and gender groups: white women, black men, black women, Hispanic men, Hispanic	Age, average household income at ZIP code of residence, geographic region, clinical characteristics (12 months prior to index admission): AMI, CABG, stent/PTCA, stroke/TIA, UA, CHF, AF, hypertension, PVD, diabetes, hyperlipidaemia, CKD, ESRD, COPD, Asthma, liver disease, osteoporosis, Charlson Comorbidity Index, angioedema, hyperkalemia, hypotension, sinus bradycardia, heart block, and

Study	Country/ Time period	CVD condition	Factors associated with initiation	Effect size (Odds Ratio, 95% CI)	Factors not associated with initiation	Covariates included in model
					women, Asian men, other men, other women	rhabdomyolysis/other myopathy prescriptions of β-blockers, ACEIs/ ARBs, and statins in the 6 months prior to the index AMI, AMI type (subendocardial or transmural infarction), procedures (CABG, stent/PTCA, cardiac catheterization, infusion of thrombolytic, infusion of platelet inhibitors) and complications (heart failure, cardiogenic shock, acute renal failure, hypotension, cardiac dysrhythmias) during the index AMI hospitalization, and total intensive care unit (ICU) and inpatient stays for the index AMI
Lindhardsen et al. (2012)	Denmark (2002-2009)	MI	Rheumatoid arthritis (reference: no RA)	0.69 (0.58-0.82)	Na	Sex, age, SES, comorbidity
Rosenson et al. (2017)[110]	USA (2011-2014)	MI	History of CHD	Medicare 0.92 (0.86-0.99)	High-intensity statin initiation Older age group, race, low income subsidy/dual eligible (applies to Medicare only); history of: diabetes, CHD (MarketScan	Covariates explored in analysis
			Cardiologist care	Medicare 0.93 (0.88-0.99)		
			Total number of medications taken (reference: <5) 5-9 medications ≥10 medications	MarketScan 0.94 (0.90-0.98) 0.93 (0.87-0.98) Medicare 0.96 (0.92-1.00) 0.92 (0.87-0.98)		

[110] Effect sizes reported as Relative Risk (RR)

Study	Country/ Time period	CVD condition	Factors associated with initiation	Effect size (Odds Ratio, 95% CI)	Factors not associated with initiation	Covariates included in model
					only), stroke, HF, PAD, CKD, dementia; Charlson index, depression, Hospitalisation in year prior to MI, Cardiologist care (MarketScan only), use of non-statin lipid-lowering therapy	
Setoguchi et al. (2007) [111]	USA (1995-2004)	MI	Year of discharge	1.18 (1.17-1.19)	CKD, depression, peripheral vascular disease, diabetes mellitus, cardiac surgery	Co-morbidities (previous MI, coronary artery diseases, heart failure, cerebrovascular diseases, peripheral vascular diseases, atrial fibrillation, aortic aneurysms, diabetes, hypertension, chronic pulmonary diseases, gastrointestinal bleeding or peptic ulcer diseases, liver diseases, chronic kidney diseases, dialysis, malignancy, rheumatoid arthritis, osteoarthritis, human immunodeficiency virus
			Increasing age	0.97 (0.97-0.97)		
			Heart failure	0.93 (0.90-0.97)		
			Chronic pulmonary diseases	0.90 (0.87-0.93)		
			Malignancy	0.95 (0.90-0.99)		

[111] Effect estimates reported as Risk Ratios (RR)

Study	Country/ Time period	CVD condition	Factors associated with initiation	Effect size (Odds Ratio, 95% CI)	Factors not associated with initiation	Covariates included in model
			Dementia	0.86 (0.80-0.93)	during the index hospitalisation	infection, dementia, depression, other mental diseases, obesity, and alcohol abuse); length of stay; and procedures, including angiography (including percutaneous coronary interventions) and revascularization surgery or the infusion of thrombolytic agents during the index hospitalization
			Cerebrovascular diseases	1.07 (1.03-1.11)		
			Liver diseases	0.48 (0.24-0.96)		
			Hypertension	1.16 (1.11-1.22)		
			Length of MI hospitalisation	0.99 (0.98-0.99)		
			Dialysis	0.81 (0.69-0.94)		
			Atrial fibrillation	0.85 (0.82-0.89)		
			Alcohol abuse	0.82 (0.75-0.91)		
			Other mental disorders	0.87 (0.81-0.94)		
			Angiography during index hospitalisation	1.53 (1.46-1.60)		
			Black/African American patients (vs. White and others)	0.86 (0.80-0.93)		

Table A.12 Study characteristics and determinants of statin adherence investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with good adherence**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with adherence**	**Covariates included in model**
Booth et al. (2017)[112] **Adherence after re-initiation discontinuation gap of 90 days*	USA (2007-2012)	MI	Statin intensity at re-initiation (reference: low)	Moderate: 0.95 (0.90-1.01) High: 0.80 (0.75-0.86)	Na	Demographics (ie, age, race/ethnicity, sex, low income subsidy, area-level median income, geographic region), characteristics prior to the myocardial infarction hospitalization (ie, cardiologist care, diabetes mellitus, stroke, chronic kidney disease, heart failure, coronary heart disease, status of statin use, and non-statin lipid-lowering medication use), and characteristics during the MI hospitalization (length of hospitalization, coronary stent insertion, newly diagnosed heart failure, diabetes mellitus, and chronic kidney disease) and statin intolerance within 182 days after statin re-initiation
			Change in statin intensity at re-initiation (reference: none)	Up-titration: 0.97 (0.90-1.05) Down-titration 1.10 (1.05-1.16)		
			Statin type at re-initiation (reference: same)	Different: 1.10 (1.06-1.14)		
Colantonio et al. (2017)[113]	USA (2007-2012)	MI	Women	0.91 (0.88-0.94)	Age group (66-70 vs. 71-75); history of: CKD, heart failure, cancer, depression, stent during MI hospitalisation	Covariates explored in analysis
			Race/ethnicity (reference: white)	Black: 0.75 (0.70-0.80) Hispanic: 0.68 (0.59-0.78) Asian: 0.98 (0.88-1.09) Other: 0.87 (0.79-0.96)		

[112] Effect size in Relative Risks (RR)

[113] Effect size in Prevalence Ratio (PR); adherence at two years post-MI discharge

Study	Country/ Time period	CVD condition	Factors associated with good adherence	Effect size (Odds Ratio, 95% CI)	Factors not associated with adherence	Covariates included in model
			Rural residence	1.03 (1.00-1.06)		
			Year of MI (reference: 2007)	2008: 1.07 (1.01-1.14) 2009: 1.11 (1.04-1.18) 2010: 1.18 (1.11-1.25) 2011: 1.24 (1.17-1.32) 2012: 1.46 (1.39-1.54)		
			Charlson Comorbidity Index (reference: 0)	1-3: 0.92 (0.88-0.97) ≥4 0.87 (0.82-0.91)		
			Dual Medicare/Medicaid coverage	1.09 (1.06-1.13)		
			Cardiologist care	0.95 (0.92-0.99)		
			History of diabetes	0.95 (0.92-0.98)		
			History of stroke	0.92 (0.87-0.97)		
			History of CHD	0.93 (0.89-0.97)		

Study	Country/ Time period	CVD condition	Factors associated with good adherence	Effect size (Odds Ratio, 95% CI)	Factors not associated with adherence	Covariates included in model
			New high-intensity users	0.65 (0.63-0.67)		
			Any hospitalisation	0.93 (0.90-0.97)		
			Polypharmacy	0.92 (0.89-0.96)		
			Post-MI Cardiac rehabilitation	1.10 (1.06-1.15)		
			Outpatient visits (per 5 visits)	1.02 (1.01-1.03)		
			Outpatient cardiologist visits (reference: 0)	1: 1.11 (1.06-1.17) 2: 1.15 (1.09-1.20) ≥3: 1.12 (1.07-1.18)		
			Had a medical coverage gap	1.21 (1.18-1.23)		
			Recurrent MI	0.88 (0.81-0.95)		
Fang et al. (2014)[114]	USA (2007-2009)	MI	Hospital referral regions (HRRs)	Crude ICC mean: 0.041 (0.031,0.052)	Na	Patient socio-demographic and clinical characteristics, the adjusted proportion of patients adherent across HRRs.

[114] Effect size measured as intracluster (intraclass) correlation coefficient (ICC)

Study	**Country/ Time period**	**CVD condition**	**Factors associated with good adherence**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with adherence**	**Covariates included in model**
				Adjusted c-statistic: 0.614		
Lauffenburger et al. (2014)	USA (2007-2009)	MI	Race/ethnicity and gender (reference: white men)	White women: 1.05 (1.01-1.09) Black men: 0.73 (0.67-0.79) Black women: 0.72 (0.66-0.89) Hispanic men: 0.77 (0.66-0.89) Hispanic women: 0.71 (0.61-0.83) Other women: 0.74 (0.58-0.95)	Other race/ethnicity and gender groups: Asian men, Asian women, Other men	Age, average household income at ZIP code of residence, geographic region, clinical characteristics (12 months prior to index admission): AMI, CABG, stent/PTCA, stroke/TIA, UA, CHF, AF, hypertension, PVD, diabetes, hyperlipidaemia, CKD, ESRD, COPD, Asthma, liver disease, osteoporosis, Charlson Comorbidity Index, angioedema, hyperkalemia, hypotension, sinus bradycardia, heart block, and rhabdomyolysis/other myopathy prescriptions of β-blockers, ACEIs/ ARBs, and statins in the 6 months prior to the index AMI, AMI type (subendocardial or transmural infarction), procedures (CABG, stent/PTCA, cardiac catheterization, infusion of thrombolytic, infusion of platelet inhibitors) and complications (heart failure, cardiogenic shock, acute renal failure, hypotension, cardiac dysrhythmias) during the index AMI hospitalization, and total intensive care unit (ICU) and inpatient stays for the index AMI

Table A.13 Study characteristics and determinants of persistence/discontinuation with statin therapy investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with discontinuation**	**Effect size** (Hazard ratio, 95% CI)	**Factors not associated with discontinuation**	**Covariates included in model**
Booth et al. (2017)[115]	USA (2007-2012)	MI	Statin intensity (reference: low)	Moderate: 0.93 (0.89-0.96) High: 0.95 (0.91-0.99)		Demographics (i.e., age, race/ethnicity, sex, low-income subsidy, area-level median income, geographic region), characteristics prior to the myocardial infarction hospitalization (i.e., cardiologist care, diabetes mellitus, stroke, chronic kidney disease, heart failure, coronary heart disease, status of statin use, and non-statin lipid-lowering medication use), and characteristics during the MI hospitalization (length of hospitalization, coronary stent insertion, newly diagnosed heart failure, diabetes mellitus, and chronic kidney disease) and statin intolerance within 182 days after the myocardial infarction hospital discharge
Gislason et al. (2006) [116]	Denmark (1995-2002)	MI	Gender (reference: women)	Men: 1.14 (1.07-1.22)	Concomitant use of loop diuretics and Antidiabetics	Covariates explored in analysis
			Age (reference: 30-59 years)	60-69 years: 0.88 (0.82-0.94) 70-79 years: 0.99 (0.90-1.08) ≥80 years: 1.40 (1.16-1.68)		
			Concomitant treatment	Beta-blocker: 0.90 (0.83-0.96)		

[115] Effect size in Relative Risks (RR)
[116] Effect size in Relative Risks (RR)

Study	Country/ Time period	CVD condition	Factors associated with discontinuation	Effect size (Hazard ratio, 95% CI)	Factors not associated with discontinuation	Covariates included in model
				ACE-inhibitor: 0.87 (0.81-0.94)		
			Calendar year (reference 1995-1996)	1997-1998: 1.07 (0.97-1.19) 1999-2000: 1.36 (1.23-1.51) 2001-2002: 1.04 (0.92-1.17)		
Glader et al. (2010)[117]	Sweden (2005-2008)	Stroke	***Association between factors and persistence*** Gender (reference: women)	Men: 0.91 (0.82–1.01), p=0.07	Age, diabetes, atrial fibrillation, low mood and follow-up at hospital outpatient clinic at three months' follow-up	Covariates explored in analysis
			Recurrent stroke (reference: No)	Yes: 0.77 (0.68-0.88) Missing: 0.62 (0.33-1.18)		
			Stroke unit care (reference: No)	1.25 (1.06-1.46)		
			Treatment before stroke onset (reference: No)	1.28 (1.15-1.42)		
			At 3-months' follow-up: living	Institutional living: 1.64 (1.32-2.04)		

[117] Effect sizes in Odds Ratios (ORs); examined relationshipw between persistence and statin use instead of discontinuation.

Study	**Country/ Time period**	**CVD condition**	**Factors associated with discontinuation**	**Effect size** (Hazard ratio, 95% CI)	**Factors not associated with discontinuation**	**Covariates included in model**
			situation (reference: living at home)	Missing: 0.96 (0.69-.1.32)		
			Self-perceived general health (reference: Good)	Poor: 0.69 (0.59-0.80) Missing: 0.70 (0.55-0.90)		
Hudson et al. (2007)[118]	Canada (QC) (1999-2004)	MI	Age (reference: 65-69)	Men <45: 2.01 (1.79-2.26) 45-49: 1.71 (1.48-1.98) 50-54: 1.78 (1.56-2.03) 55-59: 1.53 (1.00-1.32) 60-64: 1.11 (0.97-1.27) 70-74: 1.02 (0.90-1.15) 75-79: 1.05 (0.92-1.20) 80-84: 1.21 (1.02-1.43) ≥85: 1.42 (1.12-1.80) Women	Congestive heart failure, cerebrovascular disease, diabetes, renal disease, cardiac dysrhythmias, COPD, hypertension, malignancy (women), dementia (women), Cardiologist (compared to family physicians) (women), Internist,	Covariates explored in analysis

[118] Effect sizes in Hazard Ratios (HR)

Study	**Country/ Time period**	**CVD condition**	**Factors associated with discontinuation**	**Effect size** (Hazard ratio, 95% CI)	**Factors not associated with discontinuation**	**Covariates included in model**
				<45: 1.70 (1.27-2.28) 45-49: 1.19 (0.87-1.62) 50-54: 0.95 (0.73-1.24) 55-59: 1.05 (0.83-1.31) 60-64: 1.00 (0.82-1.23) 70-74: 0.92 (0.77-1.09) 75-79: 0.99 (0.83-1.17) 80-84: 1.10 (0.91-1.33) ≥85: 1.52 (1.22-1.91)	Number of other cardiac drugs between discharge and first prescription of the study drug, Length of stay > 8 days (women), Fiscal years (women), Number of physician visits in the year prior to the index AMI (women),	
			Length of stay > 8 days	Men 0.83 (0.77-0.89)		
			Malignancy	Men 1.39 (1.11-1.74)		
			Dementia	Men 1.73 (1.16-2.58)		

Study	Country/ Time period	CVD condition	Factors associated with discontinuation	Effect size (Hazard ratio, 95% CI)	Factors not associated with discontinuation	Covariates included in model
			Cardiologist (compared to family physicians)	Men 1.09 (1.02-1.18)		
			Fiscal years (reference: 1999)	Men 2002: 0.84 (0.75-0.94) 2003: 0.74 (0.65-0.84)		
			In-hospital revascularisation procedures	Men 0.92 (0.85-0.99) Women 0.86 (0.78-0.96)		
			Number of physician visits in the year prior to the index AMI (reference: zero)	Men 1-6: 0.91 (0.82-1.01) 7-11: 0.88 (0.77-0.99) >11: 0.99 (0.87-1.13)		
			Number of hospitalisations in the year prior to the index AMI	Men 1.07 (1.02-1.12) Women 1.06 (1.01-1.12)		

Study	**Country/ Time period**	**CVD condition**	**Factors associated with discontinuation**	**Effect size** (Hazard ratio, 95% CI)	**Factors not associated with discontinuation**	**Covariates included in model**
Lindhardsen et al. (2012)[119]	Denmark (2002-2009)	MI	Rheumatoid arthritis (reference: no RA)	1.26 (1.07-1.48)	Na	Sex, age, SES, comorbidity

[119] Effect sizes in Odds Ratios (ORs)

A.10 Characteristics of studies included in the systematic review of antiplatelet therapy use

The following **Tables A.14-A.17** provide an overview of the characteristics and findings of studies reporting rates of antiplatelet therapy use at different stages of the treatment pathway.

