Treatment optimisation in older primary care patients – A focus on antihypertensive medication reduction

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This thesis is dedicated to
Jolet
I am glad you are here with me

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Abstract

Background

Antihypertensive treatments are widely used among older adults to effectively reduce morbidity from cardiovascular disease. However, these treatments are also associated with potential harms, and the evolving risk-benefit balance in ageing patients has raised questions about the necessity of indefinite treatment. Recent guidelines have suggested discontinuing antihypertensive therapy for some older patients. However, robust evidence to support this approach is still lacking. Therefore, this thesis aims to address this gap by examining the association between reducing antihypertensive treatment and long-term outcomes in older patients.

Methods

This thesis comprises four empirical chapters. The first is a systematic review that identifies and synthesises outcomes following the cessation of cardiovascular medications. The second chapter develops a method to detect sustained changes in complex pharmacotherapeutic regimens using routinely collected primary care data from the Clinical Practice Research Datalink (CPRD) GOLD dataset. The third chapter investigates patient characteristics associated with the continuation or discontinuation of treatment. Finally, the fourth chapter examines long-term outcomes following the reduction of antihypertensive treatment.

Results

The systematic review found no evidence of a short-term association between antihypertensive treatment discontinuation and all-cause hospitalisation. Using a representative English primary care cohort treated with antihypertensives, a novel algorithm was developed to detect sustained changes in longitudinal data, resulting in the successful identification of treatment reduction. Over time, one-third of patients on antihypertensive treatment reduced their medication. Patients who were older, experienced polypharmacy, or had lower blood pressure were more likely to reduce treatment, whereas those with additional cardiovascular risk factors were more likely to continue. Treatment reduction was associated with a decrease in all-cause hospitalisation; however, it was also associated with increases in all-cause mortality and cause-specific hospitalisation.

Conclusion

This work established that antihypertensive treatment is routinely reduced in primary care and that this intervention is potentially associated with a reduction in all-cause hospitalisation but increased cause-specific harm in a generalisable older population. These findings suggest that discontinuation of antihypertensive treatment should potentially be avoided in patients who tolerate the therapy well. Future research should focus on identifying specific patient populations, specific drug classes, clinical conditions, and strategies for managing long-term preventive pharmacological interventions to better guide treatment decisions.

Contents

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List of Abbreviations

3-HMG CoA . 3-hydroxy-3-methylglutaryl coenzyme A

ACE . . . . . Angiotensin Converting Enzyme.

ACEi . . . . . Angiotensin Converting Enzyme inhibitor.

AHA . . . . . American Heart Association

AHT . . . . . Antihypertensive Treatment.

APC . . . . . Admitted Patient Care

ARB . . . . . Angiotensin Receptor Blocker.

AT_1 . . . . . angiotensin II receptor type 1

BB . . . . . Beta Blocker.

BIHS . . . . . British and Irish Hypertension Society

BMC . . . . . BioMed Central

BMI . . . . . Body Mass Index.

BNF . . . . . British National Formulary

BP . . . . . Blood pressure

CAA . . . . . Centrally acting agents.

CCB . . . . . Calcium Channel Blocker.

CI . . . . . Confidence interval

CPRD . . . . . Clinical Practice Research Datalink.

CVD . . . . . Cardiovascular disease

CYP450 . . . . Cytochrome P450

DDD . . . . . Daily defined dose

dob . . . . . Date of birth

eFI . . . . . Electronic frailty index

ESC . . . . . European Society of Cardiology

ESH . . . . . European Society of Hypertension

EHR . . . . . Electronic healthcare records

GFR . . . . . Glomerular Filtration Rate

GRADE . . . Grading of Recommendations Assessment, Development and Evaluation

GI . . . . . Gastrointestinal

GP . . . . . General Practice/General practitioner

HES . . . . . Hospital Episode Statistics

HR . . . . . Hazard Ratio.

ICD-10 . . . . International Classification of Diseases (10^{th})

IMD . . . . . Index of multiple deprivation

IQR . . . . . Interquartile range

ISAC . . . . . Independent Scientific Advisory Committee

LDL . . . . . Low-density lipoproteins

MHRA . . . . the Medicines and Healthcare products Regulatory Agency

MICE . . . . . Multiple Imputation by Chain Equations

MLTCs . . . . Multiple Long-term Conditions (MLTCs)

mmHg . . . . . Millimetres of mercury

NHS . . . . . National Health Service

OAC . . . . . Oral Anticoagulant.

ONS . . . . . Office for National Statistics

OR . . . . . Odds Ratio

PIM . . . . . Potentially Inappropriate Medication

PRISMA . . . Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

PROSPERO . International Prospective Register of Systematic Reviews.

RAAS . . . . . Renin–angiotensin–aldosterone system

RCT . . . . . Randomised Clinical Trial

RR . . . . . Relative Risk

SD . . . . . Standard Deviation

SE . . . . . Standard Error

UTS . . . . . Up to standard

VA . . . . . Veterans Affairs

1
Introduction

1.1 The burden of modern medicine

For the last hundred years, the life expectancy at birth has increased substantially: where the life expectancy in the early 1920s was around 50 years, it has now risen to approximately 80 years [1, 2]. Both economic prosperity and the rise of modern medicine have been established as major drivers of this change [1, 3, 4]. In addition to increased life-expectancy at birth, there has been an increase in survival at older ages [5]. This has led to an ageing population, in which many are living with multiple long-term conditions and require long-term medical care [6–9]. Therefore, maintaining good health, especially in older people, requires management of risk-factors, co-morbidities, and concurrent disease management strategies [10–12].

Management strategies for the most common chronic conditions in older age, like hypertension, diabetes, and arthritis, often revolve around long-term pharmacological interventions aimed at preventing debilitating disease [13–28]. With many of the age-related disease treatments falling in the category of prevention, older patients are exposed to an ever-growing list of long-term treatments due to escalation of management strategies, for example to off-set disease progression [29–32]. Preventive medications are categorised as pharmacological treatments aimed at reducing the risk of developing disease, for example developing stroke in patients with either high blood pressure (managed with antihypertensive medication) or atrial fibrillation (managed with oral anticoagulants) [33, 34]. Each disease or risk factor carries an inherent risk of resulting in the outcome which was sought to be prevented with preventive medication. However, not all patients develop the disease of interest when not managed. Additionally, the therapies have varying effectiveness in reducing risk of outcome; for example, roughly 140 older patients have to be treated with antihypertensive medication to prevent one stroke in patients with hypertension, while 25 patients with atrial fibrillation need to be treated with anticoagulants to prevent one stroke [35, 36]. This also means that a proportion of patients are exposed to potential treatment harms, while they might never had experienced the harmful outcome. This results in a peculiar balance that needs to be struck in

the benefit and harms of individual medication and in how many patients we are willing to expose to long-term treatment. Furthermore, additional drugs might be prescribed to manage risks associated with the primary pharmacological intervention or to treat misidentified drug side-effects, leading to prescribing cascades [37–40].

The chronic exposure to multiple pharmaceutical interventions can be summarised in the much-debated term "polypharmacy" [31, 41]. Much of this debate around this term is centred around the threshold of the number of active prescriptions, the type of drugs to include, and the clinical consequences of exposure [42, 43]. Another interpretation of polypharmacy is the use of medications that are not indicated. This can potentially lead to the misinterpretation of the term polypharmacy, because of the existence of the term "overtreatment" and the necessity of a clinical interpretation [44, 45]. Studies assessing the impact of the exposure to polypharmacy, exclusively observational, are sensitive to "confounding by indication", resulting in unknown overestimation of the harm associated with polypharmacy [43, 46–49]. As discussed, the accumulation of chronically prescribed medication throughout life is often inevitable and can be deemed "a necessary evil" [50]. Better yet, correct implementation of guidelines could be seen as clinically appropriate [51]. A clinical approach is the sub-classification of polypharmacy in two, not mutually exclusive, groups of "appropriate polypharmacy" and "problematic polypharmacy", thereby accommodating for the practical clinical nuance [52, 53]. In this thesis, the term polypharmacy is used to denote patients who are using five or more concurrent prescriptions, which is generally accepted as the threshold [54]. However, it is not a reflection of either appropriateness or inappropriateness of the number of therapies a patient is receiving. In this work, it is recognised that the exposure to multiple medications can lead to increased complexity of treatment. Therefore, in the absence of clinical assessment with regards to appropriateness, this term could be used as an indicator for the potential of increased harm due to treatment.

In addition to being prone to multiple long-term conditions (MLTCs), how the body interacts with medication, better known as pharmacokinetics, changes as people get older. These changes could lead to changes in drug exposure over time, which might require personalised tailoring of treatment [55, 56]. The principles and subsequent effects of pharmacokinetics can best be explored through ADME, an acronym that summarises the four main determinants in drug exposure: Absorption, Distribution, Metabolism, and Excretion [57]. In general, absorption of medication remains relatively unchanged in older adults. Therefore, this generally does not affect drug treatment to the extent some the other pharmacokinetic properties do [55, 58]. However, increased gastric pH in older people may lead to reduced uptake of poorly water-soluble drugs, which has been explored *in vitro* but the *in vivo* clinical implications seem to be limited [58–60]. The pharmacokinetic term "distribution" deals with the localisation of drugs within the body, mainly over the simplified two-compartment model, which includes a central compartment that encompasses the circulatory system and a peripheral compartment that includes the tissues. The distribution across these compartments is affected by a complex system of equilibrium, perfusion, and protein-binding, which are all determined by individual chemical properties of drugs [61]. Changes in fat composition and blood protein content in older patients will lead to altered distribution of drugs between the central and peripheral compartments. Importantly, this can lead to drug toxicity due to increased free plasma concentrations [62–64]. The metabolism of medication is focused on the alteration of chemical moieties with the primary goal of facilitating elimination of the compound. Metabolism leads to the deactivation of many active drugs to inactive metabolites, leading to a decrease in the blood concentration of the active medication [65]. Changes in metabolism might especially affect medication called pro-drugs, which require modification through the metabolic process to change into the active drug moiety [66]. Although some changes in the liver, the main organ involved in drug metabolism, have been shown in older patients with regards to mass and perfusion, changes in drug metabolic activity due to the ageing process seem to be limited[55, 58, 67]. Finally, excretion of

active substances through the renal pathway is heavily-reliant on healthy renal function, including good perfusion and glomerular filtration rate (GFR) [68]. It has been well-established that in older adults, renal function is altered, manifesting in reduced GRF which leads to increased blood concentrations of renally-cleared drugs[58, 69]. Combined or individual decline of any of the systems associated with the body's ability to deal with medication exposure often leads to increased drug exposure and the increased potential of drug toxicity/adverse effects. Since these effects can be gradual, periodic evaluation of treatments in older adults is very important for the safe usage of medications and best treatment of older adults[58, 70].

Increasing prevalence of MLTCs, changes in clinical practice, problematic polypharmacy, and changes in physiology all predispose to the potential for chronic therapy to no longer be appropriate in older patients, known as potentially inappropriate medication (PIM) [52, 71–73]. Early classification and recognition of the problems caused by PIMs can be traced back to work done by Beers *et al.* in the early 90s [74, 75]. In recent years multiple screening tools have been developed to detect PIMs in older patients. The Beers criteria and STOPP/START criteria are the most well-known examples of this, both providing explicit criteria and guidances on management treatment [76–78]. Management strategies for PIMs are centred around dose management (for example, in the case renal insufficiency), avoiding the prescription of certain classes of medication, discontinuation of therapy, or switching to alternative classes; all of this is done with the aim of reducing the inappropriateness of therapy and preventing unnecessary harm. Discontinuation of treatment has more recently been referred to as "deprescribing". Deprescribing is defined in the literature as: 'the process of withdrawal of an inappropriate medication, supervised by a healthcare professional, with the goal of managing polypharmacy and improving outcomes' [79]. However, the term "deprescribing" is not appropriate to describe medication reduction as it is studied in this thesis. First, at this time, it has only been questioned but not established if continued antihypertensive treatment is inappropriate in older general practice patients [80,

81]. Second, throughout this work, it is unclear if discontinuation of treatment was clinically-led and, as an extension of this, if the intention of discontinuation was to manage polypharmacy and improve outcomes. Finally, as a personal observation, the term deprescribing is often applied incorrectly by generalisation of the intervention as whole, while this is not appropriate [82, 83]. For example, a study on the safe and effective deprescribing of proton pump inhibitors, a medication mainly used to treat acid reflux, only reflects the appropriateness of deprescribing of this specific class of medication and not the intervention "deprescribing" as a whole. Appropriateness of drug therapy is ever-changing due to new insights and discoveries or questioning the current clinical paradigm. One group of therapies for which the appropriateness has been questioned and where therapy optimisation could potentially improve patient outcomes in context of an ageing and frail population are medications used to prevent CVD [80, 81, 84, 85].

1.2 Cardiovascular disease and older individuals

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity globally and in the UK [86–89]. Increased age is associated with an increased risk of CVD; in addition, CVD and its risk-factors are prevalent in older individuals [13, 90–92]. Important modifiable risk factors of CVD are hypertension and hyperlipidaemia, which can be managed through the means of life-style and chronic pharmacological interventions (antihypertensives and statins, respectively) [21, 22, 93]. Furthermore, thrombocyte aggregation inhibitors, also known as antiplatelets, are used in the secondary prevention of CVD after experiencing a stroke or myocardial infarction (MI) [20, 23, 94]. Lastly, in patients with atrial fibrillation oral anticoagulants are indicated to prevent strokes [18].

1.2.1 Hypertension

Hypertension is defined as a state in which blood pressure is considered too high [21, 95]. Blood pressure is subject to the cardiac phases: a systolic phase, when the heart contracts to move blood throughout the circulatory system, and the diastolic phase, when the heart relaxes to refill with blood for next cycle [96]. Blood pressure is considered normal when systolic blood pressure is less than 120 mmHg and diastolic blood pressure is below 70 (<120/70 mmHg), blood pressures ranging from 120 up to 140 systolic and 70 to 90 diastolic are considered elevated, and $\geq$ 140/90 is considered hypertensive [21, 97]. Increased age is associated with an increased prevalence of hypertension, with the prevalence of hypertension exceeding 70 % in people of 65 year and older [98].

Pharmacological management of hypertension is aimed at reducing hypertension-related organ damage and reducing cardiovascular disease by lowering blood pressure [21, 33, 97]. A large individual patient data meta-analysis showed that lowering systolic blood pressure by 5 mmHg reduced cardiovascular events by about 10% which was consistent for patients up to 85 years old [35, 93]. Treatment targets for relatively healthy younger older adults (<74 years of age) are getting lower and maintenance of systolic blood pressure in the range of 120-129 mmHg is now recommended if treatment is well-tolerated [21]. In recent years, work has been done to examine an even more intensive blood pressure management approach with blood pressure targets ranging from 110-130 mmHg, which further reduces CVD outcomes [99–101]. A recent meta-analysis on treatment targets in the older population showed that conventional targets are appropriate, but also highlights a clear gap in evidence in patients over the age of 80 years [102].

The collective group of pharmaco-active agents used to manage elevated blood pressure is called antihypertensive medications or antihypertensives [103]. The specific classes, mechanisms of action, and side effects are discussed at a later point. Patient guidelines provide structured recommendations to support clinical practice

and guide selection of appropriate classes[21, 97]. As with everything, there are several potential exceptions to this structure, which include change of medication due to age, other medications, and co-morbidities [21, 97, 103]. Since there are a large number of these exceptions which are not necessarily relevant in this thesis, these can be found in the guidelines of the National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology [21, 97, 103]. However, the class-specific benefits for some of the drug classes that are included in these exceptions will be discussed in the pharmacology subsection independent of specific implementation recommendations. The generalised recommended structure when drug treatment is indicated is the initiation a single agent (also known as monotherapy) either from the family of calcium channel blockers (CCB) or angiotensin converting enzyme inhibitors (ACEi). When treatment monotherapy is not sufficient, addition of another class is recommended, either the class not selected for the initial treatment or thiazide/thiazide-like diuretics (medication choice flowchart is summarised in Figure 1.1). Combination treatment is characteristic of hypertension management and it is generally accepted that class escalation is more effective at reducing blood pressure than dose escalation of monotherapy [21, 104, 105].

1.2.2 Antihypertensive agents

The different classes compromising the group of antihypertensives will be discussed, including their class mechanism of action and associated side effects (See Figure 1.2). Additionally, the side effects related to the hypotensive effect will be discussed separately. While this will provide the reader with the basis needed for this thesis, this overview is by no means meant to be comprehensive. Comprehensive reviews on pharmacological mechanisms and associated adverse effects are available for further reference [103, 106–108]. The classes discussed throughout this thesis are: Angiotensin-converting-enzyme(ACE) inhibitors, alpha-blockers, angiotensin II receptor type 1 blockers(ARB), beta-blockers, calcium-channel blockers, thiazide and thiazide-like, central-acting, renin-inhibitors, and vaso-active drugs. While

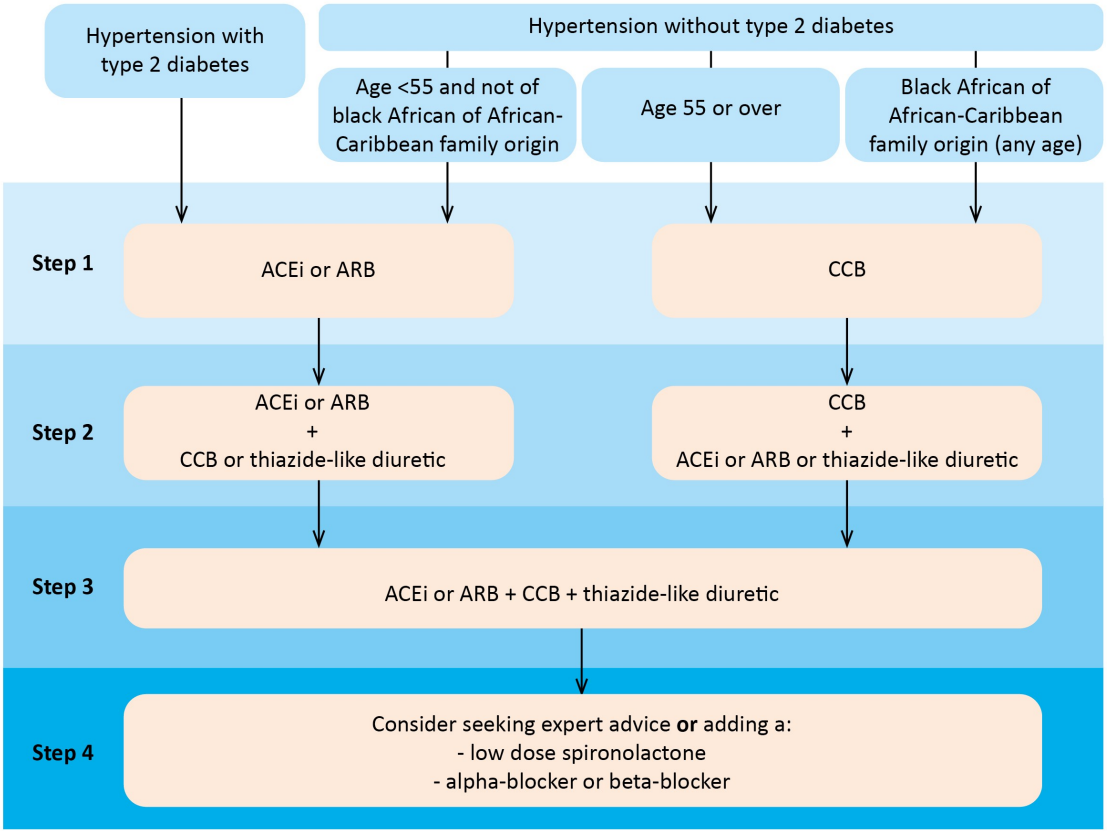


Figure 1.1: Antihypertensive drug choice flowchart. ACEi, Angiotensin Converting Enzyme inhibitor; ARBs, angiotensin receptor blocker; CCB, calcium channel blockers. Adapted from NICE Hypertension guideline 2023 [97].

there are other classes of drugs that elicit a blood pressure lowering effect, this thesis focusses on drugs which primary use is the treatment of hypertension [21, 33, 73]. Therefore, drugs like loop-diuretics are excluded and will not be discussed [109]. Finally, aldosterone antagonists are excluded although they are utilised in hypertension care. This implementation has changed since the recent discovery and re-introduction of this class; therefore, the use of this drug class is restricted to a very specific subset of hypertensive patients [110, 111].

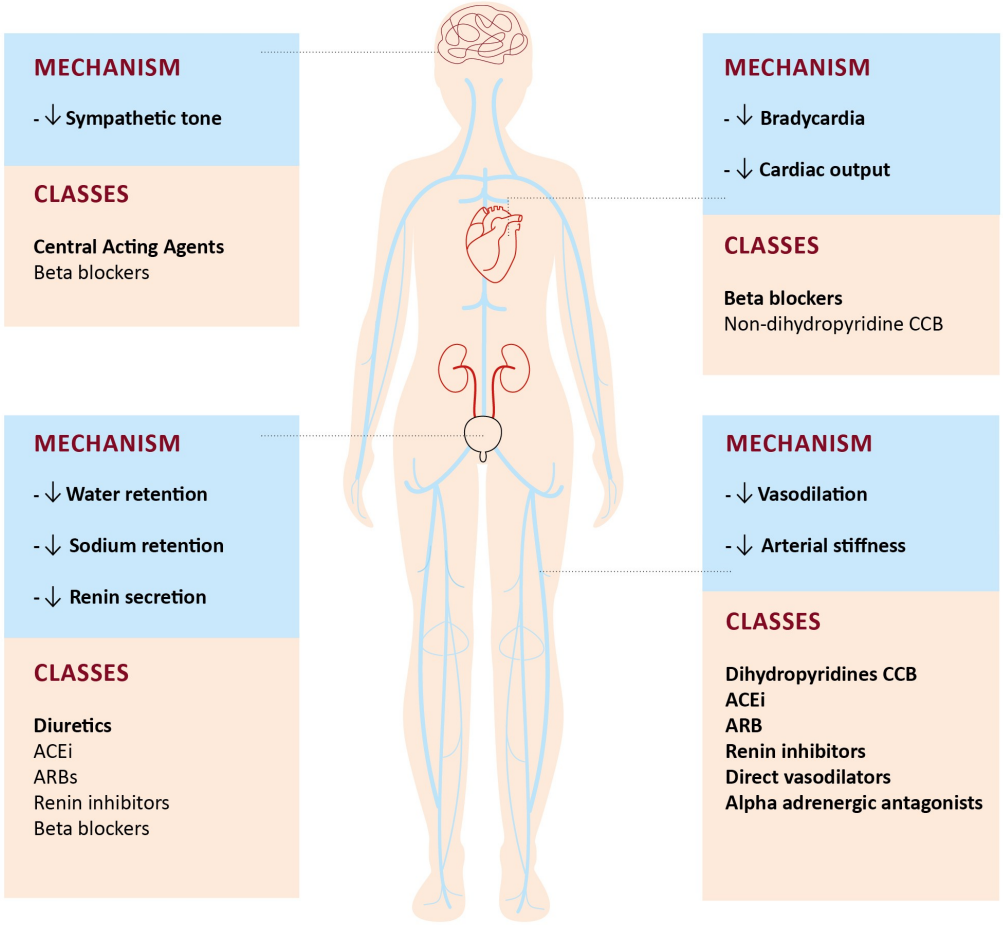


Figure 1.2: Blood pressure control, main mechanisms, organs, and associated pharmacological classes. Main pharmacological class mechanisms are specified in bold. ACEi, Angiotensin Converting Enzyme inhibitor; ARBs, angiotensin receptor blocker; CCB, calcium channel blockers. Adapted from [103].

1.2.2.1 Angiotensin Converting Enzyme inhibitors

Mechanism of Action

Angiotensin Converting Enzyme (ACE) inhibitors (ACEi) elicit their effect by inhibiting the conversion of angiotensin I to the active peptide angiotensin II through ACE [112–114]. Angiotensin II is considered the main active peptide in the renin-angiotensin-system (RAS) which plays an instrumental role in blood pressure homeostasis [113]. Angiotensin II is potent vasoconstrictor acting directly

on smooth muscles through the angiotensin II receptor type 1 (AT_1). Through inhibition of ACE the concentration and effect of angiotensin II is reduced leading to vasodilation and subsequent reduction in blood pressure [115, 116]. In addition to the direct blood pressure lowering effect, angiotensin II is responsible for the production and secretion aldosterone, a mineralocorticosteroid that affects sodium and water retention [117]. Additionally, ACE is involved in the inactivation of bradykinin, a vasodilatory peptide, although this hypotensive effect is attenuated over time [114, 118, 119].

In addition to their blood pressure lowering effect, ACEi have renal protective effects due to reduction of glomerular pressure, prevent maladaptive remodelling of the heart after myocardial infarctions, and reduce the pre- and after-load, making them essential in patients with co-morbidities like type 2 diabetes, heart failure, or previous myocardial infarctions [21, 120–124].

Side-effects

The most well-known side-effect of ACEi is the development of a persistent cough, which develops after initial initiation with medications of this class [125]. It is generally considered that the accumulation of bradykinin in the lungs is the cause of this side-effect, due to high concentration of ACE in endothelial cells of the lungs [119, 126]. Management of ACEi-induced cough is cessation of ACEi and treatment with angiotensin receptor blockers (ARB) [97, 127].

Differential vasodilation of the afferent and efferent arteriole of the glomerulus is associated with a reduction in glomerular pressure resulting in a reduced glomerular arteriolar flow [128], which can potentially lead to renal insufficiency. However, the decrease in filtration rate is reversible after withdrawal of treatment [103, 128, 129]. Furthermore, the use of ACEi has been associated with acute kidney injury (AKI), a condition that is described by a sudden loss of kidney function [130–132].

Finally, due to reduced production and secretion the aldosterone, water and sodium retention is disrupted leading to increased excretion of sodium and retention of potassium [133]. Excessive blood concentrations of potassium can lead to hyperkalemia (potassium levels >5.0 mmol/L), which is associated with arrhythmias, hospitalisation, and mortality [134–136].

1.2.2.2 Alpha adrenergic antagonists

Mechanism of Action

Adrenergic innervation through the hormones (nor)epinephrine acting on α/alpha receptors (and β/beta receptors discussed later) play a vital role in peripheral vascular resistance [137, 138]. Alpha-1-receptors, a subgroup of the aforementioned alpha receptors, cause vasoconstriction when activated in vascular smooth muscles cells by increased uptake of calcium [138, 139]. Antagonism of the sympathetic innervation at the level of alpha-1-receptors results in a reduction of peripheral resistance and thus a decrease of blood pressure [140]. Although alpha adrenergic antagonist were the first pharmaceutical agents considered in the treatment of hypertension, their use has been limited since studies have shown reduced efficacy and increased side-effects compared to other antihypertensive agents [141–143].

Side-effects

Alpha-1 adrenergic receptor antagonist are well-known to cause orthostatic hypotension [142, 144, 145]. Orthostatic hypotension is characterised by a complex of symptoms of dizziness, syncope, and visual disturbances (blurring) [146]. In turn this can increase the risk of falls and fall-related complications, making these agents undesirable in older patients whom are more likely to fall regardless [78, 147–150].

In addition to its effects on smooth muscle cells of the vasculature, alpha-1 adrenergic receptor effects the relaxation of the musculature surrounding the bladder [151]. In male patients it can exhibit positive effects especially in the

management of benign prostate hyperplasia [152]. However, this bladder muscle relaxation is also known to cause urinary incontinence, especially in female patients, which has a considerable impact on quality of life [153, 154].

1.2.2.3 Angiotensin receptor blockers

Mechanism of Action

As previously discussed, angiotensin II elicits a myriad of physiological effects by increasing blood pressure through direct and indirect mechanisms. These effects are achieved by binding of angiotensin II to the effector cells through AT_1 receptors [117, 155]. Angiotensin receptor blockers (ARB) are a group of drugs that are selective antagonist for the AT_1 receptor and inhibit binding of angiotensin II affecting its ability to elicit its effects, reducing blood pressure due to vasodilation and reduced salt and water retention [156, 157]. ARBs antagonise further down the RAS pathway and do not interfere with ACE, which negates for example the effects on bradykinin accumulation [156].

Side-effects

Similarly to the side-effect profile of ACEi and inhibition of the RAS-pathway, ARBs are know to decrease the GFR, potentially leading to renal insufficiency and kidney related injuries [103, 158]. Furthermore, ARBs reduce the production and secretion of aldosterone, resulting in a loss of retention of water and sodium and eventual hyperkalemia [136].

1.2.2.4 Beta adrenergic blockers

Mechanism of Action

Beta blockers, specifically selective beta-1 receptor blockers, elicit their effects through different mechanisms. The main mechanism is the reduction of cardiac output by reduction of heart rate, resulting in reduced blood pressure [159, 160].

Newer generation of beta blockers, with mixed adrenergic blocking capabilities, have additional vasodilatory properties as a result of affinity for alpha-1 receptors [161]. Finally, renin release is in part regulated by sympathetic innervation, mediated through beta-1 receptors on juxtaglomerular cells in the kidney [162–164].

Side-effects

Adrenergic receptors are present throughout the body. Therefore, antagonism of these receptors can elicit a wide range of adverse drug reactions. Although the reduction of heart rate is part of the intended effect, too much reduction can cause bradycardia [103, 165]. Symptoms of bradycardia include syncope, fatigue, dizziness, and possible confusion states due to reduced perfusion of the brain [166].

Due to blockade of the sympathetic tone at the heart muscle cells, the heart is less efficient in responding to sudden drops in blood pressure, leading to orthostatic hypotension [145]. Similar to alpha-1-receptor antagonism, orthostatic hypotension can lead to a cascade of detrimental effects including falls and fractures [167, 168].

1.2.2.5 Centrally acting agents

Mechanism of Action

Centrally acting agents (CAAs) is collective term for various medications that reduce the sympathetic tone by mainly activating alpha-2-receptors in the brain [103, 169]. Peripherally sympathetic innervation results in vasoconstriction through activation of alpha-1-receptors by noradrenaline on smooth muscle cells surrounding the vasculature throughout the circulatory system [170]. By lowering the sympathetic tone centrally, the peripheral release of noradrenaline is restricted and thus its vasoconstrictive effects are reduced, resulting the immediate lowering of blood pressure [169, 170]. The long-term reduction of blood pressure associated with CAAs has been associated in reduction of cardiac output after prolonged drug exposure [103, 171].

Side-effects

Centrally acting agents have an unfavourable side effect profile, which makes their clinical use, especially in older patients, very limited or should preferably be avoided where possible [21, 169, 172]. Side effects are mediated through both central effect and peripheral activation of alpha-2-receptors, and and are very common even at clinically-accepted therapeutic doses [103, 169, 172].

Central side effects of CAA treatment include sedation, cognitive impairment and slowing, and deliriums [172, 173]. Sedation as a result of treatment is reported in over a third of patients taking treatment and is associated with increased risk of falls and subsequent fractures [172, 173].

Peripherally, therapeutic doses of CAA commonly result in dry mouth by inhibiting saliva excretion and constipation by reducing smooth muscle contractility [169]. Furthermore, due to reduction of the sympathetic tone, there is an increased risk of developing orthostatic hypotension, which increases the risk of falls and fractures [146, 174].

1.2.2.6 Calcium channel blockers

Mechanism of Action

Calcium channel blocker (CCB) are generally utilised in first or second line treatment of hypertension [21, 97]. Calcium channel blockers are often referred to as non-dihydropyridine derivates (diltiazem and verapamil), which have limited utility in hypertension management, or dihydropyridine derivates based on their chemical structure [103, 175]. In this thesis the focus is solely on the dihydropyridine derivates. Therefore, the reader can be assured that only dihydropyridines are implied anywhere were CCB is mentioned and not specified. As the name implies, CCBs exert their effect by blocking calcium channels [103, 175]. Calcium channels, specifically found on smooth muscle cells of the circulatory vasculature, are responsible for the uptake

of calcium ions increasing intracellular calcium, which is necessary for smooth muscle cells to contract and increase blood pressure [176]. Inhibition of calcium uptake through blockade of calcium channels leads to vasodilation due to relaxation of vascular smooth muscle cells and reduction of blood pressure [175].

Side-effects

The pharmacological effect of CCB is vasodilation leading to lower blood pressures. However, vasodilation in peripheral tissue can lead to flushing and redness in the face [175]. Furthermore, a side-effect that remains poorly understood is the development of oedema that can occur in various anatomical regions and seems to be more prevalent with amlodipine [103, 175, 177].

Vasodilatory side effects of CCBs also induce syncope, headaches, and hypotension [175]. However, all of these effects are associated with peak blood concentration, and sustained release preparations containing CCBs reduce the likelihood of experiencing these side effects [175, 178].

1.2.2.7 Renin antagonist

Mechanism of Action

Renin antagonist inhibit the catalytic function of renin, the rate-limiting step in the RAS-pathway, which is responsible for the conversion of angiotensinogen to angiotensin I, the precursor to the potent vasocontrictor angiotensin II. Renin inhibition is one of the earliest steps in the RAS-pathway where pharmacological antagonism is possible [179]. In clinical studies, the renin-inhibitor aliskiren has shown similar blood pressure reductions as ARBs. However, it had limited efficacy in reducing cardiovascular events. Therefore, its use in clinical practice has been minimal [180–182].

Side-effects

Side effects of renin are generally considered to be similar to those experienced on ACEi or ARBs. This means that treatment with renin antagonist can lead to hyperkalemia and reduction of GFR [103, 183, 184]. However, these side effects are generally less common compared to ACEi [183, 184].

1.2.2.8 Thiazide and thiazide-like diuretics

Mechanism of Action

Thiazides and thiazide-like diuretics, hereafter collectively referred to as thiazides, are agents that increase diuresis [103, 185]. Similar to CCB, thaizides are a collection of agents with a similar pharmacological effect. However, in contrast to CCB,the systemic effect of thiazides is similar and class heterogeneity is driven mainly by pharmacokinetic effects [185]. Thiazides elicit blood pressure reducing effect through blocking the sodium-chloride co-transporter in the kidneys [185, 186]. Due to blockade of the channel, sodium is not reabsorbed, which in turn causes a loss of water through urinary excretion [185, 186].

Side-effects

Thiazides, by reducing the reuptake of sodium, can cause electrolyte abnormalities mainly hyponatraemia and hypokalaemia [185, 187]. The risk of developing electrolyte abnormalities increases with age and lower body weight [148, 187]. Hyponatraemia, if left untreated, can cause symptoms such as weakness, vomiting, dizziness, confusion, and - more severely - seizures and coma [187].

Renal effects of thiazides are not limited to their primary target (sodium chloride co-transporter), but also interact with renal urate transporters [188]. This increases serum uric acid concentrations, which can lead to gout in some patients [188].

1.2.2.9 Vaso-active drugs

Mechanism of Action

Direct-acting vasodilators, or vaso-active drugs, have direct vasodilatory effects that lead to fast reduction in blood pressure. However, in response to the induced blood pressure reduction, blood pressure regulatory mechanisms are activated leading to increase sympathetic tone and RAS-activity. This makes these agents unsuitable for long-term management of hypertension and as such are no longer recommended in first-line long-term management [21, 103].

Side-effects

The two drugs, minoxidil and hydralazine, representative for this class of antihypertensives mediate their effect differently [103]. Although the associated side-effects to are similar as they are closely related to the regulatory response [103]. Activation of both the sympathetic nervous system and RAS-system lead to tachycardia due to beta-receptor stimulation in the heart, and fluid and sodium retention due to increased aldosterone production and secretion [103, 108, 133, 162].

1.2.2.10 Side-effects

Overarching side-effects, regardless of antihypertensive medication class, are related to the inherent hypotensive properties of these therapies. Reduction in systolic blood pressure, whilst the aim of treatment, could potentially also lead to hypotension, syncope, and falls [103, 147]. These side-effects could have a great impact on patients lives and negatively impact disability-free survival [189].

All the side-effects described here are commonly associated with antihypertensive treatment or commonly associated with the pharmacological effect of the class they belong to. However, this is not an indication of how common these side-effects are in the general population. Most of the side-effects associated with treatment are rare in the general population [147, 148]. However, this is not true for all subgroups of the population; for example, the risk of side-effects is higher in older patients,

which is the subgroup of interest in this thesis [130, 148]. Furthermore, side-effects related to the pharmacological effect often present during the initial exposure to new treatment [130, 190]. This means that if the treatment is generally tolerated well, the likelihood of these side-effect occurring after continued exposure is reduced.

1.2.3 Other cardiovascular medications in this thesis

While the main focus of this thesis is the study of the discontinuation of antihypertensive agents, three other groups of medications used in the management of cardiovascular disease that might be potential targets for cessation are included in Chapter 2. These groups are statins, anticoagulants, and antiplatelets.

Statins are the cornerstone of the management of atherosclerosis and hyperlipidaemia [22]. Statins elicit their lipid lowering effect by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (3-HMG CoA) reductase, a key enzyme in the melavonate pathway, which is essential for the production of endogenous cholesterol [191]. Additionally, melavonate is not only a precursor to cholesterol, but also to isoprenoids, which are involved in the production of pro-inflammatory cytokines, commonly associated with the pleiotropic effects of statin treatment [192, 193]. Statin treatment is generally considered safe and effective, with most notable side-effects being muscle symptoms, liver dysfunction, renal insufficiency, and eye conditions [194–196].

In patients with atrial fibrillation oral anticoagulants are often prescribed to reduce their risk of stroke [34]. Oral anticoagulants can be further subdivided in coumarin-derivatives and direct oral anticoagulants (DOACs). The use of anticoagulants are associated with an increased risk of minor and major bleeds due to the interruption of haemostasis to reduce the formation of blood clots [197, 198].

Finally, antiplatelets are indicated in the secondary prevention of cardiovascular disease, for example in patients with previous stroke or myocardial infarction [20, 23].

Antiplatelets reduce platelet aggregation, which is essential for thrombus formation, by inhibiting platelet activation through their individual class mechanisms [199]. Platelet aggregation is essential in haemostasis and disruption of the physiological balance is associated with an increased risk of bleeding [200, 201].

1.3 Medication discontinuation

The health impacts of discontinuing treatment has been explored for various drug classes (e.g. sleep medication and acid reflux medication), in different populations (e.g. older and frail), and to varying intensity (e.g. poly-deprescribing, stopping more than one medication) [82, 202–205]. Although medication discontinuation is recognised as an inherent aspect of long-term care and essential to therapy optimisation, there is a lack of evidence on outcomes in general practice patients [83, 206, 207]. Therefore, evidence in relation to outcomes and the discontinuation of specific drug groups or classes is now essential, as viewing medication discontinuation (or deprescribing) as a general intervention is potentially not appropriate [83].

Guidelines on general management of multi-morbidity, CVD, and hypertension have recommended using clinical judgement when prescribing in older individuals [15, 33, 97]. Furthermore, the Geriatric Cardiology Leadership Council of the American College of Cardiology published a perspective paper on reducing treatment used in the prevention of CVD, citing the lack of evidence to support safe implementation of medication reduction [80]. Therefore, this thesis aims to synthesise existing evidence from both randomised and observational studies on the reduction of cardiovascular preventive medication, while also contributing new insights into its long-term outcomes in older patients in general practice.

1.4 Types of evidence

This thesis aims to gather evidence on the safety and efficacy of reducing medications used for the prevention of CVD, with a particular focus on antihypertensive medication. Evidence is drawn from both published RCTs, generally considered the gold standard, and observational studies [208, 209]. Although observational studies are often regarded as lower in quality compared to RCTs, well-conducted observational research can provide valuable insights, particularly in the absence of RCTs with long-term follow-up that are sufficiently powered to detect associations [209, 210].

One key distinction between RCTs and observational studies that is central to this work is the element of randomisation. In RCTs, treatment assignment is random, which means that current patient characteristics or prior history do not influence whether a patient receives the intervention (or - in the case of this thesis - has their treatment reduced or not) [211]. In contrast, observational studies rely on naturally occurring exposures, where treatment decisions are influenced by patient-specific factors rather than random chance [212]. This results in an unequal distribution of patient characteristics between exposed and unexposed groups.

When patient characteristics are associated with both the exposure (medication reduction) and the outcome (e.g., mortality), they act as confounders. Various statistical methods can be used to adjust for confounding in observational studies, but accurately accounting for all associated patient characteristics remains a challenge [213, 214]. In the case of cardiovascular medication discontinuation, relevant patient characteristics are not well-defined, necessitating their careful identification and consideration in any analyses [215].

1.5 Aims and objectives of the thesis

This thesis will answer the following questions:

1. What evidence for the safety and efficacy of reducing preventative cardiovascular drugs is currently available?

By assessing the available evidence and where possible apply meta-analyses to aggregate estimators of multiple studies, an overview can be made of the current landscape of cardioprotective medication reduction. Furthermore, it allows for the identification of gaps in the current knowledge and evidence as well as where to apply this thesis.

2. How can we identify patients whose antihypertensive treatment is reduced in routinely collected health care data?

Currently, there are limited methods available to analyse prescription data over large periods of time, where treatment does not consist of monotherapy. The development of a method to detect sustained changes in prescriptions is essential to identify patients whose treatment is reduced.

3. What are the characteristics of the patients associated with the reduction of antihypertensive treatment?

Currently, it is unclear which patient characteristics are associated with stopping antihypertensive treatment in routine clinical care. One of the reasons for this is the lack of clear and concise clinical guidelines, which in turn can be attributed to a lack of evidence on long-term results after reducing treatment [33, 97]. The elucidation of patient characteristics associated with discontinuation of antihypertensive treatment is essential to adjust any models examining outcomes in observational data.

Finally, and the main question of this thesis is:

4. What are the long-term benefits and harms of reducing antihypertensive treatment in older primary care patients?

1.6 Structure of the thesis

The thesis consists of four results chapters to answer the previously identified thesis questions. Where the beginning (Chapter 2) of the thesis is focussed on the broader question of cessation of medication used in the prevention of CVD, the subsequent chapters presenting the observational work focus on antihypertensive treatment discontinuation.

Chapter 2 presents the results of a systematic review and meta-analysis which gives insight into the current available evidence on cessation of four different drug groups, namely anticoagulants, antihypertensives, antiplatelets, and statins.

Chapter 3 presents the development of a novel method for detecting sustained changes in complex pharmacotherapeutic regimens in the CPRD Gold database. The method developed in this chapter is used to detect reduction in antihypertensive treatment in a cohort of older English primary care patients, which is further analysed in chapters 4 and 5.

Chapter 4 presents the results of a nested case-control study that aims to explore the patient characteristics associated with reducing antihypertensive treatment.

Finally, chapter 5 presents the long-term outcomes of reducing antihypertensive treatment in older primary care patients using a retrospective cohort design.

2

Safety and efficacy of cardiovascular medication reduction in older patients: a systematic review and meta-analysis

2.1 Chapter overview

This chapter presents the results of a systematic review and meta-analysis of the literature comparing the reduction of four different cardiovascular (antihypertensives, statins, antiplatelets, and oral anticoagulants) preventive treatment with usual care, or continued treatment, in older patients (75 years and over).

The primary outcome was all-cause hospitalisation for all drug groups. Secondary outcomes included all-cause mortality, cardiovascular hospitalisation, and cardiovascular mortality. Pooled treatment effects were generated using random-effects meta-analyses.

Twelve studies (four RCTs and eight observational studies) provided data from 377,425 (range: 106 – 166,465) patients, mean follow-up was 12-weeks to 6.5-years. Six studies examined antihypertensive therapy reduction (n=177,578 patients), three examined statin discontinuation (n=195,611), one examined antiplatelet withdrawal (n=2,346), and two examined anticoagulant cessation (n=2,159). There was no evidence of an association between antihypertensive treatment discontinuation and all-cause hospitalisation (2 studies, 954 patients; risk ratio, 1.10 [95%CI 0.63-1.93]; I^2=0%). However, antihypertensive medication reduction was associated with an increased risk of all-cause mortality (4 studies, 10,940 patients; relative risk, 1.36 [95%CI, 1.14-1.62]; I^2=86%).

The number of studies included per group in this analysis was small and the contribution of RCTs was limited to antihypertensive medication reduction only (n=1,229). Withdrawing preventive cardiovascular medications may be associated with overall poorer health outcomes but these findings were primarily driven by observational studies that had important methodological limitations. Additionally, there was very limited reporting of outcomes that may be associated with potential benefits of reducing preventive cardiovascular medication.

2.2 Introduction

Cardiovascular disease is the leading cause of morbidity and mortality worldwide [216]. Preventive cardiovascular medications reduce the risk of cardiovascular disease events and are widely recommended by clinical guidelines [22, 34, 94, 217–221]. While these medications have led to a decrease in cardiovascular mortality over the last 5 decades [222], they have also caused a dramatic increase in the number of concurrent medications patients are prescribed [41].

Cardiovascular medication is mostly prescribed for older patients, who often also have multiple long-term conditions (MLTCs) which they take medications for [11]. This means that they are more likely to be exposed to polypharmacy, which could either be appropriate or problematic as discussed in detail in Chapter 1) [41, 43, 47, 52, 54]. As described in detail in Chapter 1, in recent years questions have been asked about the appropriateness of using cardiovascular medication in older patients with frailty and multi-morbidity, who are often excluded from drug trials [41, 80, 223]. In patients experiencing problematic polypharmacy, medication reduction has been suggested as a method to improve outcomes [80, 224, 225]. Indeed, for some patients it may become less important for them to maximise longevity and more important to take fewer medications, have fewer adverse effects, remain functionally independent, and optimise other patient-centred outcomes. However, there is currently little evidence to inform cardiovascular medication reduction in practice [80], and both national and international guidelines advise using clinical judgement in the management of patients with multi-morbidity and/or frailty [33, 224].

Previous systematic reviews on this topic did not include important recent randomised controlled trials, did not perform meta-analyses, or limit their population to older patients (aged 65 and over), but not the very old (aged 75 and over) [206, 207, 226], resulting in uncertainty with regards to the safety and efficacy of cardiovascular medication reduction in older adults. Additionally, because of the potential high

risk posed by reducing preventive medication and questions around acceptability of this practice, observational studies could provide valuable evidence, albeit it being of lower quality compared to randomised studies [227].

2.3 Chapter Aim

The objective of this systematic review was to evaluate the association between preventive cardiovascular medication reduction and clinical outcomes including all-cause hospitalisation (efficacy outcome), cardiovascular disease, and death (safety outcomes). Cardiovascular medication groups included in this were antihypertensives, statins, antiplatelets, and oral anticoagulants.

2.4 Methods

This systematic review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis [228]. The protocol was registered with PROSPERO (registration number: CRD42020208223) and has been published BioMed Central (BMC) Systematic Reviews (Appendix A.1) [229].

2.4.1 Data Sources and Searches

The search strategy was developed for Embase (OvidSP) [1974-present], MEDLINE (OvidSP) [1946-present] and Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) for articles published from database inception to March 7, 2023. Terms included in the strategy were *deprescribing, reduction, withdrawal, cessation, antihypertensive, anticoagulant, antiplatelet, antihyperlipidemic, frail, and elderly.* The full search strategies are included in the appendices (Appendix A.2). No language restriction was applied to the search. The search strategy was reviewed by an information specialist (Nia Roberts). Reference management software (EndNote 20, Clarivate Analytics, US) was used for de-duplications. Titles and abstracts were

screened for relevance using online review management software (Rayyan) by two independent reviewers: Rik van der Veen (RV) and either Isabel Henderson (IH) or Joseph Lee (JL) [230]. Full text papers were independently screened against inclusion and exclusion criteria by two reviewers (RV and Lucy Goddard (LG)), with differences assessed, reviewed, and resolved by consensus or the third reviewer (James Sheppard (JS)).

2.4.2 Eligibility Criteria

The inclusion and exclusion criteria for the current study were summarised in table 2.1. Studies were considered eligible if they were randomised controlled trials or non-randomised studies of interventions (prospective and retrospective cohort studies, and case-control studies) where at least half of the participants were aged 75 years and above or provided subgroup analysis for this population, compared cardiovascular medication reduction with a control, and provided information on any of the pre-specified outcomes of interest. Cardiovascular medication was defined as either antihypertensives (e.g. calcium channel blockers), lipid lowering agents (e.g. statins), antiplatelets (e.g. aspirin), or oral anticoagulants (e.g. vitamin K antagonists). Controls were defined as placebo, usual care, or medication continuation. Studies were considered ineligible if they were case reports or compared cardioprotective medication reduction with an inappropriate control (e.g. diet changes). Inappropriate controls were defined as no control or other interventions (e.g. physiotherapy, healthy lifestyle interventions, or withdrawal of multiple drugs in different groups). Exclusion criteria for this study were: single-arm studies, studying medication reduction in the context of end-of-life care, temporary withdrawal, or explicitly in response to adverse events.

Table 2.1: Table of inclusion and exclusion criteria for the following domains: Patients, Intervention, Comparators, Outcomes, and Study Designs

	Inclusion Criteria	**Exclusion Criteria**
Patients	Patient population >75 years of age Median/mean >75 years old Subgroup analysis >75 years old	Patients receiving palliative care (end-of-life)
Intervention/ Exposure	Reduction, withdrawal, discontinuation, deprescribing of preventative cardiovascular therapies: Antihypertensives, statins, antiplatelets, and oral anticoagulants	Studies in which medication reduction is reactive in nature, e.g. patients experiencing adverse events or symptoms of the drug therapy, and studies that are looking at temporary withdrawal (e.g. in preparation for major surgical interventions) or as part of a run-in phase prior to randomisation in a clinical trial
Comparators	Usual care Placebo-controlled Active maintenance of current therapy	No comparator High vs low reduction
Outcomes	All-cause hospitalisation, all-cause mortality, cardiovascular events, cardiovascular mortality, quality of life, non-fatal myocardial infarction, non-fatal stroke, falls, fractures, cognitive functioning, bleeding events, renal functioning, electrolyte abnormalities, medication burden, drug reinstatement, time-in-hospital, blood pressure changes, and frailty status	N/A
Study designs	RCTs, Controlled cohort studies, Case-control	

2.4.3 Data Extraction

Two reviewers (RV and LG) independently extracted data using a standardised data extraction form. Extracted data included study characteristics, baseline demographics of study participants, description of intervention, and intervention effect estimates. Discrepancies were checked and resolved by consensus or the third reviewer (JS).

2.4.4 Outcomes

The primary outcome of this study was all-cause hospitalisation, including accident and emergency admissions, planned admissions, and inpatient stays of any duration. The aim of medication reduction in the population of interest is to reduce hospitalisation due to adverse drug effects or inappropriate polypharmacy. Conversely, reducing preventive medication has the potential to cause hospitalisation for the disease the initial treatment targeted. All-cause hospitalisation is a very widely reported outcome, and unlike specific events, applies to both serious adverse effects of polypharmacy and medication reduction.

Secondary outcomes were all-cause mortality, hospitalisation due to cardiovascular events, cardiovascular mortality, quality of life, non-fatal myocardial infarction, non-fatal stroke, falls, fractures, cognitive functioning, bleeding events, renal functioning, electrolyte abnormalities, medication burden, drug reinstatement, time-in-hospital, blood pressure changes, and frailty status.

2.4.5 Risk of Bias Assessment

Risk of bias was assessed using Cochrane Risk of Bias 2-tool or Risk of Bias in Non-Randomised Studies of Interventions-tool, depending on the study design [231, 232]. Assessments were performed independently by two reviewers (RV and LG), and discrepancies were resolved by a third reviewer (JS). The five domains that were

assessed, for randomised controlled trials, were those associated with bias that arise from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results [231]. Assessment of bias domains for non-randomised studies of interventions were: pre-intervention (bias due to confounding and bias in selection of participants into the study), at intervention (bias in classification of interventions), and post-intervention (bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result) [232].

2.4.6 Data Synthesis and Analysis

Pooled treatment effects were calculated using random-effects meta-analysis. For dichotomous outcomes, risk ratios (RRs) and 95% CIs were estimated for each study or extracted adjusted hazard ratios were used. The common measure of association adopted was risk ratios with hazard ratios considered equivalent where outcomes were rare. For continuous outcomes (blood pressure and quality of life), the mean change from baseline to follow-up was analysed. Outcomes expressed on the same scale were aggregated using mean difference, continuous outcomes on different scales were aggregated using standardized mean difference (Hedges g). Standard errors were obtained from the lower and upper limit values of the 95% confidence interval and substituted in the following equation: (upper limit – lower limit)/3.92 [233]. The variability across studies due to heterogeneity was investigated using forest plots and I^2 statistics. The proportion of patients maintaining medication reduction at end of follow-up (intervention success), was calculated using inverse variance methodology on logit transformed proportions.

All statistical analyses were performed using the Meta package in R statistical software version 4.0.3 [234, 235].

2.5 Results

A total of 24,161 unique articles were retrieved using the search strategy from database inception to March 7, 2023. After title and abstract screening, 122 articles were identified as potentially relevant. Twelve studies were included after full-text review (Figure 2.1). Only three out of the twelve included articles reported data on the primary outcomes: two antihypertensive medication reduction RCTs and one observational study examining the effects of discontinuing statin therapy [236–238]. The remaining nine studies, two RCTs and seven observational studies, reported secondary outcomes only, and were analysed in their respective drug groups [123, 239–246].

2.5.1 Study characteristics

Eligible studies included a total of 377,425 patients, with follow-up ranging from 3 - 78 months. The mean age range of participants was 75 to 84.8 years and 74,928 (19.9%) were female (Table 2.2). A total of six antihypertensive medication reduction studies (n = 177,578) were included, four of these were RCTs (n = 1,233) and two were observational studies (n = 176,345) [123, 236, 237, 239–241]. Three studies examined the effect of discontinuing statin therapy, all of these were observational studies (n = 195,611) [238, 242, 243]. A single observational study was included that studied the effects of aspirin withdrawal (n = 2,346) [244]. Finally, two studies were included examining the effects of oral anticoagulation withdrawal, all of which were observational studies(n = 2,159) [245, 246]. Out of the twelve included studies, six studies were conducted in primary care, four in a hospital outpatient setting, and in two studies the setting was unclear (Table 2.2).

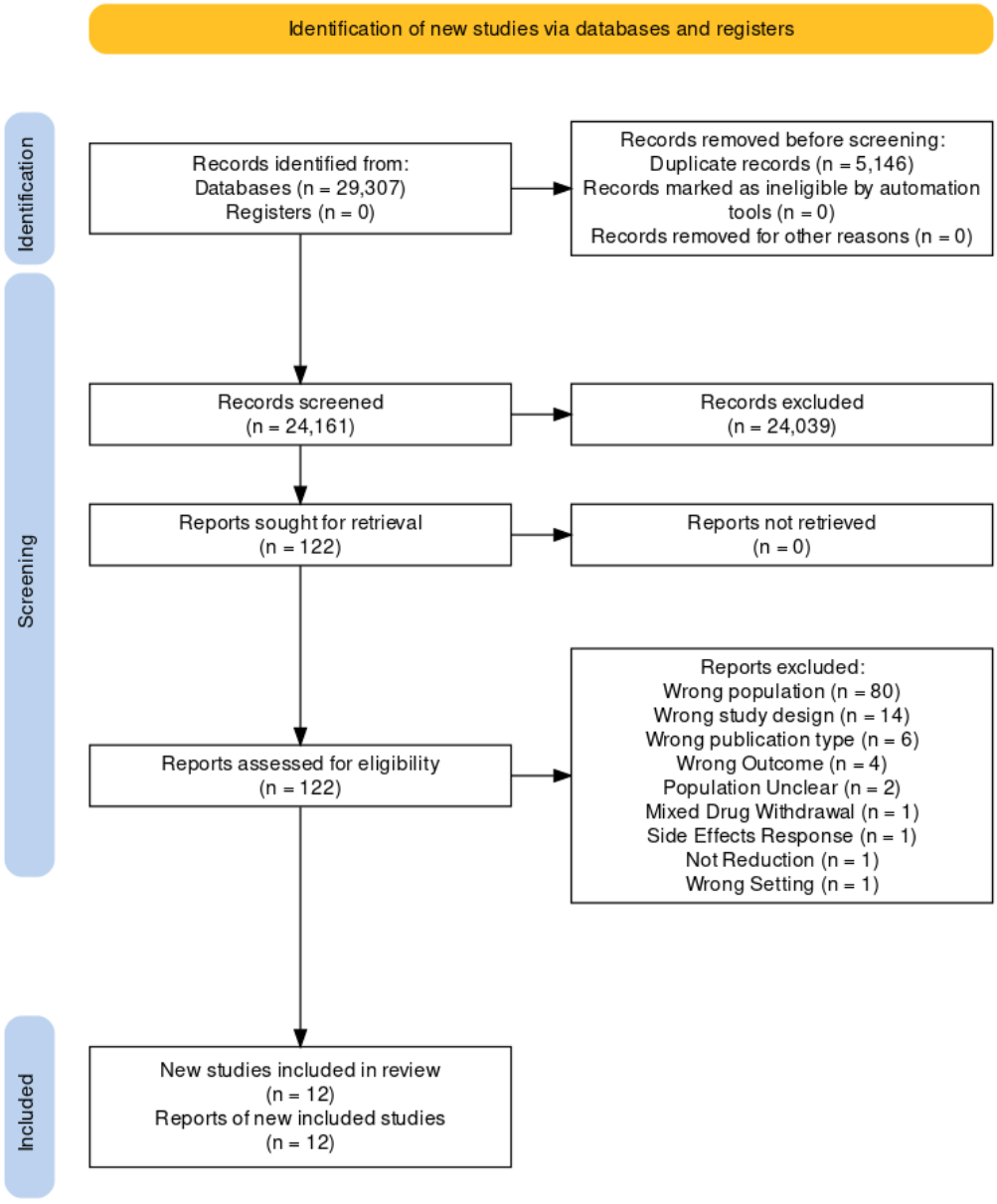


Figure 2.1: PRISMA flow chart of study selection.

Table 2.2: Descriptive table of included studies

Drug Group	Author, Year	Country	Design	Setting	Study Period	Follow-up	No. of Patients	No. of Patients Intervention/ exposure	No. of Patients Control/ continuation	Age, mean (SD), y	Female, No. (%)	Intervention/ Exposure Description	Comparator Description	Primary Outcome
Antihypertensive	Aubert, 2021 [240]	USA	Obsv	Primary Care	2011 - 2013	9 months	166,465	72,672	93,793	75.2 (7.5)	3,034 (1.8%)	Dose decrease	No dose change	Composite outcome of hospitalisation (acute CVD event. syncope, or fall) (aAR; 18.3% vs 14.8%)
	Burr, 1977 [239]	Wales	RCT	Hospital	-	12 weeks	106	54	52	82	93 (87.7)	Diuretics withdrawal	Diuretics continuation	Ankle oedema (OR; 0.57 (95% CI 0.0 - 4.5))
	Gilstrap, 2017 [123]	USA	Obsv	Hospital	Jan '05 - Dec '13	-	9880	308	9572	78 (7.82)	4079 (41.3)	ACE/ARB Discontinuation	ACE/ARB Continuation	All-cause mortality at 30 days (aHR; 1.92 (95% CI 1.32 - 2.81))
	Moonen, 2015 [237]	Netherlands	RCT	Primary Care	Jun '11 - Aug '13	16 weeks	356	180	176	81.3 (4.45)	209 (58.7)	Discontinuation of antihypertensive medication	Continuation of antihypertensive medication	Change in overall cognition compound score (difference; 0.02 (95% CI -0.19 - 0.23))

Table 2.2 continued from previous page

Statins	Sheppard, 2020 [236]	UK	RCT	Primary Care	Mar '17 - Sep '18	12 weeks	569	282	287	84.8 (3.4)	276 (48.5)	Removal of one antihyper-tensive drug	Usual care	Systolic blood pressure <150 mmHg (RR; 0.98 (97.5% 1-sided CI, 0.92 - inf))
	Walma, 1997 [241]	Nether-lands	RCT	Primary Care	-	6 months	202	102	100	76 (1)	151 (74.8)	Withdrawal of all diuretic treatment	Contin-uation of diuretic treatment	Clinical occurrence requiring diuretic treatment (risk difference; 36% (95% CI 22% - 50%))
	Giral, 2019 [242]	France	Obsv	Primary Care	2012 - 2014	Mean: 2.4 years	120,173	17,204	102,969	75	71,118 (59.2)	Statin discontin-uation	Statin contin-uation	Cardiovascular hospitalisation (HR; 1.33 (95% CI 1.18 -1.50))
	Rea, 2021 [238]	Italy	Obsv	-	Oct '13 - Jun '18	Mean: 2.4 years	8,020	4,010	4,010	76.3 (6.35)	3,141 (39.2)	Statin discontin-uation	Statin contin-uation	All cause mortality (HR; 1.15 (95% CI 1.02 - 1.30))

Table 2.2 continued from previous page

Antiplatelets	Thompson, 2021 [243] [primary]	Denmark	Obsv	-	Jan '11 - Dec '16	-	27,463	8,311	19,152	Median; 79 (77-83)	18,134 (66.0)	Statin discontinuation	Statin continuation	MACE (SHR; 1.32 (95% CI 1.18 - 1.48))
	Thompson, 2021 [243] [secondary]						39,955	9,853	30,102	80 (77-84)	18,717 (46.8)			MACE (SHR; 1.28 (95% CI 1.18 - 1.39))
	Rodriguez, 2011 [244]	UK	Obsv	Primary Care	Jan '00 - Dec '07	Mean(SD): 3.2(2.2) years	2,346	174	2,172	$\geq$ 75	-	Recent discontinuation of low dose aspirin	Continuation of low dose aspirin	Non-fatal myocardial infarction (RR; 1.96 (95% CI 1.27 - 3.02))
Oral Anticoagulants	Gallego, 2013 [245]	Spain	Obsv	Hospital	Jan '09 - Dec '09	Mean(SD): 2.3(0.45) years	529	116	413	75.6 (9.66)	271 (51)	Aceno-coumarol withdrawal	Aceno-coumarol continuation	Thrombotic/ cardiovascular events (HR; 2.72 (95% CI 1.56 - 4.72))
	Rivera-Caravaca, 2017 [246]	Spain	Obsv	Hospital	May '07 - Dec '07	Mean(SD): 6.23(2.67) years	1,361	136	1,225	76 (7.42)	698 (51.3)	OAC discontinuation	OAC continuation	Adverse CVD events (HR; 1.45 (95% CI 1.01 -2.08))

2.5.2 Risk of Bias

Risk of Bias was assessed in all included studies (figure 2.2). The risk of bias for the RCTs studying the effects of antihypertensive medication withdrawal was deemed low for one study [241], some concerns for one study [237], and high in two studies [236, 239]. Of the two observational studies on antihypertensive medication withdrawal, one had a low risk of bias [123] and one a moderate risk of bias [240]. The three observational studies concerning statin discontinuation all had low-risk of bias [238, 242, 243]. The observational study on antiplatelet cessation had a moderate risk of bias [244]. Finally, the two observational studies on anticoagulant discontinuation both had a high risk of bias [245, 246].

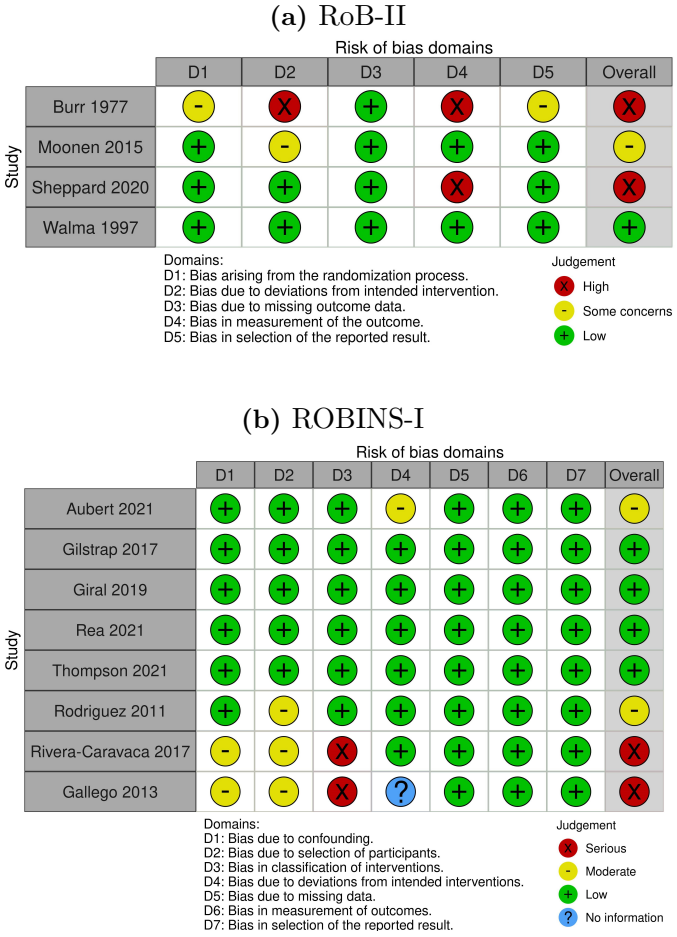


Figure 2.2: Risk of bias in the included studies. RoB-II, risk-of-bias tool for randomized trials; ROBINS-I, Risk Of Bias In Non-Randomized Studies - of Interventions.

2.5.3 Antihypertensive reduction outcomes

2.5.3.1 Primary Outcome

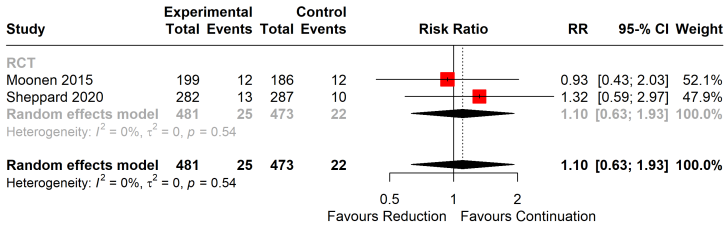
All-cause hospitalisation was reported for two RCTs of antihypertensive medication reduction [236, 237]. Out of total of 954 participants, 25 events occurred in those reducing cardiovascular medication and 22 in the control groups, after 12-15 weeks of follow-up. There was no evidence of an association between antihypertensive medication reduction and all-cause hospitalisation (relative risk, 1.10 [95% CI, 0,63-1.93]; heterogeneity, I^2=0%; Figure 2.3a).

2.5.3.2 Secondary Outcomes

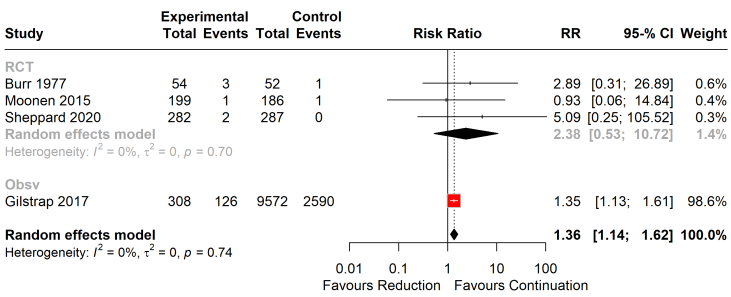
There was no evidence from the RCTs that antihypertensive medication reduction was associated with all-cause mortality (relative risk, 2.38 [95% CI, 0.53-10.72]; heterogeneity, I^2=0%; Figure 2.3b), cardiovascular hospitalisation (relative risk, 1.46 [95% CI, 0.42-5.15]; heterogeneity, I^2=0%; Figure 2.3c), and cardiovascular mortality (relative risk, 2.02 [95% CI, 0.26-15.56]; heterogeneity, I^2=0%; Figure 2.3d), although numbers of outcome events were low. In the observational studies there was evidence of an association with all-cause mortality (relative risk, 1.35 [95% CI, 1.13-1.61]; Figure 2.3b) and no evidence of an association with cardiovascular hospitalisation (adjusted hazard ratio, 1.07 [95% CI, 0.92-1.25]; Figure 2.3c). In a combined analysis of both RCT and observational studies, there was evidence of an association for all-cause mortality (risk ratio, 1.36 [95% CI, 1.13-1.62]; heterogeneity, I^2=0%; Figure 2.3b) and no evidence for an association for cardiovascular hospitalisation risk ratio, 1.07 [95% CI, 0.92-1.25]; Figure 2.3c), although heavily weighted towards the observational studies.

For individual outcomes there was no evidence from RCTs for an association of antihypertensive medication withdrawal and strokes (relative risk, 3.84 [95% CI, 0.43-34.60]; heterogeneity I^2=0%; Figure 2.4a), myocardial infarctions (relative risk, 0.98 [95% CI, 0.14-6.89]; heterogeneity I^2=0%; Figure 2.4b), and falls (relative

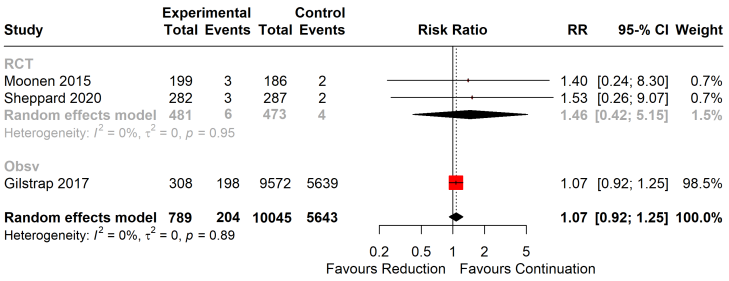
(a) All cause hospitalisation



(b) All cause mortality



(c) Cardiovascular hospitalisation



(d) Cardiovascular mortality

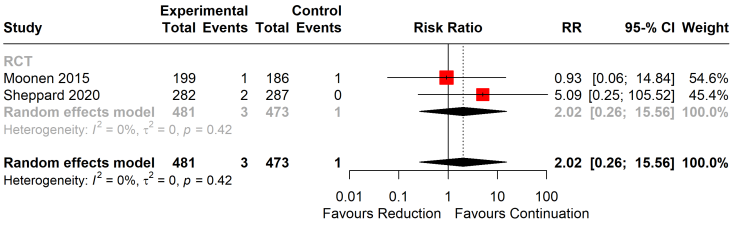


Figure 2.3: Association of antihypertensive medication reduction on hospitalisation and mortality. CI, confidence interval; RR, relative risk.

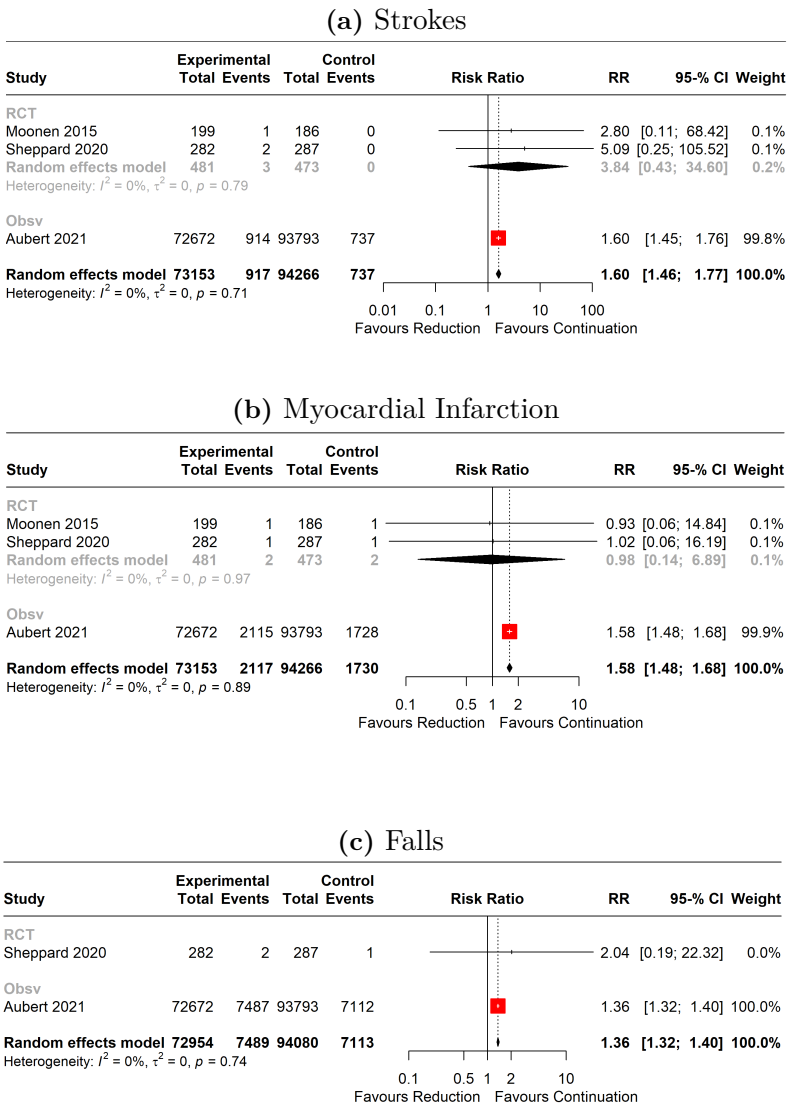


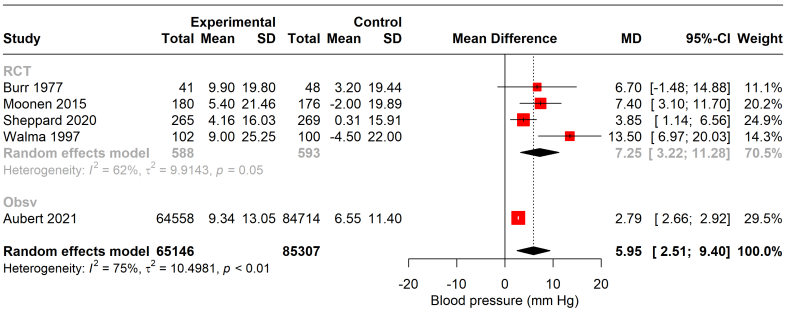
Figure 2.4: Association of antihypertensive medication reduction on strokes, myocardial infarctions, and falls. CI, confidence interval; RR, relative risk.

risk, 2.04 [95% CI, 0.19-22.32]; Figure 2.4c). Evidence was found in observational data that reduction was associated with an increase in strokes (relative risk, 1.60 [95% CI, 1.45-1.76]; Figure 2.4a), myocardial infarctions (relative risk, 1.58 [95% CI, 1.48-1.68]; Figure 2.4b), and falls (relative risk, 1.36 [95% CI, 1.32-1.40]; Figure 2.4c). Combined analysis, completely driven by the weight of the observational study, showed evidence of an association for strokes (risk ratio, 1.60 [95% CI, 1.46-1.77]; heterogeneity I^2=0%; Figure 2.4a), myocardial infarction (risk ratio, 1.58 [95% CI, 1.48-1.68]; heterogeneity I^2=0%; Figure 2.4b), and falls (relative risk, 1.36 [95% CI,

1.32-1.40]; heterogeneity I^2=0%; Figure 2.4c).

Only five antihypertensive studies had data available on the association of medication reduction and changes in blood pressure, all the RCTs and one observational study [236, 237, 239–241]. Antihypertensive medication reduction was associated with an increase in systolic (MD (mmHg), 7.25 [95% CI, 3.22-11.28]; heterogeneity, I^2=62%; Figure 2.5a) and diastolic blood pressure (MD (mmHg), 2.92 [95% CI, 1.75-4.10]; heterogeneity, I^2=0%; Figure 2.5b) although significant heterogeneity was observed for change in systolic blood pressure (Figure 2.5a).

(a) Change in systolic blood pressure



(b) Change in diastolic blood pressure

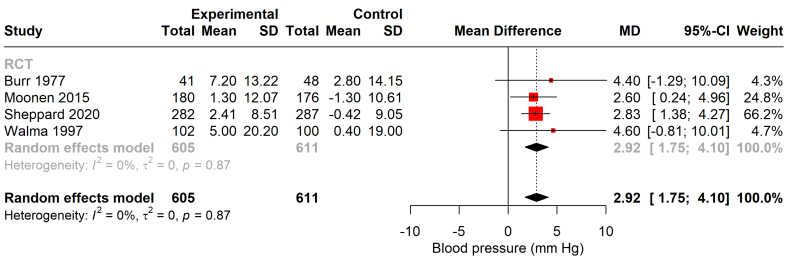


Figure 2.5: Association of antihypertensive medication reduction and changes in blood pressure measurements. CI, confidence interval; MD, mean difference; SD, standard deviation.

Only one study measured changes in cognitive function and no evidence of an association was found with medication reduction [237].

Outcome data were sought for renal functioning, electrolyte abnormalities, medication burden, and change in frailty status, but these outcomes were not measured in any of the included studies.

2.5.4 Statin reduction outcomes

2.5.4.1 Primary Outcome

All-cause hospitalisation was reported for one study of statin discontinuation [238]. Out of 8,020 participants, a total of 2,209 events occurred in those discontinuing statin treatment and 2,055 in the continuation group. Statin discontinuation was associated with a modest increase in all-cause hospitalisation (relative risk, 1.12 [95% CI, 1,05-1.19])[238].

2.5.4.2 Secondary Outcomes

The relation between statin discontinuation and mortality due to any cause was assessed in two studies, including three patient populations [238, 243]. Discontinuation of statin treatment was associated with an increased risk of all-cause mortality (risk ratio, 1.84 [95% CI, 1.17-2.90]; heterogeneity, I^2=98%; Figure 2.6a), although very significant heterogeneity was observed I^2=98%; Figure 2.6a).

Cardiovascular hospitalisation was assessed in all three included statin discontinuation studies, resulting in four included patient populations [238, 242, 243]. Statin treatment discontinuation was associated with an increased risk of cardiovascular hospitalisation (risk ratio, 1.26 [95% CI, 1.18-1.35]; heterogeneity, I^2=44%; Figure 2.6b), although significant heterogeneity was observer I^2=44%; Figure 2.6b).

A single study provided information on the association of statin discontinuation and cardiovascular mortality, providing a primary prevention and secondary prevention study population [243]. Statin treatment discontinuation was statistically significantly associated with an increase in cardiovascular mortality (risk ratio,

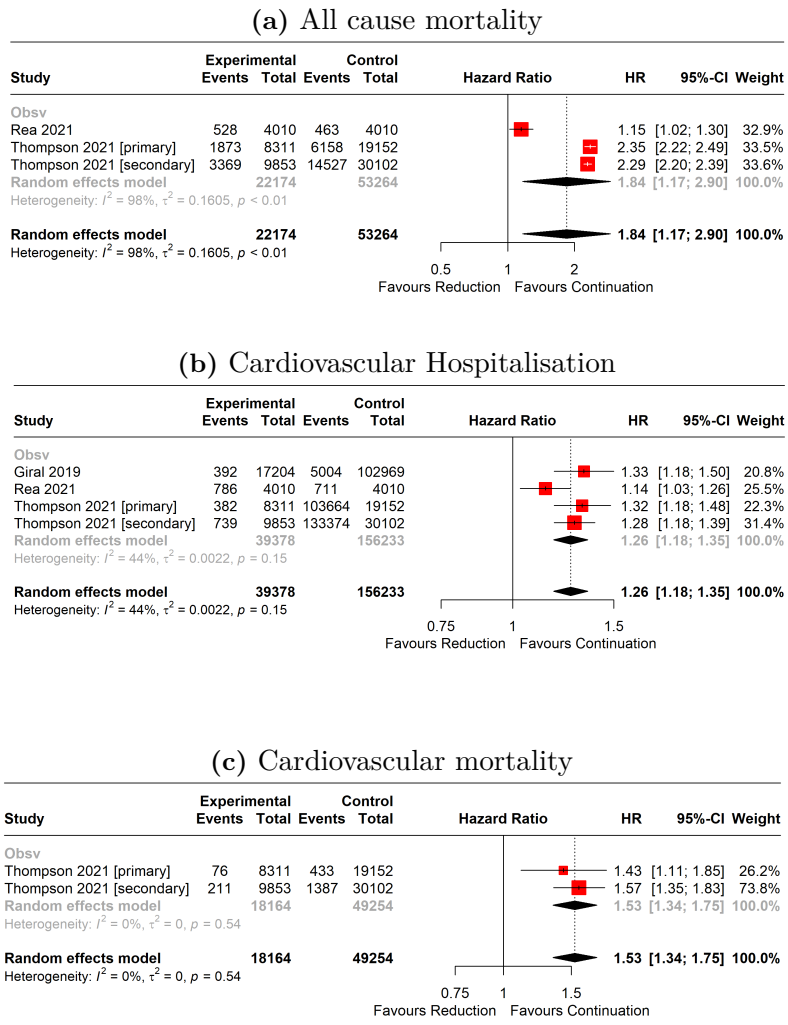


Figure 2.6: Association of statin discontinuation on all cause mortality, cardiovascular hospitalisation, and cardiovascular mortality. CI, confidence interval; HR, hazard ratio.

1.53 [95% CI, 1.34-1.75]; heterogeneity, I^2=0%; Figure 2.6c. The risk increase was similar in both primary (adjusted hazard ratio, 1.43 [95% CI, 1.11-1.85]; Figure 2.6c) and secondary prevention cohorts (adjusted hazard ratio, 1.57 [95% CI, 1.35-1.83]; Figure 2.6c).

Stroke and myocardial infarction risk was assessed in two studies, providing data from three cohorts (n = 75,438)[238, 243]. Statin discontinuation was significantly associated with increased stroke risk (risk ratio, 1.30 [95% CI, 1.20 - 1.41]; heterogeneity, I^2=1%; Figure 2.7a) and myocardial infarction risk (risk ratio,

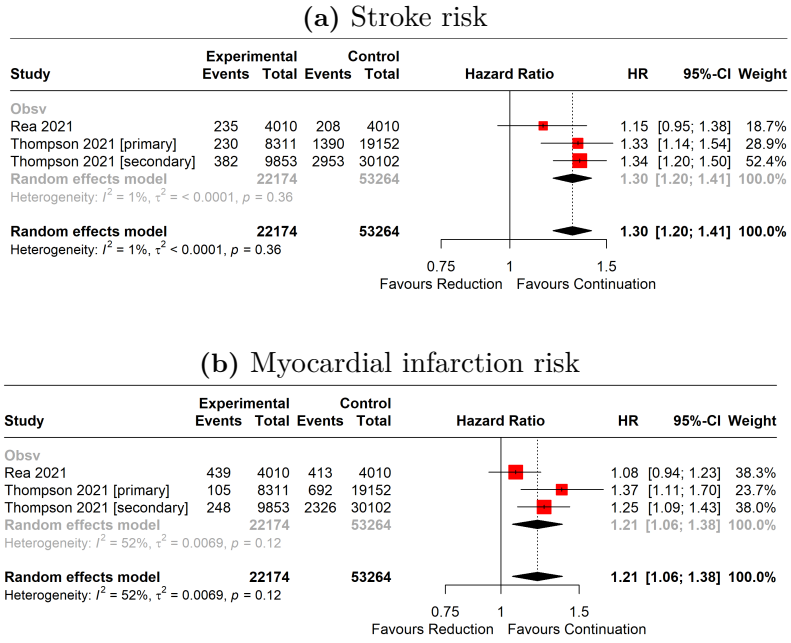


Figure 2.7: Association of discontinuing statin treatment and risk of strokes and myocardial infarction. CI, confidence interval; HR, hazard ratio.

1.21 [95% CI, 1.06 - 1.38]; heterogeneity, I^2=52%; Figure 2.7b).

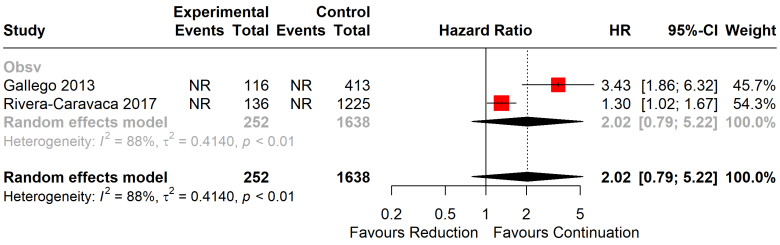
2.5.5 Antiplatelet reduction outcomes

A single observational study on antiplatelet reduction was included, examining the association between discontinuing aspirin used in the secondary prevention of cardiovascular events and stroke [244]. The primary outcome of all-cause hospitalisation was not reported in this work. In 2,346, patients 339 stroke events occurred (adjusted risk ratio, 1.96 [95% CI, 1.27-3.02]).