Table A.14 Characteristics of studies included in the systematic review of antiplatelet therapy prescriptions on hospital discharge

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Prescriptions on discharge (%)	Rate adjustment	Determinants	QA Score
Basra et al. (2018)	USA/ ACTION Registry-Get With The Guidelines (GWTG)	2013-2014	MI	167,455	Proportion of individuals (%) who received antiplatelet therapy on hospital discharge	Clopidogrel 51.1 Ticagrelor 16.7 Prasugrel 13.9 No P2Y12 18.2	Crude rates	No	8
Becker et al. (2000)	USA/National Registry of Myocardial Infarction (NRMI), not representative of all US hospitals	1994-1996	MI	220,171	Proportion of individuals (%) who received antiplatelet therapy on hospital discharge	Aspirin 69	Crude rates displayed by time period, age group and gender	No	7
Hawkins et al. (2013)	England & Wales/ MINAP & GPRD	1999-2007	MI	MINAP data: 51,755	Medication receipt during hospitalisat-on or at discharge	Aspirin 2003: 94 2007: 97	Crude rates reported by, age group, gender and SES	No	6
Lawesson et al. (2011)	Sweden / national quality register SWEDE-Heart	1998-2006	MI	30,077	Proportion of individuals (%) who	Aspirin 1998-2000: 76 2004-2006: 86	Crude rates reported by time period and gender	Yes	9

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Prescriptions on discharge (%)	Rate adjustment	Determinants	QA Score
					received antiplatelet therapy on hospital discharge	Other platelet inhibitors 1998-2000: 7 2004-2006: 70			
O'Brien et al. (2012)	USA / ARIC: retrospective surveillance study of hospitalized CHD, in four communities	1987-2008	MI	30,986	Medication receipt during hospitalisat-on or at discharge	Aspirin Overall: 82 2002-2008: 89 Other antiplatelet therapies Overall: 28 2002-2008: 63	Crude rates reported by time period, gender and STEMI vs. NSTEMI	No	8
Radovanovic et al. (2012)	Switzerland / AMIS (Acute Myocardial Infarction in Switzerland) Plus project	1997-2011	MI	21,620	Proportion of individuals (%) who received antiplatelet therapy on hospital discharge	Aspirin 2011 (men): 98 2011 (women): 97	Crude rates displayed by time period and gender	Yes	9
Redfors et al. (2015)	Sweden / one county, national quality register SWEDE-Heart	1995-2014	MI	48,118		Aspirin Overall: 81 Other antiplatelet therapies Overall: 43	Cruder rates reported by gender	Yes	9
Rezaei et al. (2017)	Austria/13 Austrian health insurance funds covering 98%	2009-2014	MI	32,830	Proportion of individuals (%) who	DATP 45	Cruder rates	No	8

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Prescriptions on discharge (%)	Rate adjustment	Determinants	QA Score
	of the Austrian population				received antiplatelet therapy on hospital discharge	Of those who were prescribed treatment: Clopidogrel 56.8 Prasugrel 20.4 Ticagrelor 22.9%			
Sahlen et al. (2016)	Sweden/ SWEDE-HEART national registry	2012-2013	MI	28,639	Proportion of individuals (%) who received antiplatelet therapy on hospital discharge	Aspirin 92 Other ATP 86 DATP breakdown: Clopidogrel 39.5 Prasugrel 1.9 Ticagrelor 44	Crude rates	No	8
Simpson et al. (2002)	Canada/QC, administrative hospital discharge summary database for the province of	1996-1998	MI	14,057		Aspirin 65	Crude rates	No	6

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Prescriptions on discharge (%)	Rate adjustment	Determinants	QA Score
	Quebec (Med-Echo)								

Table A.15 Characteristics of studies included in the systematic review of antiplatelet therapy initiation since hospital discharge

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Antiplatelet therapy initiators (%)	Rate adjustment	Determinants	QA score
Green et al. (2013)	Denmark / Danish nationwide compulsory registries	2009-2012	MI	28,449	Prescription fill 180 days prior to index admission or within 30 days since index discharge	DATP *Overall* 2009: 68 2012: 73 *Patients with PCI* 2009: 87 2012: 91 *Patients without PCI* 2009: 49 2012: 52	Crude rates	No	7
Hoer et al. (2013)	Germany / one big statutory health insurance (SHI) fund covering 7M beneficiaries	2007-2009	MI	45,188	Prescription fill within 100 days since discharge	STEMI Aspirin: 49 Clopidogrel: 65 No initiation: 21 NSTEM Aspirin: 32 Clopidogrel: 39 No initiation: 40	Crude rates reported by STEMI vs. NSTEMI	No	8
Hudson et al. (2007)	Canada (QC)/ Quebec provincial discharge	1999-2004	MI	34,735	Rate of prescriptions within 30 days after discharge	Any ATP 1999-2004: 83	Crude rates, reported by gender	No	8

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Antiplatelet therapy initiators (%)	Rate adjustment	Determinants	QA score
	summary database								
Mangiapane et al. (2011)	Germany/one statutory health insurance fund, i.e., Techniker Krankenkasse	2001-2006	MI	30,028	Drug prescription within 90 days since discharge	Aspirin 66 Clopidogrel 61	Crude rates	No	6
Sorenson et al. (2012)	Denmark/ National Patient Register	2002-2005	MI	46,190	Drug prescription within 30 days since discharge	MI with PCI 2000: Clopidogrel 80.4 2005: 93.7 MI without PCI 2000: Clopidogrel 2.8 2005: 39.3	Crude rates	Yes	8
Tuppin et al. (2010)	France / SNIIRAM based on general health insurance	2006	MI	14,007	Filled a prescription within 180 days since discharge	Aspirin 84 Clopidogrel 80	Crude rates for overall population; rates adjusted for age and	No	7

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Time interval	Antiplatelet therapy initiators (%)	Rate adjustment	Determinants	QA score
	scheme covering 70% of population						gender and reported by diabetes status reported		
Zhu et al. (2011)	USA/Market-Scan commercial claims database	2005-2006	MI + PCI	10,465	At least one record of drug use within 12 months since index discharge	Clopidogrel 92.8	Crude rates	Yes	7

Table A.16 Characteristics of studies included in the systematic review of antiplatelet therapy adherence

Study	Country/ Data Source	Time period	CVD Condition	N	Adherence measure	Adherence definition	Follow-up in months	Adherent (%)	Determinants	QA score
Simpson et al. (2002)	Canada/QC, administrative hospital discharge summary database for the province of Quebec (Med-Echo)	1996-1998	MI	14,057	PDC since initiation	≥ 80%	12	Aspirin 71	No	6
Zhu et al. (2011)	USA/Market-Scan commercial claims database	2005-2006	MI + PCI	10,057	MPR since discharge	≥ 80%	12	Clopidogrel 66.8	Yes	7

Table A.17 Characteristics of studies included in the systematic review of antiplatelet therapy persistence

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/Definition	Follow-up in months	Discontinuation (%)	Determinants	QA score
Glader et al. (2010)	Sweden/ National RIKS-Stroke registry	2005-2008	Stroke	14,904	Persistence: Drug purchase at least once during each 4-month interval after hospital discharge.	Up to 2 years	ATP 79.3% (i.e. 20.7% discontinued) at 12 months; 63.7% (i.e. 36.3% discontinued) at 24 months.	Yes	5
Hudson et al. (2007)	Canada (QC)/ Quebec provincial discharge summary database	1999-2004	MI	34,735	Discontinuation: Failure to renew a medication for more than 60 days after continuous exposure since the initial prescription.	Up to 6 years, but rates reported for year 2 & 5	Antiplatelet agents: 2 years: 22% of women and 25% of men 5 years: 36% of women and 39% of men	No	8
Sorenson et al. (2012)	Denmark/ National Patient Register	2002-2005	MI	46,190	Discontinuation: Treatment gap of >30 days	9	MI + PCI: Clopidogrel 26.3 No PCI: Clopidogrel 26.9	Yes	8

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/Definition	Follow-up in months	Discontinuation (%)	Determinants	QA score
Zhu et al. (2011)	USA/Market-Scan commercial claims database	2005-2006	MI + PCI	10,465	Discontinuation: Average time in days to discontinuation; treatment gap of >30 days	12	Clopidogrel 240.8 days (SE 126.7 days)	No	7

Table A.18 Characteristics of studies included in the systematic review of antiplatelet therapy utilisation

Study	Country/ Data Source	Time period	CVD Condition	N	Measure/ Definition	Utilisation rate (%)	Rate adjustment	Determinants	QA Score
Bohn et al. (2016)	Germany & Austria / Diabetes population based on national registries	2006-2015	MI and stroke	29,325	Registry record of antiplatelet prescription	Antiplatelet therapy MI patients with diabetes: 52 Stroke patients with diabetes: 34	Crude rates reported by gender and CVD type	No	6
Wettermark et al. (2008)	Sweden / two counties only; national patient registry	2005-2006	Stroke	12,362	At least one dispense record of aspirin and/or clopidogrel in the year 2005-2006 among individuals previously discharged for stroke	Aspirin: 59 Clopidogrel: 7	Crude rates for overall use; rates also reported by gender, age group and year of discharge	No	7

A.11 Determinants of antiplatelet therapy use reported in the included studies

The following **Tables A.19-A.22** provide an overview of the characteristics and findings of studies reporting determinants of antiplatelet therapy use at different stages of the treatment pathway.

Table A.19 Study characteristics and determinants of antiplatelet therapy prescriptions on discharge investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with prescribing**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with prescribing**	**Covariates included in model**
Lawesson et al. (2011)	Sweden (1998-2006)	MI	Gender (female)	Aspirin 1998-2000: 0.96 (0.85-1.08) 2004-2006: 0.85 (0.74-1.0) Other antiplatelet therapies 1998-2000: 1.01 (0.86-1.18) 2004-2006: 0.83 (0.78-0.95)	N/a	Age, smoking, previous MI, percutaneous coronary intervention, coronary artery bypass grafting, stroke, hypertension, diabetes mellitus, COPD, heart failure, chronic kidney disease, PAD, dementia, cancer within 3 years, therapies on arrival, interventional hospital and year of inclusion
Radovanovic et al. (2012)	Switzerland (1997-2011)	MI	Gender (female)	Aspirin 0.84 (0.68-1.03)	N/a	Age, Killip classes>2, risk factors (smoking, dyslipidemia, hypertension, diabetes) and comorbidities (Charlson weighted index ≥2) and admission year

Table A.20 Study characteristics and determinants of antiplatelet therapy initiation investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with initiation**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with initiation**	**Covariates included in model**
Sorenson et al. (2012)	Denmark (2002-2005)	MI without PCI	Gender (women)	Clopidogrel 0.86 (0.78, 0.95)	Age; diabetes with complication; chronic renal failure; malignancy; shock, pulmonary oedema; ACE inhibitor use; antidiabetic treatment use; type of hospital.	All covariates included in model.
			Cerebral vascular disease	Clopidogrel 0.81 (0.67-0.98)		
			Cardiac dysrhythmia	Clopidogrel 0.82 (0.71-0.96)		
			Acute renal failure	Clopidogrel 0.50 (0.30-0.82)		
			Beta blocker use	Clopidogrel 1.90 (1.69-2.13)		
			Statin use	Clopidogrel 2.51 (2.24-2.83)		
			Loop diuretics	Clopidogrel 0.89 (0.80-1.00)		
			Vitamin-K antagonists	Clopidogrel 0.48 (0.39, 0.57)		
			Acetylsalicylic acid	Clopidogrel 1.86 (1.60, 2.16)		
		MI + PCI	Cerebral vascular disease	Clopidogrel 0.48 (0.36-0.63)	Gender; age; diabetes with complication; chronic renal failure; malignancy;	All covariates included in model.
			Cardiac dysrhythmia	Clopidogrel 0.70 (0.58-0.85)		
			Acute renal failure	Clopidogrel 0.51 (0.26-1.00)		

			Shock	Clopidogrel 0.50 (0.31-0.81)	pulmonary oedema; antidiabetic treatments; type of hospital.	
			Beta-blocker use	Clopidogrel 2.14 (1.85-2.48)		
			ACE-inhibitor use	1.16 (1.02-1.31)		
			Statin	Clopidogrel 1.20 (1.72-2.32)		
			Loop diuretic use	Clopidogrel 0.49 (0.43-0.56)		
			Vitamin-K antagonists	Clopidogrel 0.52 (0.42-0.64)		
			Acetylsalicylic acid	Clopidogrel 1.68 (1.44-1.96)		
Zhu et al. (2012)	USA (2005-2006)	MI + PCI	No Stent during PCI	Clopidogrel 3.28	Prior all-cause hospitalizatio n; renal disease; gender; COPD; prior depression; UA/NSTEMI	All covariates included in the model.
			Atrial Fibrillation	Clopidogrel 1.91		
			Hypertension	Clopidogrel 1.50		
			Diabetes	Clopidogrel 1.49		
			Age < 55 (vs. 55 years or older)	Clopidogrel 0.83		
			Prior clopidogrel use	Clopidogrel 0.54		
			Prior BSI use	Clopidogrel 0.44		

Table A.21 Study characteristics and determinants of antiplatelet adherence investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with non-adherence**	**Effect size** (Odds Ratio, 95% CI)	**Factors not associated with non-adherence**	**Covariates included in model**
Zhu et al. (2012)	USA (2005-2006)	MI + PCI	Prior clopidogrel use	Clopidogrel 1.40	Prior depression; renal disease; gender; hypertension; UA/NSTEMI; atrial fibrillation	All covariates included in the model.
			Prior all-cause hospitalisation	Clopidogrel 1.34		
			No stent during PCI	Clopidogrel 1.32		
			COPD	Clopidogrel 1.31		
			Age < 55 (vs. 55 years or older)	Clopidogrel 1.29		
			Diabetes	Clopidogrel 1.17		
			Prior BSI use	Clopidogrel 0.82		

Table A.22 Study characteristics and determinants of persistence with antiplatelet therapy investigated in the included studies

Study	**Country/ Time period**	**CVD condition**	**Factors associated with discontinuation**	**Effect size** (Hazard ratio, 95% CI, unless otherwise noted)	**Factors not associated with discontinuation**	**Covariates included in model**
Glader et al. (2010)	Sweden (2005-2008)	Stroke	***Association between factors and persistence*** (**Odds ratio, 95% CI**) Gender (reference: women)	Men: 0.92 (0.85-0.99)	Recurrent stroke, stroke unit care, treatment before stroke onset, diabetes, support by next of kin, and follow-up at hospital outpatient clinic at three months' follow-up	Covariates explored in analysis
			Age (reference: <65)	65-74 years: 1.08 (0.97-1.21) 75-84: 1.18 (1.06-1.31) >85: 1.37 (1.20-1.57)		
			Atrial fibrillation (reference: no)	Yes: 0.78 (0.70–0.87) Missing: 1.34 (0.82–2.16)		
			Treatment before stroke onset (reference: No)	1.28 (1.15-1.42)		
			At 3-months' follow-up: living situation (reference: living at home)	Institutional living: 1.78 (1.55–2.05) Missing: 0.81 (0.67–0.99)		

Study	**Country/ Time period**	**CVD condition**	**Factors associated with discontinuation**	**Effect size** (Hazard ratio, 95% CI, unless otherwise noted)	**Factors not associated with discontinuation**	**Covariates included in model**
			Low mood (reference: No)	Yes: 0.92 (0.83–1.02) Missing: 1.16 (0.98–1.39)		
			Self-perceived general health (reference: Good)	Poor: 0.79 (0.70–0.89) Missing: 0.77 (0.64–0.91)		
Sorenson et al. (2012)	Denmark (2002-2006)	MI (with and without PCI)	Gender (men)	Clopidogrel 0.88 (0.78-0.98)	Age; cerebral vascular disease; diabetes with complication; acute and chronic renal failure; malignancy; shock, pulmonary oedema; PCI; beta blocker; ACE inhibitor use; statin; antidiabetic treatment use; loop diuretics; acetylsalicylic acid; type of hospital	All covariates included in model.
			Vitamin K antagonists use	Clopidogrel 1.24 (1.01-1.52)		

B

National Scottish Health Datasets and Statistical Methods

B.1 Overview of British National Formulary (BNF) codes

Table B.1 Overview of British National Formulary (BNF) codes used in the analyses

BNF code	Description
2	**Cardiovascular System**
2.9	**Antiplatelet drugs**
0209000A0	Aspirin
0209000C0	Clopidogrel
0209000L0	Dipyridamole
0209000V0	Dipyridamole & Aspirin
0209000Y0	Prasugrel
0209000Z0	Ticagrelor
2.12	**Lipid-regulating drugs**
0212000AI	Atorvastatin
0212000M0	Fluvastatin Sodium
0212000X0	Pravastatin Sodium
0212000AA	Rosuvastatin Calcium
0212000Y0	Simvastatin
0212000AC	Simvastatin & Ezetimibe

Reference: British National Formulary (BNF), The National Institute for Health and Care Excellence (NICE)

B.2 Exclusion of individuals hospitalised for more than 90 days

The total number of individuals with a hospital length of stay (LOS) > 90 days is 4,752 (i.e. 2.7% of the total ASCVD population (N=172,730)), of whom 78.9% were discharged with a diagnosis of ischaemic stroke.