2.5.6 Oral anticoagulant reduction outcomes

Two studies examined the effect of oral anticoagulant reduction in older adults [245, 246]. A total of 2,159 patients (follow-up range: 2.5-6 years) provided outcome data, all observational in nature, for the secondary outcome of all-cause mortality (risk ratio, 2.02 [95% CI, 0.79-5.22]; heterogeneity, I^2=88%; Figure 2.8a) and stroke

(a) All-cause mortality risk



(b) Stroke risk

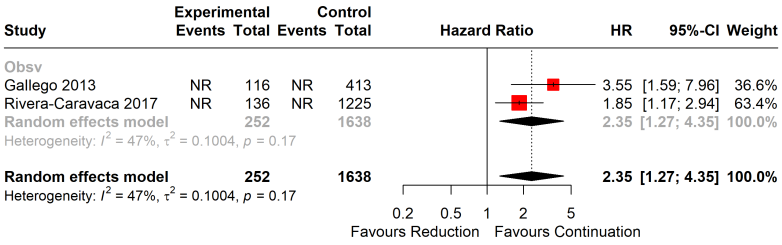


Figure 2.8: Association of discontinuing oral anticoagulants and all-cause mortality and stroke risk. CI, confidence interval; HR, hazard ratio; NR, not reported.

risk (risk ratio, 2.35 [95% CI, 1.27-4.35]; heterogeneity, I^2=47%; Figure 2.8b). Where an increased stroke risk was statistically associated with reduction of oral anticoagulants, the change in all-cause mortality was not statistically significantly associated with reduction, however both outcomes had high statistical heterogeneity of 47% and 88% respectively.

2.6 Discussion

The clinical implications of reducing various different groups of preventative cardiovascular medication in older patients are poorly understood in terms of both benefits and risks. Therefore, this systematic review and meta-analysis was performed to examine studies of preventive cardiovascular medication reduction in older patients, namely antihypertensives, antiplatelets, statins, and anticoagulants. Very few included studies reported data on all the clinical outcomes of interest. In general, in observational studies reduction of medication was associated with an increased risk of harm. For antihypertensive medication, where data from RCTs were available,

there was no evidence of this association. However, there remains substantial uncertainty around the evidence, as it is unclear whether these findings are a result of the low number of events reported in RCTs or because of bias due to residual confounding in observational studies.

The literature search was as comprehensive as possible, with a total of 24,141 articles assessed for eligibility (figure 2.1), although studies could have been missed in the search strategy or not been published. However, no analysis of publication bias was conducted, due to the low number of studies included in the meta-analysis (less than ten), which severely limits the statistical power of the Egger's test and the ability to interpret funnel plots [247, 248].

2.6.1 Comparison with Previous Literature

Previous systematic reviews focusing on antihypertensive medication reduction concluded that such a strategy might be safe, despite examining similar data to the present study [206, 226]. Similarly to the present study, these studies were limited by the number of events and patients included in the RCTs [206]. Different to the present review was the inclusion of only randomised controlled trials, focused solely on withdrawal of antihypertensive therapy used in primary prevention, and including younger patients (<75 years old). The results of the present meta-analysis addresses the effect of reducing cardiovascular medications more generally in an older population and whether such a strategy should be considered in the context of management of problematic polypharmacy. The rationale for focusing on older people is that they may be more likely to benefit from medication reduction due to physiological changes that would predispose them to adverse drug events [56, 249]. Older patients also often have more morbidities and take more prescriptions increasing their chances of experiencing problematic polypharmacy and so have greater competing risks, potentially reducing the importance of preventing CVD [41].

These findings showed that blood pressure was significantly increased after reduction of antihypertensive treatment, with a mean difference of 7.8 mm Hg and 3.1 mm Hg for systolic and diastolic blood pressure, respectively. However, substantial heterogeneity was observed for changes in systolic blood pressure, which may be explained by variation in the type of reduction intervention studied. Some studies implemented cessation of all antihypertensive medication, with either no or high (>180 mmHg systolic blood pressure) thresholds for drug re-initiation [239, 241]. While other studies reduced treatment up to target blood pressure levels (150 mmHg), with the option of having residual treatment [236, 237]. This intervention differences translate into a potential increase in systolic blood pressure of between 3 and 13 mm Hg, this is a significant amount of uncertainty. Subsequently, whether this increase in blood pressure would translate into an increase in CVD is unclear, due to competing risks in this population. The synthesis of the limited data identified in this review suggests that harm cannot be discounted: recent results from a large individual patient data meta-analysis found that a reduction in systolic blood pressure by 5 mm Hg was associated with a decrease in major cardiovascular events of around 10%, consistent for both primary and secondary prevention [93]. Age-stratified analysis by the same group showed that the beneficial effect of lowering blood pressure remained up to at least 84 years of age [35]. Taking into account the observed systolic blood pressure increase on reducing antihypertensive treatment and the consistent reduction in major cardiovascular events associated with treatment, one might expect that adequately powered trials of antihypertensive reduction would demonstrate cardiovascular harm, as observed in observational data. This also assumes that the effects of giving a new treatment are the same as removing a treatment that has been prescribed for prolonged periods of time, this remains unclear. Furthermore, this effect can be population specific and further observational studies could be utilised to identify these particular populations.

Contrary to the outcomes found in antihypertensive studies, the studies focused on the remaining drug groups all suggested harm after discontinuing the respective

medication, albeit the number of studies was limited and were all observational in nature. Additionally, valuable information from these studies are missing (e.g. reduced hospitalisation from side-effects), specific sub populations are not explored (e.g. frail vs non-frail), or need to be replicated in larger observational studies (e.g. Rodriguez *et al.* was limited to only 2,346 patients).

Statin treatment discontinuation all showed substantial indicators for increased cardiovascular harm in terms of increased mortality and hospitalisation, in both primary and secondary prevention populations. While this warrants discouragement of pursuing statin discontinuation in the general population of older adults, it does not provide an answer to the outcomes in highly vulnerable populations (e.g. frailty or at increased risk of harm). Further research on statin discontinuation therefor could focus on determining the effects of statin discontinuation in frail older adults, as this patient population is of specific interest in medication reduction/deprescribing literature because they are assumed to be more susceptible and effected by stressors like medication related adverse events [250–252].

Two randomised controlled trials, which did not meet the current study's eligibility criteria, examined the effect of cardiovascular medication reduction and suggest reduction might be safe [253, 254]. The ECSTATIC-trial (n=1067, 2-year follow-up) looked at reducing preventive cardiovascular medication in a younger population, aged 40-70, without any previous CVD [253]. In this cohort 65% of the intervention arm stopped their medication, but both intention-to-treat and per-protocol analysis showed that reduction of preventive cardiovascular medication was not associated with a difference in risk increase of cardiovascular risk score, albeit an intermediate outcome and a low-risk population [253]. Kutner *et al.* examined the effects of discontinuing statins in patients with a life-expectancy prognosis of one month to a year. In this particularly vulnerable patient group, there was no evidence of a difference in the primary outcome of 60 day mortality (23.8% vs 20.3%; [90% CI, -3.5% to 10.5%]; P= .36), but quality of life was higher in the discontinuation arm of the study (mean McGill QOL score, 7.07 vs 6.74; P= .03) [254]. After a

planned interim analysis of the study changes were made to the study protocol in terms of primary outcome and subsequent power calculations. However, it is very likely that the analyses were underpowered to detect any differences between groups.

2.6.2 Interpretation of findings and clinical implications

Medication reduction, ranging from dose reduction to complete withdrawal of all medications in a specific domain, is increasingly being recommended, under certain conditions, in routine clinical practice without a robust evidence base [33, 224, 255, 256]. While recognising the importance and essential practice of medicine optimisation in patients to prevent harm and reduce unnecessary therapeutic load, it is important to do so with the best possible evidence available. Although previous reviews have suggested that antihypertensive medication reduction may be safe [206, 226], the current results suggest that there remains considerable uncertainty about the long-term effects, regardless of drug group, of such an intervention. When observational data is considered in addition to RCTs, there seems to be a signal for harm in the general older population. Therefore, it should not currently be implemented in routine clinical practice, based on age alone, in primary care patients living in the community without additional research to determine which patients might benefit from reducing preventive cardiovascular medication.

2.6.3 Limitations

This study has several limitations. The key limitation of the present work is the short follow-up of randomised studies included in the analysis and the lack of outcome events, which prevents us from drawing firm conclusions. Therefore, larger studies with longer follow-up would be preferable to be able to definitively establish the safety and efficacy of preventive cardiovascular medication reduction. However, where randomised studies are not available, observational studies can be helpful.

The inclusion of observational data introduces bias from confounding by indication. All but one study adjusted for covariates in their analysis to reduce the impact of confounding by indication [242]. However, it remains possible that these attempts were unsuccessful, and as there is no way of verifying the success of covariate adjustment, the observational studies included in this review may still be subject to bias from unmeasured confounding. Indeed, it is likely that the reasons for stopping medication in the observational studies were different from those in the RCTs. One of these reasons which likely affect the study of Aubert *et al.*, is that patients who were at an increased risk of falls were more likely to have their antihypertensive treatment reduced (in order to reduce the fall risk), this results in a disproportionately high number of patients with increased fall-risk in the intervention arm compared to the control group. Therefore, the increase in falls observed in this study could be incorrectly attributed to the intervention (antihypertensive reduction). However, in reality, this is likely caused by confounding (fall-risk) which was not properly addressed. Additionally, observational research to date have used inappropriate study designs, which need to be addressed to strengthen the use of observational data [215]. For example, most studies have used a fixed time-point (e.g., consultation within the study period) or time-window (e.g., 2 years after turning 75) in which the reduction event should have taken place, resulting in respectively a small population who could experience the reduction event in the observation period or limited follow-up time. Sensitivity analysis excluding observational studies from the meta-analysis did not alter point estimates, but due to the limited number of reported outcomes these were no longer statistically significant. Therefore, aggregate outcomes including results from observational sources should be interpreted as observational in nature, in particular those weighted heavily towards the observational data such as in our analysis of cardiovascular hospitalisation outcomes.

In addition to measured statistical heterogeneity, significant clinical heterogeneity is observed in intervention implementation and included patient characteristics,

likely contributing to differences observed in the included outcomes. First and most notably, in antihypertensive medication reduction most varying interventions were included. Where aspirin and statin treatment is binary in nature, meaning it is either present or not, antihypertensive treatment consist of many different classes that could be used by themselves (monotherapy) or in-combination (polytherapy) [217]. This results in either differences in which drug class is reduced, for example Walma *et al.* and Burr *et al.* focused solely on the reduction of diuretic treatment, where Moonen *et al.* and Sheppard *et al.* focused on antihypertensive medication reduction holistically where any class could be reduced [236, 237, 239, 241]. This means that the latter will provide a more generalised effect of reducing antihypertensive medication in older patients compared to a class specific effect. Although a generalised effect of antihypertensive medication discontinuation is an interesting exposure to study, there might be differential outcomes associated with discontinuation of the various antihypertensive classes that cannot be studied with the current available evidence. Therefore, research of the effect of discontinuation of specific classes could potentially be more appropriate [257]. Furthermore, due to the often polytherapeutic nature of high blood pressure treatment and measurement thresholds, a single prescription or multiple prescriptions could be stopped, or medication could be withdrawn up to a maximum increase of systolic blood pressure or threshold (e.g. max 150 or 180 mm Hg) [236, 237, 239, 241]. Additionally, taking the variations in these specific interventions, care could be given to have at least a single prescription remaining after implementation of the reduction intervention, as seen in the study of Sheppard *et al.* [236]. Second, cardiovascular preventive therapy can be initiated either before a cardiovascular event has taken place or after, known as primary and secondary prevention respectively. This distinction was particularly profound in the studies examining the effect of discontinuing statin therapy, where Giral *et al.* and one cohort in Thompson *et al.* included only patients receiving statin therapy as primary prevention [242, 243]. Conversely, the other cohort in Thompson *et al.* only included patients receiving secondary prevention treatment [243]. Finally, Rea *et al.* similarly to the patients included in the antihypertensive trials, included

a mix of both primary and secondary prevention intervention [238]. The difference of receiving statin therapy in either primary or secondary prevention is the absolute risk these patients have to experience cardiovascular outcomes [258]. Finally, and in a similar vein to primary and secondary prevention, specific patients populations were selected, most notably in the observational antihypertensive studies, which influences heterogeneity. The two observational trials included very specific patients groups, while completely appropriate, limiting the generalisability to all primary care patients. Aubert *et al.* included patients with low to very low systolic blood pressure (<130 mm Hg), whom are potentially at a higher risk of hypotension related adverse events like falls and fractures [240]. Additionally, it is postulated that a low to very low systolic blood pressure carries a higher cardiovascular risk due to the assumed J-shaped relation between cardiovascular risk and blood pressure [259], although more recent work disputes this association [93]. The other observational study, of Gilstrap *et al.*, provides a very specific population of heart failure patients with reduced ejection fraction whom have been hospitalised for acute decompensated heart failure [123]. Baseline risk for rehospitalisation is very high in this group of patients and not comparable with the other patients included in this work from other studies [260].

While studies that focused solely on reducing drugs in patients in end-of-life care were excluded, it is very likely that some of these patients could have been part of the included studies. While it is recognised that generalised medication reduction could be beneficial and the essence of palliative care in this specific population, the motivation to initiate stopping treatment is diametrically opposed to those who have no life-limiting disease, as there is still apparent benefit from preventing long-term cardiovascular events in these patients [261, 262]. Therefore, this was the population targeted in our review, with the aim of producing results that could be helpful for conversations with patients who are not known to be nearing the end-of-life and would of course bring their own priorities and preferences to the consultation.

Outcomes reported as hazard ratios or relative risks were combined in the meta-analyses conducted. While in essence these values represent different forms of risks, e.g., instantaneous risk over time, and therefore should be interpreted within the context they were analysed, it is possible to combine different relative risks using generic inverse variance methodology, where the incidence of the event in question is low [263]. For our data this seems to be the case with the caveat that follow-up was short.

2.7 Conclusion

The current evidence is not sufficient to guide the clinical practice of routine cardiovascular medication reduction, regardless of drug group, in older patients with problematic polypharmacy. Existing randomised studies report point estimates which suggest medication reduction could be harmful but were limited by study size, number of events, or the duration of follow-up. Observational studies for the four included drug groups in this work all showed increased harm, although the quality of this evidence was generally low. Further research focusing on long-term patient outcomes centred around cardiovascular outcomes as well as (the potential reduction of) often reported side-effects of cardiovascular medications within different patient populations is essential to determine benefit/risk. Although these studies would preferably be RCTs, well-designed observational studies should be considered (and might be more appropriate) to protect patients from potential harmful interventions in light of the concerns raised in the current work and questions with regards to equipoise [227]. Several steps would need to be taken to answer such a question in observational data (Chapter 5. First, medication reduction needs to be accurately defined and patients that do and do not meet these criteria need to be identified (Chapter 3) [215]. Then, the characteristics associated with the reduction of medication need to be determined to adequately to adjust for confounding (Chapter 4.4.4. This means that for each of the four drug groups examined in this chapter, a method to establish discontinuation has to be developed, in addition to the fact

that patient characteristics associated with discontinuation are likely to be different for each drug group, and other outcomes need to be studied. This would result in four separate projects and therefore discontinuation of antihypertensive medications was chosen as the first group to study in older primary care patients.

These data suggest that if reduction of problematic polypharmacy in a patient is considered important, a physician may wish to consider alternative management strategies or other drug candidates for potential withdrawal.

2.8 Key Points

- In this systematic review and meta-analysis, antihypertensive medication reduction was not associated with a change in the primary outcome of all-cause hospitalisation.
- Statin, antiplatelet, and anticoagulant therapy discontinuation was associated with increased cardiovascular harm.
- A substantial knowledge gap still exist in terms of long-term outcomes after discontinuation, outcomes in different subgroups, and measurement of benefits.

3

Identification of sustained changes in complex pharmacotherapeutic regimes in electronic health record data: methodology development

3.1 Chapter overview

This chapter presents the results of a new method to identify patients in whom antihypertensive treatment has been reduced using electronic health record data. In the GOLD database of the Clinical Practice Research Datalink (CPRD), 737,385 patients over the age of 65 that were prescribed antihypertensive treatment were used to develop and test an algorithm to identify sustained changes in total number of antihypertensive prescriptions.

A rule-set was developed to ascertain sustained prescription changes in routinely collected health care data. The rule-set describes a period of time where treatment is stable for a period of three months (Rule 1) followed by a stable period of three months (Rule 2) where treatment is lower than the previous period of three months (Rule 3). This set of rules was implemented through four motifs to facilitate the automated analysis of millions of lines of prescriptions data.

After acquiring monthly prescription exposure per patient per month, patterns were determined that were associated with treatment discontinuation. Using a three-month window of sustained reduction in total antihypertensive prescriptions, 232,851 patients (31.6%) were determined to have experienced a first time reduction event. During follow-up, a total of 79,555 (34.2%) of these patients had their treatment reintroduced.

3.2 Introduction

Chapter 2 has established that there is a lack of evidence on the long-term consequences of reducing antihypertensive treatment. The RCTs that were included in the systematic review in Chapter 2 revealed several issues, including short follow-up times and a low number of clinical events and patients [236, 239, 241]. Furthermore, the included observational studies still had short periods of follow-up

(<1 year) and included specific patient populations, thereby limiting generalisability of the results [123, 240]. Well-conducted observational studies can be used to provide evidence in the absence - and potential inappropriateness - of large long-term RCTs, especially if the intervention has the potential to cause harm [209, 212, 227]. Examples of successful implementation of observational study designs to evaluate the effect of discontinuing cardiovascular medication are reported in Chapter 2 [123, 238, 240, 242–246].

Most observational studies have focused on simple pharmaceutical interventions, in which a single class of medications (e.g. statins or proton pump inhibitors) are solely used to treat a specific disease, symptom, or risk factor [238, 242, 243, 264–266]. This results in a straightforward interpretation of prescription data, namely determination if any medication is present and identify the gaps between prescription end and subsequent prescription start. However, the treatment of hypertension is more complex. Guidelines for the treatment of hypertension recommend target blood pressure thresholds that are to be met depending on age [217]. If patients are not able to meet treatment targets with a single agent (also referred to as monotherapy), guidelines advise escalation of the number of agents used, often resulting in multiple agents used to achieve blood pressure control in clinical practice [97]. Furthermore, co-morbidities of patients play a role in the selection of preferential agents, increasing the variance of agents used in the general population [97, 217]. Lastly, patients who experience side-effects are often switched to alternative treatment. A classic example of therapeutic switching is the change from an angiotensin converting enzyme inhibitor (ACEi) to an angiotensin receptor blocker (ARB), for patients who develop persistent coughs on the former drug class [267].

The multi-drug nature of the treatment of hypertension, as well as the common class switching within the group of antihypertensive treatments, makes the analysis of antihypertensive prescriptions (or any intervention relying on combination therapy)

challenging, as one cannot look for gaps between individual classes and prescription windows might not perfectly align [97, 268]. First, combination therapy does not allow for easy interpretation if antihypertensive treatment is present or not, as treatment reduction means that residual treatment is possible if patients started on two or more different antihypertensive medications. Second, interpreting data per class does not account for class switching, as one class might be stopped indefinitely, whilst another class might have been started, meaning that the overall antihypertensive load remains the same, which would falsely indicate discontinuation. Due to the nature of routinely collected primary care data, it is subject to real-world oddities; one of the most important factors of this is the timing of requesting repeat prescriptions. Repeat prescriptions are (ideally) requested before the previous stock has ran out or (non-ideally) after the previous stock theoretically ran out. However, this is more likely than not not on the date we expect or estimate the stock to run out [268]. These gaps before and/or after the estimated prescription end date can cause artificial fluctuation in the number of concurrent prescriptions at certain time points, while - in reality - treatment remains the same.

Recent work done on identification of antihypertensive medication reduction in observational data sets have not resulted in methods that can be applied to UK general practice data sets, but were excellent for the data set they were implemented in. One looked at specific antihypertensive class discontinuation without taking into account the possibility of class switching [123]. Others were able to leverage database specific strengths of the Veterans Administration (VA) dataset to identify antihypertensive medication discontinuation, where detailed information on dosage is readily available and - in the case of the nursing homes dataset - prescribing and dispensing information was available on a day-to-day basis[240, 269, 270]. In the case of Aubert *et al.*, a validated method was used that utilised a single consultation within a predefined observation period resulting in a limited period in which medication changes could occur [240, 271, 272]. Odden *et al.* was able to use a rolling two-week reduced treatment window, without taking temporal increases

into account, utilising the day-to-day prescribing and dispensing [269].
However, these approaches used for identification were not universal[269] and/or resulted in a significant loss of follow-up time [271, 272], meaning that they are not applicable to routinely collected primary care with many years of follow-up data. Therefore, there remains an unmet need for the development of a method that would be able to use all these requirements and is more readily applicable to anonymised primary care datasets to determine medication changes and their long-term clinical impacts general practice patients [215].

3.3 Chapter Aim

The objective of this study was to develop a universal method to determine sustained changes in the number of prescriptions that can be used to identify medication reduction or, inversely, to identify medication intensification in datasets consisting of routinely collected data. Having established this new method, the second aim of this chapter was to use this method to create a matched cohort of patients that discontinue and conversely, continue antihypertensive treatment in the CPRD Gold dataset.

3.4 Methods

3.4.1 Data Source

The protocol for this study was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA) (protocol reference number: 21_000385) (Appendix A.3).

The method that was developed for this work used electronic health records from the Clinical Practice Research Datalink (CPRD) - GOLD: an anonymised ongoing primary care records database covering 6.9% of the UK population, divided in thirteen regions, of which ten are in England, these data are representative of

the UK population [273]. CPRD maintains two databases containing routinely collected primary care data: GOLD and Aurum [273, 274]. The CPRD GOLD database has been extensively used for epidemiological research for the greater part of three decades and collects its data from general practices in the UK utilising Vision software [273]. The quality of the data is variable as data entry into Vision is done by GPs during usual consultations, which is why CPRD provides a data quality measurement known as up to standard (UTS). UTS is the latest date at which each individual practice is considered to have continuous high quality data suitable for research. This consideration is based on two measurements: 1) gaps in data, an analysis of data recorded in the practice over time, and 2) death recording, an analysis based on number of deaths recorded in a practice [273].

All included patients in this work were eligible for linkage to the Office for National Statistics Death Registration Data and Hospital Episode Statistics admitted patient care, and practice level Index of Multiple Deprivation data. For this study data was used from 01-01-1998 to 31-12-2019 where UTS data was available.

3.4.2 Prescription data structure

CPRD prescription information can be obtained from the therapy file. Therapy files are provided for each individual patient at each practice. Prescription information included in the therapy files are a patient identifier, CPRD product code, British National Formulary code, quantity of the product, dose, pack size, and number of days prescribed. Additional information is available for instructions for usage, like frequency (e.g. one tablet daily or take once in the morning) [273]. While information on dosage is technically available, this is often missing and provided in free text, meaning that this is not readily available for large cohorts with many years of prescription data.

3.4.3 Cohort Selection

3.4.3.1 Patient eligibility

Patients were eligible for analysis by the algorithm if they fulfilled all of the following three requirements: 1) at least one active antihypertensive prescription, 2) were at least 65 years of age, and 3) their practice was UTS, whichever happened last. Patients were ineligible if they could not be linked to additional datasets and had less than twelve months of follow-up time between cohort entry and cohort exit (total observation period). Cohort entry was defined as the first point in time where patients met all eligibility criteria, meaning for patients 65 and over that were prescribed antihypertensive treatment before UTS, the UTS date was cohort entry. For all other patients the cohort entry date was either when they turned 65 years of age or were prescribed their first antihypertensive medication. Cohort exit was defined as either the end of data collection, the date of transfer of the patient out of the practice area, or the patient's death, whichever came first.

3.4.4 Algorithm development

3.4.4.1 Preparation of prescription data

For each patient in the potentially eligible population, exposure to each antihypertensive drug class was determined from cohort entry to cohort exit (observation period). In short, a previously developed list of antihypertensive medications was subdivided into the following classes (a detailed list is provided in appendix A.4): Angiotensin-converting-enzyme (ACE) inhibitors, alpha-blockers, angiotensin 2 receptor blockers (ARB), beta-blockers, calcium-channel blockers, thiazide and thiazide-like, and other (central-acting, renin-inhibitors, and vaso-active drugs) [148]. For each medication prescription, the prescription end date was determined using quantity (qty) prescribed and prescribed usage (e.g. take 1 daily) to determine days covered by therapy. Patients that had missing data with regards to qty or prescribed usage for any of the antihypertensive classes were removed from the eligible cohort. An example of this would be a prescription for 30 tablets of enalapril taken once a

day issued on 01-01-2010, with the direction of a single tablet a day a quantity of 30 tablets will cover this patient for 30 days, up to 31-01-2010 as expected prescription end date. For each individual patient the amount of prescriptions per class was counted from cohort entry to cohort exit at fixed monthly intervals. Counting was achieved by checking for the prescriptions at these fixed dates that covered that period. Specifically, it was checked if the start date came before the interval date and end date after the interval date. Finally, a summation of all individual classes for each interval resulted in a total antihypertensive prescription-load per month (Figure 3.1 provides a visual representation of a single patient using dummy data).

3.4.4.2 Pattern recognition approach

A set of algorithm requirements were determined *a priori*, namely, this method should be:

- Able to analyse the data over time, irrespective of patient start date or total observation time. This should not be dependent on a specific baseline visit or strict time window.
- Able to distinguish prescription stability before and after intervention of interest. The method should be able to deal with variations caused by the limitation of the use of real world data.
- Able to deal with potential changes in therapeutic intensity occurring between cohort entry and cohort exit opposite to the effect of interest [275].
- Able to deal with a high variation of numeric values (total prescribed medications) [276].

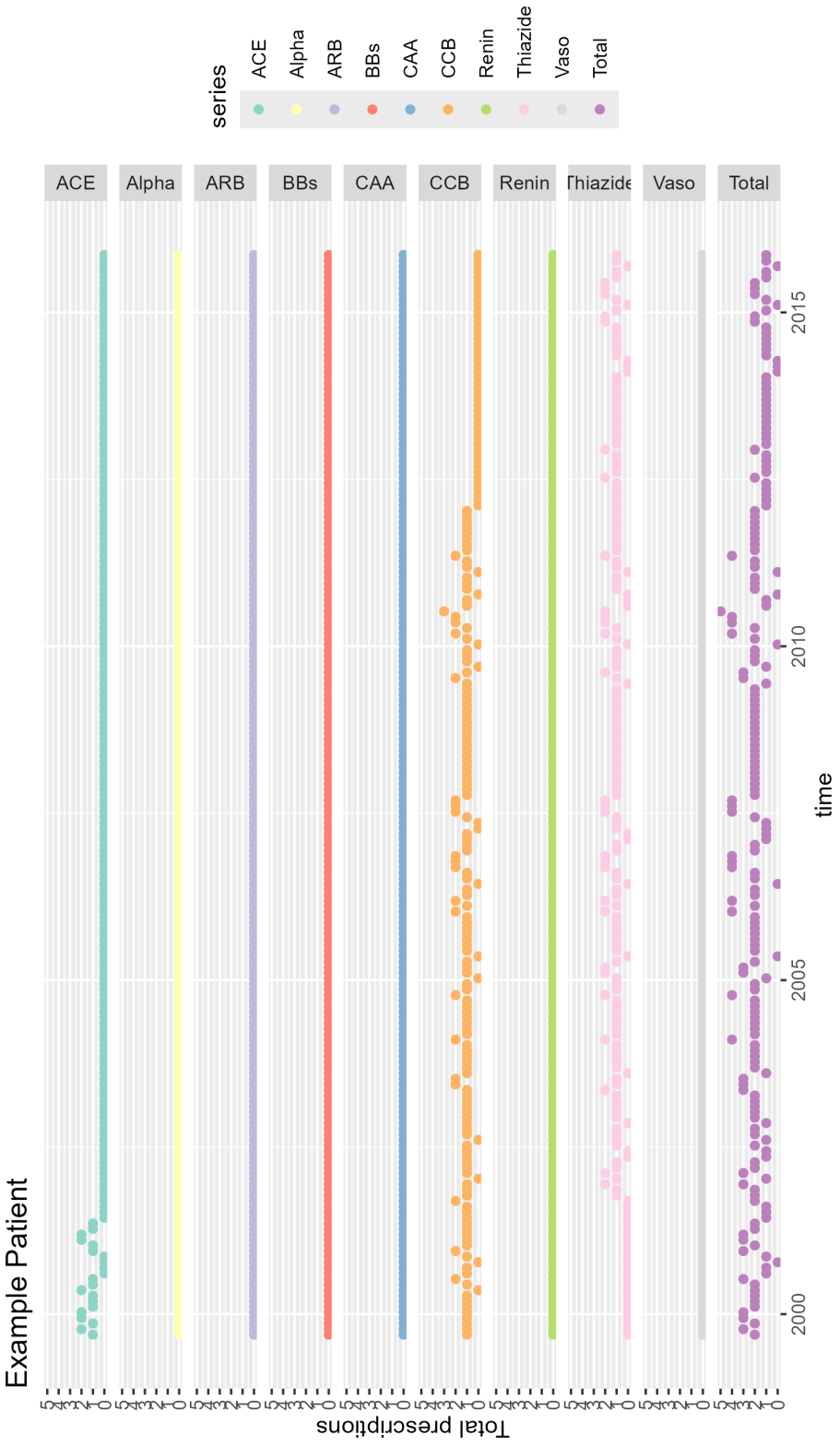


Figure 3.1: Visualisation of monthly prescription exposure per class and total antihypertensive prescriptions. Each dot represents a monthly count. ACE, Angiotensin-converting-enzyme inhibitors; Alpha, alpha-blockers; ARB, angiotensin 2 receptor blockers; BBs, beta-blockers; CAA, central-acting agents; CCB, calcium-channel blockers; Renin, renin-inhibitors; Thiazide, thiazide and thiazide-like agents; Vaso, vaso-active drugs.

These requirements will remain consistent regardless whether they are applied to the detection of discontinuation or intensification. In this work, they were applied for each patient within a cohort of patients taking antihypertensive medication to detect medication discontinuation. Additionally, they were applied for each patient within a cohort of patients who discontinued treatment to detect medication reinstatement.

Combining the previously determined algorithm requirements with expert opinion, published literature, and prescription information from a single practice, the following set of rules was applied to detect medication reduction [240, 242, 269]:

- Rule 1: A three-month window of pre-intervention therapeutic stability
- Rule 2: A three-month window of post intervention therapeutic stability
- Rule 3: Any decrease in antihypertensive prescriptions between the pre-intervention window (Rule 1) and post-intervention window (Rule 2)

For rule 3, the latest time-point in the pre-intervention window and the earliest time-point of the post-intervention window is used to determine change between the two time periods.

3.4.4.3 Algorithm design

Based on visual inspection of antihypertensive counts of patients in a single CPRD Gold practice, patterns of sustained change were determined. From these patterns motifs were derived, where a primary motif reflects the simplest representation of the rule set (Figure 3.2; top left) and three motifs that incorporate a break in continuity to facilitate the observed real world variation (Figure 3.2).

These four motifs formed the basis for equation 3.1 and equation 3.2 used in the algorithm. Equation 3.1 is the simplest application of the primary motif. Equation 3.2 incorporates an error term to deal with the variation represented by the other

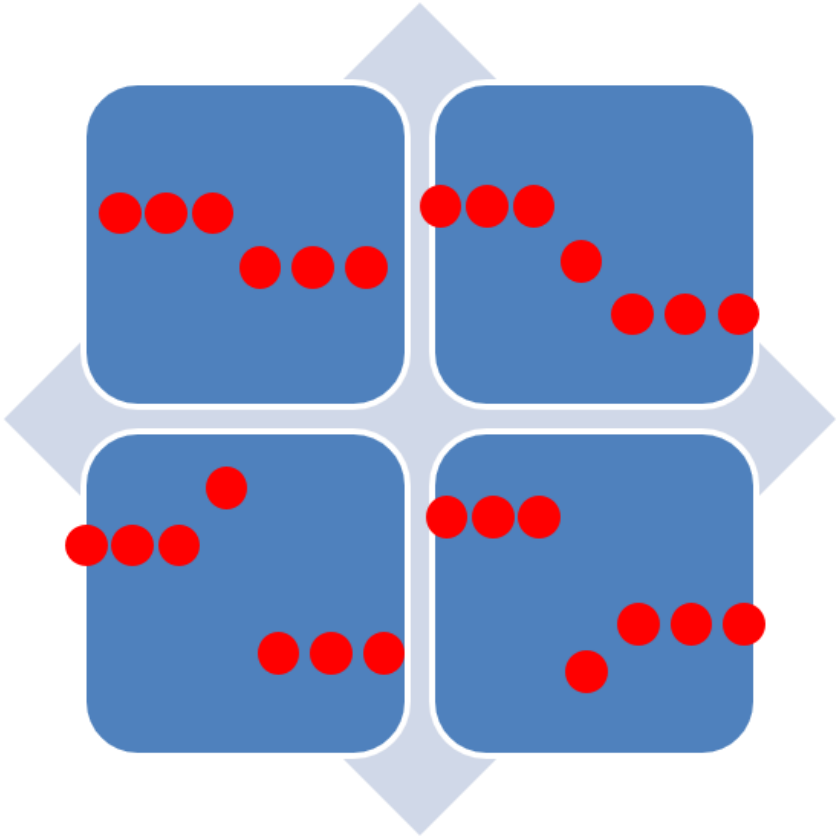


Figure 3.2: Visualisation of discontinuation patterns in the four motifs used in the algorithm. Each dot represents a month.

motifs. Detailed derivation of the equations, and examples of application of the algorithm and code, can be found in Appendix A.6. R programming language code for the application of equations for automated processing of longitudinal data is available in Appendix A.7.

In these equations, y is the total prescriptions of antihypertensives at time-point t, ce the date of cohort entry, and the time interval i in months.

$$y(t = ce + i) = y(t = ce + i + 1) = y(t = ce + i + 2) > y(t = ce + i + 3) = y(t = ce + i + 4) = y(t = ce + i + 5) \quad (3.1)$$

$$y(t = ce + i) = y(t = ce + i + 1) = y(t = ce + i + 2) > y(t = ce + i + 4) = y(t = ce + i + 5) = y(t = ce + i + 6) \quad (3.2)$$

3.4.4.4 Algorithm application

The designed algorithm was applied to potentially eligible population. Detailed explanation of code functionality is provided in Appendix A.6. In short, the algorithm parses through total antihypertensive prescription counts per patient from cohort entry until cohort exit and tries to identify the presence of any of the four motifs previously described, as visualised in Figure 3.2. This is a brute-force algorithmic approach to pattern recognition as developed for parsing of text ('strings'), which consists of a systematic approach to check if the statement (in this case the equation) is true or not [277]. A patient is identified as having their antihypertensive treatment reduced at the point at which one of the patterns is matched to a similar pattern in the total antihypertensive data. The moment the reduced treatment starts, which is defined as the first month when the treatment is lower compared to the previous three-month window, is defined as the index date.

The algorithm direction of effect (rule 3) to identify intensification, was subsequently applied to all patients that discontinued antihypertensive treatment. All prescription data from the index date (first moment of reduced treatment) until cohort exit was parsed to determine antihypertensive treatment reinstatement.

Figure 3.3: Visualisation of incidence sampling matching methods. Each patient enter the cohort at different time point, based on eligibility criteria. Patient 1 (P1) discontinues antihypertensive treatment at arbitrary time point 1 (t(1), index date), P2 and P3 are selected as controls at the same time. P2 and P3 continue in the risk-set, while patient P1 is removed from the risk-set. At a later arbitrary time point (t(2)) P3 discontinues their treatment (t(2) case index date) and is matched to P4 and P5. Patient 3 is removed from the risk-set at t(2). P2, P4, and P5 do not experience any antihypertensive medication discontinuation and are removed from the risk-set when the exit the cohort (first date out of date of death, latest available data, or transfer out of practice).

3.4.4.5 Matching

Patients identified as stopping treatment were matched using incidence density sampling, which is an established matching method used in nested case-control designs [278]. Patients become part of the risk-set from cohort entry until either cohort exit or when they experience the outcome of interest, which - in this case - is the discontinuation of antihypertensive treatment. The index date for cases is determined as the first date of reduced treatment and is derived from the algorithm. Incidence density sampling matches cases to controls based on a flexible time: whenever a case is identified, a control is sampled from patients in the risk-set. The case is removed from the risk-set at the time of experiencing the outcome and can not be matched to any cases at a later time point. Controls remain at risk and can therefore still be identified as cases at a later time-point [278].

Practice was used as a matching variable to account for potential prescriber preference [279]. Using this method allows for matching of controls using active time (or at time-at-risk) to circumvent the problem of the controls not having an index date. Matched controls within the same matched-set inherit the index date of the patient that discontinued treatment from that set (e.g. a patient is identified to have stopped treatment at 01-01-2010, all matched controls will have the same index date at 01-01-2010). Because matching occurs using the at-risk set, a control matched at an earlier time point (e.g. 01-01-2010) is not removed from the risk-set and will remain eligible to discontinue antihypertensive treatment, at which point it will be removed from the risk-set. In short, this means some patients are both control and discontinuer , at two different time-points. Figure 3.3 visualises the concept of incidence density sampling, including time at risk.

3.4.5 Variable definitions

All baseline characteristics were determined from information recorded prior to the index date, with only data within a specific time frame before the index date

being considered. The specific time frames for each variable are discussed in detail in later sections. Code lists used to generate the variables included in the analysis are available at: `https://github.com/RikvdVeen/DPhil_thesis2025/tree/main/AHT_reduction`. Baseline characteristics comprised patient demographics, clinical readings, medication usage, and co-morbidities. Variables were selected based on previously published work on cardiovascular medication discontinuation and expert opinion [242, 269, 271, 280].

3.4.5.1 Patient demographic definitions

Age and sex were determined based on CPRD patient data files. Ethnicity was based on data available through CPRD and linkage with basic inpatient Hospital Episode Statistics (HES) data, categories included were: White, Black, South Asian, and mixed other. Patient-level Index of Multiple Deprivation (IMD) data was obtained as quintiles (ranging from most deprived to least deprived). Smoking and alcohol consumption were derived from a combination of clinical (smoking and drinking status) and additional CPRD files (alcohol units). Smoking was categorised into non-smokers, current smokers, and ex-smokers. Alcohol categories were based on a combination of drinking status (yes/no) and daily units of alcohol consumed and were as followed: non-drinker, occasional drinker (<1 daily units), light drinker (between 1 and 2 daily units), moderate drinker (between 2 and 6 daily units), heavy drinker (>6 daily units), and unknown amount (alcohol units undefined).

3.4.5.2 Clinical readings

Weight category was determined using BMI, where the latest measured weight in the last five years was accepted and the most recent height. For blood pressure (systolic and diastolic), the most recent blood pressure measurement in the last year before the index date was taken; if this was not available, this was considered missing. Similarly, hypercholesterolemia was determined on a LDL-measurement taken within the last year with a measurement of 2.5 mmol/L or higher considered

as positive. In the UK, adults with hypertension should have a yearly review of cardiovascular risk factors, which includes monitoring of blood pressure and lipids [97]. Therefore, the most up-to-date laboratory and clinical readings should be available for these patients, with the most recent readings being the most relevant.

3.4.5.3 Medication history definitions

Prescription history of antihypertensives was based on the number of prescriptions before discontinuation (index date - 1 month). The presence of other cardiovascular medications was determined by any prescription in the four months preceding the index date. Polypharmacy was determined based on the number of active chronic prescriptions in the four months before the index data, medications included in chapters one to thirteen of the British National Formulary (BNF) were used to determine total chronic prescription load [281]. The BNF is a reference book containing monographs on all licensed medications in the UK, in which medications are categorised in individual chapters. Patients were determined to have polypharmacy if five or more active prescriptions were present, which was based on previous literature and similar studies conducted in CPRD [54, 282]. All included drug classes can be found in appendix A.5.

3.4.5.4 Co-morbidity definitions

Co-morbidities were defined as any historical read code of diseases of interest, with the exception of cancer and recent hospitalisation. Cancer was defined as a recent diagnoses of a cancer in the last year based on CPRD clinical files, which was based on an observation in the work of Giral *et al*[242]. Recent hospitalisation was defined as at least a single hospital admission in the last year based on HES data linkage.

3.4.6 Statistical Analysis

The baseline characteristics were described of the overall cohort, control, and discontinuation cohort at the time of index. Categorical and binary variables were presented as percentages. Continuous variables were either represented as median with interquartile range or mean with standard deviation, depending the distribution of the data. No comparative statistics were performed in this chapter. All analyses were performed using R statistical software version 4.0.3 [235].

3.4.7 Data management

All data management and algorithm development was done using R Studio version 2023.06.2 and R statistical software version 4.0.3 [235].

3.5 Results

3.5.1 Testing and review of automated detection of medication reduction

To assure no false positives were detected using this algorithmic approach, the algorithm was first tested in a single practice. This practice consisted of 2,676 eligible patients, where the algorithm identified 751 patients experiencing discontinuation of antihypertensive medication. Since no testing method was available, manual verification of all patients identified by the algorithm to have discontinued antihypertensive treatment determined that no false-positives were identified (i.e. people who did not discontinue treatment, but were flagged by the algorithm). No additional analysis was done to determine the number of false-negatives. Therefore, there will be patients that discontinued treatment that will remain undetected due to the nature of their irregular prescription patterns. However, changing the algorithm to identify patients by incorporating more error terms, or different patterns of prescribing, could have resulted in an increase in false-positives, which is something

that was determined to be undesirable.

3.5.2 Patient Characteristics

After successfully establishing the pattern recognition algorithm, this algorithm was used to detect decreases in antihypertensive medications in a total of 737,385 patients that were previously determined to be potentially eligible for further analysis (see patient flow diagram in figure 3.4). A total of 232,851 (31.6%) patients were identified to have had a reduction of their antihypertensive medication during the observation time. Even though patients could technically have had multiple reductions in the observation time, only the first reduction was recorded and used for this analysis. Out of 232,851 patients that discontinued treatment, 79,555 (34.2%) patients had their treatment reinstated during follow-up, with a median time to reinstatement at 111 weeks.

In order to identify appropriate control patients, incidence density sampling matching method was used (as explained in method section 3.4.4.5). Following the implementation of this method, 394,760 control patients were identified. 92,974 (23.6%) of these control patients became cases at a later time point. Table 3.1 provides the baseline characteristics of the overall, exposed, and non-exposed populations at time of index. Although matching was limited to practice, the general baseline characteristics were similar, with a similar median age (76.40 years (IQR: 70.48 - 82.88 years) vs 75.18 years (IQR: 69.96 - 81.27 years), proportion of females (57% vs 56%), and mean systolic blood pressure (138.9 mmHg (SD: 20.44 mmHg) vs 140.5 mmHg (SD: 18.63 mmHg)), respectively for patients who discontinued antihypertensive treatment and matched controls. When age was stratified into 5-year intervals, a greater proportion of older patients were observed in the discontinuation cohort. Notable differences in patient characteristics included higher rates of recent hospitalisation, recent cancer diagnoses, cognitive impairment, hypotension, and polypharmacy in the discontinuation group.