Over the duration of these admissions, the patient's actual residence status is unclear (e.g. whether staying in hospital or only attending rehabilitation sessions in hospital). However, the medication prescription information available in the study includes only medicines prescribed and dispensed in the community and does not include medicines dispensed in hospital.

Using an alternative definition of 'initiation' in order to account for the unclear patient status, with initiation defined as a patient being prescribed a statin within 180 days since index admission date and then subsequently dispensed a statin within 60 days since prescription:

- Out of 4,752 individuals with LOS>90 days, 2,648 individuals (56%) were prescribed a statin by a GP within 180 days since index admission. And of these, 2,276 individuals (86%) were dispensed the statin within 60 days since prescription date. Therefore, the initiation rate in this population group would appear to be 48%.

However, this does not necessarily reflect the real initiation rate because:

- There may be individuals prescribed statin at the hospital.
- There may be individuals who were actually prescribed statins within 181 (or more) days since admission but would be excluded in the current definition.
- Furthermore, due to the absence of a discharge date, patients are treated differently. For example, a patient who is hospitalised for 179 days only has one day to fill the prescription to be categorised as an 'initiator,' whereas another patient who is hospitalised for 90 days would have an additional 90 days to fill the prescription.

When using the final discharge date reported in the data, which may be the date of discharge from rehabilitation, the statin initiation rate in this population is 64% (as presented in **Table B.2**). However, this is also a likely underestimate of the true initiation rate, as the majority of ASCVD patients with LOS < 90 days who discontinue treatment tend to do so after 1.5 years (as documented in **Chapter 5**) and a large proportion of individuals within this population with LOS > 90 days are hospitalised/receiving rehabilitation at hospital for a length of 2 to 5 years.

Therefore, it is difficult to estimate the final initiation rate for this specific population and neither approach presented above is optimal. Consequently, individuals with LOS > 90 days were excluded from the analyses. **Table B.2** provides a comparative overview of the baseline characteristics of (1) the total ASCVD population as defined in Chapter 4, (2) individuals with hospital LOS > 90 days, and (3) ischaemic stroke patients with a hospital LOS ≤ 90 days.

Table B.2 Baseline characteristics of individuals hospitalised for an ASCVD[120]-related event at index discharge, by hospital length of stay and CVD type

	ASCVD population LOS ≤90 days	ASCVD population LOS > 90 days only	Ischaemic stroke population LOS ≤90 days (subpopulation of the ASCVD population LOS ≤90 days)
N (%)	167,978	4,752	32,873
Age on discharge (mean, SD)	67.4 (12.7)	73.9 (12.7)	70.8 (13.4)
Sex (Female)	65,707 (39.1)	2,512 (52.9)	15,851 (48.2)
Ethnic group			
White	143,578 (85.4)	3,965 (83.4)	28,069 (85.3)
Other	2,373 (1.4)	34 (0.72)	294 (0.9)
Missing	22,027 (13.1)	753 (15.8)	4,510 (13.8)
SIMD[121] deprivation quintile (2009)			
1 (most deprived)	26,294 (15.7)	1,055 (22.3)	5,223 (15.9)
2	30,896 (18.4)	1,075 (22.7)	5,841 (17.8)
3	34,330 (20.4)	916 (19.3)	6,492 (19.8)
4	37,290 (22.2)	929 (19.3)	7,343 (22.3)
5 (least deprived)	39,168 (23.3)	764 (16.1)	7,974 (24.2)
Urban/Rural Classification[122]			
Large urban areas	54,126 (32.2)	1,687 (35.5)	11,115 (33.8)
Other urban areas	60,563 (36.0)	1,551 (32.6)	11,731 (35.7)
Accessible small towns	16,042 (9.6)	448 (9.4)	3,126 (9.5)
Remote small towns	6,772 (4.0)	224 (4.7)	1,282 (3.9)
Accessible rural	19,314 (11.5)	517 (11.0)	3,637 (11.1)
Remote rural	11,161 (6.7)	318 (6.7)	1,982 (6.1)

Number (%) reported unless otherwise specified.

[120] ASCVD = Atherosclerotic cardiovascular disease; CVD = cardiovascular disease

[121] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones.

[122] Scottish Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.

	ASCVD population LOS ≤90 days	ASCVD population LOS > 90 days only	Ischaemic stroke population LOS ≤90 days (subpopulation of the ASCVD population LOS ≤90 days)
Health Board			
Ayrshire & Arran	13,853 (8.2)	354 (7.4)	2,571 (7.8)
Borders	4,192 (2.5)	120 (2.5)	864 (2.64)
Dumfries & Galloway	5,425 (3.2)	145 (3.1)	1,037 (3.2)
Fife	11,358 (6.8)	422 (8.8)	2,407 (7.3)
Forth Valley	8,884 (5.3)	326 (6.8)	1,605 (5.0)
Grampian	16,589 (9.9)	590 (12.4)	2,640 (8.0)
Greater Glasgow and Clyde	36,676 (21.8)	839 (17.7)	7.523 (22.9)
Highland	11,830 (7.1)	304 (6.4)	2,013 (6.2)
Lanarkshire	22,332 (13.3)	375 (7.9)	4,517 (13.7)
Lothian	21,373 (12.7)	772 (16.2)	4,662 (14.2)
Tayside	13.275 (7.9)	426 (8.9)	2,697 (8.2)
Other (Orkney, Shetland, Eileanan Siar Western Isles)	2,191 (1.3)	79 (1.6)	337 (1.0)
ASCVD-related hospitalisation prior to 1 October 2009	67,114 (39.9)	1,802 (37.9)	10,751 (32.7)
Charlson Comorbidity Index (within 12 months prior and incl. index event)			
0 (no-comorbidities)[123]	30,748 (18.3)	16 (0.34)	Not applicable
1	77,177 (45.9)	1,985 (41.7)	18,541 (56.4)
2	33,709 (20.1)	1,169 (24.6)	7,624 (23.2)
3	14,937 (8.9)	832 (17.5)	3,862 (11.8)
4 or more comorbidities	11,407 (6.8)	750 (15.8)	2,846 (8.7)
Mental health inpatient/day case within 12 months prior to index admission	2,994 (1.8)	766 (2.5)	819 (2.5)

[123] Absence of comorbidities as defined by CCI: in the case of the ASCVD and PAD populations, this means that individuals were not hospitalised for any other of the 17 specified conditions. In the case of the MI and stroke populations, this means that individuals were not hospitalised for at least one out of 16 specified conditions in addition to their index hospitalisations, and that every individual has at least one comorbidity (i.e. MI or stroke).

	ASCVD population LOS ≤90 days	ASCVD population LOS > 90 days only	Ischaemic stroke population LOS ≤90 days (subpopulation of the ASCVD population LOS ≤90 days)
At least one statin prescription in last 12 months prior to index admission[124]	93,103 (55.4)	1,943 (40.9)	14,338 (43.6)
ASCVD event at index discharge			
Myocardial infarction	50,420 (30.0)	190 (4.0)	Na
Ischaemic Stroke	32,928 (19.6)	3,750 (78.9)	32,873 (100)
Peripheral arterial disease	15,156 (9.0)	368 (7.7)	Na
Other ASCVD	69,676 (41.4)	444 (9.4)	Na
Initiation of statin therapy post index admission (yes)	136,855 (81.5)	3,043 (64.0)	26,501 (80.6)

[124] For individuals with index hospitalisations in 2009, information on prior medication use is available from 1 April 2009 and onward, thereby contributing a minimum of 6 months and up to 12 months of medication history. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

C

Rates and determinants of statin use for the secondary prevention of cardiovascular disease

C.1 Statin therapy initiation rates by ASCVD type

Table C.1 Myocardial infarction: statin therapy initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
Statin initiation rates (%)	**87.2**	**88.6**	**88.8**
Men	89.4	91.0	91.1
Women	83.4	84.2	84.5
Individuals aged 18 – 49 years	91.5	93.4	93.3
Individuals aged 50 – 59 years	93.1	93.3	94.5
Individuals aged 60 – 69 years	91.2	93.4	92.9
Individuals aged 70 – 79 years	86.7	87.7	88.6
Individuals aged 80 – 89 years	76.5	76.3	78.1
Individuals aged 90 years or older	59.9	55.3	51.9
Proportion of all statin initiators being dispensed high-intensity statin[125] (%)	**37.0**	**45.9**	**72.6**
Men	39.0	48.3	76.6
Women	33.3	41.4	64.6
Individuals aged 18 – 49 years	46.6	54.8	84.5
Individuals aged 50 – 59 years	44.4	52.1	82.1
Individuals aged 60 – 69 years	40.6	48.0	78.5
Individuals aged 70 – 79 years	33.3	43.2	66.9
Individuals aged 80 – 89 years	23.3	32.4	50.9
Individuals aged 90 years or older	12.3	22.6	38.6

[125] In line with NICE's classification of statin intensity, statins are defined as 'high-intensity' if they reduce LDL-C levels by a minimum of 40%, and 'low/medium-intensity' if LDL-C level reduction is below 40%.

Table C.2 Ischaemic stroke: statin therapy initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
Statin initiation rates (%)	**79.0**	**80.2**	**82.5**
Men	81.8	83.2	85.7
Women	76.2	76.9	79.0
Individuals aged 18 – 49 years	75.1	78.7	77.8
Individuals aged 50 – 59 years	83.7	87.4	89.1
Individuals aged 60 – 69 years	86.2	86.2	89.5
Individuals aged 70 – 79 years	80.7	82.9	85.1
Individuals aged 80 – 89 years	74.6	73.0	78.0
Individuals aged 90 years or older	52.0	57.8	49.6
Proportion of all statin initiators being dispensed high-intensity statin[126] (%)	**24.9**	**33.3**	**50.9**
Men	25.8	33.8	53.6
Women	24.0	32.8	47.8
Individuals aged 18 – 49 years	27.4	33.1	54.0
Individuals aged 50 – 59 years	31.7	37.8	58.0
Individuals aged 60 – 69 years	29.4	37.4	56.3
Individuals aged 70 – 79 years	26.1	34.4	51.3
Individuals aged 80 – 89 years	17.2	28.7	43.6
Individuals aged 90 years or older	8.6	16.8	33.4

[126] In line with NICE's classification of statin intensity, statins are defined as 'high-intensity' if they reduce LDL-C levels by a minimum of 40%, and 'low/medium-intensity' if LDL-C level reduction is below 40%.

Table C.3 Peripheral arterial disease: statin therapy initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
Statin initiation rates (%)	**70.4**	**71.4**	**66.9**
Men	71.7	73.3	69.2
Women	67.8	67.9	62.6
Individuals aged 18 – 49 years	54.1	51.3	38.8
Individuals aged 50 – 59 years	69.8	72.2	66.3
Individuals aged 60 – 69 years	73.8	78.3	72.2
Individuals aged 70 – 79 years	74.2	74.0	72.1
Individuals aged 80 – 89 years	65.8	65.0	61.8
Individuals aged 90 years or older	45.5	39.6	43.4
Proportion of all statin initiators being dispensed high-intensity statin[127] (%)	**29.5**	**34.4**	**40.0**
Men	29.3	34.6	39.7
Women	30.1	33.9	40.5
Individuals aged 18 – 49 years	32.2	33.3	38.8
Individuals aged 50 – 59 years	35.1	38.7	42.7
Individuals aged 60 – 69 years	33.0	38.7	42.4
Individuals aged 70 – 79 years	28.7	33.4	40.9
Individuals aged 80 – 89 years	18.2	25.8	34.2
Individuals aged 90 years or older	22.6	15.5	15.5

[127] In line with NICE's classification of statin intensity, statins are defined as 'high-intensity' if they reduce LDL-C levels by a minimum of 40%, and 'low/medium-intensity' if LDL-C level reduction is below 40%.

Table C.4 Other atherosclerotic cardiovascular disease: statin therapy initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
Statin initiation rates (%)	**77.8**	**78.6**	**78.8**
Men	81.0	82.6	82.5
Women	72.8	72.2	72.2
Individuals aged 18 – 49 years	67.7	69.1	67.2
Individuals aged 50 – 59 years	81.1	80.4	81.5
Individuals aged 60 – 69 years	83.3	83.6	83.8
Individuals aged 70 – 79 years	80.0	80.6	80.5
Individuals aged 80 – 89 years	65.6	69.3	69.8
Individuals aged 90 years or older	40.3	45.0	41.8
Proportion of all statin initiators being dispensed high-intensity statin[128] (%)	**35.3**	**38.6**	**51.1**
Men	35.8	39.3	52.8
Women	34.4	37.4	48.0
Individuals aged 18 – 49 years	43.0	41.0	61.9
Individuals aged 50 – 59 years	41.8	44.2	57.5
Individuals aged 60 – 69 years	37.5	41.0	53.9
Individuals aged 70 – 79 years	31.6	35.8	48.0
Individuals aged 80 – 89 years	24.4	30.3	37.4
Individuals aged 90 years or older	13.9	22.3	25.7

[128] In line with NICE's classification of statin intensity, statins are defined as 'high-intensity' if they reduce LDL-C levels by a minimum of 40%, and 'low/medium-intensity' if LDL-C level reduction is below 40%.

C.2 Determinants of statin therapy initiation by CVD type

Table C.5 Associations of patient characteristics with statin therapy initiation among individuals with ASCVD, by CVD type (multivariable logistic regression models)

	Myocardial infarction		**Ischaemic stroke**		**Peripheral arterial disease**		**Other ASCVD**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Female (vs. male)	0.77***	0.73-0.82	0.79***	0.75-0.84	0.91	0.84-1.00	0.67***	0.64-0.70
Age (vs. 60-69 years old)								
<50	0.98	0.87-1.10	0.55***	0.49-0.62	0.60***	0.51-0.71	0.63***	0.59-0.69
50-59 years	1.18**	1.06-1.32	0.99	0.88-1.12	0.89	0.78-1.02	0.96	0.90-1.02
70-79 years	0.66***	0.60-0.72	0.71***	0.65-0.78	1.00	0.90-1.11	0.82***	0.77-0.87
80-80 years	0.34***	0.31-0.37	0.47***	0.43-0.52	0.78***	0.68-0.88	0.51***	0.48-0.54
≥ 90 years	0.13***	0.11-0.15	0.20***	0.17-0.23	0.50***	0.37-0.66	0.23***	0.20-0.27
Deprivation quintile (vs. 5, least deprived)								
4	1.08	0.97-1.19	1.05	0.95-1.16	1.02	0.88-1.18	0.99	0.92-1.06
3	0.94	0.85-1.04	1.03	0.93-1.13	1.08	0.95-1.25	0.98	0.91-1.05
2	0.95	0.86-1.04	0.97	0.88-1.07	1.07	0.94-1.23	1.00	0.93-1.07
1	0.88*	0.80-0.97	0.94	0.86-1.03	0.94	0.82-1.08	0.94	0.88-1.00
Charlson Comorbidity Index (vs. no comorbidities)[1]								
1	N/a	N/a	N/a	N/a	N/a	N/a	0.99	0.94-1.04
2	0.71***	0.66-0.76	0.78***	0.73-0.84	0.93	0.83-1.04	0.96	0.90-1.03
3	0.56***	0.51-0.61	0.72***	0.66-0.79	0.91	0.79-1.05	0.70***	0.64-0.77
4 or more	0.40***	0.37-0.44	0.58***	0.53-0.64	0.67***	0.58-0.78	0.63***	0.57-0.70
Receiving specialist mental health care	0.40***	0.33-0.48	0.49***	0.40-0.54	0.75	0.54-1.05	0.53***	0.46-0.61

	Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
History of prior CVD or statin use (vs. no prior CVD, no prior statin)								
Prior CVD, no prior statin	0.34***	0.31-0.37	0.52***	0.48-0.57	0.55***	0.48-0.63	0.35***	0.32-0.37
No prior CVD, prior statin	1.53***	1.39-1.68	1.97***	1.81-2.14	7.98***	7.14-8.92	5.93***	5.59-6.28
Prior CVD, prior statin	1.24***	1.15-1.35	1.63***	1.51-1.77	7.84***	7.06-8.72	5.00***	4.74-5.27
Discharge year (vs. 2009-11)								
2012-14	1.10**	1.03-1.18	1.08*	1.00-1.15	1.08	0.98-1.19	1.06*	1.01-1.11
2015-17	1.11**	1.03-1.19	1.29***	1.20-1.39	0.96	0.86-1.06	1.14***	1.08-1.20

Note: (***): p<0.001; (**): p<0.01; (*): p<0.5; [1] In the case of myocardial infarction, stroke and peripheral arterial disease, the reference group is 'one comorbidity' as the Charlson Comorbidity Index classifies the presence of these conditions as a comorbidity.

C.3 Determinants of high-intensity statin therapy initiation by CVD type

Table C.6 Associations of patient characteristics with high-intensity statin therapy initiation (vs. moderate/low intensity therapy) among individuals with ASCVD, by CVD type (multivariable logistic regression models)

	Myocardial infarction		**Ischaemic stroke**		**Peripheral arterial disease**		**Other ASCVD**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Female (vs. male)	0.87***	0.83-0.91	1.00	0.94-1.05	1.16**	1.06-1.26	1.00	0.97-1.04
Age (vs. 60-69 years old)								
<50	1.32***	1.23-1.42	0.98	0.87-1.10	0.88	0.71-1.09	1.28***	1.19-1.38
50-59 years	1.17***	1.10-1.24	1.07	0.98-1.17	1.09	0.96-1.24	1.16***	1.11-1.22
70-79 years	0.73***	0.69-0.78	0.79***	0.73-0.85	0.86**	0.78-0.95	0.76***	0.73-0.80
80-80 years	0.43***	0.40-0.46	0.57***	0.53-0.62	0.54***	0.47-0.61	0.52***	0.49-0.56
≥ 90 years	0.24***	0.20-0.28	0.35***	0.29-0.42	0.42***	0.27-0.66	0.28***	0.22-0.36
Deprivation quintile (vs. 5, least deprived)								
4	1.09*	1.02-1.17	1.11*	1.01-1.22	1.01	0.87-1.17	0.95	0.90-1.01
3	1.13***	1.05-1.21	1.04	0.95-1.14	0.99	0.85-1.14	0.99	0.93-1.05
2	1.00	0.93-1.07	1.04	0.95-1.14	1.09	0.95-1.26	1.02	0.96-1.08
1	0.93*	0.87-0.99	1.00	0.92-1.09	1.03	0.90-1.19	0.98	0.93-1.04
Charlson Comorbidity Index (vs. no comorbidities)[1]								
1	N/A	N/A	N/A	N/A	N/A	N/A	1.33***	1.27-1.39
2	0.88***	0.84-0.92	1.15***	1.07-1.23	1.14*	1.02-1.27	1.50***	1.42-1.58
3	0.77***	0.71-0.82	1.09	1.00-1.19	1.18*	1.03-1.35	1.55***	1.43-1.68
4 or more	0.79***	0.73-0.86	1.14*	1.03-1.26	1.13	0.98-1.31	1.53***	1.39-1.68
Receiving specialist mental health care	0.76**	0.63-0.92	0.72**	0.58-0.88	0.72	0.48-1.09	0.92	0.79-1.07

	Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
History of prior CVD or statin use (vs. no prior CVD, no prior statin)								
Prior CVD, no prior statin	0.89**	0.82-0.97	1.08	0.96-1.20	1.11	0.84-1.29	1.02	0.91-1.14
No prior CVD, prior statin	1.44***	1.36-1.52	2.16***	2.02-2.32	1.60***	1.36-1.87	1.15***	1.09-1.22
Prior CVD, prior statin	1.83***	1.73-1.94	2.71***	2.52-2.92	2.76***	2.36-3.23	2.02***	1.91-2.13
Discharge year (vs. 2009-11)								
2012-14	1.44***	1.38-1.51	1.54***	1.44-1.66	1.25***	1.13-1.37	1.17***	1.12-1.22
2015-17	6.35***	6.01-6.71	4.11***	3.83-4.41	1.86***	1.67-2.07	2.38**	2.27-2.49

Note: (***): p<0.001; (**): p<0.01; (*): p<0.5; [1] In the case of myocardial infarction, stroke and peripheral arterial disease, the reference group is 'one comorbidity' as the Charlson Comorbidity Index classifies the presence of these conditions as a comorbidity.

C.4 Subgroup analyses of determinants of statin initiation

Statin initiation among individuals with and without a prior history of ASCVD

Between 1 October 2009 and 3 July 2017, of the 100,864 (60%) patients hospitalised for their first ever ASCVD event, 83.2% initiated statin treatment. This compares with an initiation rate of 78.7% ($p<0.001$) in the 67,160 patients who had had ASCVD-related hospitalisations prior to April 2009 and their index hospitalisation in the time period from April 2009 to July 2017 (**Table C.7**).

The results of each subgroup analysis (**Figure C.1** and **Figure C.2**) are consistent across both subgroups, as well as with the findings from the original ASCVD population that includes both individuals with and without history of prior ASCVD (**Chapter 5, Figure 5.1**), meaning that the same patient characteristics are associated with statin initiation as previously discussed in **Chapter 5, Section 5.5.2**. For example, women without a history of ASCVD had 34% lower odds of initiating statin (OR 0.66 [0.64-0.69]), while women with previous ASCVD hospitalisations had 20% lower odds of initiating statin compared to men (OR 0.80 [0.77-0.84]). Patients without ASCVD history and aged 80 to 89 years or 90 years and older were significantly less likely to initiate treatment compared to individuals aged 60-69 years, with similar findings reported in patients with prior ASCVD (e.g., individuals aged 80-89 years: OR 0.45 [0.42-0.47] without prior ASCVD, vs. OR 0.56 [0.53-0.60] in individuals with prior ASCVD). Similarly, patients without previous ASCVD events and with a history of mental health hospitalisations had 59% lower odds of initiating therapy than those without mental health-related admissions (OR 0.41 [0.36-0.46]), compared to having 41% lower odds among patients with prior ASCVD (OR 0.59 [0.52-0.67]). Time trends in statin initiation were less pronounced in patients experiencing their first ever ASCVD event when compared to individuals with prior ASCVD history (time period 2012/14 compared to 2009/11: OR 1.05 [1.00-1.09] in patients without ASCVD history vs. 1.17 [1.11-1.22] in patients with prior ASCVD); time period 2015/17 compared to 2009/11: OR 1.06 [1.02-1.11] among patients without prior ASCVD vs. 1.31 [1.24-1.37] in patients with a history of ASCVD).

Table C.7 Statin initiation rates among individuals with and without prior ASCVD history

Study population	Statin therapy		
	Total, N	Initiation, N (%)	No initiation, N (%)
Total ASCVD population	167,978	136,855 (81.5)	31,123 (18.5)
Individuals with no history of ASCVD event prior to index admission	100,864	83,994 (83.2)	16,870 (16.8)
Individuals with history of ASCVD event at any point in time prior to index admission	67,114	52,861 (78.7)	14,253 (21.3)

Figure C.1 Associations of patient characteristics with statin initiation among individuals with first ever ASCVD since 1 October 2009 (a multivariable logistic regression model)

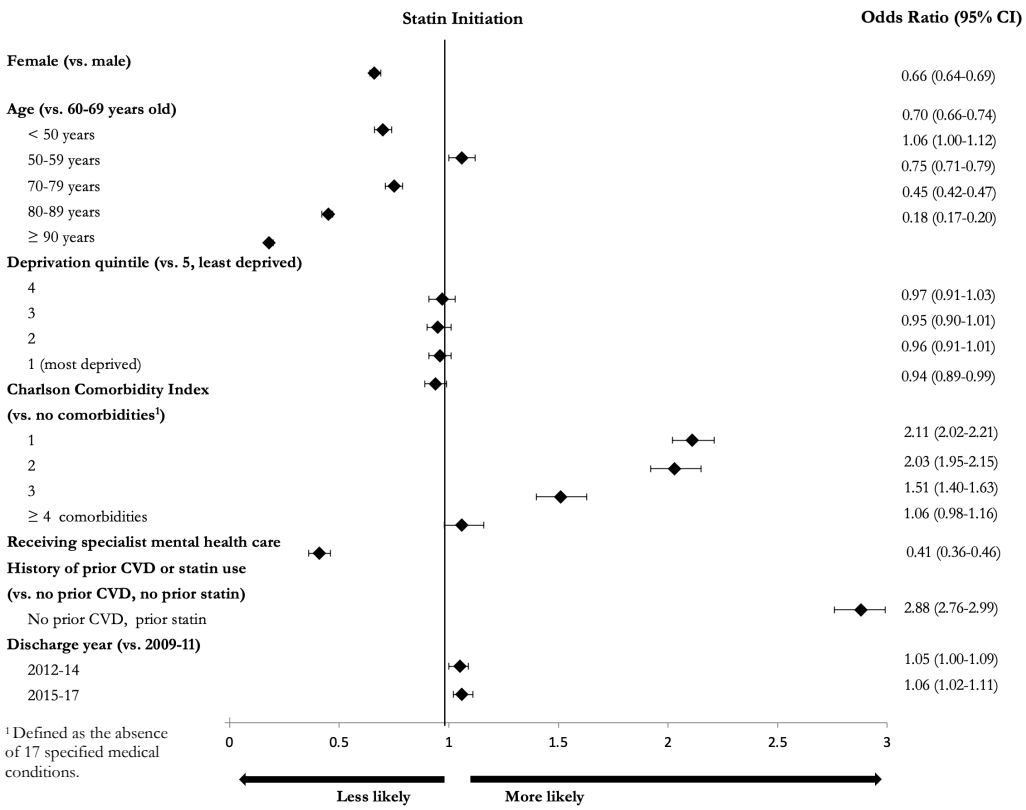
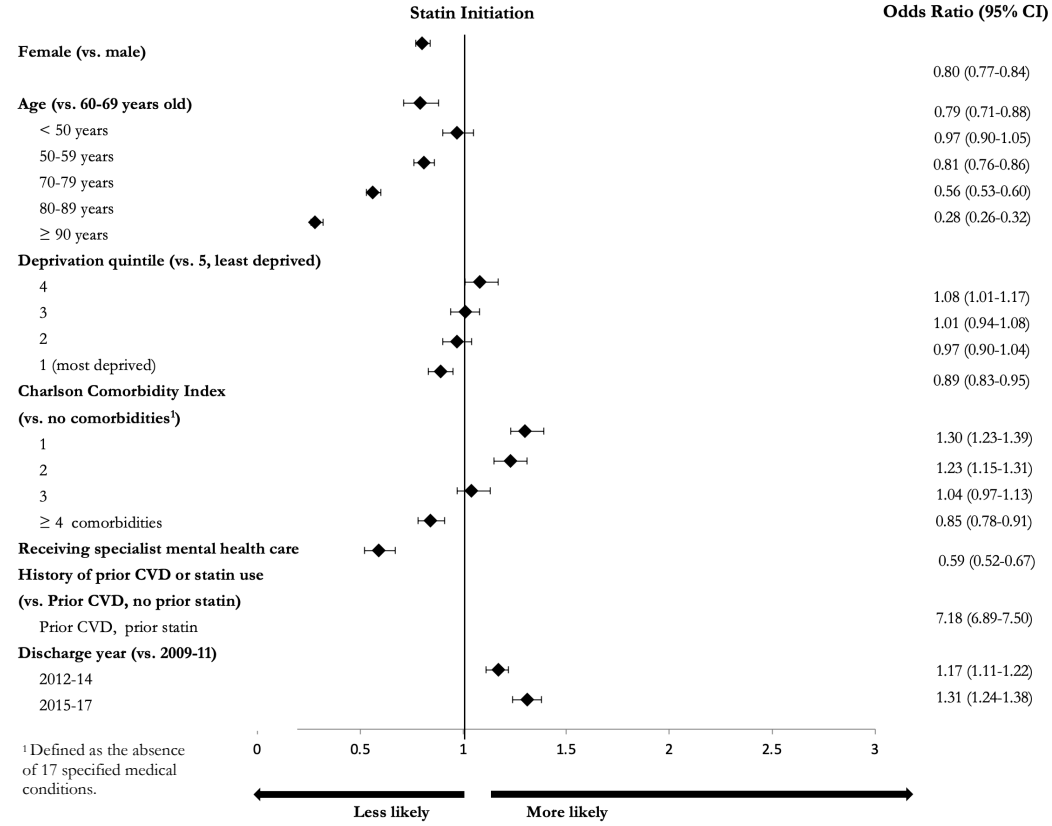


Figure C.2 Associations of patient characteristics with statin initiation among individuals with a history of ASCVD prior to 1 October 2009 (a multivariable logistic regression model)



* OR not pictured in figure due to scale.