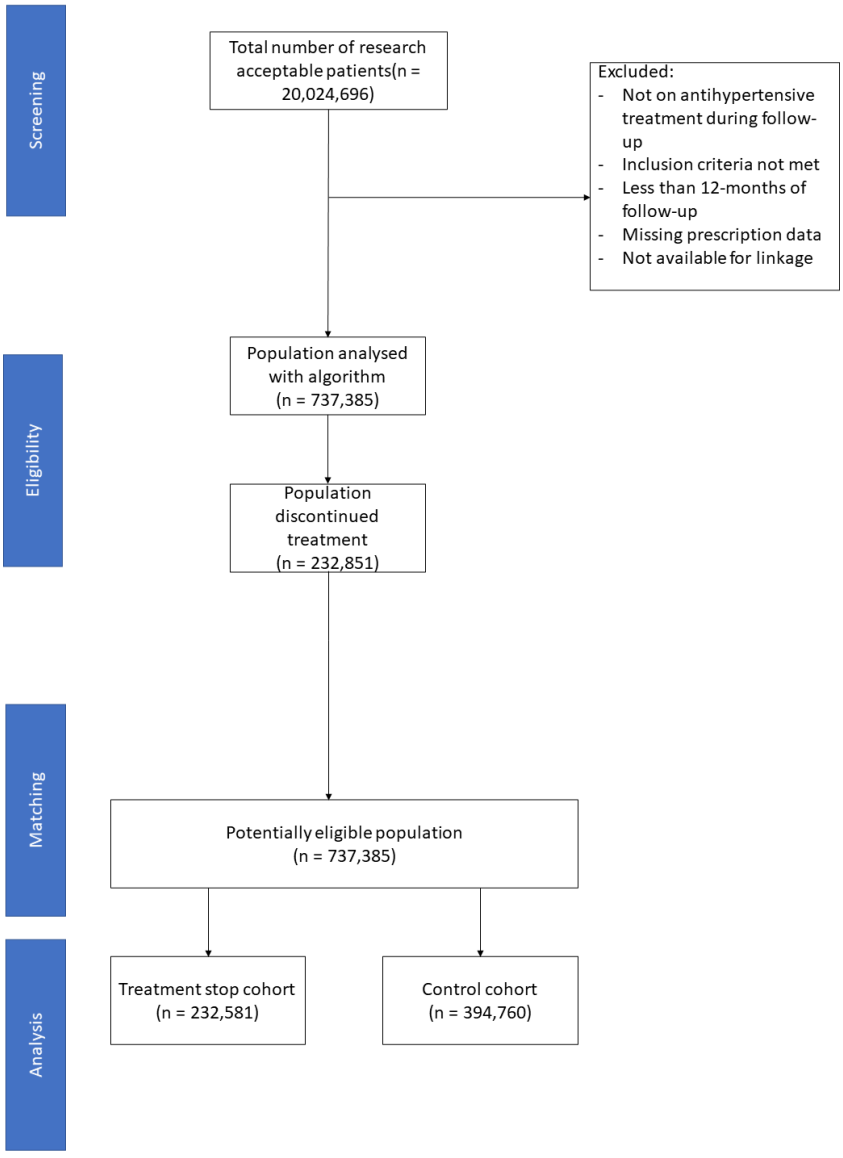


Figure 3.4: Patient flow chart of study. Patient over 65 years of age with an active antihypertensive prescription were included with at least twelve months of follow-up. Practices had to be up-to-standard an eligible for linkage to additional data sources HES, ONS, and IMD.

Table 3.1: Baseline characteristics of patients overall, control cohort, and reduction cohort at index

Variable	Overall, N = 627,341[1]	Controls, N = 394,760[1]	Reduction, N = 232,581[1]
Age	75.60 (70.15, 81.86)	75.18 (69.96, 81.27)	76.40 (70.48, 82.88)
Age (stratified)			
65-70	152,296 (24%)	99,154 (25%)	53,142 (23%)
70-75	144,548 (23%)	94,851 (24%)	49,697 (21%)
75-80	131,049 (21%)	83,821 (21%)	47,228 (20%)
80-85	103,215 (16%)	62,941 (16%)	40,274 (17%)
85-90	63,533 (10%)	36,435 (9.2%)	27,098 (12%)
90-95	26,296 (4.2%)	14,198 (3.6%)	12,098 (5.2%)
95+	6,404 (1.0%)	3,360 (0.9%)	3,044 (1.3%)
Gender, female	356,089 (57%)	222,884 (56%)	133,205 (57%)
Ethnicity			
Black	5,175 (0.8%)	3,017 (0.8%)	2,158 (0.9%)
Mixed Other	7,891 (1.3%)	4,831 (1.2%)	3,060 (1.3%)
South Asian	7,068 (1.1%)	4,210 (1.1%)	2,858 (1.2%)
White	552,301 (88%)	347,762 (88.1%)	204,539 (88%)
Missing	54,906 (8.8%)	34,940 (8.8%)	19,966 (8.6%)
Index of Multiple Deprivation Score			
1 (least deprived)	121,027 (19%)	78,370 (20%)	42,657 (18%)
2	129,288 (21%)	83,725 (21%)	45,563 (20%)
3	119,188 (19%)	75,643 (19%)	43,545 (19%)
4	98,979 (16%)	61,967 (16%)	37,012 (16%)
5 (most deprived)	78,937 (13%)	47,596 (12%)	31,341 (13%)
Missing	79,922 (13%)	47,459 (12%)	32,463 (14%)
Smoking Status			
Current	60,803 (10%)	37,971 (10%)	22,832 (10%)
Ex	178,539 (28%)	113,423 (29%)	65,116 (28%)
Non-smoker	333,366 (53%)	210,122 (53%)	123,244 (53%)
Missing	54,633 (9%)	33,244 (8%)	21,389 (9%)
Alcohol Consumption Status			
Heavy drinker	5,990 (1%)	3,701 (1%)	2,289 (1%)
Light drinker	73,574 (12%)	47,661 (12%)	25,913 (11%)

Table 3.1 continued from previous page

Variable	Overall, N = 627,341[1]	Controls, N = 394,760[1]	Reduction, N = 232,581[1]
Moderate drinker	41,642 (7%)	27,145 (7%)	14,497 (6%)
Non-drinker	143,603 (23%)	88,234 (22%)	55,369 (24%)
Occasional drinker	157,353 (25%)	101,058 (26%)	56,295 (24%)
Unknown amounts	122,374 (20%)	77,375 (20%)	44,999 (19%)
Missing	82,805 (13%)	49,586 (13%)	33,219 (14%)
Weight Category			
Healthy	77,782 (12%)	47,858 (12%)	29,924 (13%)
Obese	75,160 (12%)	49,290 (12%)	25,870 (11%)
Overweight	106,787 (17%)	69,239 (18%)	37,548 (16%)
Severe obesity	7,485 (1%)	4,767 (1%)	2,718 (1%)
Underweight	5,650 (1%)	2,964 (1%)	2,686 (1%)
Missing	354,477 (57%)	220,642 (56%)	133,835 (58%)
Systolic Blood Pressure (mmHg)	139.9 (19.34)	140.5 (18.63)	138.9 (20.44)
Missing	87,842 (14%)	56,827 (14%)	31,015 (13%)
Diastolic Blood Pressure (mmHg)	77.0 (10.64)	77.3 (10.40)	76.6 (11.03)
Missing	87,793 (14%)	56,797 (14%)	30,996 (13%)
Hypercholesterolemia	106,658 (17%)	68,004 (17%)	38,654 (17%)
Missing	420,553 (67%)	261,989 (66%)	158,564 (68%)
Antihypertensive (classes)			
Angiotensin Converting Enzyme	210,250 (34%)	126,732 (32%)	83,518 (36%)
Alpha Blockers	42,602 (6.8%)	24,674 (6.3%)	17,928 (7.7%)
Angiotensin Receptor Blocker	80,117 (13%)	48,505 (12%)	31,612 (14%)
Beta Blockers	193,498 (31%)	114,755 (29%)	78,743 (34%)
Central Acting Agents	6,238 (1.0%)	3,288 (0.8%)	2,950 (1.3%)
Calcium Channel Blockers	208,818 (33%)	123,974 (31%)	84,844 (36%)
Renin	185 (<0.1%)	99 (<0.1%)	86 (<0.1%)
Thiazide	198,064 (32%)	112,088 (28%)	85,976 (37%)
Vaso-active drugs	1,166 (0.2%)	712 (0.2%)	454 (0.2%)
Number of unique antihypertensive prescriptions			
1	350,746 (56%)	227,475 (58%)	123,271 (53%)
2	189,124 (30%)	115,332 (29%)	73,792 (32%)
3+	87,471 (14%)	51,953 (13%)	35,518 (15%)
Statin	238,923 (38%)	154,569 (39%)	84,354 (36%)

Table 3.1 continued from previous page

Variable	Overall, N = 627,341[1]	Controls, N = 394,760[1]	Reduction, N = 232,581[1]
Antiplatelet Therapy	221,476 (35%)	137,294 (35%)	84,182 (36%)
Oral Anticoagulant	43,780 (7.0%)	26,633 (6.7%)	17,147 (7.4%)
Polypharmacy (>5 prescriptions)	352,106 (58%)	212,324 (56%)	139,782 (61%)
Atrial Fibrillation	67,608 (11%)	40,118 (10%)	27,490 (12%)
Ischaemic Heart Disease	231,033 (37%)	144,159 (37%)	86,874 (37%)
Cerebrovascular Disease	62,241 (9.9%)	36,832 (9.3%)	25,409 (11%)
Heart Failure	41,871 (6.7%)	24,634 (6.2%)	17,237 (7.4%)
Hypertension	449,948 (72%)	286,324 (73%)	163,624 (70%)
Hypotension	54,005 (8.6%)	30,992 (7.9%)	23,013 (9.9%)
Diabetes	108,603 (17%)	69,244 (18%)	39,359 (17%)
Chronic Kidney Disease	92,213 (15%)	55,366 (14%)	36,847 (16%)
Cognitive impairment	25,888 (4.1%)	13,317 (3.4%)	12,571 (5.4%)
Parkinsonism	12,886 (2.1%)	7,214 (1.8%)	5,672 (2.4%)
Cancer	11,176 (1.8%)	5,774 (1.5%)	5,402 (2.3%)
Recent hospitalisation	184,377 (29%)	98,977 (25%)	85,400 (37%)

[1]Median (IQR); n (%); Mean (SD)

3.6 Discussion

3.6.1 Summary of Results

It is difficult to determine the long-term consequences of reducing antihypertensive treatment due to the length of follow-up in available clinical trials, leaving an unmet need for the determination of these long-term consequences. Observational studies can provide more insight in the absence of trial data. However, determination of medication reduction in a complex intervention like the treatment of hypertension in electronic health record data has been challenging. Therefore, an algorithm was developed that allows for the detection of sustained prescription changes to facilitate the detection of medication discontinuation in complex pharmaceutical interventions in observational data. This algorithm was then applied to a CPRD-derived cohort, which consisted of patients over the age of 65 that were on at

least one antihypertensive prescription. Furthermore, patients had to be eligible for further linkage (death statistics, deprivation, and hospitalisation), the practice had to be up-to-standard, and patients had to have at least twelve months of observation time (as measured from cohort entry to cohort exit). The motifs that were developed to form the basis of the algorithm were based on the total antihypertensive prescription load as determined by a summation of the individual drug classes (summarised in appendix A.4).

In this cohort of representative English primary care patients treated with antihypertensive agents, 232,581 (31.6%) out of 737,385 patients discontinued treatment. Notable differences in characteristics were observed among those who discontinued, including older age, higher rates of recent hospitalisation, cancer diagnosis, hypotension, cognitive impairment, and polypharmacy. These differences could suggest that patients discontinuing treatment may represent a more vulnerable subgroup, potentially influenced by co-morbidities, frailty, or clinician concerns about the safety of continued therapy. However, the presented difference in this chapter are unadjusted and are analysed in more detail in Chapter 4 as there may be potential confounders in any analyses of long-term antihypertensive medication reduction outcomes.

3.6.2 Strengths and Limitations

The algorithm was based on two consecutive periods of three months of stable therapy where the first three months total prescription intensity was higher compared to the subsequent three months (see equation 3.1). This is a different approach to others who recently have sought to define antihypertensive discontinuation in electronic health record data [240, 269]. Where these approaches are viable to their selected dataset specifically (both extracting from the US Veteran Affairs (VA) facilities dataset or a subset thereof), they lack generalisability to other settings as both rely on specific strengths that the VA dataset has compared to

CPRD. VA covers veterans whom are predominantly male but offers high-resolution data due to day-to-day prescribing and dispensing information, [270, 273] which enabled the study of Odden *et al.* to detect the reduction of antihypertensives after a period of two weeks with a high degree of certainty [269]. In contrast, while CPRD offers lower-resolution prescription data, it provides excellent coverage of all patients attending general practices across the UK, enabling researchers to conduct epidemiological studies in primary care patients. This includes examining associations between treatments and outcomes, investigating potential causes of outcomes, and estimating incidence and prevalence of conditions [273].

While the algorithm provides a method to detect if medication reduction took place, it only provides an approximation of when this occurred. Obtaining a correct index date or "time zero" is a known problem of medication reduction research in routinely collected data [215]. This is caused by two distinct problems encountered in the CPRD data set or any general practice electronic health record data set. To exemplify these two problems, we will have a patient that will be stopping treatment, regardless of whom initiates the intervention (patient-led or clinician-led). This patient has received their final prescription and will not request a renewal, however the thesis is that it is likely that the patient stops within this time-window and not at the end as the prescription supply runs out. The second thesis is that tapering is poorly reported or hard to discern [283]. In practice it is not uncommon to gradually reduce the dose before complete cessation to prevent any direct withdrawal syndromes, for example, where dose tapering is indicated for the discontinuation of beta blockers [284, 285]. Tapering, like direct cessation, is likely to occur in any time of the last active prescription window. When it occurs, the patient might be advised to half the current dose for a period of time, before complete cessation. This intervention is only possible if the pharmaceutical product can safely be halved, in other cases a new prescription will be added for a lower dose drug. In the latter case, the prescription window is moved and the algorithm will adjust accordingly. In the former case, there will be an additional period of unknown therapeutic exposure.

The index date in the current work is determined at the first month the therapy is lowered. While this will in all likelihood not be the true time zero, by using the first month after the prescription reduction the assumption is made that the therapy has been ceased at this time point. This means that this time point is the latest we assume the reduction has taken place, thereby increasing the certainty of events happening after this to be related to stopping. Further limitations on outcome assessment will be discussed in chapter 5.

Another inherent limitation is the use of a grace period to prevent misclassification of prescription exposure gaps as stopping. In this work, a gap of at least three month is used similarly to other studies that were either conducted in CPRD or that assessed the effects of stopping cardiovascular medication [240, 242, 286]. This means that patients that pass away before the three months have been completed will not be classified as discontinued. This leads to the drawback that all patients that discontinue antihypertensive treatment survive at least the first three months after index, creating immortal time bias [287]. One approach to reduce immortal time bias would be the addition of a minimum follow-up period of three-months to the control group. This would allow for a better comparison between cases and controls and would ensure that controls had the same opportunity to discontinue treatment as cases. Additionally, it potentially also reduces selection bias as the control group now includes patients that die early; by applying three-month follow-up, the control group is less biased by "early" deaths, leading to more comparable groups (internal validity). However, adding a three-month window could potentially lead to skewing to healthier controls and - in extension - to exclusion of certain populations (e.g. frailer or comorbid patients in general) who are at increased risk of discontinuing treatment. We predict that most of these patients will fall into one of the two following categories. First, some patients could have stopped treatment, which might have influenced their speed of passing. A second category of patients that have their medications reduced and passing relatively quickly thereafter, would likely include those that stop their therapy in response to critical illness and overall

futility of continued treatment of preventive therapy. The implications on the interpretation of outcomes will be discussed in chapter 5.

Due to the inclusion of two three-month intervals, various edge cases are impossible to detect. First, patients who initiate new treatment will need to use this new prescription for at least three months to satisfy the stability requirement. This means that patients who initiate treatment and discontinue this treatment within three months will not be flagged by the algorithm. In this work, this type of reduction is considered to be likely due to patients not tolerating treatment, and the occurrence and outcomes associated with this category of patients were not of interest in this thesis. While the implementation of the three-month stability window before reduction was introduced to deal with naturally occurring variations, it also has the advantage that it prevents these patients being flagged. Would one want to ascertain treatment tolerability, prescriptions of a specific class that are new (e.g. no previous history) can be tracked specifically. Second, the algorithm is unable to detect medication that was stopped more gradually; either a single prescription over a period of two months or multiple prescriptions at monthly intervals. Alternatives to the double three-month window were considered to be able to catch these patients. This revolved around the extension of the window of decreased prescription load from three to six months. Although this would lead to more certainty with regards to actual medication reduction taking place, this would also result in selection of patients who were able to tolerate treatment reduction (selection bias). Furthermore, increasing the window to six months would require more "error terms" to deal with the naturally occurring variations. The placement of these "error terms" at specific months as represented in the motifs would become increasingly complex, and - after thorough consideration - was considered impractical.

Whilst the CPRD GOLD data set indicates that it provides data on dosages, actual extraction of this information is far from trivial [273]. Therefore, number of prescriptions was used in this work as an indication of antihypertensive treatment intensity, which does not consider the dosage of these prescriptions. The initial aim

was to work with daily defined dose (DDD). However, this had to be abandoned due to problems determining dosage. DDD is a technical unit of measure, where two drugs of different classes can be compared using a dimensionless unit reflecting strength based on indication [288], allowing a direct comparison between various treatment regiments. This is because there are several problems that could arise using number of prescriptions instead of DDD. First, patients who are on two low dose antihypertensives could be switched to a single high dose antihypertensive. While this would be a decline of a single prescription in prescription numbers, this could be a one-to-one switch where the two low dose therapeutics equated to a single high dose treatment when using the DDD system. In this example, you would get a misclassification of antihypertensive medication discontinuation as the overall antihypertensive potential effect does not change. It is assumed that this switch is uncommon, but not improbable. Furthermore, an overall decline of antihypertensive effect might still happen as the synergistic effect of combination therapy is lost [289, 290]. Additionally, it is undetermined what the strength of the reduction is, meaning that in our current work it is unclear if only high or low dose antihypertensives are withdrawn. In this work the assumption is made that there is an equal distribution of both low and high dose discontinuation. The use of DDD would allow various alternative strategies to be explored, namely dose reduction as well as low-vs-high dose reductions.

As this algorithm is designed to work with various data types, including DDD because its detection of change is dependent on the intensity information delivered (either DDD or number of prescriptions). Therefore, the same rule-set could be applied, with minor adaptations if and when this information were to become available. The only significant change that needs to be implemented is with regards to the third rule. The third rule states that the number of prescriptions (or DDD) needs be greater at an earlier time point. Due to the fact that number of prescriptions can only be integers, the equation remains simple as the change can only be whole number with one the smallest integer possible. When using

DDD, each prescription is converted to a numeric value between 0.25 and 2.00, with extremes being possible. This has an advantage that a threshold value (tv) needs to be implemented, changing equation three to $y(t = ce+i+2)-y(t = ce+i+3) > tv$. Future work should explore this approach, including the use of different values for the threshold value, which will allow for better differentiation of specific discontinue subgroups (e.g extreme discontinuation where tv is greater than one or moderate discontinuation where tv is between a half and one).

Finally, due to the observational nature of the data analysed, the algorithm was only able to determine that antihypertensive medication reduction occurred. Currently, no method exists that can determine who initiated the discontinuation of any treatment. As a result, the cohort of patients identified as having stopped their treatment includes both those whose medication was reduced under clinical supervision and those who discontinued treatment independently. The implications of this for subsequent analyses will be discussed in the respective chapters.

3.6.3 Comparison with existing literature and previous findings

To my knowledge, this study is the first that has attempted to use an algorithmic approach to determine medication discontinuation in routinely collected general practice electronic health record data. The method development dataset consisted of 737,385 patients from ten different regions within England. All patients over the age of 65 and on antihypertensive treatment were included, making this a representative population of older patients on antihypertensive treatment receiving long-term care in English General Practice (GP).

In a recent years the wider public's' perception of what constitutes an algorithm has changed, due to the introduction of artificial intelligence and machine learning systems in everyday life [291]. However, the definition remains the same and herein

used, where an algorithm is "a set of predetermined instructions to solve a specific problem" [292]. When applied to big datasets and computer systems, this can be further be specified to that "no human intervention is required between asking the question and reading the answer" [293].

In this study of 737,385 general practice patients 31.6% were observed to stop their medication. Indirect comparison can be done with two studies by Aubert *et al* in the VA primary care data set in primary care patients examining factors associated with and outcomes of antihypertensive deintensification [240, 271]. Both populations are predominantly male (98%) and the rate of discontinuation in the more general population was 19.9% and 20.3% in the low blood pressure cohort, for the studies Aubert *et al.* ([271]) and Aubert *et al.* ([240]), respectively. While the proportion of discontinuation is lower compared to the current work, the observation period was only two years. Similarly to this work, patients were included if they were over the age of 65 years and on antihypertensive treatment and index date was based on a baseline visit during the previously discussed follow-up time. Even though the method of detecting medication reduction and included patient population are different, a similar age was found compared to the current work with a mean age of 76.1 years (SD 7.5) and 74.9 years (SD 7.4) vs a median of 76.4 years (IQR: 70.5-82.9) [240, 271].

Comparison of the current results to studies conducted in different settings by Gilstrap *et al* and Odden *et al* showed that average ages, at time of antihypertensive treatment discontinuation, in those studies were slightly higher with 78.97 years (SD 7.77) and 78.0 years (SD 8.4), respectively [123, 269]. Interestingly, the study of Gilstrap *et al* did not exclude patients based on age. In the study by Odden *et al* 70.4% of the patients had an antihypertensive medication reduced during their stay in the VA nursing home; of these, 30.9% had treatment reintroduced [269]. The population examined in this study had a high burden of disability and morbidity, with the largest proportion of antihypertensive medication discontinuation occurring in the weeks shortly before death [269]. This pattern likely reflects decisions to

discontinue treatment due to the perceived futility of continued therapy in the context of end-of-life care.

When comparing the current work to other statin discontinuation observational studies with routinely collected general practice data, we see lower proportions of discontinuation. Giral *et al* report a total of 14% discontinuation over a period of 2.4 years [242], Thompson *et al* report 30% discontinuation among primary prevention and 25% among secondary prevention [243], and Rea *et al* report 31% discontinuation [238].

Of special interest is the comparison of drug reinstatement of those found in this work to RCT data, as most designs allowed for reintroduction of antihypertensive therapy where this was indicated, primarily for safety in the presence of elevated blood pressure. While the rate of follow-up measurements in trial settings might not be indicative of general practice, it does give a good overview of ability to remain on lower doses of treatment. In the study by Moonen *et al* 180 patients were included in the intention-to-treat intervention arm; of these, 41 (22.7%) patients restarted treatment within 16-weeks, with increased blood pressure being the most common reason [237]. However, nearly a quarter of the patients included in the intention-to-treat did not reduce their treatment at all [237]. In the study by Walma *et al* long-term diuretic treatment was reduced in 102 patients; after six months, 50 patients had restarted treatment, with 25 patients restarting in the first four weeks [241]. In the OPTiMISE trial and subsequent long-term follow-up trial OPTiMISE-X, 33.7% and 46.1% restarted treatment at 12-weeks and 4-years, respectively [236]. In this work 34.1% restarted treatment, which was determined based on the previously mentioned rule-set. This means that if changes happened within the three month window after the initial determination of deprescribing, these patient would have not been detected as medication reduction. This coincides roughly with the follow-up period in OPTiMISE, meaning that patients who potentially temporary discontinue medication were not identified [236]. During long-term

follow-up (OPTiMISE-X), an additional 16% (up to a total of 50%) of the patients had medication reintroduced [294].

The proportion of patients restarting treatment in the current study differs from the proportion reported by Sheppard *et al* [236]. During their trial, additional trial appointments were booked for patients at four weeks, where clinical readings were taken. This would potentially have allowed for earlier detection of increased blood pressure compared to routine follow-up in routine practice, in which follow-up appointments after reducing antihypertensive treatment can be delayed to the more structured and frequent monitoring protocols typically seen in clinical trials. Patients in the observation cohort who are not identified to have stopped medication because they restart within three months are more likely to not tolerate treatment reduction and possibly experience acute symptoms. Reducing the grace period might facilitate the identification of these patients. However, it will concurrently increase the likelihood of attributing low-adherence patients to the discontinuation cohort.

3.6.3.1 Future research

The algorithm developed for the detection of sustained medication changes in this work can be classified as a "brute force algorithm" [277]. The patterns that needed to be identified in patient prescription data were derived from visual inspection of prescription patterns. Further development of the algorithm could potentially be done with supervised or semi-supervised machine learning models [295, 296]. This approach will also allow for prescription files to be used directly or in combination with monthly count files which were used in this work. Due to the fact that machine learning models need some preliminary human to "know" what to look at in terms of medication discontinuation (or intensification), early pattern discovery work and development would probably need to utilise periodic prescription data. This is due to the fact that raw data entries are incomprehensible at low quantities of prescription

lines, let alone thousands of prescription entries. Machine learning models have the potential for deeper analysis of the data present in routinely collected health records, as the potential for pattern recognition by machine learning methods exceeds that of humans capabilities [296, 297].

3.7 Conclusion

Using an algorithmic approach based on simple rule-set, antihypertensive medication reduction and reinstatement was successfully determined in routinely collected general practice electronic health records. In this CPRD-derived dataset of almost 800,000 patients, approximately one third of patients reduced antihypertensive treatment during the observation time window. While this is higher than other primary care studies, the observation period was substantially longer in the current work. However, compared to nursing home residents, rates of discontinuation were markedly lower, emphasising the need to understand factors leading to discontinuation and outcomes thereafter, which will be explored in chapters 4 and 5 respectively.

3.8 Key Points

- This chapter described the successful development of a rule-set and subsequent algorithm to detect changes, both increase and decreases, in longitudinal prescription data over time in observational data.
- A third of the patients in our CPRD-derived cohort has their antihypertensive medication reduced during the observation period. Approximately 34.2 percent of these patients had their medication re-instated during the follow-up window.

4

Identification of patient characteristics associated with antihypertensive treatment reduction in older general practice patients: a nested case-control study using CPRD

4.1 Chapter overview

Antihypertensive medication is regularly stopped in primary care without proper guidance on whom to target, but it solely relies on clinical judgement. Therefore it is unclear which patients are targeted in practice. This chapter presents the results of a nested case-control analysis of patient characteristics associated with an increased or decreased likelihood of discontinuing antihypertensive medication and therefore creating an image of the patient landscape.

Out of 737,385 eligible patients from the GOLD database of the Clinical Practice Research Datalink (CPRD), 232,581 patients were identified to have discontinued antihypertensive treatment (cases) and matched to 394,760 patients that at the time of matching continued treatment (controls). Conditional logistic regression adjusted for other variables was used to calculate odds ratios. Variables comprised patient demographics, clinical readings, medication usage, and co-morbidities.

For patient demographics, increased age and black, South Asian, or mixed other compared to white ethnicity were associated with an increased likelihood of antihypertensive medication discontinuation. Furthermore, for clinical readings, a lower systolic blood pressure was associated with an increased likelihood of discontinuation. Both polypharmacy and higher antihypertensive use shortly before cessation were associated with discontinuing antihypertensive treatment. Furthermore, diagnoses related to hypotension, falls, cognitive impairment, Parkinson's disease, and cancer and recent hospitalisation were all associated with discontinuing antihypertensive treatment.

Factors associated with a decreased likelihood of discontinuing treatment were the use of other medication used to prevent cardiovascular disease, diabetes, ischaemic heart disease, heart failure, and hypertension.

Reduction of antihypertensive medication is more likely when patients were older, prescribed multiple medication, were on more than one antihypertensive, or had very low systolic blood pressure. Reduction was less likely when patients were at higher risk of experiencing cardiovascular events.

4.2 Introduction

In the previous chapter, the focus was on the development and execution of a new algorithmic method to identify patients who received antihypertensive medication and subsequently discontinued treatment. Due to the lack of evidence on whom might benefit or be at risk from reducing antihypertensive treatment and a lack of tangible guidelines advising on a pragmatic approach, it is unclear which patients are stopping treatment [33, 52]. Secondarily, due the observational nature of this and previous work, it is unclear who initiated the cessation [240, 269]. Meaning that this work includes patients who might have stopped treatment independently and these reasons might be different to those vaguely pointed to in guidelines.

Currently there is little information available on which and why patients have their antihypertensive treatment stopped in an English primary care setting. Previous work in the field of statin discontinuation showed that characteristics associated with discontinuation varied between countries [238, 242, 243]. Additionally, work done on antihypertensive medication discontinuation was done in the Veterans Affairs (VA) database consisting of almost exclusively males and focused on nursing home patients [269, 271]. Therefore, factors related to discontinuing antihypertensive medication in a general practice population need to be determined. As discussed in the previous chapter, it is currently not possible to determine if the medication discontinuation was initiated by the patient or a health care professional. Therefore, it is important to identify patient characteristics for further development of new and existing guidelines to support health care professionals in the identification of either patients to be targeted with this intervention or patients to provide additional support to increase treatment persistence. Additionally, these factors are used in the

next chapter to adjust models to determine the associations between discontinuation and outcomes (e.g. all-cause hospitalisation).

4.3 Chapter Aim

The objective of this study was to identify patient characteristics that are associated with an increased/decreased likelihood of discontinuing antihypertensive medication using electronic health record data.

4.4 Methods

CPRD GOLD dataset was used to identify a nationwide cohort of patients over the age of 65 on antihypertensive treatment. These patients were followed-up for discontinuation of antihypertensive treatment. A nested case-control analysis was conducted, nested within the cohort of patients on antihypertensive treatment. This analysis aimed to compare the characteristics of patients who discontinued treatment with those of patients who did not discontinue treatment at the time they were selected as controls.

4.4.1 Data Source and study cohort

The protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA) (protocol reference number: 21_000385).

All included patients were eligible for linkage to the Office for National Statistics (ONS) Death Registration Data and Hospital Episode Statistics (HES) Admitted Patient Care (APC), and practice level Index of Multiple Deprivation (IMD) data [298–300]. These dataset provide additional and more accurate information not available in CPRD allowing for exploration of more outcomes and the addition

of extra patient characteristics. HES APC provides information and details of all admissions to English NHS health care providers and provides ethnicity data used to define patient characteristics. Finally, the IMD dataset contains information on various domains of material deprivation. Deprivation information is available on patient-level and is available in quintiles, where the first quintile represents the least deprived population.

Patients entered the cohort when they had at least one active antihypertensive prescription and were at least 65 years of age, and their practice was up-to-standard, whichever happened last. Patients were ineligible if they had less than twelve months of follow-up time, between cohort entry and cohort exit, which was the earliest date of either last available practice data, transferred out of the practice, or death. Restrictions on minimum follow-up time was included as it was needed to facilitate the implementation of the algorithm.

4.4.2 Case and control definition

Cases were defined as patients who had reduced antihypertensive medication as identified by the algorithm developed in the previous chapter for at least 3-months compared to the previous 3-months. Case identification took place using the algorithm developed in chapter 3, where the index date was defined as the first day of the reduced treatment period. For patients with more than one discontinuation event during the observation period, only the first event was considered in the analysis. Controls were selected from the risk-set and at the time of selection had not discontinued any antihypertensive treatment.

4.4.3 Observation

Observation started at the latest of the following dates: 65^{th}birthday, practice up-to-standard, or active antihypertensive prescription. Observation continued until the earliest of the following dates: death, latest available practice data, or moved

out of practice.

4.4.4 Variable definitions

All baseline characteristics were determined from information recorded prior to the index date, with only data within a specific time frame before the index date being considered. The specific time frames for each variable are discussed in detail in later sections. Code lists used to generate the variables included in the analysis are available at: `https://github.com/RikvdVeen/DPhil_thesis2025/tree/main/AHT_reduction`. Baseline characteristics comprised patient demographics, clinical readings, medication usage, and co-morbidities. Variables were selected based on previously published work on cardiovascular medication discontinuation and expert opinion [242, 269, 271, 280].

4.4.4.1 Patient demographic definitions

Age and sex were determined based on CPRD patient data files. Ethnicity was based on data available through CPRD and linkage with basic inpatient Hospital Episode Statistics (HES) data, categories included were: white, black, South Asian, and mixed other. Patient-level Index of Multiple Deprivation (IMD) data was obtained as quintiles (ranging from most deprived to least deprived). Smoking and alcohol consumption were derived from a combination of clinical (smoking and drinking status) and additional CPRD files (alcohol units). Smoking was categorised into non-smokers, current smokers, and ex-smokers. Alcohol categories were based on a combination of drinking status (yes/no) and daily units of alcohol consumed and were as followed: non-drinker, occasional drinker (<1 daily units), light drinker (between 1 and 2 daily units), moderate drinker (between 2 and 6 daily units), heavy drinker (>6 daily units), and unknown amount (alcohol units undefined).

4.4.4.2 Clinical readings

Weight category was determined using BMI, where the latest measured weight in the last five years was accepted and the most recent height. For blood pressure (systolic and diastolic) the most recent blood pressure measurement in the last year was taken; if this was not available, this was considered missing. Similarly, hypercholesterolemia was determined on a LDL-measurement taken within the last year with a measurement of 2.5 mmol/L or higher considered as positive.

4.4.4.3 Medication history definitions

Prescription history (antihypertensives, other cardiovascular medications, and polypharmacy) were based on the prescriptions before discontinuation (index date - 1 month). Polypharmacy was determined based on the number of active chronic prescriptions in the four months before the index data, medications included in chapters one to thirteen of the British National Formulary (BNF) were used to determine total chronic prescription load [281]. The BNF is a reference book containing monographs on all licensed medications in the UK, medications are categorised in individual chapters. Patients were determined to have polypharmacy if five or more active prescriptions were present, based on previous literature and similar studies conducted in CPRD [54, 282]. All included drug classes can be found in appendix A.5.

4.4.4.4 Co-morbidity definitions

Co-morbidities were defined as any historical read code of the disease of interest, with the exception of cancer and recent hospitalisation. Cancer, was defined as a recent diagnoses of a cancer in the last year based on CPRD clinical files, due to an observation in the work of Giral *et al.* where a recent cancer diagnosis was associated with an increased likelihood of stopping treatment with statins [242]. Recent hospitalisation was defined of at least a single hospital admission in the last

year based on HES data linkage.

4.4.5 Nested Case-Control analysis

Cases were identified as patients within the study cohort who had an antihypertensive discontinuation event during follow-up. The first date of reduced treatment was considered the index date, this is when the previously (higher) number of prescriptions has finished. For each case, the maximum number of controls (with replacement) was selected as a whole number of the ratio between cases and controls available per practice. Controls were assigned the index date of their respective cases. Matching variables were limited to practice exclusively to account for potential prescriber preference. Additional variables which can be used in matching (e.g. age, gender, or blood pressure) were not used to facilitate the study of the potential differences between these characteristics in cases and controls. Cases were allowed to be selected as controls until their case-defining date. This is in accordance with incidence density sampling, which is discussed in detail in Section 3.4.4.5 and Figure 3.3 [278].

4.4.6 Statistical analysis

4.4.6.1 Nested Case-Control Analysis

Characteristics of cases and controls are presented using descriptive statistics. Conditional logistic regression was used to calculate adjusted odds ratios (aOR) and corresponding 95% confidence intervals (CIs) adjusted for age (5-year intervals), systolic blood pressure (10 mmHg bands), and all covariates listed in section 4.4.4. Logistic regression is the standard to examine the relationship of independent variables and a binary dependent outcome variable (e.g. discontinuation; yes/no) with conditional logistic regression being the standard for matched sets (e.g. practice) [301–303]. The results of both imputed data (primary analysis) and complete case

analysis (sensitivity analysis) are presented.

4.4.6.2 Missing data

Missing data was present for the following variables: ethnicity (8.9%), IMD (12.7%), smoking status (8.8%), alcohol consumption (12.8%), weight category (56%), systolic blood pressure (14.0%), and hypercholesterolemia (67%). Two approaches were utilised, imputation of missing data (primary analysis) and complete case analysis (sensitivity analysis). Complete case analysis was performed by listwise deletion, where only patients with no missing data are included in the analysis [304]. When data are not missing at random complete case analysis has the potential to be very biased [305–307].

Multiple imputation by chained equations (MICE) was used to impute missing data. MICE is a method to generate probable imputed data sets using an iterative process based on all other variables in the incomplete data set [308]. MICE can be summarised in a three-step process: imputation, analysis, and pooling. Imputation is done through different models depending on the variable being imputed, meaning binary data is imputed using logistic regression, nominal variables are imputed using polytomous logistic regression, and ordinal variables are imputed using proportional odds model [309]. The primary analysis was conducted in each imputed dataset using conditional logistic regression and the regression coefficients were combined across imputed datasets using Rubins rule [308–310].

In this work, 10 imputed datasets were created over 20 iterations using the MICE package in R [309]. All variables of the analysis were included in the imputation model. Variables with missing data were ordinal, with the exception of hypercholesterolemia (binary) and ethnicity (nominal).

4.5 Results

A total of 737,385 patients were eligible for this study. Cases were identified and matching was performed as described in Chapter 3. In summary, 232,851 cases (median age 76.40 (IQR: 70.48 - 82.88), 57% female) were identified and matched to 394,760 controls (median age 75.18 (IQR: 69.96 - 81.27), 56% female) (Figure 3.4). Baseline characteristics are described in table 3.1 and figure 4.1. Cases were on average similar to controls, with the exception of slightly more cases than controls with increased age (stratified in 5-year bands), polypharmacy (61% vs 56%, respectively), hypotension (9.9% vs 7.9%, respectively), and recent hospitalisation (37% vs 25%, respectively).

4.5.1 Nested Case-Control Analysis

4.5.1.1 Imputed data analysis

Using a nested case-control analysis with imputed data, patient characteristics associated with antihypertensive medication discontinuation were examined. Older age emerged as a significant predictor, with the likelihood of discontinuation increasing progressively from age 80 onwards (e.g., for patients aged 95 years and older: aOR, 1.43 [95% CI, 1.38–1.49]). Patients from non-white ethnic backgrounds, including Black (aOR, 1.25 [95% CI, 1.19–1.31]), South Asian (aOR, 1.24 [95% CI, 1.19–1.29]), and mixed ethnicity (aOR, 1.17 [95% CI, 1.13–1.22]), were more likely to discontinue antihypertensives compared to those of white ethnicity (Figure 4.1).

Clinical factors also played a significant role. Lower systolic blood pressure was strongly associated with discontinuation, particularly at levels below 100 mmHg (aOR, 1.93 [95% CI, 1.87–1.99]). Additional predictors included hypotension, recent hospital admissions (aOR, 1.68 [95% CI, 1.67–1.69]), cognitive impairment (aOR, 1.34 [95% CI, 1.32–1.37]), and a history of falls. Patients prescribed multiple antihypertensive medications (e.g., three or more prescriptions: aOR, 1.47 [95% CI, 1.45–1.49]) or those exposed to polypharmacy were also more likely to discontinue

treatment (Figure 4.1).

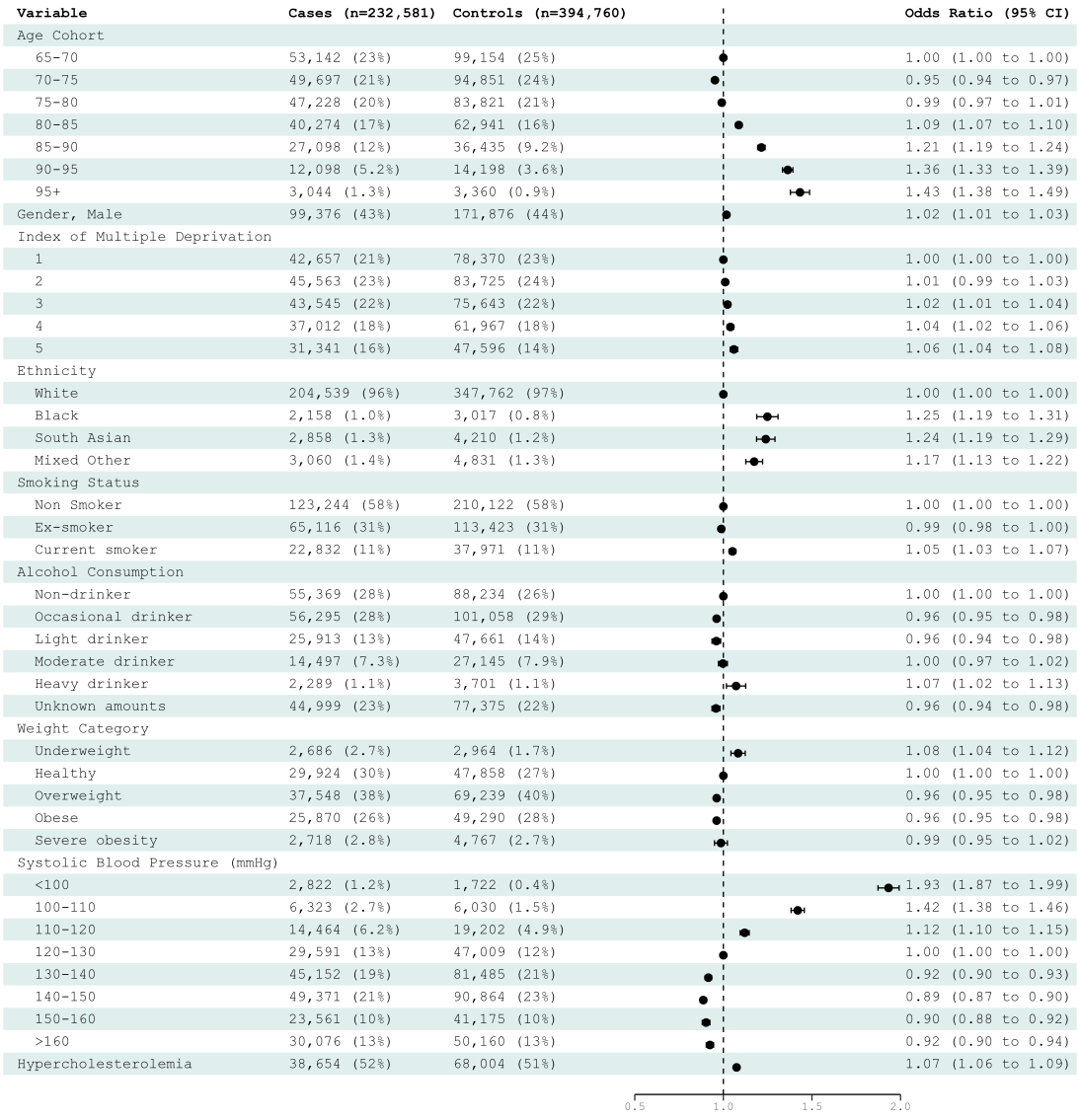


Figure 4.1: Forest plot showing adjusted Odds Ratios (aOR) of characteristics predicting antihypertensive treatment discontinuation. Adjusted Odds Ratios are based on imputation.