C.5 Determinants of statin therapy discontinuation by CVD type

Table C.8 Associations of patient characteristics with statin therapy discontinuation among individuals with ASCVD, by CVD type (multivariable Cox proportional hazards models)

	Myocardial infarction		**Ischaemic stroke**		**Peripheral arterial disease**		**Other ASCVD**	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Female (vs. male)	1.21***	1.16-1.26	1.09***	1.04-1.15	1.09*	1.02-1.17	1.19***	1.15-1.23
Age (vs. 60-69 years old)								
<50	1.18***	1.10-1.27	1.16***	1.45-1.78	1.26**	1.06-1.49	1.35***	1.26-1.45
50-59 years	0.96	0.90-1.03	1.11*	1.01-1.21	1.10	0.98-1.23	1.03	0.97-1.08
70-79 years	1.31***	1.23-1.38	1.29***	1.20-1.39	1.18***	1.08-1.29	1.23***	1.17-1.29
80-80 years	2.02***	1.89-2.15	1.92***	1.78-2.07	1.78***	1.60-1.97	1.85***	1.72-1.93
≥ 90 years	3.93***	3.53-4.37	3.45***	3.08-3.88	2.87***	2.27-3.63	3.86***	3.39-4.39
Deprivation quintile (vs. 5, least deprived)								
4	1.09**	1.02-1.16	1.05	0.97-1.13	1.10	0.97-1.24	1.07*	1.01-1.13
3	1.10**	1.03-1.18	0.99	0.92-1.07	1.14*	1.01-1.28	1.06*	1.00-1.12
2	1.02	0.95-1.09	0.89**	0.82-0.96	1.00	0.88-1.12	1.05	0.99-1.11
1	1.01	0.94-1.08	0.83***	0.77-0.90	1.06	0.94-1.20	0.97	0.91-1.03
Charlson Comorbidity Index (vs. no comorbidities)[1]								
1	N/a	N/a	N/a	N/a	N/a	N/a	0.94**	0.90-0.97
2	1.08**	1.03-1.13	1.09**	1.03-1.16	1.02	0.93-1.12	0.95	0.90-1.00
3	1.24***	1.16-1.32	1.14**	1.05-1.23	1.38***	1.24-1.53	1.15***	1.07-1.24
4 or more	1.50***	1.39-1.61	1.47***	1.35-1.60	1.60***	1.42-1.79	1.46***	1.34-1.58
Receiving specialist mental health care	1.81***	1.59-2.05	1.80***	1.59-2.05	1.69***	1.34-2.13	1.95***	1.76-2.16

	Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
History of prior CVD or statin use (vs. no prior CVD, no prior statin)								
Prior CVD, no prior statin	1.36***	1.27-1.45	1.20***	1.11-1.30	1.14*	1.01-1.30	0.98	0.92-1.06
No prior CVD, prior statin	1.01	0.95-1.08	0.96	0.90-1.03	0.94	0.84-1.04	0.79***	0.75-0.83
Prior CVD, prior statin	1.05	0.99-1.10	0.98	0.92-1.05	0.84**	0.76-0.92	0.70***	0.67-0.74
Discharge year (vs. 2009-11)								
2012-14	0.97	0.93-1.01	0.91**	0.87-0.96	0.96	0.89-1.04	0.98	0.95-1.02
2015-17	0.83***	0.78-0.88	0.78***	0.73-0.84	0.83**	0.74-0.93	0.77***	0.72-0.81

Note: (***): p<0.001; (**): p<0.01; (*): p<0.5; [1] In the case of myocardial infarction, stroke and peripheral arterial disease the reference group is 'one comorbidity' as the Charlson Comorbidity Index classifies the presence of these conditions as a comorbidity.

Table C.9 Participant characteristics of statin initiators, discontinuers and non-initiators at index discharge

Numbers are N (%) unless otherwise specified	**Total Population** 1 Oct 2009 to 31 Dec 2016	**Group 1 Initiated statin and remained on statin**	**Group 2 Initiated statin and discontinued statin**	**Group 3 Statin non-initiators**
N	151,857	113,102	11,304	27,451
Age on discharge, in years (mean, SD)	67 (12.6)	66.4 (11.9)	66.9 (13.7)	69.1 (14.8)
Female	58,921 (38.8)	40,530 (35.8)	5,025 (44.4)	13,366 (48.7)
Ethnic group				
White	129,958 (85.6)	96,440 (85.3)	9,766 (86.4)	23,752 (86.5)
Other	2,190 (1.4)	1,642 (1.4)	187 (1.6)	361 (1.3)
Missing	19,700 (13.0)	15,020 (13.3)	1,351 (12.0)	3,338 (12.6)
SIMD quintile (2009)				
5 (least deprived)	23,780 (15.6)	17,765 (15.7)	1,755 (15.5)	4,260 (15.5)
4	27,805 (18.3)	20,676 (18.3)	2,187 (19.3)	4,942 (18.0)
3	31,099 (20.5)	22,924 (20.3)	2,504 (22.1)	5,671 (20.6)
2	33,745 (22.2)	25,262 (22.3)	2,389 (21.1)	6,094 (22.2)
1 (most deprived)	35,428 (23.3)	26,475 (23.4)	2,469 (21.8)	6,484 (23.6)
Charlson Comorbidity Index				
0 (no comorbidities)[129]	28,856 (19.0)	20,822 (18.4)	2,311 (20.4)	5,723 (20.8)
1	70,643 (46.5)	53,908 (47.6)	5,130 (45.4)	11,605 (42.3)
2	30,238 (19.9)	22,945 (20.3)	2,131 (18.8)	5,162 (18.8)
3	13,007 (8.6)	9,308 (8.2)	984 (8.7)	2,715 (9.9)
4 or more comorbidities	9,113 (6.0)	6,119 (5.4)	748 (6.6)	2,246 (8.2)
Mental health inpatient/day case 12 months prior to index admission	2,799 (1.84)	1,593 (1.4)	308 (2.7)	898 (3.2)
History of CVD and statin use 12 months prior to index admission				
No CVD hospitalisation + no statin	53,944 (35.5)	37,685 (33.3)	4,780 (42.3)	11,479 (41.8)

[129] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

Numbers are N (%) unless otherwise specified	**Total Population** 1 Oct 2009 to 31 Dec 2016	**Group 1 Initiated statin and remained on statin**	**Group 2 Initiated statin and discontinued statin**	**Group 3 Statin non-initiators**
CVD hospitalisation + no statin use	13,394 (8.8)	5,462 (4.8)	1,273 (11.3)	6,659 (24.3)
No CVD hospitalisation + statin use	37,812 (24.9)	31,653 (28.0)	2,594 (23.0)	3,565 (13.0)
CVD hospitalisation + statin use	46,707 (30.8)	38,302 (33.8)	2,657 (23.5)	5,748 (20.9)

Table C.10 Associations of patient characteristics and statin use with subsequent cardiovascular event or death after index ASCVD hospitalisation (a multivariable Cox proportional hazards model), by ASCVD type

	Myocardial infarction		**Ischaemic stroke**		**Peripheral arterial disease**		**Other ASCVD**	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Status of statin use at 12 months since discharge (vs. statin initiators)								
Statin non-initiators	1.25***	1.17-1.32	1.17***	1.08-1.26	1.11*	1.01-1.22	1.09***	1.04-1.14
Statin discontinuers	1.19 ***	1.10-1.28	1.30***	1.16-1.44	1.14*	1.00-1.30	1.09**	1.02-1.17
Female (vs. male)	0.97	0.92-1.01	0.82***	0.77-0.88	0.98	0.92-1.05	0.91***	0.87-0.94
Age (vs. 60-69 years old)								
<50 50-59 years 70-79 years 80-80 years ≥ 90 years	Omitted due to age stratification		Omitted due to age stratification		Omitted due to age stratification		Omitted due to age stratification	
Deprivation quintile (vs. 5, least deprived)								
4	1.12**	1.04-1.20	1.22***	1.09-1.36	1.07	0.96-1.20	1.10**	1.04-1.17
3	1.18***	1.09-1.27	1.26***	1.13-1.40	0.99	0.89-1.11	1.12***	1.05-1.18
2	1.21***	1.12-1.30	1.30***	1.17-1.44	1.03	0.92-1.14	1.18***	1.12-1.25
1	1.28***	1.19-1.37	1.33***	1.20-1.47	1.02	0.91-1.14	1.20***	1.14-1.27
Charlson Comorbidity Index (vs. no comorbidities)[1]								
1	N/a	N/a	N/a	N/a	N/a	N/a	1.12***	1.07-1.16
2	0.55***	0.51-0.59	0.69***	0.62-0.77	2.25	0.49-10.30	1.39***	1.32-1.46
3	0.68***	0.63-0.73	0.84**	0.75-0.94	2.45	0.53-11.22	1.47***	1.37-1.57
4 or more	0.84***	0.77-0.91	0.92	0.81-1.04	2.81	0.61-12.89	1.96***	1.82-2.11
Receiving specialist mental health care	1.03	0.89-1.19	0.97	0.81-1.16	1.09	0.85-1.39	1.13*	1.01-1.27

	Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
History of ASCVD and statin use 12 months prior to index admission (vs. no ASCVD + no statin use)								
ASCVD hospitalisation + no statin use	1.89***	1.76-2.04	1.74***	1.57-1.94	1.55***	1.36-1.77	2.21***	2.05-1.38
No ASCVD hospitalisation + statin use	1.56***	1.46-1.66	1.51***	1.38-1.64	1.15**	1.03-1.29	1.36***	1.27-1.44
ASCVD hospitalisation + statin use	2.63***	1.50-2.77	2.48***	1.29-2.68	1.86***	1.67-2.08	2.46***	2.32-2.60

(***) $p<0.001$, (**) $p<0.01$, (*) $p<0.05$

D

Rates and determinants of antiplatelet therapy use for the secondary prevention of cardiovascular disease

D.1 Antiplatelet therapy (APT) initiation rates amongst atrial fibrillation patients

Table D.1 Participant characteristics of antiplatelet therapy initiators and non-initiators with a record of atrial fibrillation (AF) during index admission

	Atrial Fibrillation	
Antiplatelet therapy initiation	Yes	No
N (%)	53.1	46.9
Age on discharge, in years (mean, SD)	75.4 (10.3)	76.2 (9.5)
Hospital length of stay, in days (mean, SD)	10.5 (14.5)	13.5 (19.2)
Female	40.0	46.0
Ethnic group		
White	88.4	89.6
Other	0.8	0.7
Missing	10.8	9.8
SIMD quintile (2009)[130]		
5 (least deprived)	18.0	18.5
4	18.7	20.7
3	20.3	19.9
2	22.5	21.0
1 (most deprived)	20.5	19.8
Urban-Rural Classification[131]		
Large urban areas	32.4	34.9
Other urban areas	34.9	32.8
Accessible small towns	10.0	9.4
Remote small towns	3.9	3.9
Accessible rural	11.9	12.0
Remote rural	6.9	7.1
Charlson Comorbidity Index		
0 (no-comorbidities)[132]	10.7	10.0
1	38.8	42.0
2	26.1	23.8
3	14.1	13.5
4 or more comorbidities	10.3	10.7
Mental health inpatient/day case in the 12 months prior to index admission	1.8	1.7

[130] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones based on 2009 data. The SIMD was also published in 2012 and 2016, with limited changes in groupings in later years, and the 2009 classification was applied to patients' residence location at the time of ASCVD-related index discharge.
[131] Scottish Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes' drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.
[132] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions within 12 months prior to and including the index admission. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

Antiplatelet therapy initiation	Atrial Fibrillation	
	Yes	No
History of CVD and antiplatelet therapy (APT) use 12 months prior to index admission[133]		
No ASCVD hospitalisation + no APT use	25.9	33.5
ASCVD hospitalisation + no APT use	13.6	16.5
No ASCVD hospitalisation + APT use	21.4	28.5
ASCVD hospitalisation + APT use	39.1	21.5
Time to first primary care level prescription since index discharge, in days (mean, SD)[134]	17.5 (18.5)	Not applicable
Time from prescription to dispense, in days (mean, SD)	14.0 (15.6)	Not applicable

[133] For individuals with index hospitalisations between October 2009 and March 2010, information on prior medication use is available for the 6 to 11 months prior to index admission. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

[134] Please note that this statistic only includes individuals who initiated the prescribed treatment, as the Prescribing Information System (PIS) data do not contain prescribing information for patients who were not dispensed treatment.

D.2 Antiplatelet therapy (APT) initiation rates by ASCVD type

Table D.2 Myocardial infarction: antiplatelet therapy (APT) initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
APT initiation rates (%)	**92.2**	**93.8**	**95.1**
Men	92.9	94.7	95.7
Women	90.8	92.1	94.0
Individuals aged 18 – 49 years	93.8	95.4	95.9
Individuals aged 50 – 59 years	95.4	96.0	96.9
Individuals aged 60 – 69 years	94.5	95.8	96.3
Individuals aged 70 – 79 years	90.8	92.8	94.5
Individuals aged 80 – 89 years	86.0	88.7	91.2
Individuals aged 90 years or older	81.9	81.2	86.5

Table D.3 Ischaemic stroke: antiplatelet therapy (APT) initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
APT initiation rates (%)	**81.4**	**82.7**	**84.8**
Men	83.1	84.2	85.7
Women	79.6	81.0	83.7
Individuals aged 18 – 49 years	78.8	80.5	81.9
Individuals aged 50 – 59 years	84.5	87.8	88.4
Individuals aged 60 – 69 years	87.1	86.0	89.1
Individuals aged 70 – 79 years	80.8	83.5	85.2
Individuals aged 80 – 89 years	77.3	77.0	80.7
Individuals aged 90 years or older	71.5	77.6	71.1

Table D.4 Peripheral arterial disease: antiplatelet therapy (APT) initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
APT initiation rates (%)	**66.4**	**70.1**	**67.2**
Men	66.7	70.8	66.8
Women	65.9	68.9	67.9
Individuals aged 18 – 49 years	52.3	56.8	43.8
Individuals aged 50 – 59 years	65.3	69.3	68.0
Individuals aged 60 – 69 years	69.3	75.8	71.1
Individuals aged 70 – 79 years	68.6	70.8	69.2
Individuals aged 80 – 89 years	64.3	65.1	65.9
Individuals aged 90 years or older	59.5	63.2	58.2

Table D.5 Other atherosclerotic cardiovascular disease: antiplatelet therapy (APT) initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
APT initiation rates (%)	**79.7**	**80.7**	**81.8**
Men	81.8	83.9	84.5
Women	76.4	75.7	77.3
Individuals aged 18 – 49 years	68.5	71.3	71.5
Individuals aged 50 – 59 years	80.4	81.4	82.2
Individuals aged 60 – 69 years	82.9	84.0	85.0
Individuals aged 70 – 79 years	81.9	81.9	83.4
Individuals aged 80 – 89 years	74.1	76.0	77.0
Individuals aged 90 years or older	69.0	68.6	67.2

Table D.6 Atrial fibrillation: antiplatelet therapy (APT) initiation rates in the study population in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
APT initiation rates (%)	**58.7**	**55.7**	**44.5**
Men	60.7	58.1	48.1
Women	56.0	52.6	39.5
Individuals aged 18 – 49 years	60.7	55.3	52.7
Individuals aged 50 – 59 years	64.0	63.9	52.9
Individuals aged 60 – 69 years	60.5	58.9	51.5
Individuals aged 70 – 79 years	56.8	54.3	43.2
Individuals aged 80 – 89 years	57.6	52.8	40.2
Individuals aged 90 years or older	65.8	63.4	46.2

Table D.7 Percutaneous coronary intervention (PCI): antiplatelet therapy (APT) initiation rates in the study population (excluding individuals with atrial fibrillation) in Scotland over time and by age and gender

Index discharge year	**2009-2011**	**2012-2014**	**2015-2017**
APT initiation rates (%)	**96.0**	**97.2**	**97.2**
Men	96.2	97.3	97.3
Women	95.3	96.9	97.0
Individuals aged 18 – 49 years	95.7	96.7	95.8
Individuals aged 50 – 59 years	96.3	97.5	97.6
Individuals aged 60 – 69 years	96.7	97.6	97.5
Individuals aged 70 – 79 years	95.4	97.2	97.5
Individuals aged 80 – 89 years	94.0	95.4	95.7
Individuals aged 90 years or older	62.5	71.4	90.0

D.3 Mono- vs. dual-antiplatelet therapy (DAPT) initiation rates by ASCVD type

Table D.8 Percutaneous coronary intervention (PCI): antiplatelet therapy (APT) initiation rates by APT type in the study population[135] in Scotland over time

	PCI with drug-eluting stent			PCI with non-drug-eluting stent			PCI without stent		
	2009-2011	2012-2014	2015-2017	2009-2011	2012-2014	2015-2017	2009-2011	2012-2014	2015-2017
Monotherapy	**43.5**	**38.4*****	**34.6*****	**51.1**	**43.2*****	**30.2*****	**54.1**	**50.7*****	**29.9*****
Aspirin	11.9	10.9	10.7	26.6	20.7	11.8	30.5	24.5	7.3
Clopidogrel	31.3	24.2	18.2	24.0	21.1	13.6	22.8	20.5	15.8
Ticagrelor	0.0	2.9	4.8	0.0	0.9	4.3	0.0	4.8	6.1
Dipyridamole	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
Prasugrel	0.4	0.3	0.9	0.4	0.5	0.5	0.8	0.9	0.6
Dual Antiplatelet Therapy (DAPT)	**56.5**	**61.6*****	**65.4*****	**48.9**	**56.8*****	**69.8*****	**45.9**	**49.3*****	**70.1*****
Aspirin + Clopidogrel	56.1	47.6	32.5	48.3	50.6	38.8	44.8	41.1	36.0
Aspirin + Ticagrelor	0.0	13.4	31.0	0.0	5.8	28.8	0.0	7.9	32.9
Aspirin + Dipyridamole	0.0	0.1	0.0	0.3	0.1	0.0	0.4	0.0	0.0
Aspirin + Prasugrel	0.3	0.5	1.7	0.3	0.4	2.3	0.8	0.4	1.2

Note: Asterisks in the column 2012/2014 and 2015/2017 denote statistically significant changes in the proportion of individuals initiating treatment compared to the discharge year group prior (i.e., 2012/14 vs. 2009/11 and 2015/17 vs. 2012/14), where (***) P<0.001, (**) P<0.01, (*) P<0.5.

[135] The study population includes all individuals hospitalised for ASCVD as defined in **Chapter 4**, excluding individuals with atrial fibrillation (AF) recorded in any of the available diagnostic fields during the index hospitalisation.

Table D.9 Antiplatelet therapy (APT) initiation rates by APT type in the study population in Scotland over time and by ASCVD type

	Myocardial infarction without PCI			Ischaemic stroke			Peripheral arterial disease		
	2009-2011	2012-2014	2015-2017	2009-2011	2012-2014	2015-2017	2009-2011	2012-2014	2015-2017
Monotherapy	**46.7**	**37.5*****	**28.1*****	**69.4**	**97.0*****	**97.6**	**94.1**	**95.7****	**95.8**
Aspirin	28.5	20.3	12.5	25.5	7.8	5.1	79.9	76.9	69.8
Clopidogrel	17.9	13.1	8.9	34.9	89.0	92.4	12.6	18.0	25.5
Ticagrelor	0.0	3.8	6.4	0.0	0.0	0.0	0.0	0.1	0.1
Dipyridamole	0.1	0.0	0.0	8.9	0.2	0.1	1.7	0.7	0.5
Prasugrel	0.2	0.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0
Dual Antiplatelet Therapy (DAPT)	**53.3**	**62.5*****	**71.9*****	**30.6**	**3.0*****	**2.4****	**5.9**	**4.3****	**4.2**
Aspirin + Clopidogrel	52.8	44.1	28.9	2.6	2.6	2.1	3.0	3.5	3.8
Aspirin + Ticagrelor	0.0	17.8	41.9	0.0	0.0	0.1	0.0	0.1	0.2
Aspirin + Dipyridamole	0.3	0.1	0.0	27.9	0.4	0.2	2.8	0.7	0.2
Aspirin + Prasugrel	0.3	0.5	1.1	0.0	0.0	0.0	0.0	0.0	0.0

Table D.10 Antiplatelet therapy (APT) initiation rates by APT type in the study population in Scotland over time and by ASCV type

	Other ASCVD			Atrial fibrillation with PCI			Atrial fibrillation without PCI		
	2009-2011	2012-2014	2015-2017	2009-2011	2012-2014	2015-2017	2009-2011	2012-2014	2015-2017
Monotherapy	**85.8**	**88.2**	**84.9**	**32.4**	**24.3**	**18.2**	**46.7**	**37.5**	**28.1**
Aspirin	68.8	65.0	58.4	13.5	8.9	5.8	28.5	20.3	12.5
Clopidogrel	15.7	22.3	24.7	18.4	12.1	6.9	17.9	13.1	8.9
Ticagrelor	0.0	0.7	1.6	0.0	3.0	4.7	0.0	3.8	6.4
Dipyridamole	1.2	0.2	0.1	0.0	0.0	0.0	0.1	0.0	0.0
Prasugrel	0.1	0.0	0.1	0.5	0.3	0.7	0.2	0.3	0.3
Dual Antiplatelet Therapy (DAPT)	**14.2**	**11.8**	**15.1**	**67.6**	**75.7**	**81.8**	**53.3**	**62.5**	**71.9**
Aspirin + Clopidogrel	11.1	9.8	9.0	66.9	58.0	40.4	52.8	44.1	28.9
Aspirin + Ticagrelor	0.0	1.6	5.9	0.0	16.9	38.8	0.0	17.8	41.9
Aspirin + Dipyridamole	2.9	0.4	0.1	0.2	0.0	0.0	0.3	0.1	0.0
Aspirin + Prasugrel	0.0	0.0	0.1	0.5	0.8	2.6	0.3	0.5	1.1

D.4 Determinants of antiplatelet therapy initiation by CVD type

Table D.11 Association between antiplatelet therapy initiation and patient characteristics among individuals with ASCVD (excluding atrial fibrillation), by ASCVD type

	Myocardial infarction		**Ischaemic stroke**		**Peripheral arterial disease**		**Other ASCVD**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Female (vs. male)	0.91*	0.84-0.99	0.89**	0.83-0.95	1.02	0.93-1.11	0.69***	0.66-0.72
Age (vs. 60-69 years old)								
<50	0.83*	0.71-0.96	0.59***	0.52-0.67	0.62***	0.53-0.73	0.62***	0.57-0.66
50-59 years	1.06	0.93-1.21	0.97	0.86-1.10	0.88	0.77-1.00	0.93*	0.87-0.99
70-79 years	0.68***	0.60-0.76	0.73***	0.66-0.81	0.89*	0.80-0.99	0.87***	0.82-0.92
80-80 years	0.44***	0.38-0.49	0.54***	0.49-0.60	0.73***	0.64-0.82	0.64***	0.60-0.69
≥ 90 years	0.26***	0.22-0.32	0.43***	0.36-0.50	0.63**	0.46-0.86	0.52***	0.44-0.61
Deprivation quintile (vs. 5, least deprived)								
4	1.07	0.93-1.24	1.13*	1.00-1.26	1.00	0.87-1.15	1.04	0.96-1.11
3	0.93	0.81-1.06	1.06	0.95-1.18	1.09	0.95-1.25	1.06	0.98-1.13
2	0.93	0.82-1.07	1.04	0.93-1.15	1.10	0.96-1.26	1.04	0.97-1.12
1	0.74***	0.65-0.85	0.99	0.89-1.10	1.03	0.90-1.18	1.04	0.97-1.11
Charlson Comorbidity Index (vs. no comorbidities)[136]								
1	N/A		N/A		N/A		1.04	0.99-1.20
2	0.83***	0.75-0.91	0.95	0.88-1.04	0.96	0.86-1.06	1.08*	1.00-1.15
3	0.58***	0.51-0.65	0.85**	0.76-0.94	0.85*	0.75-0.97	0.86**	0.78-0.95
4 or more	0.49***	0.44-0.56	0.79***	0.70-0.88	0.62***	0.55-0.72	0.74***	0.67-0.83

[136] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions within 12 months prior to and including the index admission. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

	Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Receiving specialist mental health care	0.38***	0.30-0.47	0.50***	0.42-0.60	0.70*	0.50-0.97	0.64***	0.55-0.73
History of prior CVD or antiplatelet use (vs. no prior CVD, no prior antiplatelet)[137]								
Prior CVD, no prior APT	0.49***	0.43-0.55	0.50***	0.46-0.56	0.56***	0.49-0.63	0.41***	0.39-0.44
No prior CVD, prior APT	0.87*	0.76-0.99	1.09	0.99-1.21	5.96***	5.34-6.66	3.63***	3.42-3.84
Prior CVD, prior APT	0.81***	0.73-0.90	1.07	0.98-1.17	6.17***	5.56-6.85	3.83***	3.62-4.06
Discharge year (vs. 2009-11)								
2012-14	1.24***	1.13-1.35	1.09*	1.00-1.17	1.27***	1.16-1.39	1.11***	1.05-1.16
2015-17	1.54***	1.39-1.71	1.27***	1.17-1.38	1.22***	1.11-1.36	1.27***	1.20-1.34

Note: (***): p<0.001; (**): p<0.01; (*): p<0.5.

[137] For individuals with index hospitalisations between October 2009 and March 2010, information on prior medication use is available for the 6 to 11 months prior to index admission. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

Table D.12 Association between antiplatelet therapy initiation and patient characteristics among individuals with MI (excluding atrial fibrillation), by percutaneous coronary intervention (PCI) status

	Myocardial infarction with PCI		Myocardial infarction without PCI	
	OR	95% CI	OR	95% CI
Female (vs. male)	0.98	0.75-1.29	0.92	0.85-1.00
Age (vs. 60-69 years old)				
<50	0.81	0.55-1.18	0.84*	0.72-0.99
50-59 years	1.02	0.73-1.43	1.06	0.92-1.23
70-79 years	0.99	0.69-1.41	0.66***	0.58-0.75
80-80 years	0.67	0.42-1.05	0.45***	0.39-0.51
≥ 90 years	0.06***[138]	0.01-0.22	0.29***	0.24-0.35
Deprivation quintile (vs. 5, least deprived)				
4	1.11	0.73-1.68	1.08	0.93-1.26
3	0.87	0.59-1.28	0.96	0.83-1.11
2	0.86	0.58-1.28	0.97	0.84-1.12
1	0.68[139]	0.46-1.00	0.79**	0.69-0.91
Charlson Comorbidity Index (vs. no comorbidities)[140]				
1	N/A		N/A	
2	1.00	0.75-1.34	0.83***	0.75-0.91
3	0.76	0.50-1.15	0.58***	0.51-0.65
4 or more	0.60*	0.36-0.99	0.50***	0.44-0.57
Receiving specialist mental health care	0.50	0.20-1.28	0.38***	0.31-0.48
History of prior ASCVD or antiplatelet use (vs. no prior ASCVD, no prior antiplatelet)[141]				
Prior ASCVD, no prior APT	0.53***	0.36-0.80	0.49***	0.44-0.56
No prior ASCVD, prior APT	0.83	0.55-1.27	0.87	0.76-1.00
Prior ASCVD, prior APT	0.66*	0.48-0.92	0.84**	0.75-0.94
Discharge year (vs. 2009-11)				
2012-14	1.39*	1.05-1.85	1.21***	1.10-1.33
2015-17	1.26	0.93-1.71	1.57***	1.41-1.75

Note: (***): p<0.001; (**): p<0.01; (*): p<0.5.

[138] The study population only included 13 individuals aged 90 years or older, who were hospitalised for MI and underwent PCI.

[139] P=0.053, p<0.1.

[140] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions within 12 months prior to and including the index admission. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

[141] For individuals with index hospitalisations between October 2009 and March 2010, information on prior medication use is available for the 6 to 11 months prior to index admission. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

Table D.13 Association between dual-antiplatelet therapy (DAPT) initiation[143] and patient characteristics among individuals with percutaneous coronary intervention (PCI) (excluding atrial fibrillation)

Percutaneous coronary intervention (PCI)		
	OR	95% CI
Female (vs. male)	0.92[142]	0.85-1.00
Age (vs. 60-69 years old)		
<50	1.22**	1.07-1.38
50-59 years	1.03	0.94-1.13
70-79 years	0.83***	0.75-0.91
80-80 years	0.82*	0.70-0.96
≥ 90 years	0.88	0.32-2.45
Deprivation quintile (vs. 5, least deprived)		
4	1.03	0.92-1.14
3	0.92	0.82-1.03
2	0.90	0.90-1.00
1	0.82**	0.73-0.92
Charlson Comorbidity Index (vs. no comorbidities)		
1	1.71***	1.56-1.87
2	1.64***	1.48-1.83
3	1.43***	1.22-1.67
4 or more	1.55***	1.26-1.91
Receiving specialist mental health care	1.22	0.80-1.86
History of prior ASCVD or antiplatelet use (vs. no prior ASCVD, no prior antiplatelet)		
Prior ASCVD, no prior APT	0.55***	0.47-0.64
No prior ASCVD, prior APT	0.15***	0.14-0.17
Prior ASCVD, prior APT	0.13***	0.12-0.15
Discharge year (vs. 2009-11)		
2012-14	1.33***	1.22-1.45
2015-17	1.63***	1.49-1.78

[142] P=0.053, p<0.1.

[143] In the case of percutaneous coronary intervention (PCI), the outcome analysed is the initiation of dual-antiplatelet therapy vs. monotherapy, as indicated by a (*).

D.5 Subgroup analyses of determinants of antiplatelet therapy initiation

Antiplatelet therapy initiation among individuals with and without a prior history of ASCVD (excluding patients with atrial fibrillation)

Between 1 October 2009 and 3 July 2017, of the 92,490 (61%) patients hospitalised for their first ever ASCVD event, 85.1% initiated antiplatelet therapy treatment. This compares with an initiation rate of 81.9% in the 58,238 patients who had ASCVD-related hospitalisations prior to study start in October 2009 and their index hospitalisation in the time period from April 2009 to July 2017 (**Table D.14**).

The results of each subgroup analysis (**Figure D.1** and **Figure D.2**) are consistent across both subgroups, as well as with the findings from the original ASCVD population that includes both individuals with and without history of prior ASCVD (**Chapter 6, Figure 6.1**), meaning that the same patient characteristics are associated with statin initiation as previously discussed in **Chapter 6, Section 6.1.2**.

Table D.14 Antiplatelet initiation rates among individuals with and without prior ASCVD history (excluding individuals with atrial fibrillation)

Study population	Antiplatelet therapy		
	Total, N	Initiation, N (%)	No initiation, N (%)
Total ASCVD population	150,728	126,338 (83.8)	24,390 (16.2)
Individuals with no history of ASCVD event prior to index admission	92,490	78,669 (85.1)	13,821 (14.9)
Individuals with history of ASCVD event at any point in time prior to index admission	58,238	47,669 (81.9)	10,569 (18.1)

Figure D.1 Associations of patient characteristics with antiplatelet therapy initiation among individuals with first ever ASCVD (excluding atrial fibrillation) since 1 October 2009 (a multivariable logistic regression model)

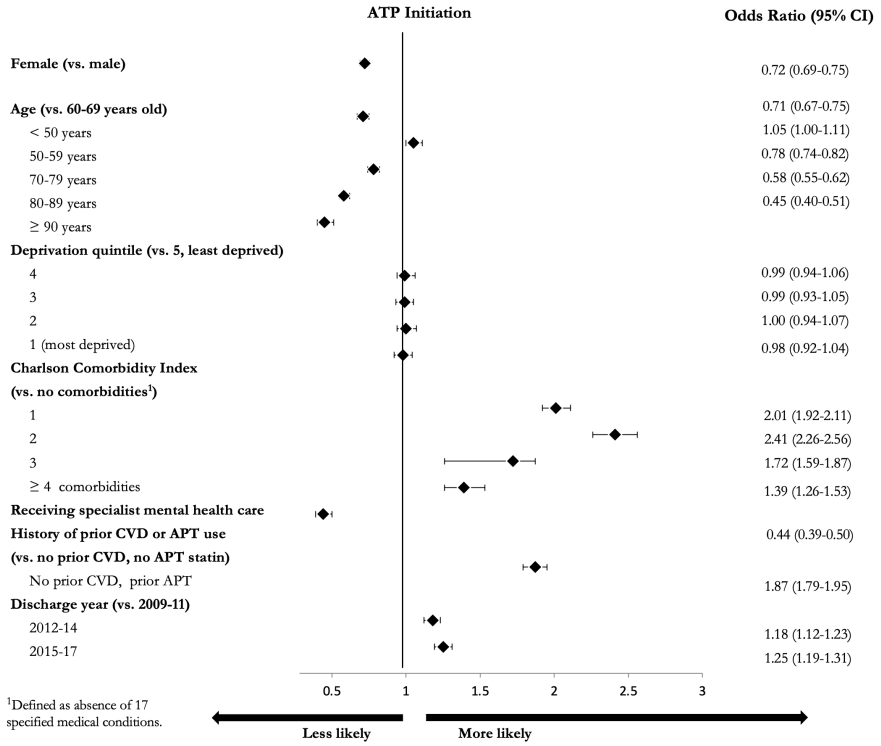
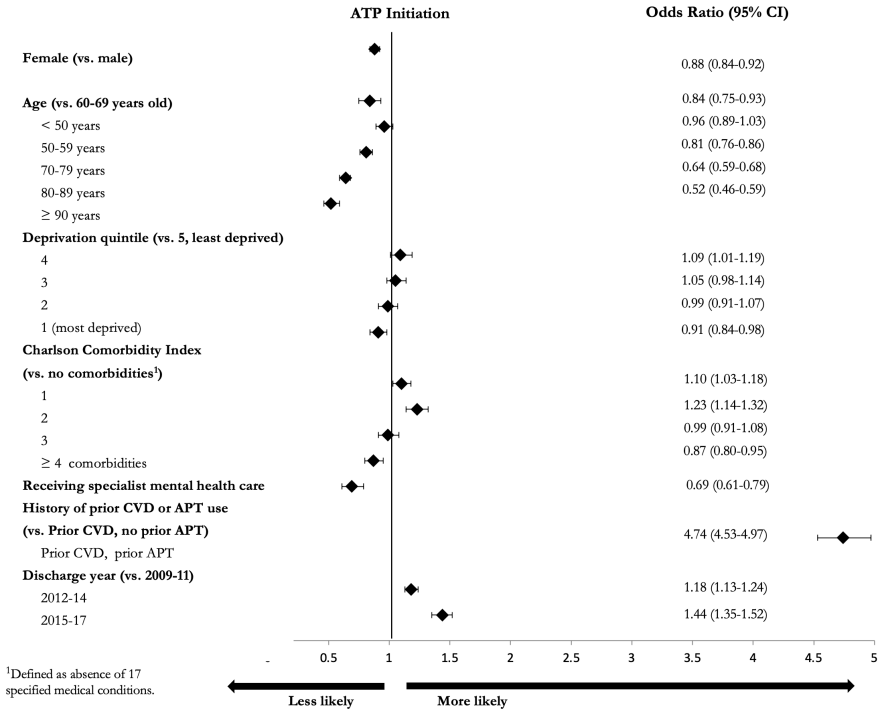