In contrast, factors associated with a reduced likelihood of discontinuation included higher systolic blood pressure (e.g., 140–150 mmHg: aOR, 0.89 [95% CI, 0.87–0.90]), active prescriptions for statins (aOR, 0.88 [95% CI, 0.87–0.90]) or anticoagulants, and comorbid conditions, such as history of different types of CVD (with the exception of stroke (aOR, 1.05 [95% CI, 1.03–1.07])), diabetes, and

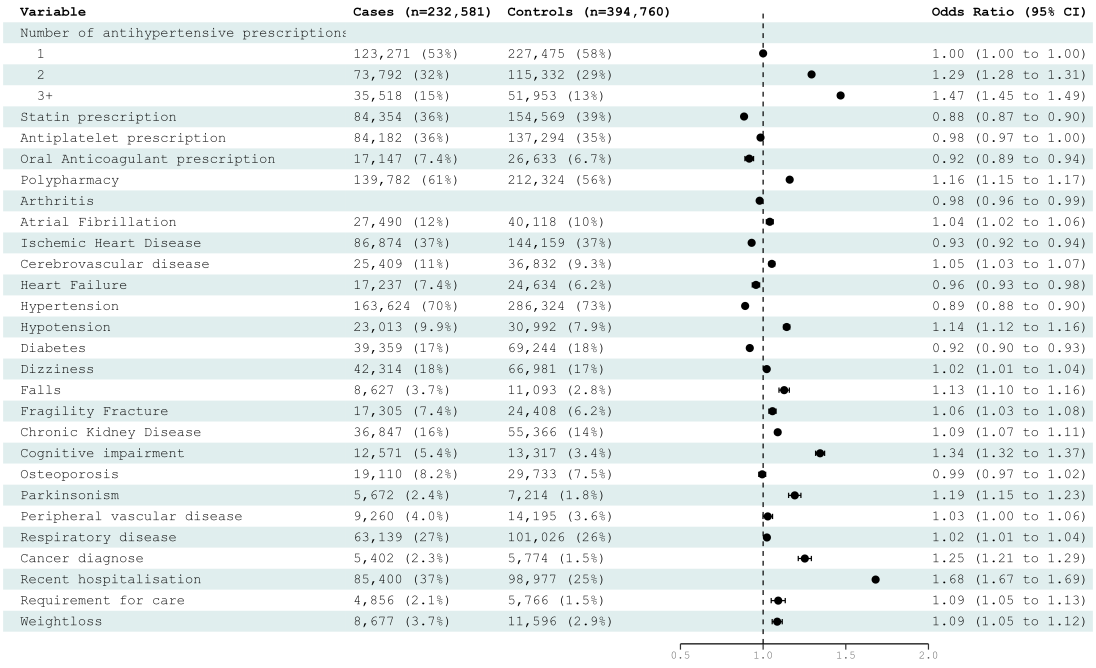


Figure 4.1: Forest plot showing adjusted Odds Ratios (aOR) of characteristics predicting antihypertensive treatment discontinuation (cont.).

hypertension (Figure 4.1).

4.5.1.2 Complete case analysis

Using listwise deletion a total of 98,017 patients remained with complete case data available to perform a nested case-control analysis. Due to the reduced power, the confidence intervals for most characteristics were wide and most outcomes were not statistically significant. Noticeable exceptions associated with an increased likelihood of discontinuing antihypertensive medication were increased age (age 65-70 used as reference group, 85-90 years; aOR, 1.21 [95% CI, 1.11-1.32]), 90-95; aOR, 1.29 [95% CI, 1.11-1.49]), decreased systolic blood pressure (120-130 mmHg as reference, <100 mmHg; aOR, 2.25 [95% CI, 1.80-2.80]), increased number of antihypertensive prescriptions (three or more prescriptions vs one; aOR, 1.72 [95% CI, 1.62-1.82]), recent cancer diagnosis (aOR, 1.47 [95% CI, 1.26-1.70]), and recent hospitalisation (aOR, 1.68 [95% CI, 1.61-1.76]).

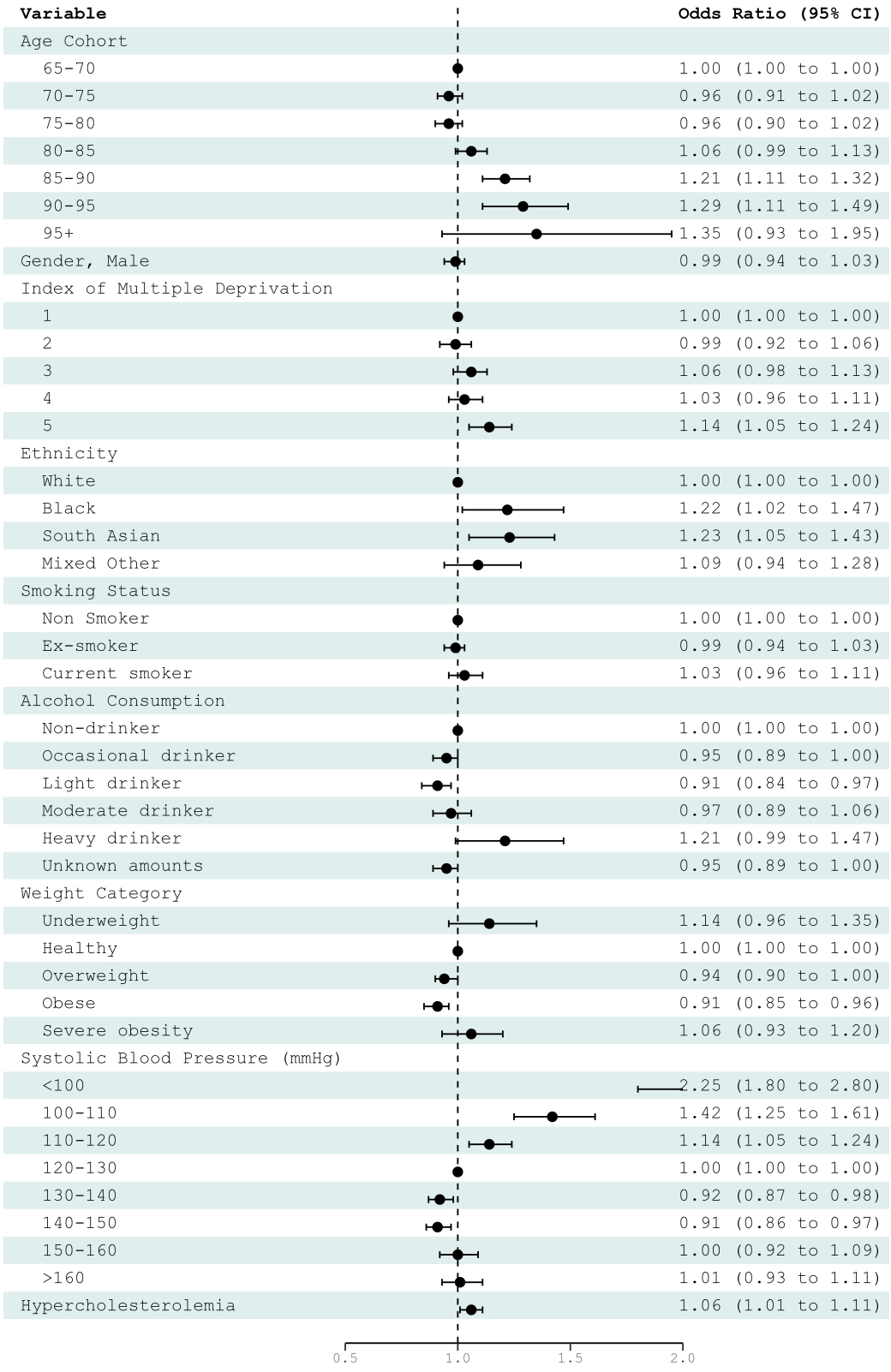


Figure 4.2: Forest plot showing adjusted Odds Ratios (aOR) of characteristics predicting antihypertensive treatment discontinuation. Adjusted Odds Ratios are based on complete case data.

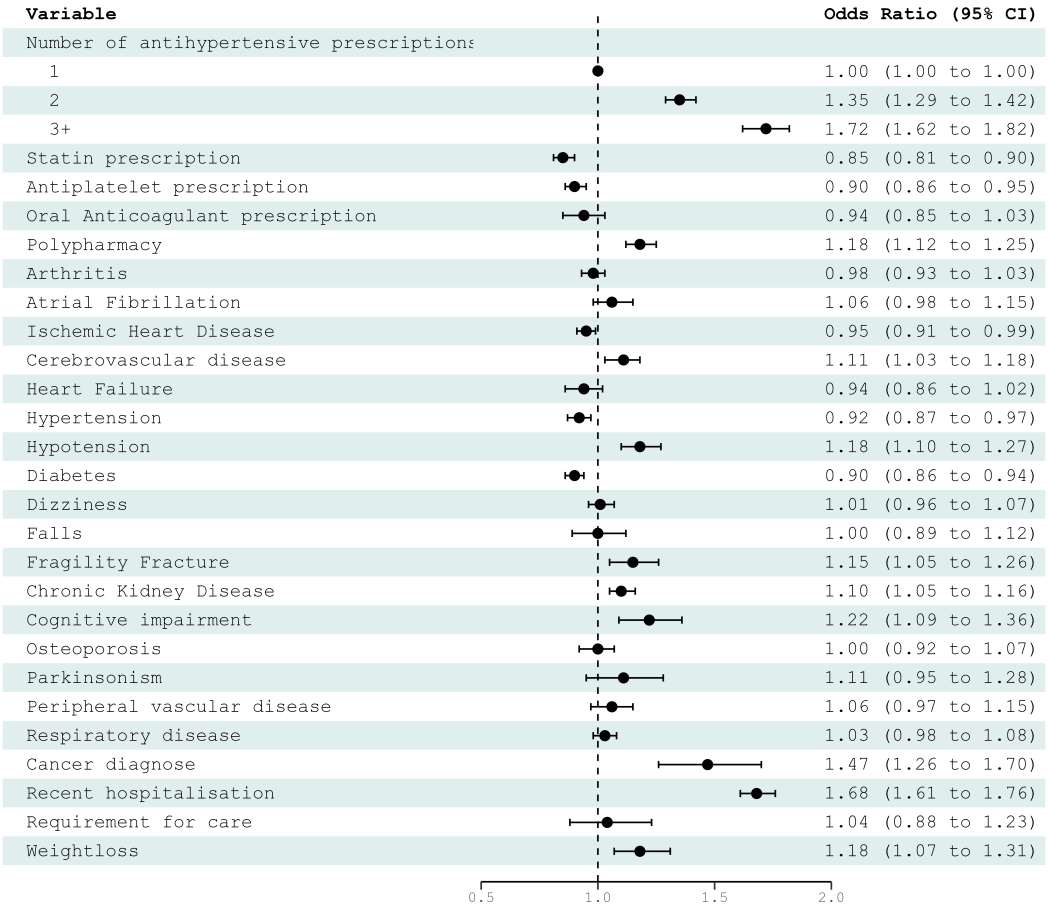


Figure 4.2: Forest plot showing adjusted Odds Ratios (aOR) of characteristics predicting antihypertensive treatment discontinuation (cont.).

4.6 Discussion

4.6.1 Summary of Results

In this large observational study of older patients on antihypertensive treatment in the CPRD GOLD data set, a nested case-control study was performed to determine which factors are associated with stopping or reducing treatment. Older age, lower systolic blood pressure, higher number of antihypertensive prescriptions, decreased cognitive function, recent cancer diagnosis, and recent hospitalisation were all associated with discontinuing antihypertensive treatment. Inversely, cardiovascular risk factors like increased systolic blood pressure, other cardiovascular medication prescriptions, hypertension, previous CVD, and diabetes were associated with a

reduced likelihood of discontinuing antihypertensive treatment.

Hypertension management, as supported by national and international guidelines, focus on attaining blood pressure targets (<140 mmHg and <150 mmHg systolic blood pressure, for patients under and over the age of 80 years, respectively) [21, 97]. Furthermore, co-morbidities associated with increased cardiovascular risks are widely recognised and are used to identify patients at higher risk of morbidity[217, 311]. Thus, the presence of co-morbidities and unattained systolic blood pressure targets have the potential to impact treatment decisions made by clinicians, especially when the treatment is essential in the management of cardiovascular disease [93]. The decreased likelihood of discontinuing antihypertensive treatment found in patients at increased risk of cardiovascular events in the current analysis reflects this. Although the associations were modest, the associations were consistent for all cardiovascular risk factors, with the exception of history of stroke (see Figure 4.1).

Recent hospitalisation was a strong indicator of discontinuing antihypertensive treatment (aOR, 1.68 [95% CI, 1.67-1.69]). While it is unclear what the mechanism behind this phenomenon is in the context of this work, it is known that medication erroneously is discontinued after hospitalisation [312, 313]. Methods to reduce these errors in practice are being implemented in the form of medication reconciliation and the effects of this might be obscured by due the large follow-up time [314, 315]. An alternative hypothesis is that medication related side-effects that required hospital admission are increased in older populations, either in the context of adverse drug reactions or drug-drug interactions [316, 317]. Therefore, discontinuation could be a result of appropriate management of adverse drug events instead of medication prescribing errors. In this work, no additional analyses have been undertaken to elude the specific mechanism underpinning discontinuation after hospital admission or if there are differences between pre- and post medication reconciliation as they are outside of the scope of this thesis and this is currently not feasible in these

datasets.

4.6.2 Strengths and Limitations

One of the strengths of this analysis is the large cohort of patients being treated with hypertensives, which is representative of both England and of a primary care setting [273]. It is the first study that assesses the factors associated with discontinuation of any antihypertensive treatment in primary care patients; most other studies have focused on cessation of treatment with a specific agent or persistence in new-users [318, 319]. While these studies offer valuable information with regards to treatment persistence, they do not take into consideration therapy switching. Therefore, these studies only provide information on class persistence, but not overall continuation and discontinuation of antihypertensive treatment.

Due to the large size of the analysis cohort, almost all of the explored characteristics were statistically significant in the imputation cohort. However, this does not necessarily imply clinical significance for these findings [320]. An example of this could be the association between male and female patients and their likelihood of discontinuing treatment (or being discontinued) (aOR 1.02; 95% CI, 1.01-1.03). This means that some caution is needed for the interpretation of these results, as it leaves the door open for over-interpretation of the results. Additionally, the current analyses only represent associations as confounding has not been rigorously addressed. Therefore, it is important to consider each factor separately and decide the difference or change that would be necessary to make this clinically relevant. This is also important in the context of the analysis carried out in the next chapter.

Another strength is the method of matching: using incidence density sampling allows for selection of controls at the time a case is identified. Where any patient at risk of developing the outcome of interest, in this case at risk of discontinuation of antihypertensive treatment, can be selected as a control as long as they have not yet

stopped treatment themselves [278, 321]. When compared to cumulative incidence sampling, in which controls are sampled from patients that remain on treatment until the end of the observation period, incidence density sampling provides less biased estimates, because patients in each pair are more similar [322]. Matching variables were limited to practice level only, meaning controls were sampled from the same general practice to account for practice or prescriber preferences [279]. Additionally, due to the fact no additional matching variables were selected, it allowed for the exploration of all the characteristics of interest. Finally, due to the limited number of matching variables, all patients within a practice were eligible to be selected, maximising the amount of controls per case increasing statistical power [323].

Blood pressure is collected regularly for patients who are treated with antihypertensive medication in the NHS [324]. Blood pressure is an important clinical outcome of cardiovascular management and due to associations seen in previous work [217, 269]. Therefore, in this work the latest blood pressure reading less than a year old was used to establish the approximate blood pressure at the index date. Due to this constraint there was 14.0% missing data for systolic blood pressure, which was imputed using MICE. This percentage is acceptable and results in very minimal biased results as reflected by similar associations found in the complete case and imputed analyses (e.g. 100-110 mmHg; aOR 1.42 (95% CI 1.38-1.46) imputed vs aOR 1.42 (95% 1.25-1.61) complete case) [325]. Therefore, it is a strength of this work to have a large proportion of recent systolic blood pressure information available to evaluate the effect of systolic blood pressure on the continuation of discontinuation.

The implementation of MICE to impute missing values allowed for a larger retention of the study cohort, thereby maintaining a large enough sample size for analyses. However, when a large proportion of data is missing, the imputations may be less reliable and the results may still be biased despite the use of MICE

[325]. Compared to complete case analysis (obtained through listwise deletion, presented in Figure 4.2) the full study cohort is maintained and therefore preserves statistical power. Moreover, complete case analysis can lead to biased results, where MICE preserves variability in the data reducing bias [304]. Furthermore, and more importantly, it is unclear if the mechanism behind the missing data is that data is missing at random (or missing completely at random), which justifies the use of MICE. A comprehensive model was built to try and address this limitation [131, 148, 326, 327]. However, missing data could potentially have been informative as they could be associated with underlying factors such as health seeking behaviour. This is known as "missing not at random" (MNAR). This case can be made specifically for missing data on blood pressure. As previously described, blood pressure is routinely collected in the NHS as part of the Quality and Outcomes Framework (QOF), where the aim is to obtain readings on an annual basis [324]. Missing data in this case could be related to other factors associated with discontinuation, like interactions with the health system (continuity of care/health seeking behaviour) or poor adherence. The impact of this could be analysed in a sensitivity analysis by adding missing data as an additional variable (e.g. has systolic blood pressure measurement 1 or 0, where 0 is the missing category). This approach has been recommended to improve imputation performance when MAR assumptions may be violated, by allowing the missing information to inform the prediction of other variables [308, 328]. The results of the imputed analysis and complete case were broadly similar, with less precision in the complete case analysis, providing additional support that missing data did not have a large impact on these findings. For variables measured within a time period before the index date (e.g. blood pressure) missing data could have been supplemented by taking the last observation forward, because this can create bias as these measurement might poorly reflect change in status over-time [304, 329]. As with any observation study there is a potential for residual confounding. Of special interest here is the increased risk of discontinuation in patients with a history of stroke, which is in contrast to reduced risk of discontinuation with history of other CVDs. This is an unexpected association, especially in the established

benefit of antihypertensives in the secondary prevention of stroke [93]. Although great care has been taken in developing an extensive list of patient characteristics based on previous literature and feedback from clinicians, there might still be the potential for unmeasured confounding [330].

As described in detail in the previous chapter, the algorithm might miss patients who do not fall within the algorithm-specific parameters. This means that the control arm might include undetected patients who did reduce antihypertensive treatment, which will dilute the overall measured effect. This is because there will be a bias towards the null-effect due to the presence of cases in the controls will lead to the control group resembling the case cohort [331, 332]. It is unknown how many cases ended up undetected and how much this attenuated the measured effects.

Finally, in this work it is unclear which party initiated the stopping of treatment or if there was consensus/discussion about this. This is important to distinguish, because from the clinical expertise of a medical professional, one would assume that the patients who stop in concordance with the doctor's clinical judgement might either benefit or experience the least harm from the stopping intervention when compared to patients stop on their own accord. This is over simplification of clinical practice and it is hard to test this assumption, as we are not able to distinguish between the forms of stopping. It is therefore difficult to distinguish which characteristics are associated with the choices of clinicians and which are association with the wishes of the patient.

4.6.3 Comparison with existing literature and previous findings

As shown in my systematic review (chapter 2), few studies appear to have been published on the subject of discontinuing antihypertensive treatment. Results from the Odden *et al.* study using the VA (nursing homes) dataset shows similarities

in likelihood of discontinuing medication [269]. In both analyses, cognitive decline, lower systolic blood pressure, and higher cholesterol were associated with an increased likelihood of discontinuing antihypertensive medication. However, while in our analysis increased age and use of multiple medication was associated with increased likelihood of discontinuation of antihypertensive medication, in Odden *et al.* age and increased medication use was associated with lower odds of discontinuation. Odden *et al.* hypothesise that this is because the actual need or perceived need of the use of medication in these patients is higher and therefore they are less likely to have their treatment reduced. It is difficult to pinpoint to which point or points exactly contribute to the observed difference, as both cultural differences and differences in the type of patient populations might contribute to this difference of effect. In another part of the VA dataset Aubert *et al.* looked at factors associated with discontinuation of antihypertensive medication, mainly focused on geriatric/frail patients and systolic blood pressure [271]. Similarly to our work decreased blood pressure was associated with increased likelihood of discontinuation. Aubert *et al.* also found an increased likelihood to discontinue in patients that were considered geriatric or frail. While our work did not focus on frail patients, patients with decreased cognitive functioning were included and also had a modestly increased likelihood of discontinuing medication.

Antihypertensive treatment in the context of cardiovascular risk management allows for comparison to other cardiovascular medication used in the prevention of cardiovascular disease, specifically we can look at the characteristics associated with statin cessation. It is important to note that the context of statin discontinuation has to be prefaced by the fact that the use of statins is much more divisive when compared to other medications, which might partly be due role that social media has been proven to play a role in therapy persistence [333, 334]. Meaning that in additional to pure clinical considerations, patients beliefs play an important role in the continued use of all medications, but especially with statins. Additionally, the use of statins can be viewed in the context of primary or secondary prevention of

cardiovascular disease, while this is less relevant in the context of blood pressure management [93]. In the work by Giral *et al.* statin discontinuation was studied in the context of primary prevention. They found that recent hospitalisation, dementia, and metastatic solid tumours were associated with an increased likelihood of statin cessation. Additionally, discontinuation of statins often happened in the context of other cardiovascular medication being discontinued [242]. While concurrent medication discontinuation was not explored in our current work, these findings are congruent with our findings related to antihypertensive medication discontinuation.

4.6.4 Implications for future research and clinical practice

In this work patient characteristics, like blood pressure, age, number of concurrent medications, cancer diagnosis, and recent hospital admission were identified as associated with a greater likelihood of discontinuing antihypertensive treatment. By themselves these factors have little to no impact on clinical practice. They are merely a reflection of what has been happening in clinical practice but it does not provide insights on the appropriateness of the intervention studied. Once we combine the results from this chapter with the results from the upcoming chapter, we can start exploring the impacts of the intervention. However, regardless of the impact on the general population of older patients on antihypertensive treatment, differential outcomes are hypothesised for different subgroups of patients, specifically the very old patient (90 years and older) or those who are multiple concurrent antihypertensive treatments [80]. Therefore, these results do provide clinicians target populations to provide either support in continued drug treatment or to reduce antihypertensive treatment.

Future work could explore different characteristics of patients stopping specific subgroups of antihypertensives. This work focusses on the overall "antihypertensive" effect. However, it is known that different antihypertensives have different side-effect profiles (as explored in the introduction), meaning that there could be different

antihypertensives targeted in response to for example fears of side-effects. For example, in response to hyperkalemia, ACE or ARB treatment might be preferential to be discontinued as these cause increased potassium blood concentration levels compared to for example a thiazide-like diuretic. Additionally, co-morbidities play a role in initial selection of specific antihypertensives (e.g. in patients with diabetes) or specific antihypertensives might be used after experiencing a cardiovascular event (e.g. myocardial infarction [23, 217].

Furthermore, there are various subgroups that can be created within the context of discontinuation beyond the type of antihypertensive medication concerned. First, there are the patients who reduce treatment but have residual treatment (e.g. go from two to one prescription) or those who stop multiple medications. These two groups could also be combined, where we have patients who stop multiple prescriptions, but remain on one (or more) treatments or cease all antihypertensive medication. Secondly, there is a group of patients who remain on reduced levels of treatment as stated in the previous chapter, but also a substantial amount of patients restarts therapy during follow-up. Exploration of the differences in baseline characteristics between these populations might be of interest in combination with outcome data and optimise treatment for patients in different age brackets. While this is beyond the scope of the current work due to the exponential complexity arising from the formation of these groups, this analysis could give us interesting insights into the various different forms of treatment discontinuation.

To facilitate the exploration characteristics associated with class specific discontinuation or number of prescriptions discontinued, further development of the algorithm (as described in Chapter 3) is required. The current iteration of the algorithm uses the total number of prescriptions and associated patterns to determine if treatment is reduced, when treatment is reduced the only information stored is the date of discontinuation. Further iterations of the algorithm should additionally store the underlying class-specific prescription data and the absolute change in total

prescriptions (e.g. if treatment goes from three to two prescriptions, this value would read one). This would potentially allow for the comparison of the stable period with the reduced period. In the case of class-specific reduction, this would mean a comparison of whether the class was present before and after. However, special consideration should be given to the possibility of class switching occurring in the same period of time. As an example, a patient could be on an ACEi and thiazide-like diuretic in the period before reduction and in the reduced phase on ARB only (ACEi to ARB class switch); this could potentially flag that two classes were discontinued, although total prescriptions only show a single prescription reduction. Resolution of this problem is a separate issue and requires further study.

4.7 Conclusion

This nested case-control study suggests that patients that are prescribed antihypertensive medication that were identified to have discontinued their treatment are more likely to stop if they are older, experience lower than normal systolic blood pressure, experienced polypharmacy, or were prescribed more than one antihypertensive. Likewise, cognitive impairment, recent cancer diagnosis, or recent hospitalisation also increased likelihood of discontinuing treatment. Finally, the knowledge gained in this chapter will be used to adjust for confounding in the next chapter to enable the exploration of the clinical impact associated with discontinuation of treatment.

4.8 Key Points

- Increased age and lower systolic blood pressure are associated with discontinuing antihypertensive treatment. Furthermore, increased use of both medication in general and antihypertensive medication were associated with an increased likelihood of discontinuing treatment.

- Recent hospital admission and recent cancer diagnosis were associated with discontinuation of antihypertensive medication.
- A modest decrease in likelihood of discontinuing antihypertensive treatment was found for cardiovascular risk factor like diabetes and ischaemic heart disease.

5

Long-term outcomes after reducing antihypertensive medication prescriptions in older general practice patients: a retrospective cohort analysis using CPRD

5.1 Chapter overview

This chapter presents the results of the analysis of long-term outcomes of discontinuing antihypertensive treatment in older primary care patients using a retrospective cohort design.

Out of 737,385 eligible patients from the GOLD database of the Clinical Practice Research Datalink (CPRD), 232,581 cases were identified and matched to 394,760 controls. Using multivariate Cox proportional hazard models with adjustment for confounders, adjusted hazard ratios were estimated for the association between antihypertensive medication discontinuation and clinical outcomes. The primary outcome was all-cause hospitalisation, with secondary outcomes focussing on all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, heart failure, cognitive decline, acute kidney injury, electrolyte abnormalities, hypotension, syncope, falls, and fractures.

For the primary outcome, there was a statistically significant decrease in all-cause hospitalisation after discontinuing antihypertensive treatment (aHR, 0.93 [95% CI, 0.92-0.94]), with the associations being consistent in different subgroups. There was an increased risk of all secondary outcomes after stopping treatment, with no evidence of an association between antihypertensive discontinuation and myocardial infarction. Although the primary outcome suggests that discontinuation of antihypertensive treatment was beneficial, all other outcomes other than myocardial infarction suggest that it might be harmful.

In conclusion, in this cohort of older patients treated with antihypertensive medication, discontinuation of antihypertensive treatment was associated with a modest decrease of all-cause hospitalisation, which is contrasted by an increased risk of both safety and efficacy outcomes.

5.2 Introduction

In older primary care patients, antihypertensive medications are extensively and effectively used to prevent cardiovascular disease [35, 93, 335, 336]. At the start of treating patients with antihypertensive medication, benefit-risk assessments are made, as treatment is not without risk [147]. In older individuals, striking the right balance is difficult, due to uncertainty due to a lack of evidence around long-term treatment effects and increased risk for adverse outcomes [80, 147]. In recent years there have been increased efforts in increasing medication safety and a reduction iatrogenic disease, with among other interventions an increased interest in reducing antihypertensive treatment in older patients [80]. Discontinuation of antihypertensive treatment is also mentioned as a consideration for frail older patients with very low systolic blood pressure in the latest European Society of Hypertension guideline on hypertension management [33]. However, currently there is not enough long-term evidence to support the discontinuation of antihypertensive treatment [206]. In the systematic review and meta-analyses presented in Chapter 2 of this thesis, it was established that little evidence exists regarding the long-term safety and efficacy of reducing antihypertensive treatment in older patients. While the systematic review included the largest and several smaller RCTs conducted in the field of antihypertensive medication reduction, combined they involved too few patients and had follow-up periods that were too brief to identify differences in clinically relevant outcomes [236, 237, 239, 241].

The design and execution of large RCTs is difficult [337]. Large trials powered on clinical endpoint take considerable time and money to complete, in addition to practical limitations like recruitment rate and ethical considerations [337–340]. In the absence of large RCTs evidence can be provided by well conducted observational studies, but in the context of reducing treatment they need to be able to accurate define stopping treatment and manage confounding [210, 215]. In the two previous chapters, patients who discontinue antihypertensive treatment were identified (Chapter 3 and the characteristics associated with discontinuation were examined

(Chapter 4). Building on these results, the objective of this chapter was to determine the long-term effects of antihypertensive medication reduction on clinical outcomes. The primary outcome all-cause hospitalisation was selected as an all-encompassing outcome with regards to treatment cessation in general, but specifically of preventative therapies, where potential benefits of stopping (e.g. reduced hospitalisation due to falls) has to be weighed at the potential of negative outcomes (e.g. increased hospitalisation due to CVD) with regard to the initial treatment benefits [242, 294]. Secondary outcomes were selected to focus on both safety and efficacy aspects of withdrawing antihypertensive therapy, with secondary safety outcomes including cardiovascular and all-cause mortality, stroke, myocardial infarction, and heart failure and secondary safety outcomes including cognitive functioning, acute kidney injury, electrolyte abnormalities, hypotension, syncope, falls, and fractures [93, 147]. In order to capture the real-world implications of discontinuing antihypertensive medication, this chapter uses a retrospective observational approach using primary care data from the CPRD-Gold dataset. This design enables the analysis of long-term outcomes in an older population treated with antihypertensives that is representative of patients seen in routine clinical practice.

5.3 Chapter Aim

The aim of this study was to determine the long-term outcomes of reducing antihypertensive medication compared to continued use, in primary care patients in England.

5.4 Methods

CPRD GOLD dataset was used to identify a nationwide cohort of patients over the age of 65 on antihypertensive treatment. These patients were followed up

for discontinuation of antihypertensive treatment. A retrospective analysis was performed to determine the outcomes after patients stopped antihypertensive treatment.

5.4.1 Data Source and study cohort

The protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA) (protocol reference number: 21_000385).

All included patients were eligible for linkage to the Office for National Statistics (ONS) Death Registration Data and Hospital Episode Statistics (HES) Admitted Patient Care (APC), and practice level Index of Multiple Deprivation (IMD) data [298–300]. These datasets provide additional and more accurate information not available in CPRD allowing for exploration of more outcomes and the addition of extra patient characteristics. The ONS dataset contains information on data of death and cause of death, where cause of death is coded according to World Health Organisation (WHO) International Classification of Diseases (ICD-10). HES APC provides information and details of all admissions to English NHS health care providers where clinical diagnoses are coded using ICD-10. Finally, the IMD dataset contains information on various domains of material deprivation, deprivation information is available on patient-level and is available in quintiles, where the first quintile represents the least deprived population.

Patients entered the cohort when they had at least one active antihypertensive prescription and were at least 65 years of age, and their practice was up-to-standard, whichever happened last. Patients were ineligible if they had less than twelve months of follow-up time, between cohort entry and cohort exit, which was the earliest date of either last available practice data, transferred out of the practice, or death. Restrictions on minimum follow-up time was included as it was needed to

facilitate the implementation of the algorithm.

5.4.2 Exposure definition

Patients were classified as having reduced antihypertensive medication if there was a reduction that was sustained for at least 3 months compared to the prior 3 months. The exposure was identified using the algorithm developed in Chapter 3, with the index date based on the first month of reduced treatment. For patients who experienced more than one discontinuation event during follow-up, only the first discontinuation was included in the analysis to avoid multiple exposures per individual. Patients who continued antihypertensive treatment without reduction during the same period served as the comparison group.

5.4.3 Outcome variables and follow-up

The primary outcome was all-cause hospitalisation based on linked data provided by Hospital Episode Statistics (HES) admitted patient care. Secondary outcomes of interest were: all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, heart failure, cognitive functioning, acute kidney injury, electrolyte abnormalities, hypotension, syncope, falls, and fractures based on HES admitted patient care.

ICD-10 codes for all outcomes are available in the Appendix A.8. All-cause hospitalisation was based on any hospital admission after the index date regardless of ICD-10 code.

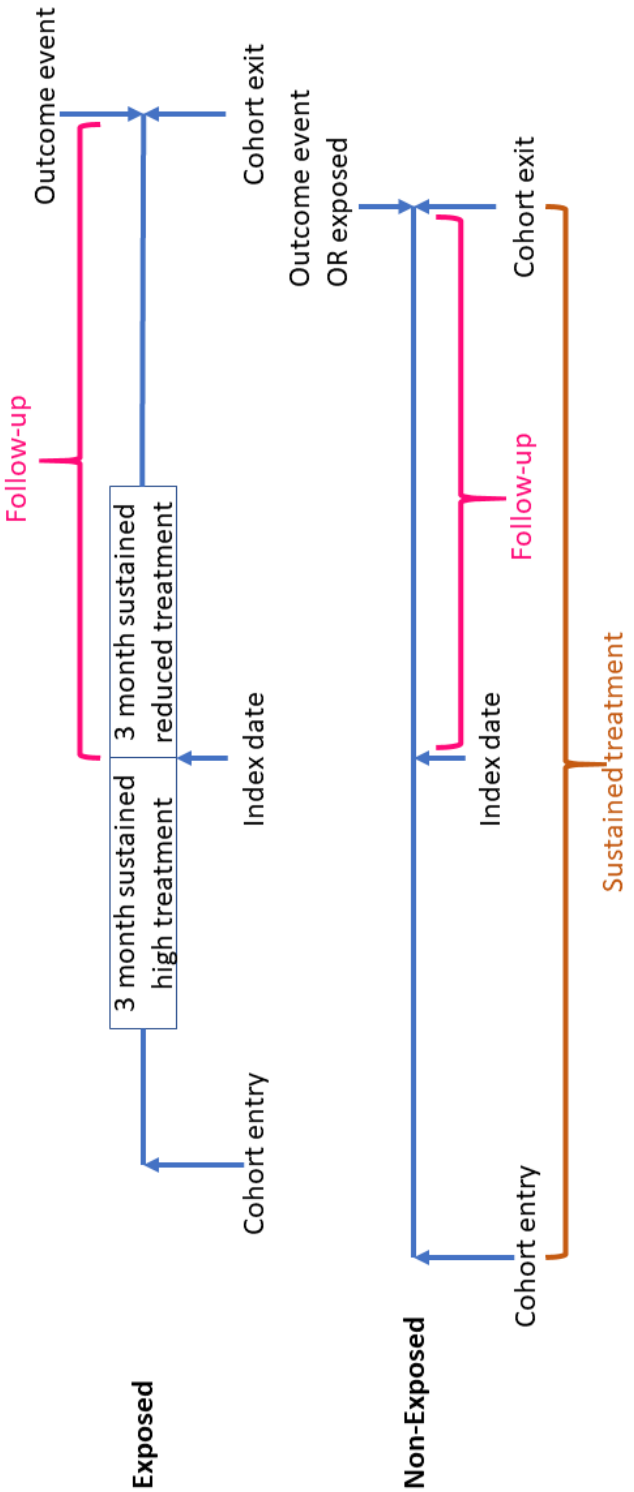


Figure 5.1: Cohort design of observational study. Cohort entry; latest of practice up-to-standard (UTS), patient 65 years, and active antihypertensive prescription. Exposed index date determined by algorithm, index date is the first month when antihypertensive treatment was discontinued. Follow-up started until outcome or cohort exit (censor). Cohort exit for exposed patients was determined as the earliest occurrence of death (if not outcome), transfer out of practice, or latest available data. Non-exposed patients were matched to exposed patients using incidence density sampling, controls had to be active at the same period and belong to the same practice. Cohort exit for non-exposed patients was determined as the earliest occurrence of death (if not outcome), transfer out of practice, latest available data, or discontinuation of antihypertensive treatment (exposure). Data available from 01-01-1998 until 31-12-2019.

Follow-up started from the index date (first month of reduced treatment for exposed patients and the index date of matched exposed patients for controls) and continued until the first of the four following scenarios occurred: outcome, death (if not outcome), transferred out of the practice, or latest available practice data. There was no restriction on the maximum length of follow-up. If controls discontinued antihypertensive medication (exposed) during follow-up, their follow-up time was censored at the moment they were exposed (index date as exposed). The cohort design is illustrated in Figure 5.1.

5.4.4 Variable definitions

All baseline characteristics were determined from information recorded prior to the index date, with only data within a specific time frame before the index date being considered. The specific time frames for each variable are discussed in detail in later sections. Code lists used to generate the variables included in the analysis are available at: `https://github.com/RikvdVeen/DPhil_thesis2025/tree/main/AHT_reduction`. Baseline characteristics comprised of patient demographics, clinical readings, medication usage, and co-morbidities. Variables selected for adjustment of the models was based on patient characteristics associated with discontinuation of antihypertensive medication as determined in Chapter 4 and clinical expert opinion [242, 269, 271, 280].

5.4.4.1 Patient demographic definitions

Age and sex were determined based on CPRD patient data files. Ethnicity was based on data available through CPRD and linkage with basic inpatient Hospital Episode Statistics (HES) data, categories included were: white, black, South Asian, and mixed other. Patient-level Index of Multiple Deprivation (IMD) data was obtained as quintiles (ranging from most deprived to least deprived). Smoking and alcohol consumption were derived from a combination of clinical (smoking and drinking status) and additional CPRD files (alcohol units). Smoking was categorised into

non-smokers, current smokers, and ex-smokers. Alcohol categories were based on a combination of drinking status (yes/no) and daily units of alcohol consumed and were as followed: non-drinker, occasional drinker (<1 daily units), light drinker (between 1 and 2 daily units), moderate drinker (between 2 and 6 daily units), heavy drinker (>6 daily units), and unknown amount (alcohol units undefined).

5.4.4.2 Clinical readings

Weight category was determined using BMI, where the latest measured weight in the last five years was accepted and the most recent height, classification is based on a national classification scale [341]. For blood pressure (systolic and diastolic) the most recent blood pressure measurement in the last year was taken; if this was not available, this was considered missing. Similarly, hypercholesterolemia was determined on a LDL-measurement taken within the last year with a measurement of 2.5 mmol/L or higher being considered positive.

5.4.4.3 Medication history definitions

Prescription history (antihypertensives, other cardiovascular medications, and polypharmacy) were based on the prescriptions before discontinuation (index date - 1 month, to index date - 4 months). Polypharmacy was determined based on the number of active chronic prescriptions in the four months before the index data. Medications included in chapters one to thirteen of the British National Formulary (BNF) were used to determine total chronic prescription load [281]. Patients were determined to have polypharmacy if five or more active prescriptions were present, based on previous literature and similar studies conducted in CPRD [54, 282]. All included drug classes can be found in appendix A.5.

5.4.4.4 Co-morbidity definitions

Co-morbidities were defined as any historical read code of the disease of interest, with the exception of cancer and recent hospitalisation. Cancer, was defined as a recent diagnoses of a cancer in the last year based on CPRD clinical files, based on an observation in the work of Giral *et al*[242]. Recent hospitalisation was defined of at least a single hospital admission in the last year based on HES data linkage. Cognitive impairment was defined using read codes list, based on the work of Clegg *et al.* [342].

5.4.5 Statistical analysis

5.4.5.1 Missing data

Missing data was present for the following variables: ethnicity (8.9%), IMD (12.7%), smoking status (8.8%), alcohol consumption (12.8%), weight category (56%), systolic blood pressure (14.0%), and hypercholesterolemia (67%). Multiple imputation by chained equations (MICE) was used to impute missing data. MICE is a method to generate probable imputed data sets using an iterative process based on all other variables in the incomplete data set [308]. In this work 10 imputed data sets were created over 20 iterations using the MICE package in R [309]. All variables of the analysis were included in the imputation model, including the outcome variable (binary) and time until outcome (continuous). Variables with missing data were ordinal, with the exception of hypercholesterolemia (binary) and ethnicity (nominal). The model coefficients were estimated from each imputation dataset and combined using Rubin's rules [310].

5.4.5.2 Cox Proportional Hazard Model

A cox proportional hazard model was used to estimate the hazard ratio of anti-hypertensive medication discontinuation vs continuation, controlling for baseline confounding. Outcomes were coded as binary variables, where 0 indicated censoring

(e.g. death or latest available data) and 1 indicated the occurrence of the outcome of interest (e.g. all-cause hospitalisation). These codes were used as the dependent variable in the Cox proportional hazards model. The following baseline covariates, based on work done in the Chapter 4, were used to adjust the model: age, gender, ethnicity, smoking status, systolic blood pressure, BMI, number of antihypertensive prescriptions, polypharmacy, statin treatment, oral anticoagulants prescription, antiplatelet prescription, heart failure, ischaemic heart disease, cerebrovascular disease, cognitive functioning, hypertension, hypotension, diabetes, chronic kidney disease, fragility fracture, recent cancer diagnosis, recent hospitalisation, weight loss, requirement for care. These covariates were selected based on positive and negative clinical significant associations with antihypertensive treatment discontinuation as discussed in the results section of Chapter 4. To account for potential correlations among patients within the same practice, a cluster-robust variance estimator was applied, with clustering based on practice ID. This adjusts the standard errors to reflect similarities within practices, providing more accurate results [343, 344].

5.4.5.3 Subgroup analysis

Subgroup analysis for the primary outcome was performed for the following subgroups: age (stratified), systolic blood pressure (stratified), number of antihypertensives. With age stratification spanning 5 year, starting at 65 years, and ending at 95 (95 and over). Systolic blood pressure is stratified in intervals of 10 mm Hg and blood pressures lower than 100 and 160 and over were grouped separately. Subgroups were picked *a priori* and refined based on patient characteristics associated with antihypertensive medication discontinuation as determined in Chapter 4.

Additionally, an exploratory subgroup analysis was performed using inclusion criteria from the OPTiMISE trial to compare to all-cause hospitalisation and all-cause mortality of the current work to OPTiMISE-X, the long-term follow-up results of the OPTIMISE trial [236, 294]. This subgroup, OPTiMISE Eligible, consisted

of patients aged 80 years and over, with a systolic blood pressure of 150 mmHg or lower, and on at least 2 antihypertensive medications [236].

5.4.5.4 Sensitivity analysis

The primary analysis contains all eligible patients, including control patients whom were exposed patients at a later time point. In the primary analysis the control (non-exposed) time is censored at the time the exposed time starts. To assess the impact of censoring time of controls, the following sensitivity analyses were conducted: 1) Time censoring was dropped for controls who were exposed at a later time meaning that control time was extended, and 2) patients who are both controls and exposed were removed as controls. Finally, the impact of clustering on practice level was explored.

5.5 Results

A total of 737,385 patients were eligible for this study. Cases were identified and matching was performed in Chapter 3. A total of 627,341 patients were included in this analysis, including 232,851 cases (median age 76.40 (IQR: 70.48 - 82.88), 57% female) and 394,760 matched controls (median age 75.18 (IQR: 69.96 - 81.27), 56% female) (Figure 3.4). Baseline characteristics are described in table 3.1 and figure 4.1. The mean and median follow-up for the total population were 4.9 years (SD: 4.1 years) and 3.8 years (IQR: 1.7 - 7.1 years), respectively.

5.5.1 Primary Outcome

During follow-up, a total of 425,873 (68%) hospital admissions for any cause occurred, with 173,836 (75%) of these admissions in patients discontinuing antihypertensive treatment and 252,037 (64%) in those continuing treatment.

Outcome	Events Exposed (n=232,581)	Events Control (n=394,760)	aHR (95% CI)
Primary Outcome			
All cause hospitalisation	173,836 (75%)	252,037 (64%)	0.93 (0.92 to 0.94)
Secondary Safety Outcomes			
All cause mortality	62,129 (27%)	63,440 (16%)	1.17 (1.15 to 1.18)
CVD Mort	21,231 (9%)	22,912 (6%)	1.10 (1.08 to 1.13)
Stroke	32,591 (14%)	35,855 (9%)	1.15 (1.13 to 1.17)
Myocardial Infarction	23,359 (10%)	29,754 (8%)	1.00 (0.97 to 1.02)
Heart Failure	34,920 (15%)	39,212 (10%)	1.08 (1.06 to 1.10)
Secondary Efficacy Outcomes			
Cognitive functioning	24,579 (11%)	22,521 (6%)	1.25 (1.23 to 1.28)
Acute kidney injury	28,431 (12%)	31,852 (8%)	1.07 (1.04 to 1.09)
Electrolyte abnormalities	15,225 (7%)	17,551 (4%)	1.04 (1.01 to 1.07)
Hypotension	14,235 (6%)	15,367 (4%)	1.10 (1.07 to 1.13)
Syncope	14,507 (6%)	16,474 (4%)	1.11 (1.09 to 1.14)
Falls	14,589 (6%)	13,831 (4%)	1.16 (1.12 to 1.20)
Fracture	23,925 (10%)	26,983 (7%)	1.11 (1.09 to 1.13)

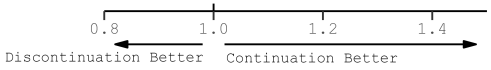


Figure 5.2: Primary analysis of the association between discontinuing antihypertensive medication and all-cause hospitalisation and secondary outcomes. All outcomes are based on hospital admission (HES), except for mortality (ONS). The analyses were adjusted for age, gender, ethnicity, smoking status, systolic blood pressure, BMI, number of antihypertensive prescriptions, polypharmacy, statin treatment, oral anticoagulants prescription, antiplatelet prescription, heart failure, ischaemic heart disease, cerebrovascular disease, cognitive functioning, hypertension, hypotension, diabetes, chronic kidney disease, fragility fracture, recent cancer diagnosis, recent hospitalisation, weight loss, requirement for care. aHR; adjusted Hazard Ratio, 95 % CI; 95% confidence interval.

In the primary multivariable Cox proportional hazards analysis, adjusted for all covariates, antihypertensive medication reduction was associated with a statistically significant reduction in the risk of all-cause hospitalisation (aHR, 0.93 [95% CI, 0.92-0.94]) compared to those who continued treatment (Figure 5.2).

5.5.2 Secondary outcomes

Discontinuing antihypertensive treatment was associated with an increased risk of all-cause mortality (aHR, 1.17 [95% CI, 1.15-1.18]), cardiovascular mortality (aHR, 1.10 [95% CI, 1.08-1.13]), stroke (aHR, 1.15 [95% CI, 1.13-1.17]), and heart failure (aHR, 1.08 [95% CI, 1.06-1.10]) (Figure 5.2). No evidence of an association between discontinuation and risk of myocardial infarctions (aHR, 1.00 [95% CI, 0.97-1.02]) was found.

With regards to secondary efficacy outcomes, antihypertensive medication discontinuation was associated with an increased risk of cognitive functional decline (aHR, 1.25 [95% CI, 1.23-1.28]), acute kidney injury (aHR, 1.07 [95% CI, 1.04-1.09]), electrolyte abnormalities (aHR, 1.04 [95% CI, 1.01-1.07]), hypotension (aHR, 1.10 [95% CI, 1.07-1.13]), syncope (aHR, 1.11 [95% CI, 1.09-1.14]), falls (aHR, 1.16 [95% CI, 1.12-1.20]), and fractures (aHR, 1.11 [95% CI, 1.09-1.13]) (Figure 5.2).

5.5.3 Subgroup and sensitivity analyses

5.5.3.1 Subgroup analyses all-cause hospitalisation

In the subgroup analyses for all-cause hospitalisation there was little difference in different age categories, number of antihypertensive prescriptions, baseline systolic blood pressure, or recent hospitalisation (Figure 5.3). However, for patients who had a recent cancer diagnosis, antihypertensive treatment discontinuation was associated with increased all-cause hospitalisation (aHR, 1.08 [95% CI, 1.04-1.13]) (Figure 5.3).

5.5.3.2 Comparative analysis with OPTiMISE-trial

The all-cause hospitalisation and mortality outcomes of patients meeting the age (>80 years), systolic blood pressure (<150 mmHg), and number of active antihypertensive medication (>2) were compared to the complete population and the outcomes in the OPTiMISE-X study (Figure 5.4). The risk of all-cause hospitalisation was slightly increased in the OPTiMISE Eligible population (aHR, 0.97 [95% CI, 0.95-0.99]) when compared to the complete population (aHR, 0.93 [95% CI, 0.92-0.94]) and fell within the 95% confidence interval for all-cause hospitalisation as measured in the OPTiMISE-X study (aHR, 0.93 [95% CI, 0.76-1.13]). No difference in association was found for all-cause mortality between the total population and OPTIMISE Eligible population. All-cause mortality was increased in the OPTIMISE Eligible population (aHR, 1.18 [95% CI, 1.15-1.22]) compared to that observed in the OPTIMISE-X study (aHR, 0.80 [95% CI, 0.57-1.12]).

5.5.3.3 Sensitivity analyses all-cause hospitalisation

To assess the robustness of the assumptions made in the primary analysis, sensitivity analyses were performed. All the primary analyses utilised clustering on practice level, to account for potential differences between practice level preferences in regards to stopping or continuing treatment. Removal of clustering had no effect on the point estimate or 95 % confidence intervals (aHR, 0.93 [95% CI, 0.92-0.94]).

Furthermore, patients could be controls even if they turned into exposed patients at a later time point. In the primary analyses, time was censored at the moment the patients were exposed to treatment discontinuation. Restricting the analysis to only include controls whom never experience discontinuation was similar to inclusion of these controls (aHR, 0.95 [95% CI, 0.94-0.96]). Removal of the time-censoring at the moment of discontinuation resulted in an increased risk of hospital admission for any cause (aHR, 1.02 [95% CI, 1.01-1.03]).

Subgroup	Events Exposed	Number of Exposed	Events Controls	Number of Controls	aHR (95% CI)
All Patients	173,836	232,581	252,037	394,760	0.93 (0.92 to 0.94)
Age Cohort (Years)					
65 - 69	36,628	53,142	57,620	99,154	0.90 (0.89 to 0.91)
70-74	37,025	49,697	59,556	94,851	0.91 (0.90 to 0.92)
75-79	36,880	47,228	55,745	83,821	0.94 (0.93 to 0.95)
80-84	31,541	40,274	42,880	62,941	0.95 (0.94 to 0.97)
85-89	20,979	27,098	24,849	36,435	0.97 (0.95 to 0.99)
90-94	8,826	12,098	9,386	14,198	0.96 (0.93 to 0.99)
≥95	1,957	3,044	2,001	3,360	0.95 (0.89 to 1.01)
Antihypertensive Prescriptions (n)					
1	93,372	123,271	147,363	227,475	0.93 (0.92 to 0.93)
2	54,721	73,792	72,453	115,332	0.93 (0.92 to 0.94)
≥3	25,743	35,518	32,221	51,953	0.94 (0.92 to 0.95)
Systolic Blood Pressure (mmHg)					
≤100	2,304	3,101	1,495	2,246	0.95 (0.89 to 1.01)
100-110	5,305	7,131	4,845	7,357	0.96 (0.92 to 0.99)
110-120	12,137	16,458	14,533	22,630	0.94 (0.92 to 0.97)
120-130	24,939	34,267	34,203	55,044	0.93 (0.92 to 0.95)
130-140	38,150	52,502	58,316	95,093	0.95 (0.93 to 0.96)
140-150	42,387	57,023	67,167	105,764	0.93 (0.92 to 0.94)
150-160	20,818	26,946	31,973	48,089	0.92 (0.90 to 0.93)
≥160	27,796	35,153	39,505	58,537	0.91 (0.89 to 0.92)
Recent Hospital Admission					
No	104,135	147,181	178,075	295,783	0.92 (0.91 to 0.93)
Yes	69,701	85,400	73,962	98,977	0.95 (0.94 to 0.96)
Recent Cancer Diagnosis					
No	169,290	227,179	247,669	388,986	0.93 (0.92 to 0.93)
Yes	4,546	5,402	4,368	5,774	1.08 (1.04 to 1.13)

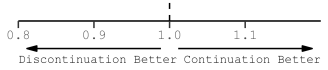


Figure 5.3: Subgroup analysis of the association between discontinuing antihypertensive medication and all-cause hospitalisation. The analyses were adjusted for age, gender, ethnicity, smoking status, systolic blood pressure, BMI, number of antihypertensive prescriptions, polypharmacy, statin treatment, oral anticoagulants prescription, antiplatelet prescription, heart failure, ischaemic heart disease, cerebrovascular disease, cognitive functioning, hypertension, hypotension, diabetes, chronic kidney disease, fragility fracture, recent cancer diagnosis, recent hospitalisation, weight loss, requirement for care. Recent hospital admission and recent cancer diagnosis were determined in the year prior to the index date. aHR; adjusted Hazard Ratio, 95 % CI; 95% confidence interval.

Figure 5.4: Comparative analysis of the association between discontinuing antihypertensive medication and all-cause hospitalisation and all-cause mortality. OPTIMISE-X is the long-term follow-up from the OPTIMISE trial [236, 294, 345]. The analyses were adjusted for age, gender, ethnicity, smoking status, systolic blood pressure, BMI, number of antihypertensive prescriptions, polypharmacy, statin treatment, oral anticoagulants prescription, antiplatelet prescription, heart failure, ischaemic heart disease, cerebrovascular disease, cognitive functioning, hypertension, hypotension, diabetes, chronic kidney disease, fragility fracture, recent cancer diagnosis, recent hospitalisation, weight loss, requirement for care. Recent hospital admission and recent cancer diagnosis were determined in the year prior to the index date. aHR; adjusted Hazard Ratio, 95 % CI; 95% confidence interval.

Figure 5.5: Sensitivity analysis of the association between discontinuing antihypertensive medication and all-cause hospitalisation. The analyses were adjusted for age, gender, ethnicity, smoking status, systolic blood pressure, BMI, number of antihypertensive prescriptions, polypharmacy, statin treatment, oral anticoagulants prescription, antiplatelet prescription, heart failure, ischaemic heart disease, cerebrovascular disease, cognitive functioning, hypertension, hypotension, diabetes, chronic kidney disease, fragility fracture, recent cancer diagnosis, recent hospitalisation, weight loss, requirement for care. aHR; adjusted Hazard Ratio, 95 % CI; 95% confidence interval.

5.6 Discussion

5.6.1 Summary of Results

In this large observational study of 627,341 primary care patients aged 65 years and over treated with antihypertensive medication, reduction of antihypertensive treatment was associated with a decreased risk of hospital admission for any cause, and an increased risk of death by any cause, death due to cardiovascular disease, hospitalisation due stroke or heart failure, worsening cognitive functioning, acute kidney injury, electrolyte abnormalities, hypotension, syncope, falls, and fractures (Figure 5.2).

While these results show that discontinuation of antihypertensive treatment is associated with both benefit, in the reduction of all-cause hospitalisation, and increased harm, in the increase of cause specific hospitalisation, it is important to explore the two possible reasons for measured effects. First, the simplest explanation is that discontinuation of antihypertensive treatment is harmful in this population. Second, as this study is observational in nature, there is the potential for unmeasured confounding that has an impact on these results, meaning that in reality outcomes could be closer to the null-effect. It also important to note that both of these statements are not mutually exclusive and each outcome can be differentially impacted. The effect of reduced blood pressure through pharmacological intervention on stroke and heart failure risk has been well established, whereas the effect on the reduction of ischaemic heart disease is only moderate [93]. Therefore, in our analysis, the impact of discontinuation of treatment reflects size of the pharmacological effect of treatment initiation. Outcomes like hypotension, syncope, and falls, on the other hand are normally associated with low systolic blood pressure, and removal of treatment is associated with raise in blood pressure. The observed worsening of secondary efficacy outcomes such as falls or hypotension following antihypertensive treatment discontinuation may reflect residual confounding. Patients who discontinue treatment, or who are selected for discontinuation by healthcare professionals, are often those who are already at higher baseline risk for these outcomes, due

to underlying frailty, a history of falls, or general decline in health status. As a result, the discontinuation group may include a greater proportion of individuals predisposed to these outcomes. Although several confounders were adjusted for in the analysis, this may not have fully accounted for unmeasured or incompletely captured factors such as functional impairment, cognitive status, or a prior fall history (those who did not lead to hospitalisation). Consequently, the associations observed between discontinuation and adverse secondary outcomes could be partly attributable to these underlying vulnerabilities rather than a direct causal effect discontinuation of antihypertensive treatment.

In this study a reduction of antihypertensive medication was associated with a decrease in all-cause hospitalisation, while hospitalisation for cause specific outcomes studied in this work all showed in an increased risk (Figure 5.2). This means that an unexplored cause of hospital admission is likely to be reduced, either as a result of discontinuing antihypertensive treatment, or as a result of another confounding mechanism not included in this study influencing the measured outcome. Using publication reports on Admitted Patient Care activity for 2023-2024 we can get a sense of general diagnoses and frequency for hospital admissions [346]. The largest contributors to hospital admissions were related to neoplasms and diseases of the digestive system (both roughly 2.5 million episodes each), closely followed by sign, symptoms, and laboratory findings (not classified elsewhere) (2 million), while diseases of the circulatory system only accounts for just shy of one million registered episodes. This could suggest that most of the reasons for hospital admissions are likely to be unrelated to medication reduction.

5.6.2 Strengths and Limitations

Using cox proportional hazard models, a well-established analytical approach, the causal relationships between antihypertensive medication discontinuation and various safety and efficacy outcomes in older primary care patients was explored

using large dataset of routinely collected primary care data linked with hospital admissions (HES), mortality (ONS), and social deprivation (IMD). As such, the results are generalisable to the older hypertensive population in primary care settings. Subgroup analyses and sensitivity analyses were performed to explore effects in different populations and to explore potential biases. However, a limitation of this study is the potential for unmeasured confounding related to patient behaviour or clinical factors not explored in Chapter 4, for which the impact cannot be directly assessed.

In this work patients were not censored when discontinued treatment was reinstated, in accordance with an intention to treat analysis; this choice comes both advantages and disadvantages. The strength of this decision is that this accounts for any subsequent changes due to initial discontinuation decision are included in the final analysis, for example where resumption of therapy causes hospitalisation or side-effects, better reflecting the impact of the intervention and how it might be delivered in clinical practice. Secondary, the risk of selection bias is reduced by including complete follow-up. It is likely that censoring at treatment resumption would probably favour the inclusion of patients with a better health status, with the assumption that poorer health status would necessitate the re-initiation of treatment. This is indirectly also a limitation leading to a biased hazard ratio as there could be a potential reversed effect where treatment resumption negates the effects of the discontinuation event. This would potentially lead to an underestimation of the observed effect. Finally, the pragmatic approach not to censor at treatment resumption was based on a lack of understanding what the impact of not being on treatment and the magnitude of treatment reduction is. These factors need to be considered in the context of the increased blood pressure due to temporary treatment cessation and in relation to the outcomes.

A potential source of bias is the introduction of immortal time bias due to the exposed population having to survive at least three months after a discontinuation

event to be flagged by the algorithm as a potential exposed patient. In this three month window the patients in the exposed cohort can not experience the outcome of death, while the controls can. Immortal time bias has the potential to lead to an underestimation of events in the exposed group and/or an overestimation in the control cohort, resulting in an overestimation of the benefit associated with, in this case, stopping antihypertensive treatment [347]. This study already identified an increase in all-cause and cause-specific mortality after stopping antihypertensive treatment. However, the immortal time bias means that this effect could be larger in reality. In contrast, all events were recorded for non-mortality related outcomes, including events those that took place in the three month window needing to establish medication reduction. Therefore, these outcomes are less likely to be affected by immortal time bias.

As previously discussed in Chapter 4, the cohort is potentially made up out of two distinct subpopulations, namely those who stop treatment under the supervision of a health care professional and those who stop on their own accord. While it is unclear what the differential risk is between these two populations, even if there is any, an assumption could be made that there is the potential for differences. This would augment the overall measured effect in this study, where the population stopping under the auspices of health care professionals could potentially experience less harm than those stopping without clinical support. This means that the outcome in the population stopping treatment in concordance with the health care populations might be closer to the null effect or potentially reversed. This could argue in favour of clinically-supported medication discontinuation under these set of assumptions, however the effect in this specific population remains unclear.

Similarly to the previous Chapter, in this work MICE is used to address missing data. Although MICE is robust method of dealing with missing data, results might still be biased, especially if data are not missing at random, this is explained in

more detail in Chapter 4 [325].

When time censoring was removed for controls who experienced antihypertensive medication discontinuation (exposure) in a sensitivity analysis, the observed association between antihypertensive medication and a reduction in all-cause hospitalization disappeared (adjusted HR, 1.02 [95% CI, 1.01–1.03]). Removing this censoring extended the control group's follow-up time to include periods during which they were exposed to the intervention. Although the absolute number of events in the control group only increased slightly, the addition of extra follow-up time reduced the relative event rate in the control group. Consequently, the difference in event rates between the exposed and control cohorts diminished, leading to the disappearance of the previously observed association [348]. Essentially, this approach makes the two cohorts more similar, as some control patients are also exposed to the intervention during their extended follow-up period.

5.6.3 Comparison with existing literature and previous findings

In Chapter 2 the literature was systematically searched for all available evidence on cardiovascular medication discontinuation and clinical outcomes in older patients. In the meta-analyses on the effects of reducing antihypertensive medication that were presented in this chapter, no association was found in RCTs due to short follow-ups and limited recorded events, resulting in the observed uncertainty with regards to the effect. The primary outcome of both this chapter and chapter 2, all-cause hospitalisation, can be compared. The meta-analysis included two trials with 12 and 15 weeks of follow-up and 954 patients in total [236, 237], while this work included 627,341 patients with a median follow-up of nearly five years. In the meta-analysis no evidence of an association was found (RR, 1.10 [95% CI, 0.63-1.93]), where in this chapter a slight reduction of all-cause hospitalisation was found (aHR, 0.93 [95% CI, 0.92-0.94]). Furthermore, comparing both RCT only and

RCT combined with observational studies meta-analyses with secondary outcomes a high level of consistency is found.

Comparison with the long-term follow-up of the OPTiMISE trial is of special interest, as it is the longest follow-up of any RCT of antihypertensive deprescribing trials to date and this trials was conducted in an English primary care population, similar to that of the population in this thesis [236, 294]. To this end, additional subgroup analyses were performed (Figure 5.4) to reflect the population eligible for the OPTiMISE trial [345]. In the long-term follow-up study of Sheppard *et al.* antihypertensive medication reduction in the intention-to-treat population there was no evidence of an association with changes in all-cause hospitalisation (aHR, 0.93 [95% CI, 0.76-1.13]) or all-cause mortality (aHR, 0.80 [95% CI, 0.57-1.12]) [294]. The effects of antihypertensive medication discontinuation on all-cause hospitalisation was similar to those found in this work, where in both the complete population and the OPTiMISE-eligible population discontinuation of treatment were statistically associated with a reduction in all-cause hospitalisation (aHR, 0.93 [95% CI, 0.92-0.94] and aHR, 0.97 [95% CI, 0.95-0.99]), respectively). In contrast, the risk of all-cause mortality was slightly higher in the present study (aHR, 1.17 [95% CI, 1.15-1.22] and aHR, 1.18 [95% CI, 1.15-1.22]), for both the complete population and OPTiMISE-eligible population respectively) when compared to that measured in OPTiMISE-X. In addition to inherent differences between RCTs and observational studies with their intrinsic risk of bias, there are additional differences between the OPTiMISE/OPTiMISE-X population and the OPTIMISE-eligible population. First, in the OPTIMISE study, patients were eligible if they had two or more antihypertensive medications and after the intervention they remained on at least a single antihypertensive prescription. In the OPTiMISE-eligible population, patients were included if they had two or more active antihypertensive prescriptions, similar to OPTIMISE, however there were no restrictions on residual treatment as these data were not available, meaning that patients could cease all antihypertensive treatment. Furthermore, as previously discussed, in the population researched in this

thesis it is not possible to distinguish between patients whom stopped treatment in accordance with their health care professional or those whom stopped by themselves. For these patients specifically it is very possible that their blood pressure might have become uncontrolled, where in the OPTIMISE trial the aim of the intervention was to ensure that participants would continue to have controlled blood pressure [345]. Uncontrolled blood pressure could reasonably lead to increased harm, as for example seen in the DANTON trial where blood pressure was allowed to exceed generally accepted 150 mmHg threshold [21, 33, 97, 349]. These differences could explain the higher mortality risk seen in this work, as residual treatment and blood pressure control as achieved in OPTIMISE could enhance patient safety compared to the patients in this cohort combined with the potential of increased harm in patients who cease treatment without consultation with health care professionals. The overall concordance of the observational outcomes and the OPTiMISE-X outcomes, increase the validity of the results of this thesis.

Comparing this work with the study by Aubert *et al.*, it is important to note the major differences in the populations and intervention studied. Patient inclusion in the study by Aubert *et al.* were similar to the current work, where patients had to be 65 years or older and at least a single antihypertensive prescription, however Aubert *et al.* restricted enrolment to only patients with systolic blood pressure of 130 mmHg or less [240]. As Aubert *et al.* sampled from the Veterans Health Administration (VHA), they were able to include dose reduction as possible outcome in addition to full prescription reduction. However, both this work and that of Aubert *et al.* show increased cause-specific hospitalisation and falls, after reducing antihypertensive treatment. However, contrary to this work where there was no association between reduction of antihypertensive medication and myocardial infarction, in the their study reduction was associated with a substantial increase in this specific outcome. Reasons to why this might be the case are unclear, but Aubert *et al.* suggest insufficient adjustment and therefore residual confounding are very likely [240]. Additionally, choices made in the selection of medication to include

in the measurement of antihypertensive prescription intensity, like loop-diuretics but more importantly nitrates, could reflect a population at a higher risk of experiencing a myocardial infarction, which could indicate some confounding by indication.

Finally, recent work by Odden *et al.* and Jing *et al.* in VA nursing home patients demonstrated that reducing antihypertensive treatment was not associated with harm in this population [350, 351]. In the study by Jing *et al.*, which followed nearly thirteen thousand patients for a median of 23 weeks (range: 9–65 weeks), the relationship between antihypertensive medication discontinuation and dementia was examined [351]. Particularly among patients with pre-existing dementia, discontinuation of antihypertensive medications was associated with less cognitive decline, a finding that largely drove the observed effects in the overall population [351]. Interestingly, this effect was not replicated in a RCT with a similar patient population and slightly shorter follow-up time [237]. In the study by Odden *et al.*, involving just over thirteen thousand nursing home patients with 20 weeks of follow-up, no association was found between reducing antihypertensive medication and hospitalizations for stroke or myocardial infarction (aHR, 0.93 [95% CI, 0.70–1.26]) [350]. Combining both stroke and myocardial infarctions might attenuate some of the observed association, as antihypertensives have a relatively low impact on myocardial infarctions. However, this does not alter the fact that these results are of interest in the care of nursing home residents. Both studies reported relatively high mortality rates during follow-up, potentially reflecting that treatment reduction often occurred in the context of life-limiting prognoses and thus potential futility of continued therapy. These findings support the consideration of antihypertensive treatment discontinuation in older, frail nursing home residents, as continued treatment may provide limited benefit in this population.

5.6.4 Implications for future research and clinical practice

This thesis has focussed on a broad older population of patients treated with antihypertensive medication. While this does examine the effect in as a generalisable as possible general practice population, more specific populations might be more appropriate. There are several subpopulations that might be of interest and potential reasons. While the following suggestions are by no means exhaustive, it will reflect some of the limitations of summarising the entire population prescribed antihypertensives as a single group. One of the pertinent populations to explore is those whom experienced a major cardiovascular incident, either non-fatal stroke or myocardial infarction, with a specific focus on treatment cessation after a set period of time after the major event. Highlighted most pertinently by exploration of patients whom experienced a myocardial infarction is the specific discontinuation of beta blocker therapy in this population. Over the last few years questions have arisen of the additional benefit of beta blocker therapy in this population, mainly due to the introduction of drugs intervening in the RAAS-pathway, which has previously been researched in the context of new initiation and as an extension of that as possible target for discontinuation [352, 353]. Similarly are the patients experiencing heart failure (with reduced ejection fraction) where specific antihypertensives, like RAAS-pathway drugs and beta-blockers, illicit more than a blood pressure reducing effect [354, 355]. The discussion with regards to class-specific analyses needs to be had and is discussed in Chapter 6.

In this work, the focus has been on any level of reduction of antihypertensive treatment, meaning that a reduction of two prescriptions is treated similarly to a reduction of single prescription. This problem is also intertwined with the patients stopping treatment and having residual treatment or not. A myriad of groups can be defined based on the reduction of prescriptions or the number of treatments remaining after treatment reduction. However, these would not necessarily be the same, for example any patient on a single prescription in this study would have stopped all treatment (as followed by the implemented algorithm definitions) but

these could arguably differ from patients that start on two or more prescriptions and cease all treatment. In other words, the same patient cohort that started on a single prescription could be different to those whom had two active prescriptions and only stopped a single prescription, where both groups had the same of treatment stopped, but one is left with residual treatment. The amount of different comparison that can be drawn-up based on these factors alone is substantial and is an inherent problem to studying antihypertensive medication cessation. Future work could focus on initially focusing on one of the two problems, e.g. solely on having residual treatment or not, or subgroups of patients whom stopped one or two prescriptions in one go, before combining. Once again here the same problem of specific drug classes might arise, either as the active treatment taken away or the residual treatment remaining.

Finally, further research should also focus on the role of the other methods of medication optimisation, dose reduction and class switching, in the management of antihypertensive pharmacotherapy. When initialising antihypertensive treatment, it is common to switch to other drug classes or up-titrate dosages, while this is generally overlooked in deprescribing research [21, 356–359]. While this is a separate question with regards to the impact of stopping or reducing treatment, all these interventions have to be seen in-context of effective pharmacotherapeutic management, whether it is in response to side-effects (reactive) or prevention of side-effects (pro-active). In Chapter 6 a more focused discussion on discontinuation in the context of pro-active and reactive management is included. Regardless of response-type, studying this more holistic intervention might not be suitable in routinely collected health care data due to previously mentioned limitations of such datasets (e.g. which includes limited data regarding prescribed dose). While a complicated design and a logistical challenge, a 4-arm drug class specific study would be an appropriate design to study this, where the arms are continued treatment, class switching, class cessation, or dose reduction.

Within the context of its limitations, the current work shows an increased association with both safety and efficacy outcomes in a broad population of older patients treated with antihypertensives whom subsequently reduce treatment. In contrast, a relative moderate decline of all-cause hospitalisation was observed. Outcomes with regards to all-cause hospitalisation remained similar in the explored subgroups, not warranting differential treatment based on age, number of antihypertensive prescriptions, systolic blood pressure, recent hospitalisation, or recent cancer diagnosis. These results, which are largely in accordance with both the meta-analysis (Chapter 2) and OPTiMISE, an English based RCT, show that caution should be taken in pro-actively discontinuation of antihypertensive treatment. This means that, in the absence of clear indications to cease treatment (e.g. orthostatic hypotension [360]) or explicit patients' wishes, antihypertensive treatment discontinuation should currently not be considered in older patients. A more detailed discussion on the clinical implications can be found in Chapter 6.

5.7 Conclusion

Good therapeutic management and optimisation is a complex interaction between indications, guidelines, multiple drug classes, clinicians education, and patients' beliefs and wishes. Therefore, based on these results and previous studies it is my belief that there is no "one size fits all" approach to reducing antihypertensive medication in patients. These data might provide context for further discussion for clinicians and patients to explore medication discontinuation where this is the patients wish or in the context of the presence of side-effects. However, pro-active antihypertensive treatment reduction on the basis of a few clinical characteristics, like age or gender, on population level might be more harmful than beneficial.

5.8 Key Points

- Antihypertensive medication discontinuation was associated with a decreased risk of all-cause hospitalisation. This was consistent in sub-group analysis.
- The risk of both safety and efficacy outcomes was increased after stopping treatment.
- The primary outcome of this study was similar to long-term follow-up of the OPTIMISE-trial.

6
Discussion

The work in this thesis was motivated by a lack of evidence in the long-term management of pharmacotherapeutic interventions aimed at preventing cardiovascular disease [80]. Most interventions aimed at the modification of risk factors like high cholesterol or increased blood pressure are initiated and, in most cases, are continued indefinitely [21, 22]. Although there has been an increased interest in stopping medication or reducing the overall medication burden in recent years, concerns about safety in trials and methodological issues in observational studies have hampered the generation of evidence and consecutive development of guideline advice [215, 227, 349]. Therefore, the aim of this thesis was to generate evidence on the long-term benefits and harms of reducing antihypertensive medication in older primary care patients.

This thesis started with a systematic review collecting evidence from previously published work on cessation of four major cardiovascular medications groups with the aim to summarise the currently available literature and, where possible, to use meta-analyses to combine outcomes. The systematic review also formed the basis of the identification of gaps in the literature with regard to long-term outcomes of discontinuation of antihypertensive treatment and refined the questions asked in the subsequent chapters. In the following chapter, the development of a method to detect sustained changes in complex longitudinal prescription data was presented, which was necessary because robust methods to detect such changes in routinely-collected prescription data from general practice electronic health records did not exist yet. This method was used to identify a cohort of patients for a case-control study and a cohort study. The aim of the case-control study was to identify patient characteristics associated with stopping or maintaining antihypertensive treatment, which was not only used for the identification of patients that could be targeted for potential discontinuation of treatment or support for continued treatment, but was also essential to identify confounders that needed statistical adjustment in the final cohort study. The final results chapter presents the cohort study, which aimed to examine the long-term benefits and harms of reducing antihypertensive

treatment in older primary care patients. The data from this thesis can be used to inform patients and clinicians about the pros and cons of continuing cardiovascular medication at an older age. Furthermore, it can used to inform the design for future studies investigating medication discontinuation.

6.1 Summary of findings

Chapter 2 of this thesis presents the findings of a systematic review with meta-analyses. Published discontinuation studies in older patients were included for four groups of medication used in the prevention of cardiovascular disease: anticoagulants, antihypertensives, antiplatelets, and statins. In total, four RCTs and eight observational studies were identified. For the cessation of anticoagulants, antiplatelets, and statins, only observational studies were identified. In all four studies, reducing any of these treatments was associated with increased harm. The studies looking at antihypertensive treatment discontinuation consisted mainly of RCTs with limited number of patients, events, and short follow-up time, where no statistical associations could be identified for discontinuation and outcomes. Finally, this systematic review also highlighted the difficulty of identifying discontinuation of multidrug therapies in routinely collected health care data, with only two observational studies on antihypertensive medication discontinuation, both of which leveraged database-specific strengths. Furthermore, studies included in this work mainly focussed on cardiovascular outcomes (e.g. strokes), mortality, and hospital admissions, with little focus on potential benefits of reducing pharmacotherapy (e.g. reduction of major bleeding on anticoagulation or acute kidney injury due to antihypertensives).

Chapter 3 presents the development of a method to identify sustained changes in routinely collected primary health care data using patterns associated with medication discontinuation. Inversely, it also allows for the identification of treatment intensification or treatment resumption, reflecting the versatility of this algorithm and the potential for wider application in pharmaco-epidemiological

research. The algorithm utilises the formation of specific patterns (or motifs) when prescription data is assessed at monthly intervals. In this chapter four motifs were used to identify patients who discontinue antihypertensive treatment, where discontinuation was defined as a sustained reduction in the number of active antihypertensive prescriptions over a period of three months compared to the previous period of three months. Using a population of older patients receiving antihypertensive treatment from the CPRD-Gold database, the algorithm detected antihypertensive treatment cessation in over a third of the population.

Chapter 4 presents the results of the case-control study. This study was used to identify patient characteristics associated with (dis)continuing antihypertensive treatment. This chapter presents three main findings. First, increased age and lower systolic blood pressure are associated with discontinuing antihypertensive treatment. Furthermore, increased use of both medication in general and antihypertensive medication specifically were associated with an increased likelihood of discontinuing treatment. Second, recent hospital admission and recent cancer diagnosis were associated with discontinuation of antihypertensive medication. Finally, a modest decrease in likelihood of discontinuing antihypertensive treatment was found for cardiovascular risk factors like diabetes and ischaemic heart disease. Due to the indeterminate nature of whom initiated the reduction (i.e. clinician or patient), this chapter could help clinicians to identify and support patients who are more likely to discontinue treatment and therefore more likely to be exposed to potential harm. Additionally, it can help support clinicians recognise intrinsic biases in deciding who can and cannot be a potential candidate for antihypertensive medication discontinuation.

Finally, Chapter 5 presents a retrospective cohort study. This study established that discontinuation of antihypertensive treatment in a general older primary care population was associated with a moderate reduction of all-cause hospitalisation, but increase in all-cause hospitalisation and mortality, cardiovascular mortality,

and cause-specific hospitalisation, including increases in potential intervention efficacy measurements (e.g. falls and fractures). The conflicting results of this chapter warrant restraint of broad implementation of antihypertensive treatment discontinuation in older primary care patients until more evidence is available, especially patients who do not experience any problems with their treatment. At the same time, it also reflects the additional research needed for patients experiencing side-effects or the management of specific drug classes in specific populations (e.g. beta blockers in secondary prevention after myocardial infarction) where the results of this work do not properly reflect outcomes of these patients.

6.2 Strengths and limitations of the Thesis

Strengths and limitations are discussed extensively in each results chapter. However, a brief overview of the main strengths and limitations of the individual chapters and, in a broader scope, the shared strengths and limitations are described below.

For chapter 2, one of the main strengths is the inclusion of both randomised trial data and data from observational studies, where the included meta-analyses provided - where possible - the aggregate of randomised, observational, and combined data. This provides a more complete overview of the available evidence, especially for interventions where there is potential of harm, or where it can be difficult to safely conduct randomised trials. Although the inclusion of observational studies in separate analyses provides additional evidence, these outcomes and meta-analyses including results from studies should be interpreted as observational in nature, meaning that they are subject to bias due to residual confounding. Furthermore, in this chapter the included RCTs all studied antihypertensives in relatively small study populations with limited follow-up time and low absolute number of events. This means that even though there was no statistical association found between reducing antihypertensive treatment and the reported outcomes, this was mainly driven by an underpowered analysis, meaning that there was significant uncertainty

about the association.

For chapters 3, 4, and 5, CPRD-Gold data was utilised, which comprises of a representative primary care population in England [273]. First, the main strength of the work presented in Chapter 3 is the versatility of the way patterns can be interpreted: while this work was interested in any antihypertensive medication reduction based on the number of prescriptions, the algorithm is agnostic to the information provided, meaning that it could have also used different dosages, different drugs classes/groups, total prescriptions, or even different databases. Furthermore, the algorithm can also be implemented to study treatment intensification, allowing its application in various different research settings or extend the treatment discontinuation/resumption research paradigm. Chapter 3 also highlights the extent of antihypertensive medication reduction taking place in primary care without robust evidence or guideline support, emphasising the need for more exploration of causes and outcomes of antihypertensive medication reduction.

One of the main limitations which stems from Chapter 3 is the inability to determine who initiated the discontinuation of treatment, which is a general limitation when examining discontinuation in observational data. This limitation persists in the subsequent chapters, where it creates some uncertainty around the patient characteristics associated with discontinuing treatment and the eventual outcomes. This limitation is mainly based on the assumption that reasons for stopping could potentially be different if it is initiated by clinicians or by patients themselves, and - as an extension to this - that the outcomes could potentially be different for clinician-led medication reduction or for patients stopping medication on their own accord. How this affects the results is unclear. A final assumption to be made here is that patients stopping on their own accord is likely to be a bigger problem in primary care patients than in nursing home patients studied by Odden *et al.*, since medication prescribing and dispensing in the Veterans Affairs (VA) Nursing homes is more tightly controlled [269, 350, 351]. While the initiator of

discontinuation remains unclear and potentially problematic, as previously discussed, Chapter 4 did show highly congruent results with regards to clinical characteristics associated with other published works, including work done in the VA database on discontinuation of antihypertensive therapy and statin discontinuation [242, 269, 271], providing validity for the results found in this thesis.

As an extension to the previous paragraph is the uncertainty if medication was discontinued in response to an adverse event or not. While one of the exclusion criteria in the systematic review was medication discontinuation in response to side-effects, this cannot be established using the observational data available in the CPRD-Gold database. Management of acute situations as a result of adverse drug reactions is different compared to prevention of future adverse drug reactions. In the situation where the adverse event has occurred (or is occurring), rapid intervention is essential and withdrawal of the causal agent is indicated [190]. Prevention of potential side-effects is a complex balance between two outcomes states that could potentially never develop: the adverse drug reaction or the targeted disease of interest outcome (e.g. stroke). Furthermore, careful consideration must be given on how to balance the difference in outcome severity of the two states (e.g. heart failure vs hyperkalemia) and how many adverse drug reactions are accepted to prevent outcomes. This benefit-risk assessment is not too dissimilar to that considered when initiating new drug treatment, but substantially differs in the assessment of harm as the likelihood of developing side-effects on established therapy is lower compared than at the time of treatment initiation [361, 362].

One of the main strengths of Chapter 5 is the alignment with existing studies summarised in Chapter 2, where results were in agreement with both meta-analysis of RCTs alone, and meta-analysis of RCTs and observational studies combined. Paradoxically, a strength of this work is the generalisability of the results due to the inclusion of a representative population of older primary care patients treated with antihypertensives. However, this sometimes poorly reflects the complex patient

sitting in front of a health care professional. While this work found that there was a general association between reducing antihypertensive treatment and increased harm, this might not be true for all patients or specific subpopulations such as the very old and frail [80].

A possible limitation throughout this work, and potentially in the field in general, is the focus on treating the medications used to treat hypertension as a singular group. As explained in the introduction of this thesis, the different classes that are used to treat hypertension exert their effects through different pharmacological pathways. This means that they have the potential to exert different positive effects and different side/adverse effects in conjunction with overall shared side effects due to the hypotensive effect (e.g. syncope). Grouping all antihypertensives together, either in observational studies or randomised trials, is a desirable approach when examining the general association between the reduction of the hypotensive-load and outcomes and is far easier to model than treating each antihypertensive treatment group separately. The main limitation of this approach, while there are pragmatic approaches to deal with this is, is that it is unclear if the cessation of specific classes is more harmful than others. This was exemplified by the recent work done on beta-blocker discontinuation in patients with previous myocardial infarctions, where cessation of this class was found to be non-inferior to continuation of treatment [353]. With regards to this work, the tracking of changes per class was explored as an option early on in this work. However, as the monthly class-specific prescription variation was too high to establish consistent treatment and developing a catch method to determine class-switching created more uncertainty, it was decided that this was beyond the scope of this thesis. However, in the future work section, a possible method for class-specific or alternative methods for detecting medication reduction will be discussed.

6.3 Implications

6.3.1 Clinical implications

This work shows that discontinuation of antihypertensive treatment occurs in older general practice patients and may potential be associated with a reduction in all-cause hospitalisation, while cause-specific outcome measures of both potential benefits and harms seemed to be negatively impacted. However, it is unclear if this discontinuation was in response to acute side-effects, patients' wishes, drug-futility, or prevention of future harm, and whether it was clinician-led or patient-led. This nuances the advice that can be given based on the findings of this work as medication discontinuation has to be considered in the context of this complex web of considerations. This means that - while the overarching advice given is based on population-level considerations, patient-level considerations might outweigh the generalised advice.

This work in a general older cohort of patients treated with antihypertensives showed that there was an association with cause-specific harm with minimal benefit when treatment was reduced. Therefore, this work suggests that antihypertensive treatment reduction should currently not be considered in all older patients, regardless of age, gender, or the use of multiple concurrent medications, if treatment is well-tolerated, in order to prevent potential side-effects or manage polypharmacy. When it is the patient's wish to take less medication, either alternative medications should be considered or the patient should be informed of the uncertain benefit or harm of stopping treatment.