Figure D.2 Associations of patient characteristics with antiplatelet therapy initiation among individuals with history of ASCVD (excluding atrial fibrillation) prior to 1 October 2009 (a multivariable logistic regression model)



D.6 Antiplatelet therapy (APT) discontinuation rates amongst atrial fibrillation patients

Table D.15 Participant characteristics of antiplatelet therapy discontinuers and non-discontinuers with a record of atrial fibrillation (AF) during index admission

	Atrial fibrillation	
Antiplatelet therapy discontinuation	Yes	No
N (%)	12,259 (23.9)	39,104 (76.1)
Age on discharge, in years (mean, SD)	75.2 (9.8)	75.6 (10.7)
Female	40.3	39.8
Ethnic group		
White	89.8	87.3
Other	0.8	0.7
Missing	9.4	12.0
SIMD quintile (2009)[144]		
5 (least deprived)	18.9	17.2
4	18.2	19.1
3	21.6	19.2
2	21.6	23.3
1 (most deprived)	19.7	21.2
Urban-Rural Classification[145]		
Large urban areas	32.1	32.7
Other urban areas	34.3	35.4
Accessible small towns	9.9	10.1
Remote small towns	3.8	4.0
Accessible rural	11.8	12.0
Remote rural	8.1	5.9
Charlson Comorbidity Index		
0 (no-comorbidities)[146]	11.2	10.3
1	39.9	37.8
2	25.7	26.5
3	13.6	14.5
4 or more comorbidities	9.6	10.9
Mental health inpatient/day case 12 months prior to index admission	2.2	1.5

[144] Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation across Scottish data zones based on 2009 data. The SIMD was also published in 2012 and 2016, with limited changes in groupings in later years, and the 2009 classification was applied to patients' residence location at the time of ASCVD-related index discharge.

[145] Scottish Government Urban Rural Classification: (1) Large urban areas: settlements of 125,0000 or more people; (2) Other urban areas: settlements of 10,000 to 124,999 people; (3) Accessible small towns: settlements of 3,000 to 9,999 people and within 30 minutes' drive of a settlement of 10,000 or more; (4) Remote small towns: settlements of 3,000 to 9,999 people and a drive time of over 30 minutes to a settlement of 10,000 or more; (5) Accessible rural: Areas with a population of less than 3,000 people, and within a 30 minute drive time from a settlement of 10,000 or more; (6) Remote rural: Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more.

[146] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions within 12 months prior to and including the index admission. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

Antiplatelet therapy discontinuation	Atrial fibrillation	
	Yes	No
History of CVD and antiplatelet therapy use 12 months prior to index admission[147]		
No CVD hospitalisation + no antiplatelet therapy	25.7	27.6
CVD hospitalisation + no antiplatelet therapy use	14.6	14.0
No CVD hospitalisation + antiplatelet therapy use	22.9	18.7
CVD hospitalisation + antiplatelet therapy use	36.8	39.8
Time to discontinuation, in years (mean, SD)	1.3 (1.4)	N/A

[147] For individuals with index hospitalisations between October 2009 and March 2010, information on prior medication use is available for the 6 to 11 months prior to index admission. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

D.7 Determinants of antiplatelet therapy discontinuation by CVD type

Table D.16 Association between antiplatelet therapy discontinuation and patient characteristics among individuals with ASCVD (excluding atrial fibrillation), by CVD type

	Myocardial infarction		**Ischaemic stroke**		**Peripheral arterial disease**		**Other ASCVD**	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Female (vs. male)	1.08***	1.03-1.14	1.01	0.96-1.07	0.99	0.91-1.07	1.16***	1.12-1.20
Age (vs. 60-69 years old)								
<50	1.10 *	1.02-1.19	1.21***	1.09-1.36	1.25*	1.05-1.49	1.22***	1.13-1.31
50-59 years	0.89**	0.83-0.96	0.92	0.83-1.01	1.01	0.88-1.15	0.96	0.91-1.01
70-79 years	1.35***	1.27-1.44	1.40***	1.30-1.51	1.27***	1.15-1.40	1.24***	1.19-1.30
80-80 years	1.90***	1.77-2.05	1.55***	1.42-1.68	1.74***	1.55-1.96	1.56***	1.47-1.66
≥ 90 years	2.87***	2.53-3.49	1.82***	1.57-.2.10	2.31***	1.74-3.06	1.91***	1.65-2.22
Deprivation quintile (vs. 5, least deprived)								
4	0.99	0.92-1.07	0.96	0.87-1.05	0.94	0.82-1.09	1.24***	1.13-1.36
3	1.03	0.96-1.11	0.89*	0.82-0.98	1.07	0.93-1.22	1.01	0.93-1.09
2	1.02	0.95-1.10	0.92	0.84-1.00	0.95	0.83-1.08	0.99	0.94-1.05
1	1.03	0.96-1.11	0.87**	0.80-0.95	1.08	0.95-1.24	0.94**	0.90-0.98
Charlson Comorbidity Index (vs. no comorbidities)[148]								
1	N/A		N/A		N/A		0.94**	0.90-0.98
2	1.11***	1.05-1.17	1.01	0.95-1.08	1.01	0.91-1.12	0.99	0.94-1.05
3	1.33***	1.24-1.43	1.08	0.99-1.18	1.15*	1.01-1.31	1.01	0.93-1.09
4 or more	1.66***	1.54-1.80	1.29***	1.16-1.42	1.40***	1.22-1.61	1.24***	1.13-1.36

[148] Absence of comorbidities as defined by CCI: in the case of the total ASCVD and other ASCVD populations, this means that individuals were not hospitalised for any of the 17 specified conditions within 12 months prior to and including the index admission. In the case of the MI, stroke and PAD populations, every individual has at least one CCI comorbidity, their index condition (i.e. MI, stroke or PAD), thus absence of comorbidity is not applicable (N/A).

	Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
Receiving specialist mental health care	1.77***	1.54-2.04	1.55***	1.34-1.80	1.50**	1.13-1.99	1.71***	1.53-1.91
History of prior ASCVD or antiplatelet use (vs. no prior ASCVD, no prior antiplatelet)[149]								
Prior ASCVD, no prior APT	1.69***	1.57-1.83	1.30***	1.18-1.43	1.11	0.94-1.33	1.34***	1.24-1.46
No prior ASCVD, prior APT	1.12**	1.04-1.21	1.06	0.98-1.14	0.75***	0.67-0.84	0.76***	0.72-0.80
Prior ASCVD, prior APT	1.14***	1.07-1.21	1.12**	1.05-1.21	0.66***	0.59-0.73	0.70***	0.66-0.73
Discharge year (vs. 2009-11)								
2012-14	0.92**	0.88-0.97	1.05	0.99-1.12	0.98	0.90-1.07	0.99	0.95-1.03
2015-17	0.82***	0.76-0.88	0.85***	0.78-0.92	0.80**	0.71-0.91	0.79***	0.75-0.84

Note: (***): $p<0.001$; (**): $p<0.01$; (*): $p<0.5$.

[149] For individuals with index hospitalisations between October 2009 and March 2010, information on prior medication use is available for the 6 to 11 months prior to index admission. For all discharges recorded after 1 April 2010, medication history is available for 12 months prior to index admission.

D.8 Long-term effects of suboptimal antiplatelet therapy use

Table D.17 Participant characteristics of antiplatelet therapy initiators, discontinuers and non-initiators at index discharge

Numbers are N (%) unless otherwise specified	**Total Population** 1 Oct 2009 to 31 Dec 2016	**Group 1 Antiplatelet therapy initiators who remained on APT**	**Group 2 Antiplatelet therapy initiators who discontinued APT**	**Group 3 Antiplatelet therapy non-initiators**
N (%)	137,013	105,407	9,800	21,806
Age on discharge, in years (mean, SD)	66.1 (12.6)	65.9 (12.2)	65.9 (13.4)	66.8 (14.1)
Female	38.4	36.7	42.1	45.2
Ethnic group				
White	85.2	85.1	85.1	85.4
Other	1.5	1.5	1.8	1.4
Missing	13.3	13.3	13.1	13.2
SIMD quintile (2009)				
5 (least deprived)	15.4	15.3	16.2	15.4
4	18.2	18.2	18.6	17.6
3	20.5	20.5	21.1	20.4
2	22.3	22.4	21.3	22.3
1 (most deprived)	23.7	23.6	22.8	24.4
Charlson Comorbidity Index				
0 (no-comorbidities)	19.9	18.8	24.5	23.1
1	47.1	47.8	44.9	44.4
2	19.4	20.1	17.2	16.5
3	8.1	7.9	7.5	8.9
4 or more comorbidities	5.6	5.3	5.9	7.1
Mental health inpatient/day case 12 months prior to index admission	1.9	1.5	2.6	3.1
History of ASCVD and antiplatelet therapy use 12 months prior to index admission				
No ASCVD hospitalisation + no antiplatelet therapy	40.0	39.7	40.2	41.3
ASCVD hospitalisation + no antiplatelet therapy use	8.5	5.9	10.5	20.6

Numbers are N (%) unless otherwise specified	**Total Population** 1 Oct 2009 to 31 Dec 2016	**Group 1 Antiplatelet therapy initiators who remained on APT**	**Group 2 Antiplatelet therapy initiators who discontinued APT**	**Group 3 Antiplatelet therapy non-initiators**
No ASCVD hospitalisation + antiplatelet therapy use	21.7	22.7	23.7	15.9
ASCVD hospitalisation + antiplatelet therapy use	29.8	31.8	25.6	22.2

Table D.18 Associations of patient characteristics and antiplatelet use with subsequent cardiovascular event or death after index ASCVD hospitalisation (a multivariable Cox proportional hazards model), by ASCVD type

	Myocardial infarction		**Ischaemic stroke**		**Peripheral arterial disease**		**Other ASCVD**	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Status of APT use at 12 months since discharge (vs. APT initiators)								
APT non-initiators	1.11**	1.02-1.21	1.11*	1.01-1.21	1.02	0.94-1.10	0.91***	0.86-0.95
APT discontinuers	1.06	0.96-1.17	1.06	0.93-1.20	1.11	0.98-1.27	0.78***	0.72-0.84
Female (vs. male)	0.97	0.92-2.02	0.83***	0.78-0.89	0.97	0.91-1.04	0.91***	0.87-0.94
Age (vs. 60-69 years old)								
<50 50-59 years 70-79 years 80-80 years ≥ 90 years	Omitted due to age stratification		Omitted due to age stratification		Omitted due to age stratification		Omitted due to age stratification	
Deprivation quintile (vs. 5, least deprived)								
4	1.12**	1.04-1.22	1.19**	1.05-1.35	1.07	0.96-1.21	1.10**	1.03-1.17
3	1.18***	1.10-1.28	1.26***	1.11-1.42	0.98	0.88-1.10	1.11**	1.04-1.18
2	1.22***	1.13-1.31	1.24***	1.10-1.39	1.02	0.91-1.14	1.17***	1.10-1.24
1	1.28***	1.18-1.38	1.33***	1.18-1.49	1.02	0.91-1.14	1.20***	1.13-1.28
Charlson Comorbidity Index (vs. no comorbidities)[150]								
1	N/a	N/a	N/a	N/a	N/a	N/a	1.12***	1.08-1.17
2	0.52***	0.48-0.56	0.68***	0.60-0.76	1.70	0.43-6.67	1.39***	1.32-1.47
3	0.65***	0.60-0.71	0.84***	0.74-0.95	1.87	0.47-7.33	1.48***	1.37-1.59

[150] In the case of myocardial infarction, stroke and peripheral arterial disease the reference group is 'one comorbidity' as the Charlson Comorbidity Index classifies the presence of these conditions as a comorbidity.

	Myocardial infarction		Ischaemic stroke		Peripheral arterial disease		Other ASCVD	
4 or more	0.81***	0.74-1.22	0.91	0.79-1.05	2.20	0.56-8.64	2.01***	1.86-2.18
Receiving specialist mental health care	1.00	0.85-1.17	0.88	0.72-1.08	1.03	0.80-1.34	1.18**	1.05-1.33
History of CVD and APT use 12 months prior to index admission (vs. no ASCVD + no APT use)								
ASCVD hospitalisation + no APT use	1.90***	1.76-2.05	1.74***	1.54-1.95	1.64***	1.45-1.84	2.13***	1.98-2.31
No ASCVD hospitalisation + APT use	1.76***	1.64-1.89	1.60***	1.45-1.77	1.24***	1.11-1.39	1.24***	1.16-1.32
ASCVD hospitalisation + APT use	2.66***	2.51-2.81	2.53***	2.33-2.76	1.93***	1.74-2.14	2.28***	2.16-2.42

(***) P<0.001, (**) P<0.01, (*) P<0.05

E

Impact of selected policies on the initiation of statin therapy

E.1 Participant characteristics: Statin type use before and after the market entry of generic atorvastatin in May 2012

A slightly higher proportion of women compared to men initiated statins other than atorvastatin before and after the market entry of generic atorvastatin (pre entry: 37.2% of other statin initiators were female while 35.7% of atorvastatin initiators were female; post entry: 38.6% of other statin initiators vs. 34.7% atorvastatin initiators). Prior to 2012, a larger proportion of individuals prescribed atorvastatin were recorded to have a previous CVD-related hospitalisation before October 2009 compared to those being prescribed other statins (57.2% vs. 42.9%), however, the rates became closer over time. Furthermore, a slightly higher proportion of elderly patients initiated statin types other than atorvastatin pre and post market entry (e.g. pre-intervention: 15.3% of other statin initiators were aged between 80 to 89 years vs. 11% of atorvastatin initiators were aged between 80 to 89 years; post-intervention: 16.5% of other statin initiators vs. 12.2% of atorvastatin initiators). A larger proportion of individuals in the atorvastatin group had comorbidities, as defined by the Charlson Comorbidity Index, compared to individuals initiating other statin types, both pre and most market entry. However, the reverse can be observed in the case of individuals reporting a history of mental health-related admissions. No differences were observed in the levels of socio-economic deprivation between individuals initiating atorvastatin versus other types of statins. Lastly, the proportion of patients treated at either small, medium or large GP practices were similar among individuals who initiated atorvastatin and those initiating other statin therapies.