Chapters 3 and4 provide insight into the extent of discontinuation taking place in primary care and into the patient characteristics associated with treatment cessation. The identification of the characteristics of patients in primary care that are more likely to discontinue treatment (or have their treatment discontinued) can help health care providers with awareness and support potential monitoring in order

to support patients to continue their treatment where appropriate. While the best way of supporting medication adherence and persistence is open for discussion and needs additional qualitative and quantitative research, one occasion where problems with treatment could be flagged is in structured medication reviews (SMR) [70, 363, 364]. Furthermore, the patient characteristics identified could be related to the tendency of clinicians to reduce treatment in, for example, older or complex patients, while this might potentially not be the best strategy. However, the advice based on the findings of this thesis should provide support for clinicians to be aware of the impacts of reducing antihypertensive treatment and consider alternative strategies.

Chapter 4 showed that previous hospital admission was strongly associated with an increased likelihood of discontinuing treatment. As discussed in the Chapter, the exact underlying mechanism is unknown and could not explored. It was also posited that it remains unclear if the implementation of medication reconciliation would have had a positive impact in reducing the amount of medication errors following hospital admission and discharge. However, it does support the necessity for continued support and close management of patients just after hospital discharge.

6.3.2 Future research

The previous section on clinical implications has emphasised the need for additional research. While some of the future research is specific to antihypertensive treatment, some points may be generalisable to the field of medication reduction.

While the studies included in this thesis related to reducing antihypertensive treatment generally showed an association with harm, it is my opinion that randomised trials on the subject still have to be conducted. Considerable uncertainty remains with regards to the benefits and harms, which can not be fully addressed by observational studies alone, due to the inherent methodological limitations of these types of studies. However, here I will posit that observational studies

on discontinuation of other medication used in the prevention of morbidity and mortality should precede randomised trials (where methodologically possible) to get an indication of direction of effect to ascertain if patients might be exposed to preventable harm [227, 365]. Nevertheless, it is important to note that in addition to the inherent biases related to observational studies, no distinction can be made between pro-active and reactive medication discontinuation. Therefore, observational studies are unable to provide all evidence that might be required or desired. Cessation of specific medication classes in a specific patient cohort should be the main focus of future research. Therefore, as discussed earlier, the only way to gain suitable evidenced that is needed to support clinical decision-making on these medication types might be studying each antihypertensive medication class separately.

This thesis has focused on discontinuing antihypertensive treatment in the context of uncertainty about the potential inappropriateness of continued treatment [80]. Evidence for a potential shift in the risk and benefit of treatment was provided in a study by Sheppard *et al.* which showed that higher age was associated with increased falls, AKI, electrolyte abnormalities, and gout [148]. Cohort studies like this are needed to provide evidence for the initiation of antihypertensive treatment in older patients. However, these studies and clinical trials in older patients only provide evidence with regards to new users [366, 367]. One pit-fall is that prevalent/experienced users are treated similarly to new users, while this is unlikely to be appropriate as the incidence of adverse drug events subsides after the initial start of treatment [368, 369]. This means that these studies are probably more appropriate to determine if treatment should be started and not necessarily if treatment should be continued.

Medication reduction is one component of good pharmacotherapeutic management; however, alternative methods are available. In both reactive and pro-active medication reduction research, the alternative methods should be included

to determine the best approach. In an ideal world, this would be done using studies with multiple intervention arms. In the context of pro-active medication discontinuation, this would be a four-arm trial containing a continuation arm, dose reduction, class-switching, and class reduction. However, combining both multiple arm trials with specific populations and specific classes would result in an impractical amount of studies needed to be conducted to provide the necessary evidence. A possible solution to this could be the exploration of these associations through master protocols [370]. One of these approaches would be the development of a platform trial, which allows for the evaluation of multiple-interventions in heterogeneous patient populations [370, 371]. Platform trials can be designed to be adaptive, which increases the flexibility by having the option of removing ineffective intervention arms [371]. Independent of the logistical complexity of attempting to design and carry out these experiments, the first priority should be conducting studies in patients that have a high-risk of experiencing adverse drug reactions, either due to previous adverse events or as predicted by prediction models. When patient populations are restricted to only those at high-risk of developing specific side-effect, the optimisation intervention can be focused on only the agents associated with the side-effect. Additionally, the impact of continued treatment in frail patients should be considered as this is a specific population that have an increased risk of iatrogenic disease [372].

The algorithm presented in Chapter 3 comprises of four motifs that reflect patterns of medication reduction in complex pharmacotherapeutic regimens. As previously described, it functions the same regardless of the intensity measurement of drug exposure that is used. In this work, the number of antihypertensive prescriptions was used as the total drug exposure, since it was not possible to convert drug exposure to "daily defined doses", which would be the preferred total drug exposure measurement as this better reflects therapeutic intensity [269, 272]. Application of the algorithm in different datasets that have easier access to dosage information should be undertaken, because dose reduction could function as an

intermediary intervention and could then be explored.
In addition to the inclusion of alternative measures of drug intensity, other complex long-term treatments can be analysed with the algorithm, such as the management of patients with type 2 diabetes. This group of patients could be of interest since escalation of oral treatments often happens in response to disease progression, while tight control is often relinquished in older patients [24, 373].

6.3.3 Conclusion

Good therapeutic management and treatment optimisation is a complex interaction between indications, guidelines, multiple drug classes, clinicians' education and experience, and patients' beliefs and wishes. Therefore, based on previous studies and the results presented in this thesis, it is my belief that there is no "one size fits all" approach to reducing antihypertensive medication in patients. These data might provide context for further discussion for clinicians and patients to explore medication discontinuation, if this is the patient's wish or in the context of the presence of side-effects. However, pro-active antihypertensive treatment reduction on the basis of a few clinical characteristics, like age or gender, might be more harmful than beneficial on a population level.

6.4 Reflection

I am a pharmacist by background. The work resulting in this thesis was motivated by my interest in medication management and enhancement of patient outcomes for those exposed to (long-term) pharmacological treatment, which is an extension of my deep passion for clinical pharmacology and toxicology. While most of the optimisation interventions have focused on initiating the correct medication at the correct time or choosing not to start treatment, studies rarely reflect on the continuation (or not) of chronic treatment to which a large proportion of the older population is exposed. With this work, I wanted to reflect on the practice of

indefinite prescriptions in relation to prevention of long-term outcomes. In the future, if possible, I would like to continue my clinical training by starting the specialty training to become a hospital pharmacist and clinical pharmacologist, with a further area of interest in toxicology and therapeutic drug monitoring. As a hospital pharmacist, I would be able to combine clinical practice with academic research, where I want to focus on studying changes in drug exposure and adverse events in relation to established therapeutic windows by examining older patients admitted with unintentional drug overdose.

The biggest take-away of conducting this research will be the impact of the time invested in developing a solid research protocol. I have previously developed protocols for small research projects; however, this is the first time conducting research spanning years. My previous research experience, mainly bachelor and master theses, revolved around the development of novel chemical entities and novel high-end pharmaceutical formulations. This type of research is substantially different to the methodologies applied in this thesis. My previous experience in conducting research has had profound impacts on the way I approached this project and how some elements of the observational study were affected by this. First, the highly experimental nature of my previous work consisted of doing a high volume of trial-and-error type experiments, or in lay language: "throw things at the wall and see what sticks", meaning that the end-goal or product was not always as relevant for day-to-day experimentation. In the current work, this scientific approach was very useful to me in the development of motifs, patterns, and the eventual algorithm, as it allowed me to just focus on the detection of medication reduction. However, notably different in the current type research is the development of a cohort suitable for analysis, with data management spanning prolonged periods of time - in my case years. In this case, trial-and-error research is quite detrimental to the overall process, as late changes to either variables or additional information to be stored from the algorithm was simply not feasible in the time given to complete this thesis. Especially in the beginning of this process, I was unaware of how my previous

research experience had shaped my approach to tackling scientific problems, and I underestimated the value of slowing down. By determining the information you need from an early stage in the project, the cohort and data management can be designed in the most suitable way to obtain the correct outcomes. Finally, this was the first time I have been involved in conducting an observational study or working with any type of large datasets. In a similar vein to the design of the study, I underestimated the time investment needed to obtain a single covariate and how tedious data management can become, especially when needing to return to a variable for a third or fourth time.

Each DPhil journey is a personal experience and different challenges need to be tackled in order to successfully complete the program. The project presented in this thesis is different to the proposed project at the start of my DPhil journey. I even started my DPhil in a different department doing wet-lab type research. Switching directions to a completely different type of research is never easy, especially coupled with a sincere sense of loss of not being able to continue doing the research project I was - and still am - deeply passionate about. Furthermore, I switched departments and projects in late January 2020, around the time a global pandemic changed the way we lived and - as an extension - how we worked. This time sadly also coincided with a period where my personal health declined and severely impacted my ability to continue with my research. As I close the chapters of my DPhil and a period of illness, I look forward to opening new and exciting chapters — both academically and, more importantly, personally.

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Appendices

A
Appendix

A.1 Published work

van der Veen et al. Systematic Reviews (2021) 10:185
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Systematic Reviews

PROTOCOL Open Access

The health impacts of preventive cardiovascular medication reduction on older populations: protocol for a systematic review and meta-analysis

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Abstract

Background: Polypharmacy is inevitable and appropriate for many conditions, but in some cases, it can be problematic resulting in an increased risk of harm and reduced quality of life. There has been an increasing interest to reduce cardioprotective medications in older adults to potentially reduce the risk of harm due to treatment; however, there is no evidence on safety and efficacy to support this practice currently. This paper describes a protocol for a systematic review on the safety and efficacy of reducing cardioprotective medication in older populations.

Methods: MEDLINE (PubMed), Embase (Ovid), and CENTRAL (Cochrane Central Register of Controlled Trials) will be searched from their inception onwards for relevant studies. Randomised controlled trials and non-randomised studies on interventions (prospective, retrospective cohort, case-control) conducted in older adults (75 years or older) examining reduction of cardioprotective medications will be included. The primary outcome of this study will be all-cause hospitalisation. Secondary outcome variables of interest are all-cause hospitalisation, mortality, quality of life, serious adverse events, major adverse cardiovascular events, falls, fractures, cognitive functioning, bleeding events, renal functioning, medication burden, drug reinstatement, time-in-hospital, and frailty status. Two reviewers will independently screen all citations, full-text articles, and extract data. Confidence in cumulative evidence will be assessed using the GRADE approach; the risk of bias will be assessed by the RoB-II tool for randomised controlled studies and ROBINS-I for non-randomised studies. Where sufficient data are available, we will conduct a random effects meta-analysis by combining the outcomes of the included studies. Sub-group analysis and meta-regression are planned to assess the potential harms and risks of different drug classes and the impacts in different patient populations (e.g. sex, cognitive status, renal status, and age).

Discussion: The study will be a comprehensive review on all published articles identified using our search strategy on the safety and efficacy of cardioprotective medication reduction in the older population. The findings will be crucial to inform clinicians on potential health outcomes of reducing cardiovascular medication in the elderly.

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Keywords: Deprescribing, Cardiovascular therapy, Aged, Problematic polypharmacy, Inappropriate prescribing, Multimorbidity, Quality of life, Adverse events, Medication reduction

Background

People are living longer and developing multi-morbidity at old age [1, 2]. As a natural consequence of applying modern treatment guidelines to treat diseases, people are exposed to evermore long-term pharmacotherapeutic interventions [2]. While this increase in pharmacological intervention unquestionably has led to an overall health benefit for patients across disease domains, the surge in interventions has created polypharmacy and problems with inappropriate prescribing in vulnerable populations [3]. The term polypharmacy inadvertently has been associated with negative health impacts, which is why several groups have sought to bring nuance by adopting two variations of polypharmacy; appropriate polypharmacy and problematic polypharmacy [2, 4]. For those patients experiencing problematic polypharmacy and/or inappropriate prescribing there may be an increased risk of adverse events, including falls, hospitalisation, and even mortality [5].

In recent years, there has been an increased interest in medication reduction to address problematic polypharmacy, known as deprescribing. Deprescribing is defined as the process of withdrawal of an inappropriate medication, supervised by a health care professional, with the goal of managing inappropriate polypharmacy and improving outcomes [6, 7]. Medication reduction in older adults is of a particular interest as they are generally not included in large randomised controlled drug efficacy trials and often are multi-morbid and/or frail, which may increase an individual's risk of adverse events from treatment [8–10].

Cardiovascular drugs have been associated with inappropriate prescribing and their pharmacological action is closely related to negative outcomes seen in problematic polypharmacy-related outcomes, i.e. antihypertensives causing hypotension resulting in syncope and/or falls, and are there for an ideal candidate for withdrawal to potentially improve patient outcomes [5, 8]. Reduction of preventative cardiovascular in drugs in older adults, either prescribed for primary or secondary prevention of cardiovascular disease, can be used to remove potentially inappropriate medications, which could mitigate unwanted risks, like adverse drug reactions [8]. However, preventative cardiovascular medication reduction might increase the risk of cardiovascular events, due to disruption of the normotensive state, increased plaque formation, increased blood coagulation, or increased platelet activity [11–14]. Therefore, the potential benefits and harms of cardiovascular medication reduction need to be balanced against the benefits and harms of continuing therapy, as well as patient wishes.

This study described in this protocol aims to look at the safety and efficacy of cardiovascular medication reduction compared to usual care in patients aged 75 years and over. There are existing systematic reviews that examine the clinical outcomes of reducing cardiovascular drugs, but these provide insufficient evidence to support clinical decision making [15–18]. One systematic review focused on the clinical outcomes of the medication reduction intervention itself, without evidence for the effect of individual drug classes [15]. A systematic review published in 2008 focused on identifying medication withdrawal studies that withdrew a single group or class of drugs, but did not include a meta-analysis due to heterogeneity of included trials [16]. A more focused systematic review looked at antihypertensive medication withdrawal in a broader age group and the proportion of the patients remaining normotensive. Due to the diversity of patients included in this review, no meta-analysis was performed for the clinical outcomes [17]. A recent systematic review reviewed the clinical outcomes of complete antihypertensive withdrawal in the older population, defined as 50 years or older, found no evidence that such an intervention was associated with mortality, heart attack, or stroke, although analyses were almost certainly underpowered [18]. Therefore, this study aims to add to existing evidence by including recently published trials omitted by other publications, inclusion of a wider range of cardiovascular medicines and reduction interventions, and a stricter age selection for patients whom we believe to be at potential increased risk of harm of continued drug exposure [5, 8].

Methods/design

The present protocol has been registered within the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42020208223) and is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist [19] (Additional File 1).

Eligibility criteria

Studies will be selected according to the following criteria: study designs, participants, interventions, comparators, outcomes, and setting.

Study designs

We will include randomised controlled trials and non-randomised studies of interventions (NRSI). Non-randomised studies of interventions that will be considered are controlled cohort studies (prospective and retrospective) and case-control studies. Studies that are excluded for this study are case reports and studies lacking a comparator.

Participants

Studies where at least of half of the population was 75 years of age will be considered for inclusion in this review. Studies including a younger population will be considered if they published a subgroup analysis of the outcomes in patients of 75 years or older. Patients receiving prescriptions either in the context of primary or secondary prevention will be considered for this systematic review. Studies will be excluded if they examine patients receiving palliative care.

Intervention

The intervention of interest in this review is deprescribing, where a healthcare professional aims to systematically reduce cardiovascular therapy in older populations to improve outcomes, manage problematic polypharmacy, or prevent adverse events. Preventive cardiovascular therapy is defined as antihypertensives (e.g. angiotensin converting enzyme inhibitors, angiotensin receptor blockers, thiazides, calcium channel blockers, alpha/beta-blockers, central acting antihypertensives), antihyperlipidemics (e.g. statins, fibrates), antiplatelets (e.g. aspirin, $P2Y_{12}$ inhibitors), and anticoagulants (e.g. coumarin-derivatives, direct acting oral anticoagulants).

Excluded are studies in which medication reduction is reactive in nature, e.g. patients experiencing adverse events or symptoms of the drug therapy, and studies that are looking at temporary withdrawal (e.g. in preparation for major surgical interventions) or as part of a run-in phase prior to randomisation in a clinical trial.

Comparator

Any study that has a suitable comparator group is considered. Comparisons are considered suitable if they are usual care, placebo-controlled, or active maintenance of current therapy.

Setting

Included settings for this review are primary care, nursing homes, and hospital care.

Hospice care setting is excluded from this review.

Outcomes

Primary outcome

The primary outcome of this study will be all-cause hospitalisation regardless of the duration of the stay.

Secondary outcomes

Secondary outcomes will include all-cause mortality, quality of life, serious adverse events, major adverse cardiovascular events (defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death), falls (including self-reported and those who need medical attention), fractures, cognitive functioning, bleeding events (major and minor), renal functioning (acute kidney injury and chronic kidney disease), electrolyte anomalies (e.g. hyperkalaemia), change in medication burden (I.e. number of medications prescribed), drug reinstatement, time-in-hospital (length of stay), and change in frailty status.

Information sources and search strategy

A search strategy using a combination of medical subject headings, publication type, key words, and abstract/title text words has been developed an example for one database (Embase) can be found in Additional File 2. After consultation with an information specialist the databases Embase, MEDLINE, and CENTRAL will be searched from their inception onwards. MEDLINE will be accessed through PubMed, Embase through Ovid, and CENTRAL through the Cochrane Library. The search terms will be adapted for use with each specific database interface. Reference lists of selected articles will be scanned to include additional papers not identified with the search strategy.

Language

No restrictions will be placed on the original publication language. A summary table of all articles requiring translation will be made available.

Study selection

Two review authors (RV and JL) will independently screen the records obtained through the search strategy. Titles and abstracts will be screened against the inclusion/exclusion criteria, before further screening of full-text articles. Differences between the two reviewers will be assessed, reviewed, and resolved by a third reviewer (JS). Study screening, selection, and recording will be done using EndNote (Clarivate Analytics, Philadelphia, USA) and Rayyan [20].

Data extraction

Two review authors will independently extract data from the included studies. Data will be extracted using a standardised Excel (Microsoft, Albuquerque, USA) form,

based on Cochrane recommendations for intervention reviews for RCTs and non-RCTs [21]. The extraction form will include information related to the reference, study methodology, participants, intervention, and outcomes. The extraction form will be piloted to ensure no data will be missing from the form. If data cannot be extracted from the original source material, the authors of the paper will be contacted to obtain the missing information.

Risk of bias assessment

Two review authors will independently assess risk of bias for each individual study using either the Cochrane risk-of-bias tool for randomised trials (RoB 2.0 tool) for randomised trials [22, 23] or Risk Of Bias in Non-randomised Studies of Interventions (ROBINS-I) for non-randomised trials [24, 25]. The RoB 2.0 tool assesses the bias that can arise in randomised trials in five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [23]. The ROBINS-I tool assesses bias within 3 domains, namely pre-intervention, at intervention, and post-intervention [25]. Any discrepancies between the two reviewers will be assessed by discussion and if not agreed, the third reviewer (JS).

Planned methods of analysis

Characteristics of included studies

Descriptive statistics and study population characteristics for all included studies will be produced and reported in a table; these will include article characteristics and clinical and methodological variables, such as average age, follow-up, and main trial outcome.

Meta-analysis

If sufficient studies for a specific drug group (antihypertensive, antiplatelet, antihyperlipidemic, and anticoagulant) are identified, we will conduct a meta-analysis for those groups. Meta-analyses will be conducted separately for randomised controlled trials and non-randomised studies of interventions. When a meta-analysis will be performed, we will use a random effects model to calculate the aggregate effect. If significant inconsistency is present in the direction of effect, a meta-analysis will not be performed.

Measures of treatment effect

Studies might utilise different methodologies to assess their outcome. To address this, we will do the following. For binary outcomes (e.g. hospitalisation) a pooled odds ratio will be calculated. For continuous outcomes that are determined through different methods (e.g. quality of life assessment), the standardised mean difference is used. For continuous outcomes that are assessed through the same test, we will use the mean difference. Data analysed using Poisson regression, count data, will be pooled similarly to other relative risk outcomes.

Assessment of heterogeneity

Clinical heterogeneity will be assessed and determined by two independent reviewers and statistical heterogeneity will be assessed by quantifying inconsistency I^2 (Cochran Q test) [26].

Sensitivity analysis

If sufficient data are available, sensitivity analyses will be performed to ascertain how or if the results change under different assumptions, namely inclusion/exclusion of specific settings (nursing home or hospital), high risk of bias studies, and studies that included a younger population.

Subgroup analysis and meta-regression

If sufficient studies (more than 10 within a specific drug group) are available, we will conduct meta-regression analyses looking at the influence of various baseline characteristics, e.g. baseline medication burden and average medication reduction. If meta-regression is not feasible, we will report where possible the subgroup analysis of the following groups: sex, age (75–84 and 85 years and over), medication classes (e.g. beta blockers), cognitive functioning (no cognitive decline vs any functional cognitive decline), renal status (stage 1-2 vs stage 3 and over), health care provider delivering the intervention (doctor, nurse practitioner, pharmacist, other), and the frailty (no frailty vs frailty).

Publication and reporting bias

Reporting biases will be assessed by comparing published reports with protocols (either published in journals or obtained from databases) and the use of contour-enhanced funnel plots to identify small-study effects where appropriate [27].

Strength of evidence assessment

To assess the certainty of the body of evidence, we will use the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) as recommended by Cochrane [28].

Statistical software

All statistical analysis will be performed using R (meta and metafor packages) [29–31].

Discussion

Despite recognition of the negative health impacts of problematic polypharmacy and increased interest in medication reduction to improve outcomes or reduce

harm in older community-dwelling older patients, evidence is still scarce to support health care professionals in decision-making. Due to the nature of the intervention, potential negative outcomes, and the principle of *primum non nocere* ('first, do no harm'), it is important to understand and summarise the short- and long-term health impacts of medication reduction. Furthermore, it is important to determine if there are any differential health outcomes in specific populations (e.g. sex, cognitive status, renal functioning) or which drugs are potentially safe to reduce [8]. The study described in this protocol seeks to summarise all currently available evidence that could help to address these questions and identify gaps in the evidence which might inform future research on this topic.

Strengths and limitations of this approach

Although great care has been taken into developing the search strategy to identify all the relevant literature, it is known that deprescribing or medication reduction studies are hard to capture due to lack of consistent and universal search terms [16, 18]. Our search strategy uses a combination of title and abstract, keyword, and subheading search terms that are generally associated with medication withdrawal or reduction studies to increase the number of relevant records identified. In addition, screening of reference lists of included records will help us identify any studies not captured by the search strategy.

Due to the scarcity of randomised evidence on cardiovascular deprescribing interventions, this study will also assess data from observational studies. Non-randomised data are inherently subject to more bias compared to randomised study data. Patient or health care professional perceptions could influence the decision to initiate medication reduction, for example patients with underlying life-limiting pathologies might be more likely to discontinue medication than those whom are not resulting in a higher mortality rate in medication discontinuation groups if not or insufficiently controlled for. Different statistical approaches have been developed to adjust for these imbalances between groups using known confounders related to the indication, but this cannot obviously not be done for unknown confounders. However, data from well-designed observational studies can still provide good estimates of potential benefits and harms with minimal risk of bias [32].

Outcomes of interest for this study can be broadly grouped in safety and efficacy outcomes. Safety outcomes in medication reduction interventions are equivalent to efficacy outcomes of therapeutic interventions, e.g. major cardiovascular events. Efficacy outcomes in this study are those outcomes that are hypothesised to improve due to reducing the cardiovascular prescription exposure, which closely resemble safety outcomes in intervention trials, e.g. bleeding or falls. All-cause hospitalisation has been chosen as the primary outcome as it can be increased both in prescribing and medication reduction interventions, when not done correctly. Furthermore, hospitalisation is an impactful experience especially in the elderly, increasing the risk of developing new diseases (both somatic and psychological) and increases their dependency, negatively affecting autonomy and increases the risk of depression [33–35].

The focus of this study is medication reduction in older people, but health care setting could potentially influence outcomes due to potential differences in health care delivery. Our hypothesis is that the direction of effect and expected effect size should be similar across settings, due to randomisation or matching. A sensitivity analysis will be included to verify this hypothesis.

If enough studies are identified, we plan to undertake meta-regression analyses. Using the average of patient characteristics as covariates in such an analysis can result in 'ecological bias' and therefore should be interpreted with caution and not used to draw conclusions about the causal effects of specific patients' characteristics. However, outcomes generated by meta-regression can be hypothesis generating and can be used to inform development of future studies [36].

Any amendments made to the protocol when conducting the review will be outlined in PROSPERO and reported in the final manuscript.

In summary, this study will provide a thorough review of all studies assessing the benefits and/or harms of cardiovascular medication reduction in older people. The results will be important for guideline developers and clinicians when making decisions on which medication prescription to withdraw and whom to consider for medication reduction interventions. Compared to results from the existing systematic reviews [15–18], this overarching summary of all relevant work will enhance decision-making as it will include a broader selection of cardiovascular drugs and outcomes to better reflect the complexity of the intervention in routine clinical practice. Results from the systematic review will be disseminated through conference abstracts, social media, and publication in a peer-reviewed journal, and a layman summary will be used for future public and patient involvement and will be made freely accessible on the website of the Nuffield Department of Primary Health Care Sciences. Findings will be used to inform researchers on potential gaps in the evidence which need to be addressed.

Abbreviations

NRSI: Non-randomised studies of interventions; RCT: Randomised controlled trial; RoB 2.0: Risk of Bias Tool for randomised trials; ROBINS-I: Risk of Bias in Non-randomised Studies of Interventions

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-021-01741-2.

Additional file 1.
Additional file 2.

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Authors' contributions

The manuscript was drafted by RV. JL, RMcM, RH, KRM, KC, and JS substantially contributed to the development of conception and design of the study and manuscript. All authors have read and approved the final manuscript. RV is the guarantor of the review

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Availability of data and materials

Not applicable

Declarations

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Not applicable

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Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

A.2 Search Strategies

A.2.1 PubMed

((("randomized controlled trial"[pt]) OR ("controlled clinical trial"[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR ("Drug Therapy"[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) OR (("Case-Control Studies"[Mesh]) OR ("Cohort Studies"[Mesh])) OR (("cohort stud*"[tiab]) OR ("cohort analys*"[tiab]) OR (prospective[tiab]) OR (retrospective[tiab]) OR ("case control"[tiab]) OR (case-control[tiab]) OR (longitudinal[tiab]))) AND (((aged[Mesh]) OR ((elder*[tiab]) OR ("older adult"[tiab]) OR ("older patient*"[tiab]) OR (frail*[tiab]) OR ("nursing home residents"[tiab]) OR ("older person*"[tiab]) OR (veteran*[tiab]) OR (centarian*[tiab]) OR (centenarian*[tiab]) OR (eldest[tiab]) OR (geriatric*[tiab]) OR (nonagenarian*[tiab]) OR (octogenarian*[tiab]) OR ("old age*"[tiab]) OR ("older age*"[tiab]) OR ("older female*"[tiab]) OR ("older male*"[tiab]) OR ("older population"[tiab]) OR ("older man"[tiab]) OR ("older men"[tiab]) OR ("older people"[tiab]) OR ("older subject*"[tiab]) OR ("older woman"[tiab]) OR ("older women"[tiab]) OR ("oldest old*"[tiab]) OR (senior*[tiab]) OR (senium[tiab]) OR (septuagenarian*[tiab]) OR (supercentenarian*[tiab]) OR ("very old*"[tiab]))) AND (((((("antihypertensive agents"[Mesh]) OR ("hydroxymethylglutaryl coa reductase inhibitors"[Mesh])) OR ("platelet aggregation inhibitors"[Mesh])) OR (anticoagulants[Mesh])) OR ((diuretic*[tiab]) OR (statin*[tiab]) OR (antiplatelet*[tiab]) OR (antithrombotic*[tiab]) OR ("cardiovascular medication*"[tiab]) OR ("oral anticoagulant*"[tiab]) OR (beta-blocker*[tiab]) OR ("ACE inhibitor*"[tiab]) OR ("lipid modifying drugs"[tiab]) OR (antihypertensive*[tiab]) OR (anticoagulant*[tiab])))) AND (((deprescriptions[Mesh]) OR ("inappropriate prescribing"[Mesh]) OR ("inappropriate prescription"[Mesh]) OR ("withholding treatment"[Mesh])) OR (("medication reduc*"[tiab]) OR ("medication discontin*"[tiab]) OR (deprescrib*[tiab]) OR ("stopping treatment"[tiab]) OR (discontin*[tiab]) OR (withdraw*[tiab]))))

A.2.2 Embase via Ovid

(("randomized controlled trial" or "controlled clinical trial").pt. or randomized.tw. or placebo.tw. or "Drug Therapy".fs. or randomly.tw. or trial.tw. or groups.tw. or (exp "Case-Control Studies"/ or exp "Cohort Studies"/) or ("cohort stud*" or "cohort analys*" or prospective or retrospective or "case control" or case-control or longitudinal).tw.) and ((exp aged/ or (elder* or "older adult" or "older patient*" or frail* or "nursing home residents" or "older person*" or veteran* or centarian* or centenarian* or eldest or geriatric* or nonagenarian* or octogenarian* or "old age*" or "older age*" or "older female*" or "older male*" or "older population" or "older man" or "older men" or "older people" or "older subject*" or "older woman" or "older women" or "oldest old*" or senior* or senium or septuagenarian* or supercentenarian* or "very old*").tw.) and (exp "antihypertensive agents"/ or exp "hydroxymethylglutaryl coa reductase inhibitors"/ or exp "platelet aggregation inhibitors"/ or exp anticoagulants/ or (diuretic* or statin* or antiplatelet* or antithrombotic* or "cardiovascular medication*" or "oral anticoagulant*" or beta-blocker* or "ACE inhibitor*" or "lipid modifying drugs" or antihypertensive* or anticoagulant*).tw.)) and (exp deprescriptions/ or exp "inappropriate prescribing"/ or exp "inappropriate prescription"/ or exp "withholding treatment"/ or ("medication reduc*" or "medication discontin*" or deprescrib* or "stopping treatment" or discontin* or withdraw*).tw.)

A.2.3 The Cochrane Library for clinical trials in CENTRAL

((("randomized controlled trial":pt) OR ("controlled clinical trial":pt) OR (randomized:ti,ab) OR (placebo:ti,ab) OR ([mh /"Drug Therapy"]) OR (randomly:ti,ab) OR (trial:ti,ab) OR (groups:ti,ab)) OR (([mh "Case-Control Studies"]) OR ([mh "Cohort Studies"])) OR ((("cohort" NEXT stud*):ti,ab) OR (("cohort" NEXT analys*):ti,ab) OR (prospective:ti,ab) OR (retrospective:ti,ab) OR ("case control":ti,ab) OR (case-control:ti,ab) OR (longitudinal:ti,ab))) AND ((([mh aged]) OR ((elder*:ti,ab) OR ("older adult":ti,ab) OR (("older" NEXT patient*):ti,ab) OR (frail*:ti,ab) OR ("nursing home residents":ti,ab) OR (("older" NEXT person*):ti,ab) OR (veteran*:ti,ab) OR (centarian*:ti,ab) OR (centenarian*:ti,ab) OR (eldest:ti,ab) OR (geriatric*:ti,ab) OR (nonagenarian*:ti,ab) OR (octogenarian*:ti,ab) OR (("old" NEXT age*):ti,ab) OR (("older" NEXT age*):ti,ab) OR (("older" NEXT female*):ti,ab) OR (("older" NEXT male*):ti,ab) OR ("older population":ti,ab) OR ("older man":ti,ab) OR ("older men":ti,ab) OR ("older people":ti,ab) OR (("older" NEXT subject*):ti,ab) OR ("older woman":ti,ab) OR ("older women":ti,ab) OR (("oldest" NEXT old*):ti,ab) OR (senior*:ti,ab) OR (senium:ti,ab) OR (septuagenarian*:ti,ab) OR (supercentenarian*:ti,ab) OR (("very" NEXT old*):ti,ab))) AND (((((([mh "antihypertensive agents"]) OR ([mh "hydroxymethylglutaryl coa reductase inhibitors"])) OR ([mh "platelet aggregation inhibitors"])) OR ([mh anticoagulants])) OR ((diuretic*:ti,ab) OR (statin*:ti,ab) OR (antiplatelet*:ti,ab) OR (antithrombotic*:ti,ab) OR (("cardiovascular" NEXT medication*):ti,ab) OR (("oral" NEXT anticoagulant*):ti,ab) OR (beta-blocker*:ti,ab) OR (("ACE" NEXT inhibitor*):ti,ab) OR ("lipid modifying drugs":ti,ab) OR (antihypertensive*:ti,ab) OR (anticoagulant*:ti,ab)))) AND ((([mh deprescriptions]) OR ([mh "inappropriate prescribing"]) OR ([mh "inappropriate prescription"]) OR ([mh "withholding treatment"])) OR ((("medication" NEXT reduc*):ti,ab) OR (("medication" NEXT discontin*):ti,ab) OR (deprescrib*:ti,ab) OR ("stopping treatment":ti,ab) OR (discontin*:ti,ab) OR (withdraw*:ti,ab)))

A.3 ISAC protocol for CPRD approval

Medicines & Healthcare products Regulatory Agency

CPRD

1 General information

Protocol reference Id
21_000385

Study title
Prevalence, prediction, and health outcomes of cardioprotective medication reduction in the older UK population

Research Area

Drug Utilisation

Pharmacoepidemiology

Does this protocol describe an observational study using purely CPRD data?
Yes

Does this protocol involve requesting any additional information from GPs, or contact with patients?
No

2

Research team

Role	Chief Investigator
Title	University Research Lecturer
Full name	James Sheppard
Affiliation/organisation	University of Oxford
Email	james.sheppard@phc.ox.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed

Role	Corresponding Applicant
Title	DPhil Student
Full name	Rik van der Veen
Affiliation/organisation	University of Oxford
Email	rik.vanderveen@phc.ox.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Profesdor
Full name	Richard Hobbs
Affiliation/organisation	University of Oxford
Email	Richard.hobbs@phc.ox.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Collaborator
Title	Medical Statistician
Full name	Constantinos Koshiaris
Affiliation/organisation	University of Oxford
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Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Associate Professor and GP
Full name	Kamal Mahtani
Affiliation/organisation	University of Oxford
Email	kamal.mahtani@phc.ox.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Collaborator
Title	Professor of Primary Care Research
Full name	Richard McManus
Affiliation/organisation	University of Oxford
Email	Richard.mcmanus@phc.ox.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Collaborator
Title	Doctoral Research Fellow
Full name	Anna Seeley
Affiliation/organisation	University of Oxford
Email	anna.seeley@phc.ox.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Medical Statistician, Epidemiologist
Full name	Ariel Wang
Affiliation/organisation	University of Oxford
Email	ariel.wang@phc.ox.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed

3
Access to data

Sponsor
University of Oxford

Funding source for the study
Is the funding source for the study the same as Chief Investigator's affiliation?
No
Funding source for the study
NIHR School for Primary Care Research

Institution conducting the research
Is the institution conducting the research the same as Chief Investigator's affiliation?
Yes
Institution conducting the research
University of Oxford

Method to access the data
Indicate the method that will be used to access the data
Institutional multi-study licence
Is the institution the same as Chief Investigator's affiliation?
Yes
Institution name
University of Oxford

Extraction by CPRD
Will the dataset be extracted by CPRD
No

Multiple data delivery
This study requires multiple data extractions over its lifespan
No

Data processors

Data processor is	Same as the chief investigator's affiliation
Processing	Yes
Accessing	Yes
Storing	Yes
Processing area	UK

4
Information on data

Primary care data

CPRD GOLD

Do you require data linkages
Yes

Patient level data

HES Admitted Patient Care
ONS Death Registration Data

NCRAS data

Covid 19 linkages

Area level data
Do you require area level data?
Yes

Practice level (UK)

Patient level (England only)

Patient Level Index of Multiple Deprivation

Withheld concepts

Are withheld concepts required?
No

Linkage to a dataset not listed

Are you requesting a linkage to a dataset not listed?
No

Patient data privacy

Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?
No

5
Protocol information

Lay Summary

Life expectancy has increased in recent decades, driven by advances in medical sciences. Diseases which would drastically lower life expectancy previously are now successfully treated with multiple drugs. Older people tend to accumulate more life-long conditions and therefore take more prescription drugs. However, taking multiple drugs may not but without risk. Some can cause side effects which might be serious. These include drugs used to prevent heart disease, such as those used to lower blood pressure and cholesterol. One way to prevent possible harm could be to reduce the number of drugs prescribed in patients where the benefits of continued treatment may be outweighed by the harms. However, the harms and benefits of reducing these drugs in patients are currently unknown.

This proposal aims to use the information from the medical records from patients in the United Kingdom to establish which drugs used to prevent heart attacks and strokes are currently stopped in current routine practice. We will also examine what events preceded the decision to stop certain prescriptions, and what outcomes occurred after the prescription was stopped. We will focus on prescriptions that are used to prevent heart disease like those who treat high blood pressure, lower cholesterol, and blood thinners. Information gathered can be used to inform general practitioners who might benefit from stopping or reducing drugs used to prevent heart attack and stroke.

Technical Summary

Background
Accumulation of multiple long-term prescription drugs has led to so called polypharmacy, which can be specified as appropriate polypharmacy and problematic polypharmacy. Problematic polypharmacy, when multiple medications prescribed inappropriately or where the intended benefit of therapy is not met, is a risk factor to develop therapeutic related harm. This is particularly important for older individuals prescribed medications for cardiovascular disease prevention, where physiological changes and frailty may make them more susceptible to adverse drug reactions. Current guidelines therefore advise using clinical judgement when prescribing in older patients, and in some circumstances, consider reducing (stopping) medications which may cause harm. However, evidence to support this is currently lacking.

Aims
This study will examine the extent to which cardioprotective medication reduction (antiplatelets, anticoagulants, lipid-lowering, and antihypertensives) occurs in routine primary care practice. Furthermore, we aim to assess which patient characteristics predict medication reduction and examine the long-term safety and efficacy of cardioprotective medication reduction.

Methods
Aim 1: Develop and validate algorithmic approach to determine first routine cardioprotective medication reduction

Aim 2: Derive predictors of cardioprotective medication reduction from population characteristics using a matched case-control design (outcome is first cardioprotective medication reduction) with conditional logistic regression. Predictors will include patient characteristics, disease and treatment status, and lab parameters.

Aim 3: Determine the long-term safety and efficacy of cardioprotective medication reduction in an UK primary care population. A matched cohort study will be used where patients will be matched based on GP practice level. The exposure is the first incidence of cardioprotective medication reduction. The primary outcome will be all-cause hospitalisation, secondary outcomes will include major adverse cardiovascular events and drug-specific adverse events. A cox proportional hazards model will be used in order to examine the relationship between medication reduction and outcomes.

Outcomes to be measured

Primary outcome
All-cause emergency hospitalisation

Secondary outcome
All-cause mortality; Stroke; Myocardial infarction; Cognitive functioning; Acute kidney injury; Electrolyte abnormalities; Falls; Fractures; Hypotension; Syncope; Cardiovascular Mortality; Worsening Heart Failure; Haemorrhage; muscle disorders; liver dysfunction; gastrointestinal and intracerebral bleeding

Specific outcomes will be examined in relation to reduction of specific drug group; anticoagulants, antihypertensives, antihyperlipidemic, or antiplatelet

Objectives, specific aims & rationale

Objective
The overarching objective of this study is to better understand the safety and efficacy of cardioprotective treatment reduction in the older population by defining treatment withdrawal and reduction in observational data, quantifying predictors of cardioprotective therapy reduction, and examining health-related outcomes after reduction.

Specific Aims
Aim 1: Develop and validate algorithmic approach to determine cardio protective medication reduction
Aim 2: Derive predictors of cardio protective medication reduction from population characteristics
Aim 3: Determine safety and efficacy of cardio protective medication reduction in an UK primary care population

Rationale
The proposed work will develop an algorithmic approach to define cardioprotective medication reduction in large data sets to better understand the safety and efficacy of cardioprotective medication reduction. Information obtained in this study will support clinicians in their decision-making process when optimising pharmacotherapy in the elderly to reduce risk and maximise benefit.

Study background

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide(1), nearly 110 million Europeans are living with CVD of which nearly 7.5 million are from the UK(2, 3). People are increasingly living longer and developing multi-morbidity at old age (4, 5). As a natural consequence of applying modern treatment guidelines to treat and prevent CVD and other conditions, people are exposed to evermore long-term pharmacotherapeutic interventions (5-8). While this increase in pharmacological intervention unquestionably has led to an overall health benefit for patients across disease domains, the surge in interventions has created polypharmacy, defined here as taking 5 or more prescription drugs, and problems with inappropriate prescribing in vulnerable populations(9).The term polypharmacy inadvertently has been associated with negative health impacts, which is why several groups have sought to bring nuance by adopting two variations of polypharmacy; appropriate polypharmacy and problematic polypharmacy (5, 10).

Medication reduction

For those patients experiencing problematic polypharmacy and/or inappropriate prescribing there may be an increased risk of adverse events, including falls, hospitalisation and even mortality (11). Medication reduction either full prescription withdrawal or dose reduction of specific drug classes could contribute to changing problematic polypharmacy to appropriate polypharmacy. Cardiovascular medication reduction in older adults is of a particular interest as they are generally not included in large randomised controlled drug efficacy trials and often are multi-morbid and/or frail, which could decrease treatment efficacy and may increase an individual's risk of adverse events from treatment(12-14). Furthermore, cardiovascular drugs have been associated with inappropriate prescribing and their pharmacological action is closely related to negative outcomes seen in problematic polypharmacy-related outcomes, i.e. antihypertensive therapy causing hypotension resulting in syncope and/or falls, and could therefore be considered for reduction in elderly patients to potentially improve outcomes(11, 12).
However, preventative cardiovascular medication reduction might increase the risk of cardiovascular events, due to disruption of the normotensive state, increased plaque formation, increased blood coagulation, or increased platelet activity (15-18). Therefore, the potential benefits and harms of cardiovascular medication reduction need to be balanced against the benefits and harms of continuing therapy, as well as patient wishes.

National guidelines recognise the central role of optimisation of an individual's prescriptions by health care professionals with the aim to improve patient outcomes(10). However, evidence on safety and efficacy of reducing cardiovascular drugs in elderly primary care patients to support clinicians is currently lacking.

Study type

Hypothesis testing

Study design

Longitudinal cohort study

Feasibility counts

There are approximately 1 million patients in England, aged 65 and over, who have had at least one antihypertensive treatment prescription, and with up-to-standard registration during the study period, 01/01/1998 to present, in CPRD GOLD and restricted to HES and ONS linkage. In this population of 1 million patients, we expect 51,000 strokes to occur during patient follow-up.