Table E.1 Baseline characteristics of individuals and their prescribers (at patient level) pre and post market entry of generic atorvastatin and by statin type

	Before market entry of generic atorvastatin in May 2012		**After market entry of generic atorvastatin in May 2012**	
	Atorvastatin users	Other statin type users	Atorvastatin users	Other statin type users
N (%)	14,656 (28.1)	37,532 (71.9)	40,074 (47.3)	44,593 (52.7)
Simvastatin*	-	63.9	-	47.1
Rosuvastatin	-	5.5	-	3.6
Pravastatin	-	2.3	-	1.8
Fluvastatin	-	0.2	-	0.1
Monthly prescription rates, mean % (range)	28.1 (22.3 – 47.9)	-	47.3 (24.3 – 73.2)	
Simvastatin	-	63.9 (39.6 – 70.7)	-	47.1 (23.4 – 69.4)
Rosuvastatin	-	5.5 (2.9 – 10.4)	-	3.5 (2.5 – 4.7)
Pravastatin	-	2.3 (1.3 – 3.2)	-	1.82 (0.8 – 5.3)
Fluvastatin	-	0.22 (0.1 – 0.5)	-	0.15 (0.1 – 0.3)
Patient Characteristics				
Sex (% female)	35.7	37.2	34.7	38.6
Age group (%)				
18-49 years	9.7	8.4	9.7	7.7
50-59 years	20.4	18.1	21.9	19.2
60-69 years	29.8	27.6	29.1	27.2
70-79 years	28.3	28.8	25.9	28.2
80-89 years	11.0	15.3	12.2	16.5
90 years or older	0.8	1.9	1.2	2.2
SIMD deprivation quintile (2009) (%)				
1 (most deprived)	24.8	23.1	22.9	23.3
2	22.8	22.5	22.1	21.9
3	20.5	20.7	20.6	19.9
4	18.2	18.3	18.6	18.6
5 (least deprived)	13.7	15.4	15.8	16.4
Charlson Comorbidity Index (within 12 months prior and incl. index event)				
0 (no comorbidities)[1]	17.9	20.6	13.5	20.1
1	44.5	45.8	50.2	46.8
2	21.5	19.8	21.7	18.9
3	9.2	8.3	8.3	8.4

	Before market entry of generic atorvastatin in May 2012		After market entry of generic atorvastatin in May 2012	
	Atorvastatin users	Other statin type users	Atorvastatin users	Other statin type users
4 or more comorbidities	6.8	5.5	6.3	5.9
Mental health inpatient/day case (within 12 months prior to index admission)	1.9	2.1	0.9	1.3
ASCVD-related hospitalisation prior to 1 October 2009 (%)	57.2	42.9	33.5	33.1
ASCVD type (%)				
Myocardial Infarction	33.8	29.8	42.1	26.4
Ischaemic Stroke	13.1	18.5	18.4	23.3
PAD	7.7	8.9	5.5	8.8
Other	45.4	42.8	34.0	41.5
Practice size (%)				
≤5,000 patients	26.4	26.2	24.6	25.9
> 5,000 patients - ≤10,000	48.6	49.7	52.5	51.3
>10,000 patients	20.1	21.6	22.7	22.5

Note: Column percentages presented, unless otherwise indicated. [1] Absence of comorbidities as defined by CCI: in the case of the ASCVD and PAD populations, this means that individuals were not hospitalised for any other of the 19 specified conditions. In the case of the MI and stroke populations, this means that individuals were not hospitalised for at least one out of 18 specified conditions in addition to their index hospitalisations.

E.2 Participant characteristics: Statin type use before and after the market entry of generic atorvastatin in May 2012

A slightly higher proportion of female patients compared to male patients initiated low/medium-intensity rather than high-intensity statin therapy in the periods before and after publication of the clinical guidelines (pre-publication: 37.9% of low/medium intensity statin were initiated by women vs. 35% of high-intensity statins were initiated by women; post publication: 39.7% of low/medium intensity statins were initiated by women vs. 34% of high-intensity statins). When examining the age distribution by statin intensity, 15.8% of low/medium-intensity statin initiators were aged 80 to 89 years compared to only 10.4% of high-intensity initiators being in the same age bracket before the guideline introduction, with similar rates after the guideline (post publication: 18.7% of low/medium intensity statin initiators were aged 80 to 89 years vs. 11.7% of high-intensity initiators). A higher proportion of individuals treated with high-intensity statins had comorbidities compared to those on low/medium intensity regimen before and after the intervention period (pre-publication: 20% of low/medium intensity initiators did not have a history of 19 conditions specified in the Charlson Comorbidity Index vs. 16.6% of high-intensity users; post publication: 21% of low/medium intensity initiators vs. 12% of high-intensity initiators). The proportion of patients treated at either small, medium or large GP practices were similar among individuals who initiated high or lower intensity statins.

Table E.2 Baseline characteristics of individuals pre and post introduction of NICE clinical guideline CG181 recommending high-intensity statin use for the secondary prevention of CVD, by statin intensity

	Before NICE clinical guideline CG181		After Nice clinical guideline CG181	
	High-intensity statin users	Low/medium-intensity statin users	High-intensity statin users	Low/medium-intensity statin users
N (%)	30,039 (32.7)	60,568 (67.3)	25,821 (55.1)	21,057 (44.9)
Mean of monthly prescription rates (range)	32.7 (24.8 – 56.2)	67.3 (43.7 – 75.2)	55.1 (38.9 – 70.4)	44.9 (29.6 – 61.1)
Patient Characteristics				
Sex (% female)	35.0	37.9	34.0	39.7
Age group (%)				
18-49 years	9.9	8.5	9.9	6.2
50-59 years	21.4	17.9	23.1	23.1
60-69 years	30.1	27.1	29.5	26.6
70-79 years	27.2	28.6	24.8	29.2
80-89 years	10.4	15.8	11.7	18.7
90 years or older	0.8	2.1	1.0	2.5
SIMD deprivation quintile (2009) (%)				
1 (most deprived)	24.4	22.9	22.9	22.9
2	22.8	22.2	21.9	21.6
3	20.8	20.5	20.2	19.9
4	17.9	18.5	18.7	18.9
5 (least deprived)	14.0	15.9	16.2	16.6
Charlson Comorbidity Index (within 12 months prior and incl. index event)				
0 (no comorbidities)[1]	16.6	20.2	12.4	21.1
1	45.2	46.1	51.9	45.9
2	22.3	19.5	21.5	18.1
3	9.2	8.5	8.1	8.3
4 or more comorbidities	6.7	5.7	6.1	6.6
Mental health inpatient/day case (within 12 months prior to index admission)	1.7	1.9	0.7	1.0
ASVD-related hospitalisation prior to 1 October 2009 (%)	50.7	38.2	29.9	32.7

	Before NICE clinical guideline CG181		After Nice clinical guideline CG181	
	High-intensity statin users	Low/medium-intensity statin users	High-intensity statin users	Low/medium-intensity statin users
ASCVD type (%)				
Myocardial Infarction	37.3	30.1	43.7	20.5
Ischaemic Stroke	13.5	19.8	19.8	26.5
PAD	7.4	8.7	4.6	9.6
Other	41.9	41.5	31.9	43.5
Practice size (%)				
≤5,000 patients	25.6	26.5	25.9	25.2
> 5,000 patients – ≤10,000	50.6	50.0	51.3	51.7
>10,000 patients	23.8	23.5	22.5	23.1

*Column percentages presented, unless otherwise indicated. [1] Absence of comorbidities as defined by CCI: in the case of the ASCVD and PAD populations, this means that individuals were not hospitalised for any other of the 19 specified conditions. In the case of the MI and stroke populations, this means that individuals were not hospitalised for at least one out of 18 specified conditions in addition to their index hospitalisations.

E.3 Sensitivity analysis: effects of the market entry of generic atorvastatin

Table E.3 Association between the market entry of generic atorvastatin and the likelihood of individuals initiating atorvastatin compared to other statin types

	Odds Ratio (95% Confidence Interval)
Time	0.98 (0.98 – 0.99) **
Intervention 1 (i.e. market entry of generic atorvastatin)	1.38 (1.31 – 1.45) **
Interaction between time and intervention 1	1.04 (1.04 – 1.05) **
Sex (female vs. men)	0.94 (0.91 – 0.95) **
Age group (vs. 60-69 years)	
18-49 years	1.30 (1.19 – 1.36) **
50-59 years	1.16 (1.11 – 1.20) **
70-79 years	0.83 (0.80 – 0.85) **
80-89 years	0.59 (0.57 – 0.62) **
90 years or older	0.40 (0.36 – 0.44) **
Charlson Comorbidity Index (vs. one comorbidity)	
No comorbidities	0.64 (0.62– 0.67) **
2 comorbidities	1.10 (1.06 – 1.13) **
3 comorbidities	1.03 (0.99 – 1.08)
4 or more comorbidities	1.09 (1.03 – 1.14) **
Mental health inpatient/day case within 12 months prior to index admission	0.78 (0.70 – 0.86) **
SIMD deprivation quintile (vs. 5, least deprived)	
4	1.03 (0.99 – 1.07)
3	1.04 (1.00 – 1.08) *
2	0.99 (0.96 – 1.03)
1 (most deprived)	0.94 (0.90 – 0.98) *
History of prior CVD or statin use (vs. no prior CVD, no prior statin)	
Prior CVD, no prior statin	0.91 (0.86 – 0.96) **
No prior CVD, prior statin	1.11 (1.07 – 1.14) **
Prior CVD, prior statin	1.60 (1.55 – 1.65) **

*p<0.05; **p<0.001; Note: Time is measured in months.

E.4 Sensitivity analysis: effects of NICE introduction of clinical guideline CG181

Table E.4 Association between the market entry of generic atorvastatin and the introduction of NICE clinical guideline and likelihood of individuals initiating high-intensity statin compared to low/medium-intensity therapy

	Odds Ratio (95% Confidence Interval)
Time	0.99 (0.99 – 1.00)
Intervention 1 (i.e. market entry of generic atorvastatin)	0.65 (0.48 – 0.88) *
Interaction between time and intervention 1	1.01 (1.00 – 1.01) **
Intervention 2 (i.e. publication of NICE guideline)	1.04 (2.94 – 1.36) **
Interaction between time and intervention 2	1.03 (1.03 – 1.03) **
Sex (female vs. men)	0.93 (0.91 – 0.95) **
Age group (vs. 60-69 years)	
18-49 years	1.23 (1.18 – 1.29) **
50-59 years	1.18 (1.14 – 1.22) **
70-79 years	0.77 (0.74 – 0.79) **
80-89 years	0.52 (0.50 – 0.53) **
90 years or older	0.31 (0.27 – 0.34) **
Charlson Comorbidity Index (vs. one comorbidity)	
No comorbidities	0.65 (0.63 – 0.67) **
2 comorbidities	1.10 (1.07 – 1.14) **
3 comorbidities	1.04 (0.99 – 1.08)
4 or more comorbidities	1.08 (1.03 – 1.14) **
Mental health inpatient/day case within 12 months prior to index admission	0.73 (0.66 – 0.80) **
SIMD deprivation quintile (vs. 5, least deprived)	
4	1.02 (0.98 – 1.06)
3	1.03 (0.99 – 1.07)
2	1.00 (0.96 – 1.04)
1 (most deprived)	0.96 (0.92 – 1.00)
History of prior CVD or statin use (vs. no prior CVD, no prior statin)	
Prior CVD, no prior statin	0.90 (0.85 – 0.95) **
No prior CVD, prior statin	1.12 (1.09 – 1.16) **
Prior CVD, prior statin	1.71 (1.66 – 1.77) **

*p<0.05; **p<0.001; Note: Time is measured in months.

E.5 Sensitivity analysis: effects of the market entry of generic atorvastatin and publication of clinical guideline CG181 versus the market entry of generic atorvastatin alone

The small, yet significant acceleration in monthly high-intensity statin initiations following the publication of the clinical guideline is further highlighted when comparing the results of the first model with two interruptions (**Figure E.1**) to the second model that only plots one interruption, namely the market entry of generic atorvastatin (**Figure E.1**). When only examining the effect of the market entry of generic atorvastatin on the uptake of high-intensity therapy, the monthly trend in high-intensity initiations increases at a rate of 0.65% for the period May 2012 to July 2017, relative to the period from October 2009 to April 2012 ($p<0.001$, 95% CI: 0.45%, 0.86%) (**Table E.3**). When including the effects of the publication of the clinical guidelines, the monthly initiation trend for the period May 2012 to June 2014 initially increases at a rate of 0.62% relative to the period before generic atorvastatin was available, followed by a further 0.15% increase in the monthly initiation trend amounting to 0.78% after the introduction of the guideline, relative to the two years prior ($p<0.05$, 95% CI: 0.71%, 0.83%).

Table E.5 Results of ITS analyses of the impact of the market entry of generic atorvastatin on the proportion of high-intensity statin prescriptions

	Proportion of high-intensity statin initiations (Coeff, 95% CI)
Intercept	35.87 (34.29, 37.45) **
Monthly change prior to market entry of generic atorvastatin	-0.42 (-0.52, -0.32) **
Step change following market entry of generic atorvastatin	3.69 (1.37, 6.01) *
Post-intervention linear trend following market entry of generic atorvastatin	0.65 (0.45, 0.86) **

*p<0.05; **p<0.001; Coeff.: Coefficient; CI: Confidence Interval

Figure E.1 Proportion of monthly statin initiators (%) using high-intensity statin over time, with generic atorvastatin entering the market in May 2012 and NICE clinical guideline CG181 being introduced in July 2014

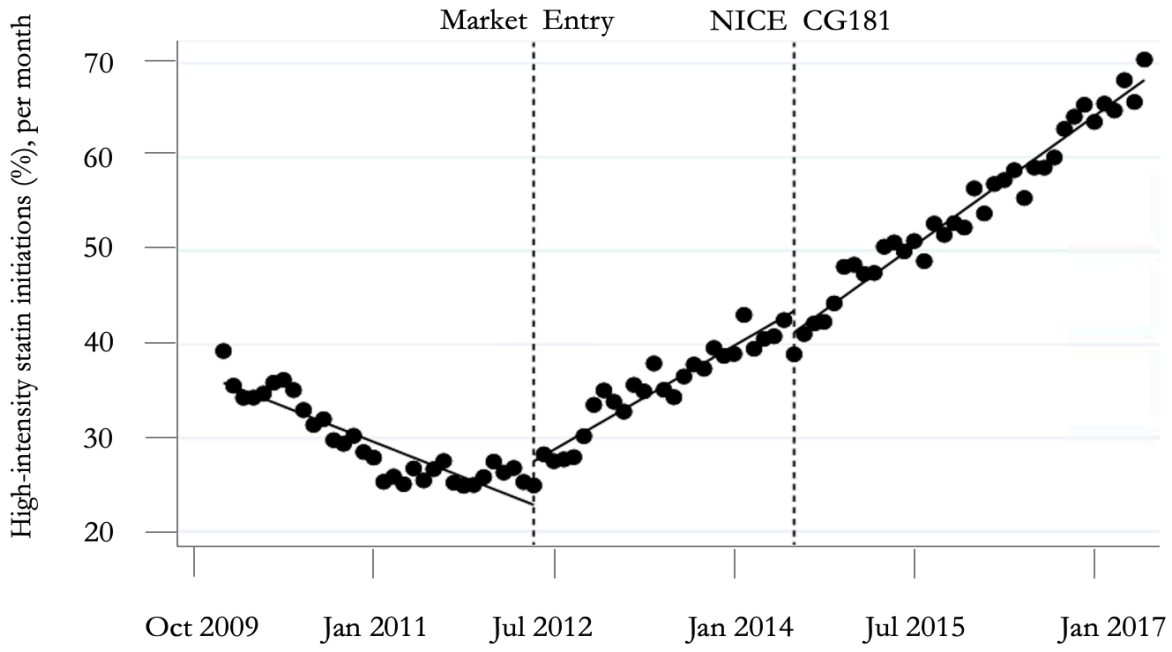


Figure E.2 Proportion of monthly statin initiators (%) using high-intensity statin over time, with generic atorvastatin entering the market in May 2012