Sample size considerations

Sample size based on the primary outcome of the study (emergency hospitalisation at 5 years). Assuming clinically significant decreased rate of emergency hospitalisation of 5%, and conservative event rate of 8% per year in the non-exposed group(19), approximately 87,203 patients (14,534 exposed vs 72,669 unexposed) and 28,847 events would be required to define the relationship between reduction and emergency hospitalisation, with 90% power and an alpha of 0.05. Secondary sample sized based on the least common outcome of the secondary outcomes listed above for antihypertensive treatment, stroke, and has been selected to ensure the sample size will be sufficient for all other outcomes. A clinically relevant decrease rate of ischaemic stroke of 5% and an event rate of 0.105% per year in the non-exposed group(20), approximately 71,078 patients (11,799 exposed vs 59,279 unexposed) and 28,847 events would be required to define the relationship between reduction and intracerebral bleeding, with 90% power and an alpha of 0.05.

Planned use of linked data and benefit to patients in England and Wales

We are planning to use linked data from ONS and HES (admitted patient care). The linked data acquired will allow us to define the primary outcome (all-cause hospitalisation) and secondary outcomes (see section D for all outcomes).

- The ONS mortality register will be used to define any outcomes which result in death, and censor follow-up at death. Specific linkages required will include data and ICD-10 coded cause of death
- Linkages to Basic Inpatient HES will be combined with data from the ONS to define all other outcomes in the study. HES data will also be used to define the study population (e.g. ethnicity where unavailable in Primary Care records). Data required from Basic Inpatient HES will include primary diagnosis, secondary diagnosis, patient characteristics (e.g. sex, ethnicity), date of admission and date of discharge. All deaths and hospital admissions occurring after a patient's index date will be included.
- A linkage to the Index of Multiple Deprivation is required to acquire patient level quintiles of multiple deprivation, to better define the study population and IMD will be used as a covariate in determining predictors, safety, and efficacy outcomes.

Policies are focusing evermore on optimising therapies through medication reviews in older individuals, especially in those whom receive multiple prescriptions to treat multiple morbidities. Currently there is very little evidence available to inform these reviews, particularly with respect to medication reduction. Using linked data, we can look at outcomes of cardioprotective medication reduction, such as the effect on hospitalisation and death. This information can be used to inform NICE guidelines subsequent policies. Due to linkage this study will only be to study patients registered to practices in England.

Definition of the study population

Definition of the study population
Individual patient data will be extracted from the medical records of all patients registered to an up-to-standard practice contributing to the CPRD GOLD.

Patients will be included for analysis if they meet the following criteria:
- Registered to a CPRD 'up-to-standard' practice
- Patients of 65 years and over
- Records are available after study start date (01/01/1998)
- Received anticoagulant, antiplatelet, antihyperlipidemic, or antihypertensive treatment for at least 3 months

Study entry criteria:
- Aim 1: Patients enter the cohort when they are at least 65 years old and have an active anticoagulant, antiplatelet, antihyperlipidemic, or antihypertensive prescription
- Aim 2 and 3: Patients will enter the exposure cohort at the point at which a cardioprotective treatment has been reduced, the index date is the start date of the period when the medication reduction has been established

Patients will exit the study if one of the following criteria has been met (whichever occurs first):
- Last date at which the most recent linked data are available from CPRD GOLD
- Date at which a given patient transfers out of a registered CPRD GOLD practice.
- Date of death
- Date at which the outcome of interest occurred

The patient age criteria has been set to include patients of 65 years and over. We expect that patients will benefit more from cardioprotective medication reduction as they get older, due to an increasing risk of adverse drug events brought about increasing frailty and multi-morbidity (12). Thus, the present analysis will focus on older adults (aged 65+ years), with sensitivity analyses comparing the effects of medication reduction in patients aged 65-74 years with those aged 75+ years.

Selection of comparison groups/controls

Aim 1: The algorithm will be developed and used in a single cohort in CPRD GOLD.
Aim 2: Case-control study – controls (1:5 cases:controls) will be randomly matched from the same practice – see Methods
Aim 3: Matched cohort analysis – controls (1:5 cases:controls) will be randomly matched from the same practice – see Methods

Exposures, outcomes and covariates

This study will examine the safety and efficacy from cardioprotective pharmacotherapy reduction. Cardioprotective pharmacotherapy aims to reduce/prevent the negative impact of modifiable risk factors, therefor safety is here defined as the complications that may arise due to exposure to these modifiable risk factors (e.g. high blood pressure), listed in the table below.
Efficacy of cardioprotective pharmacotherapy reduction is defined as a reduction in complications that may arise from the pharmacotherapeutic intervention itself, listed in table below.

Exposure (Antihypertensive therapy reduction):
ACE inhibitors
Alpha blockers
Angiotensin II receptor antagonists
Beta blockers
Calcium channel blockers
Centrally acting antihypertensives
Mixed adrenergic blockers
Potassium-sparing diuretics
Renin inhibitors

Thiazides and thiazide-like diuretics

Exposure (anticoagulant reduction)
Vitamin K antagonists
Direct acting Factor Xa inhibitors
Direct acting thrombin inhibitor

Exposure (antiplatelets reduction)
Aspirin (up to 300 mg)
Clopidogrel
Ticagrelor
Prasugrel

Exposure (antihyperlipidemics reduction)
Statins
Ezetimibe

Primary safety outcome (for all classes)
All-cause emergency hospitalisation

Secondary safety outcomes (antihypertensive therapy reduction)
All-cause mortality
Cardiovascular mortality
Stroke
Myocardial infarction
Heart failure
Chronic kidney disease
Worsening heart failure

Secondary safety outcomes (anticoagulant reduction)
All-cause mortality
Cardiovascular mortality
Stroke
Myocardial infarction

Secondary safety outcomes (antiplatelet reduction)
All-cause mortality
Cardiovascular mortality
Stroke
Myocardial infarction

Secondary safety outcomes (antihyperlipidemic reduction)
All-cause mortality
Cardiovascular mortality
Stroke
Myocardial infarction

Secondary efficacy outcomes (antihypertensive therapy reduction)
Cognitive functioning
Acute kidney injury
Electrolyte abnormalities
Hypotension
Syncope
Falls
Fracture

Secondary efficacy outcomes (anticoagulant reduction)

Haemorrhage

Secondary efficacy outcomes (antiplatelet reduction)
Haemorrhage
Dyspnoea

Secondary efficacy outcomes (antihyperlipidemic reduction)
Cognitive functioning
Diabetes Mellitus
Cataract
Liver dysfunction
Muscle disorder

Covariates (for all classes)
Age
Sex
Ethnicity
Frailty
CHA2DS2-VASc
Number of other prescription drugs
AHT dose
Cardiovascular drugs
Co-morbidity
Rheumatoid Arthritis
Diabetes Mellitus type II
Previous CVD event
Previous adverse drug reaction
CKD
End-of-life
Social deprivation
CVD risk score
Duration of therapy
Time since CVD event

Blood pressure
LDL and total cholesterol
BMI

All outcomes will be defined according to diagnostic and/or symptom codes, unless otherwise stated.

Data/statistical analysis

Aim 1: Defining medication reduction

Medication reduction of antihypertensive, anticoagulant, antiplatelet, or antihyperlipidemic is the exposure of interest. To define the exposure in CPRD, an average antihypertensive drug load will be measured on a monthly timescale.
The first exposure definition is a whole prescription reduction, as measured by the total prescriptions a patient receives of a specific class. If the medication is reduced the total numerical value will be lower, if this value remains stable for 3 months the patients is considered to have their prescription withdrawn. To account for additional prescription orders, the time-on-therapy will be extended.
For the second exposure definition, all antihypertensive treatment will be converted to a defined daily doses (DDD). The DDD is a unit of measure based on assumed average maintenance dose per day for a drug for its main indication and is commonly used for drug consumption measurement(22). For example, a patient is treated with once daily 12.5 mg hydrochlorothiazide (0.5 DDD) and once daily 5 mg amlodipine (1 DDD) this would mean that this patient is receiving 1.5 DDD of antihypertensive treatment daily.
It has been used previously in the study of antihypertensive therapy intensification and shown that there was good correlation between increasing DDD values and increase in mean number of classes used (23, 24). By converting to DDD, we can calculate an average DDD for each month and take into account drug class switches.
If the average monthly DDD decreases and is maintained for 3 months these patients will be considered having their medication reduced and thus be considered in the exposed group for subsequent analyses (25, 26). The day of medication reduction will be set as the first day of the 3-month window and will be used as the index date for further analysis.
Patients who did not experience changes in DDD or a whole prescription reduction during the research period will be assessed if they experienced class switches. Patients who had their therapy changed, for example an ACE inhibitor to an equivalent ARB, will be analysed as a subgroup.

Summary statistics will be determined for the initial population, exposed population and control population. Medication reduction rate will be reported as number of reductions per patient years and be determined for the whole population and in subgroups. Continuous baseline characteristics will be presented as mean±SD or median + IQR depending on data distribution, categorical values as frequencies and proportions.
Sensitivity analyses will be performed to assess the effects of using different cut-off thresholds values of DDD change that is accepted or using no threshold to detect cardioprotective therapy reduction.

Aim 2: Predictors of antihypertensive medication reduction

A matched case-control analysis will be conducted. Patients with a first recorded cardioprotective medication reduction will be selected as cases. The index date of the cases will be defined as the first day that medication reduction was confirmed, see aim 1 for details. Controls will be patients that did not have medication reduction and up to five controls, that were active within the same year as the case from the same practice, will be randomly matched. The index date for the controls will be set the same as their matched cases. Age and gender are not selected as matching variables, because they will be studied separately as covariates. A separate analysis will be run for each of the different methods to define medication reduction described under aim 1.
A range of different a priori covariates will be tested as predictors for cardio protective therapy reduction, the main time point considered is 12-months before the index date with additional

analysis done for 1- and 3-month intervals, based on the literature (24). The predictors need to be determined because they can both be associated with cardioprotective medication reduction and the outcomes explored under aim 3 and would need to be adjusted for. For example, a higher frailty might lead a physician to reduce medication but is also associated with an increased risk of hospitalisation.
Variables that are going to be explored included the following. Demographic variables: Age, gender, ethnicity, frailty (index-score), BMI, blood pressure (systolic and diastolic), LDL and total cholesterol, CVD risk, and social deprivation. Clinical therapeutic variables are: Cardiovascular drugs (antiplatelet, anticoagulants, antihyperlipidemic, and nitrates), number of cardioprotective medications, DDD cardioprotective therapy, time on therapy, cardioprotective therapy intensification, and polypharmacy. Clinical history variables: Previous CVD event/history (STEMI, NSTEMI, Stroke/TIA, AF, ACS, HF, and Stenting (elective)), co-morbidities (e.g. Rheumatoid Arthritis, Diabetes Mellitus type II, Cancer, CKD, COPD, dementia, etc.), End-of-life, time since CVD event, hospital admission elective, hospital admission emergency, falls, haemorrhage, fractures, and electrolyte abnormalities.
When looking at cardiovascular outcomes under aim 3 we will be adjusting for variables including, but not limited to, like standard cardiovascular risk factors like age, gender, and previous cardiovascular events and total drug load (total number of cardio protective medications). When looking at adverse drug reaction we will include, but not limited to, variables like previously adverse drug reaction like (falls, haemorrhage, etc) and total drug load (number of prescriptions of specific drug group or dosage).

Analysis will be conducted using conditional logistic regression and results will be reported as odds ratios with 95% confidence intervals. Variable selection methods will be used in order to identify which variables are the most important and these variables will be carried forward to aim 3. Odds ratios for the different time intervals will be plotted to detect any trends.

Aim 3: Benefits and harms of antihypertensive medication reduction

A retrospective cohort study will be conducted using the matched case-control cohort previously described under aim 2. Patients will be matched in a 1:5 ratio cases versus controls, controls will be selected from the same practice and had to be active within the same year. All outcomes will be assessed using cox proportional hazard models for time-to-event analysis, adjusted for all covariates including variables carried forward from aim 2, and stratified by practice. Results will be expressed as hazard ratios with 95% confidence intervals and presented for 5 years follow-up (with additional analyses for 1- and 10-year follow-up).
Poisson regression or negative binomial regression will be used according to overdispersion to model number of hospitalisations, results will be reported as incidence rate ratios (IRR) with 95% confidence intervals. Similarly to aim 2, the analysis will be done using both definitions of the exposure of medication reduction.

Subgroup and sensitivity analyses
Where possible and appropriate, analyses of treatment associations will be examined in subgroups of the population. These will include age, sex, frailty score, baseline blood pressure, baseline CHA2DS2-VASc score, baseline lipids, reduction per drug class, time periods, and patients who had class switching (see section Methods, aim 2). Subgroup definitions will be agreed by expert opinion or taken from an accompanying systematic review of previous trials, examining the same topic.

Sensitivity analyses will be performed by restricting the main analysis to patients having at least 12 months of follow-up after exposure to account for potential reverse causality.

Plan for addressing confounding

Confounding will be addressed by adjustment of covariates established in aim 2. These covariates have been selected a priori and based on previous work in the field (24). For an extended list of selected covariates see the list under section Exposures, outcomes and covariates.

Plans for addressing missing data

There is potential for missing data in this study, particularly with variables such as patient characteristics which are recorded with varying degrees of accuracy in routine practice. Where there is no record of antihypertensive, anticoagulant, antihyperlipidemic, or antiplatelet treatment, it will be assumed the patients were not exposed treatment and excluded from the population.

Where there is no record of smoking history, BMI, and alcohol consumption, values will be imputed. Likewise, those with no record of co-morbidities will be assumed to have no history of these conditions. All other covariates used in the medication prediction or outcome modelling will be imputed using multiple imputation if the missing at random (MAR) assumption seems reasonable.

Patient or user group involvement

At the time of submission this application has not been discussed with patients.
Discussions are planned to take place in September 2021 with patients aged 65 and over that take one or more of the cardio protective drugs (anticoagulant, antiplatelet, antihypertensive, or antihyperlipidemic).

Input will be sought on patients' reasons for medication discontinuation and willingness to have their medication reduced.

Plans for disseminating & communicating

All findings from the proposed research project will be published in peer-reviewed scientific journals. Findings will be presented at national and international conferences in Primary Care (e.g. Society for Academic Primary Care [SAPC], North American Primary Care Research Group), Hypertension (British and Irish Hypertension Society [BIHS], European Society for Hypertension), cardiovascular disease (European Society of Cardiology), and pharmacoepidemiology (International Society for Pharmacoepidemiology).

Social media (Twitter) will be used to draw further attention to the work.

Conflict of interest statement

The authors declare no conflicts of interest

Limitations of study design

The main limitation of the presented study will be the identification of medication reduction. Especially for hypertensive treatment reduction where there is a high variance of treatment combination and alternative methods need to be employed to compare changes (see section O, aim1). Previous research has established a 90 day or 3-month window to be used to consider medication reduction(24, 26), however in one short term RCT antihypertensive medication reduction was only maintained for 66.3% of the patients in the intervention group at 12-weeks (27). This will influence generalisability as we will be selecting patients which are more likely to maintain therapy reduction.

Converting the relevant cardiovascular therapies to DDD will facilitate the comparison of different regiments, however information is lost if therapy is managed in such a way that the DDD or number of prescriptions remains stable. Therefore we will analyse patients remaining on stable therapy to ascertain if equivalent switches have been, these patients will be used for sensitivity and subgroup analysis.

Aims 2 and 3 will use case-control and observational cohort designs respectively and are therefore inherently subjected to bias. The risk of selection bias in the observational cohort study will be limited by adjusting for a wide range of potential confounders, however there might be a risk of residual confounding.

This study focuses on potential harms and benefits from reducing cardioprotective. There is a high likelihood that some secondary outcomes may be less well recorded than others in routine electronic health records.

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Appendices

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Grant ID

A.4 List of included antihypertensives

Angiotensin Converting Enzyme Inhibitors:

- Captopril
- Enalapril
- Fosinopril
- Imidapril
- Lisinopril
- Moexipril
- Perindopril
- Quinapril
- Ramipril
- Trandolapril

Alpha blockers:

- Doxazosin
- Indoramin
- Phentolamine
- Prazosin

Angiotensin-II Receptor Blockers:

- Azilsartan
- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Valsartan
- Telmisartan

Beta blockers:

- Acebutolol
- Atenolol
- Bisoprolol
- Carteolol
- Carvedilol
- Celiprolol

- Esmolol
- Labetalol
- Metoprolol
- Nadolol
- Nebivolol
- Oxprenolol
- Pindolol
- Practolol
- Propranolol
- Sotalol
- Timolol

Calcium Channel Blockers:

- Amlodipine
- Diltiazem
- Felodipine
- Isradipine
- Lacidipine
- Lercanidipine
- Lidoflazine
- Mibefradil
- Nicardipine
- Nifedipine
- Nimodipine
- Nisoldipine
- Prenylamine
- Verapamil

Centrally acting agents:

- Clonidine
- Methyldopa
- Methyldopate
- Moxonidine
- Reserpine

Renin inhibitors:

- Aliskiren

Thiazide an thiazide like diuretics:

- Bendroflumethiazide
- Chlortalidone
- Clopamide
- Cyclopenthiazide
- Hydrochlorothiazide
- Indapamide
- Metolazone
- Xipamide

Vaso-active drugs:

- Ambrisentan
- Bosentan
- Diazoxide
- Hydralazine
- Iloprost
- Macitentan
- Minoxidil
- Nitroprusside
- Perhexiline
- Riociguat

A.5 List of included cardiovascular medications

Anticoagulant:

- Acenocoumarol
- Apixiban
- Dabigatran
- Edoxaban
- Rivoroxaban
- Warfarin

Antiplatelets:

- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor

Statins:

- Atorvastatin
- Fluvastatin
- Pravastatin
- Rosuvastatin
- Simvastatin

A.6 Detailed derivation of algorithm equations and rule set

The description of algorithm requirements, rule set, and equation stated in Sections 3.4.4.2 and 3.4.4.3 are explained in more detail below. A step-by-step explanation of non-automated and automated application of the equations and for-loop is included. First, the algorithm needs to be able to deal with large observation periods, as patients are at risk of changing treatment from cohort entry to cohort exit, which - in this case - can be anywhere between one and twenty years. To facilitate the use of an algorithm that is able to interpret data over time, the code has to be able to determine the number of active prescriptions at a specific point in time. This can be written as $y(t)$, where the active number of prescriptions (y) is dependant on a specific time (t). Because the date of cohort entry varies per patient, we also want time (t) to be a function of this date (*cohort entry*) and an independent variable (i) that can be any time variable (days, weeks, months, etc.). This allows for the algorithm the establish the number of prescriptions at certain time point from cohort entry onward ($y(t = \textit{cohort entry} + i)$, fulfilling the first algorithm requirement.

Second, the algorithm needs to be able to establish periods of stability. In the case of prescriptions, this means that the total number of prescriptions remains the same from one time point to another time point. This can be written as $y(t) = y(t + i)$, where i is a flexible predetermined time interval. However, this equation is unable to deal with possible fluctuations in prescriptions. In order to deal with fluctuations over time, multiple time points can be compared and an error term can be introduced.

The final two requirements, changes in intensity and variation of numeric values, are fulfilled simultaneously. Whilst the algorithm was developed to answer the stated questions on the discontinuation of antihypertensive treatment, the algorithm was design with a more universal applicability in mind. Depending on the specific therapeutic indication of interest, patients might be treated with a single agent (e.g. hypercholesterolemia with statins) or multiple agents (e.g. hypertension with antihypertensives or hyperglycaemia with hypoglycaemic agents). Therefore, patients could stop a single agent (e.g. statin treatment, on treatment maximum value (1) and off treatment value (0)), a single agent out of many prescriptions (e.g. stop thiazide (-1), whilst on thiazide and ACEi (2)), or multiple agents out of many prescriptions (e.g. stop thiazide and ACEi (-2), whilst on thiazide and ACEi). Furthermore, in the case where multiple agents can be used, changes in therapeutic load might occur naturally over time as a consequence of disease progression and the change of interest should not be compared to the amount of prescriptions at cohort entry. Because the equation previously described can natively be utilised to determine any number of prescriptions between cohort entry and cohort exit, by using cohort entry and a flexible time increase (i), it can assume all positive values and zero. Furthermore, it does not store or assume the cohort entry prescription load, it only uses the cohort entry as time identifier. To identify changes in therapeutic load - either increases or decreases - we can simply compare the number of prescriptions at two (sequential) time points (for example $y(t) > y(t + 1)$ for decreases and $y(t) < y(t + 1)$ for increases in total prescriptions).

The three rules of the algorithm rule set as stated in Section 3.4.4.2 are:

- Rule 1: A three-month window of pre-intervention therapeutic stability (defined in equations A.1)
- Rule 2: A three-month window of post intervention therapeutic stability (defined in equations A.2)

Table A.1: Example prescription data for two fictitious patients

Patient	Cohort entry (CE), date	Number of prescriptions, time											
		CE	CE + 1 month	CE + 2 months	CE + 3 months	CE + 4 months	CE + 5 months	CE + 6 months	CE + 7 months	CE + 8 months	CE + 9 months	CE + 10 months	CE + 11 months
A	01-01-2010	1	1	1	2	2	2	2	2	1	1	1	1
B	01-01-2015	1	1	1	2	2	2	2	2	1	2	2	2

- Rule 3: Any decrease in antihypertensive prescriptions between the pre-intervention window (Rule 1) and post-intervention window (Rule 2) (see equation A.3)

These rules can be transformed into their individual mathematical equations.

$$y(t = ce + i) = y(t = ce + i + 1) = y(t = ce + i + 2) \tag{A.1}$$

$$y(t = ce + i + 3) = y(t = ce + i + 4) = y(t = ce + i + 5) \tag{A.2}$$

$$y(t = ce + i + 2) > y(t = ce + i + 3) \tag{A.3}$$

A.6.0.1 Non-automated interpretation of prescription data

Using two example patients (table A.1) we can demonstrate how the algorithm will work. By observing the data we can see that patient A entered the cohort on the 1stof January 2010 and patient B entered the cohort on the 1stof January 2015, these dates are purely illustrative. For the convenience of this example, both patients have a similar observation period (twelve months). Patient A enters the cohort and has a single prescription for three consecutive months (cohort entry, 1; cohort entry + 1 month, 1; cohort entry + 2 months, 1), the following five months (cohort entry + 3 months up until cohort entry + 7 months) the number of prescriptions is two, before returning to a single prescription for the remainder of the observation time. Based on observation and previously outlined requirement to define medication reduction, patient A has their therapy reduced from two to one prescription between the time points cohort entry + 7 and cohort entry + 8. Even though patient A started with a single prescription and returns to a single prescription (over this limited observation period), the sustained increased therapy in the interim means that the new baseline is two prescriptions.
For patient B we can see a similar pattern, where initially the therapeutic load is a single prescription for three months, two prescriptions for the remainder of the observation period, with a single prescription at cohort entry + 8 months. The assumption is made that this unsustained change is not medication reduction (or intensification for the inverse), as this falls within the variation that was described in requirement 2.

A.6.0.2 Automated detection of medication reduction

The previous rules and equations can be used to code for a for-loop, which is a loop is used for iterating over a sequence, that will start for each patient at time of cohort entry ($t = ce$) as i will initiate at 0. If the conditions are not satisfied, i will increase by one, until either the conditions are met or the latest time point ($t = ce + i + 5$) exceeds the cohort exit date. The full R language code algorithm is available in appendix A.7 and an algorithm flow chart is included in Figure A.1. Using patients A and B from the previous example (see Table A.1), we can demonstrate how the algorithm works.

Before initialisation of the loop, the prescriptions history of the patient is loaded and the cohort entry date is stored as a static variable *ce*. After this, the conditional loop will start, where for the first cycle i is 0 and i will increase by 1 after the completion of each cycle until the latest time point required by the algorithm exceeds the cohort exit time. Using patient A and figure A.2, we can look at the first cycle (cycle(1)) and the first equation $y(t = ce + i) = y(t = ce + i + 1) = y(t = ce + i + 2)$, where $i = 0$ this can be simplified to $y(t = ce) = y(t = ce + 1) = y(t = ce + 2)$ which results in $1 = 1 = 1$. This result, $1 = 1 = 1$, can be interpreted as a Boolean statement (e.g. TRUE or FALSE), because $1 = 1$ the first condition is met (or TRUE) the algorithm will progress to verify if the other conditions are met. Next we look at the second rule $y(t = ce + 0 + 3) = y(t = ce + 0 + 4) = y(t = ce + 0 + 5)$ which is $2 = 2 = 2$, once again the condition is met. Because both initial conditions are met, the algorithm will determine if the conditions for rule three are met. Rule three, $y(t = ce + i + 2) > y(t = ce + i + 3)$ or $y(t = ce + 2) > y(t = ce + i + 3)$, will read as $1 > 2$, as one is not greater than two, this condition will not be met (or is FALSE). In short, because not all conditions are met the loop will initiate the next cycle, where i is increased by 1 ($i = 1$).

For the second cycle of the loop, due to $i = 1$, rule one will read as $y(t = ce + 1) = y(t = ce + 1 + 1) = y(t = ce + 1 + 2)$, which translates to $1 = 1 = 2$. Because $1 = 2$ is not true (or FALSE), the first condition is not met. As a result of the first condition not being met, the overall requirement of all three conditions being met is no longer possible (in the pursue of detecting medication reduction). In effect it would be ineffective to continue to verify if conditions two and three are met, so to increase speed and efficiency the current cycle will be terminated and the next cycle will start ($i = 1 + 1$).

As all elements of unsuccessful completion of the conditional loop have been discussed, results of cycle three ($i = 2$) to five ($i = 4$) will be summarised. Cycle three, $y(t = ce + 2) = y(t = ce + 2 + 1) = y(t = ce + 2 + 2)$ or $1 = 2 = 2$, next cycle ($i + 1$) due to condition one not being met. Cycle four, first condition $y(t = ce + 3) = y(t = ce + 3 + 1) = y(t = ce + 3 + 2)$ equates to $2 = 2 = 2$, therefore condition two is checked $y(t = ce + 3 + 3) = y(t = ce + 3 + 4) = y(t = ce + 3 + 5)$ or $2 = 2 = 1$, which is false and the next cycle is initiated ($i + 1$). Cycle five, condition one ($y(t = ce + 4) = y(t = ce + 4 + 1) = y(t = ce + 4 + 2)$ or $2 = 2 = 2$) is met, condition two ($y(t = ce + 4 + 3) = y(t = ce + 4 + 4) = y(t = ce + 4 + 5)$ or $2 = 1 = 1$) is unmet, start of the next cycle ($i + 1$).

For cycle six ($i = 5$), we can see that the first and second conditions are met, respectively $2 = 2 = 2$ and $1 = 1 = 1$. Once more, the algorithm will try and verify if the third and final condition is met. The third condition will read as: $y(t = ce + 5 + 2) > y(t = ce + 5 + 3)$, in the sixth cycle, which corresponds with $2 > 1$ meaning that this statement is TRUE. Now that all conditions are met, the loop will be terminated, as the presence of medication reduction has been established. However, before termination the following data or stored for further use: patient identifier and the stop date ($t = ce + i + 3$, in this example $t = ce + 8$). The stop

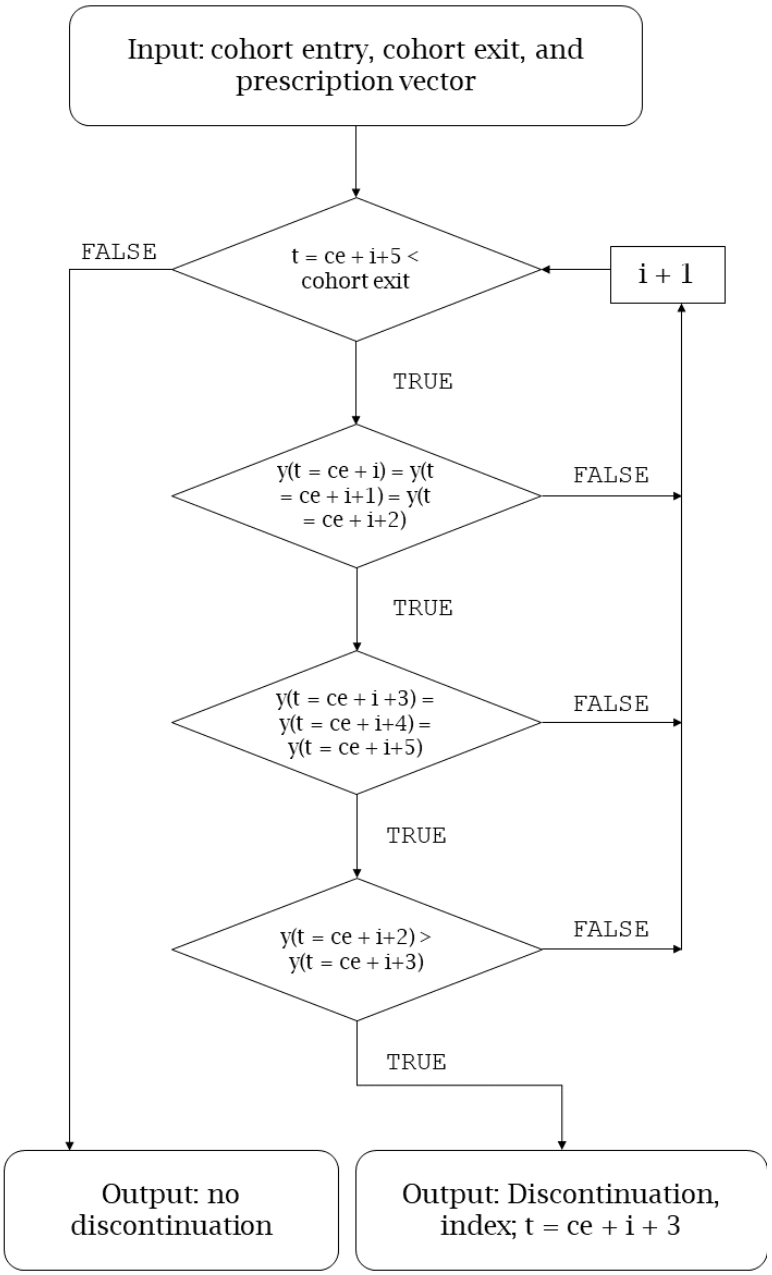

Figure A.1: Formal loop schematic. ce; cohort entry, i; loop variable

date will be used in further work as the index date for establishment of baseline characteristics, date of outcome (case-control study), and date of start exposure (cohort study).

To conclude the examples, we can demonstrate how the algorithm analysis the data of patient B, a patient that does not discontinue treatment. In this example, the final condition for loop termination becomes more apparent, where the latest time point of the third condition can not exceed the latest time point of the observed time (also described as cohort exit). Cycles one to four of patient B are identical to

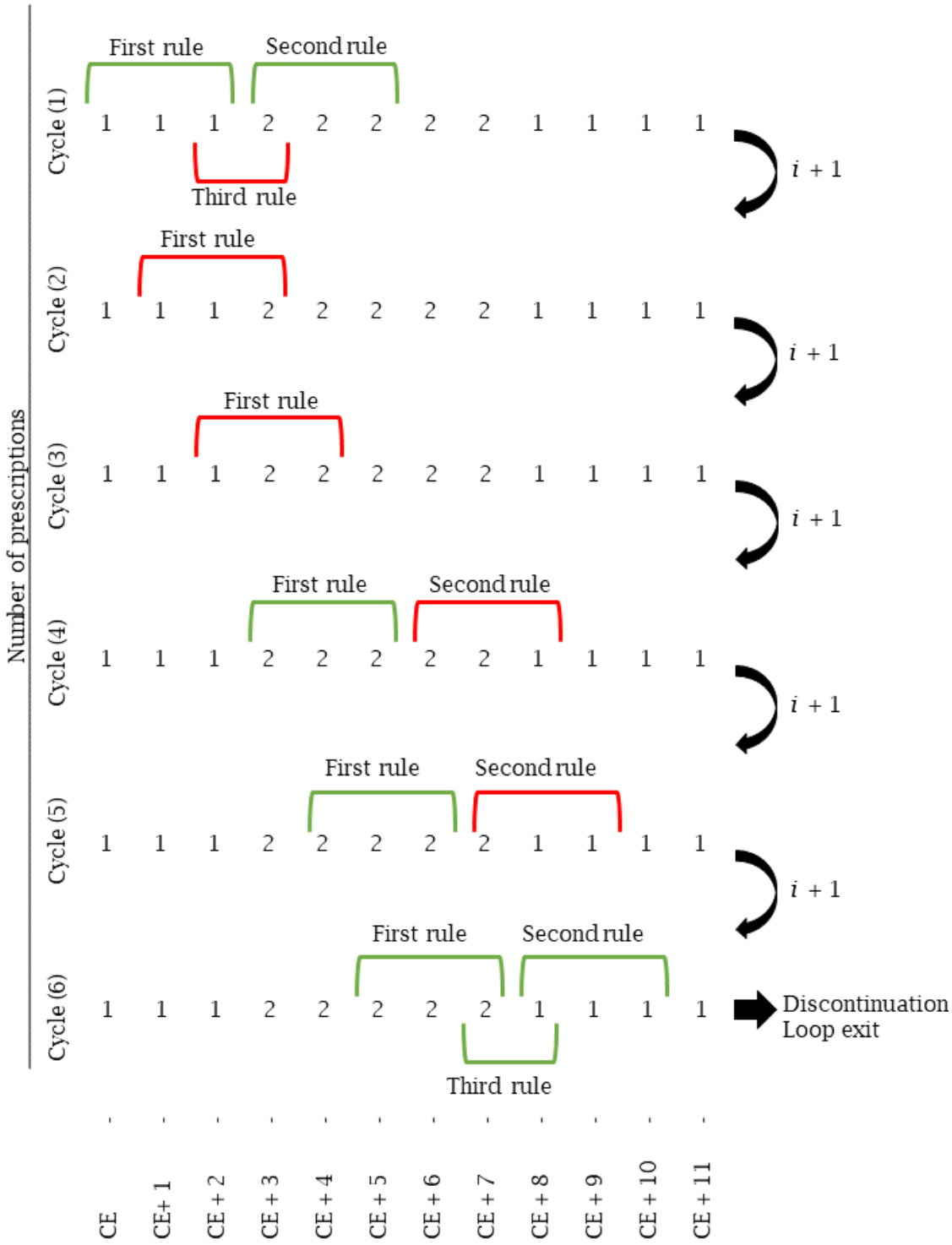

Figure A.2: Pattern verification in sample data. Green signifies that the rule or condition has been met, red signifies that the rule of condition has not been met. First rule and second rule are the same number of prescriptions for three consecutive months. Third rule is therapy is between to months is different with the first month being higher than the second month. CE, Cohort Entry; i, loop variable.

cycle one to four of patients A. Namely cycle 1, both first and second conditions are met ($1 = 1 = 1$ and $2 = 2 = 2$) and the third condition is not met ($1 > 2$); cycle 2, condition one is not met ($1 = 1 = 2$); cycle 3, condition one is not met ($1 = 2 = 2$); cycle 4, condition one is met ($2 = 2 = 2$), but two is unmet ($2 = 2 = 1$). Cycle five ($i = 4$) is where the first condition is met ($2 = 2 = 2$), but the second condition remains unmet ($2 = 1 = 2$), forcing the next cycle ($i = 5$). Cycle six, condition remains one remains met ($2 = 2 = 2$) and condition two unmet ($1 = 2 = 2$), once again forcing a next cycle ($i = 6$). For this cycle we can first check if the last time point the algorithm needs access to is available, as $y(t = ce + i + 5)$ is the highest requested value in this case $y(t = ce + 6 + 5)$, as observed in table A.1 this corresponds with the last available data point (cohort entry + 11). Therefore, this will be the last cycle of the loop. Before termination, the conditions will still need to be checked. The first conditions ($y(t = ce+6) = y(t = ce+6+1) = y(t = ce+6+2)$) is determined to be unmet ($2 = 2 = 1$), forcing a next cycle ($i = 7$). While previously demonstrated that cycle seven was the final cycle that the algorithm could function, cycle eight is initiated, but instantly terminates the loop due to the latest required time ($y(t = ce + i + 5)$ or $y(t = ce + 7 + 5)$) exceeding the latest available date (cohort entry + 11). Termination due to completing all possible cycles within the loop means that at no point in-time all three conditions were met; thus, the patient is considered a non-stopper. At termination of the loop, no stop date will be recorded.

The examples described previously all rely on the simplest form of the algorithm, a six-month period characterised by a period of two sets of three month windows where in the first set the number of prescriptions is higher compared to the second set. Due to presence of fluctuations in the prescription data, an error term was introduced. In doing so the time period now stretches over seven months, where all the previous rules still apply. However the equations underpinning the algorithm change, equation A.1 is unchanged, equation A.2 is increased by one ($y(t = ce+i+4) = y(t = ce+i+5) = y(t = ce+i+6)$), and equation A.3 now compares the latest time-point of rule 1 ($y(t = ce + 2)$) with the new earliest time-point of the adapted rule 2 equation ($y(t = ce+i+4)$) ($y(t = ce+i+2) > y(t = ce+i+4)$).

A.7 R-code for discontinuation detection

```
## Initialisation of the loop, list.patients holds the df with eligible
## patients

for (k in list.patients) {

  ## loads the total prescription data for patient
  patid.value <- k
  analysis.set <- filter(exposure, exposure$patid == patid.value)

  ## for the motifs to be able to run at least 7 months of
  ## prescription data needs to be available, set to 11
  ## during development for longer motifs (12 months)
  if (length(analysis.set$total.drug) <= 11) next

  ## i iterates over rows 1 until n ((length(analysis.set$total.drug)-6)
  ## reduced by 6 as these are added by the motif
  ## because this for-loop, loops, i increases after each try
  ## which allows for it to continue to process
  ## prescription data until there is no more data
  ## to process
  for (i in 1:(length(analysis.set$total.drug)-6)) {
  ## checks for rule 1 (3 months of stability)
    if (analysis.set$total.drug[i] == analysis.set$total.drug[i+1] &&
        analysis.set$total.drug[i+1] == analysis.set$total.drug[i+2])
{
      ## checks for follow up stability
      if (analysis.set$total.drug[i+3] == analysis.set$total.drug[i+4] &&
          analysis.set$total.drug[i+4] == analysis.set$total.drug[i+5]) {
          ## compares first 3 months with next 3 months to check if
          ## treatment is decreased
        if (analysis.set$total.drug[i+2] > analysis.set$total.drug[i+3]) {
          deprescribers <- rbind(deprescribers, analysis.set[i+2])
          deprescribers <- rbind(deprescribers, analysis.set[i+3])
          df.deprescribers <- rbind(df.deprescribers, analysis.set[i+3])
        }
      }
    }
    ## repeat however month the in between month is lower
    ## than both months, but final 3 month is still lower
    ## than initial
    if (analysis.set$total.drug[i] == analysis.set$total.drug[i+1] &&
        analysis.set$total.drug[i+1] == analysis.set$total.drug[i+2]) {
      if (analysis.set$total.drug[i+4] == analysis.set$total.drug[i+5] &&
          analysis.set$total.drug[i+5] == analysis.set$total.drug[i+6]) {
        if (analysis.set$total.drug[i+2] > analysis.set$total.drug[i+4] &&
            analysis.set$total.drug[i+4] > analysis.set$total.drug[i+3]) {
          deprescribers <- rbind(deprescribers, analysis.set[i+2])
          deprescribers <- rbind(deprescribers, analysis.set[i+4])
          df.deprescribers <- rbind(df.deprescribers, analysis.set[i+4])
        }
      }
    }
    ## repeat however month the in between month is greater
```

```
    ## than both months, but final 3 month is still lower
    ## than initial
    if (analysis.set$total.drug[i] == analysis.set$total.drug[i+1] &&
        analysis.set$total.drug[i+1] == analysis.set$total.drug[i+2]) {
      if (analysis.set$total.drug[i+4] == analysis.set$total.drug[i+5] &&
          analysis.set$total.drug[i+5] == analysis.set$total.drug[i+6]) {
        if (analysis.set$total.drug[i+2] > analysis.set$total.drug[i+4] &&
            analysis.set$total.drug[i+3] > analysis.set$total.drug[i+2]) {
          deprescribers <- rbind(deprescribers, analysis.set[i+2])
          deprescribers <- rbind(deprescribers, analysis.set[i+4])
          df.deprescribers <- rbind(df.deprescribers, analysis.set[i+4])
        }
      }
    }
    ## repeat however month the in between month is greater
    ## than final 3 months, but lower than first 3 months
    if (analysis.set$total.drug[i] == analysis.set$total.drug[i+1] &&
        analysis.set$total.drug[i+1] == analysis.set$total.drug[i+2]) {
      if (analysis.set$total.drug[i+4] == analysis.set$total.drug[i+5] &&
          analysis.set$total.drug[i+5] == analysis.set$total.drug[i+6]) {
        if (analysis.set$total.drug[i+2] > analysis.set$total.drug[i+3] &&
            analysis.set$total.drug[i+3] > analysis.set$total.drug[i+4]) {
          deprescribers <- rbind(deprescribers, analysis.set[i+2])
          deprescribers <- rbind(deprescribers, analysis.set[i+4])
          df.deprescribers <- rbind(df.deprescribers, analysis.set[i+4])
        }
      }
    }
  }
}
```

A.8 ICD-10 for outcomes

Table A.2: Variables and corresponding ICD-10 codes used to determine outcomes in Chapter 5

Outcome	**ICD-10**
Acute Kidney Injury	S37.0, N19, N17, N17.0, N17.1, N17.2, N17.8, N17.9
Fall	W01, W05, W06, W07, W08, W10, W18, W19, R29.6
Fracture	S02, S02.0, S02.00, S02.01, S02.1, S02.10, S02.11, S02.2, S02.20, S02.21, S02.3, S02.30, S02.31, S02.4, S02.40, S02.41, S02.5, S02.50, S02.51, S02.6, S02.60, S02.61, S02.7, S02.70, S02.71, S02.8, S02.80, S02.81, S02.9, S02.90, S02.91, S12, S12.0, S12.00, S12.01, S12.1, S12.10, S12.11, S12.2, S12.20, S12.21, S12.7, S12.70, S12.71, S12.8, S12.80, S12.81, S12.9, S12.90, S12.91, S22, S22.0, S22.00, S22.01, S22.1, S22.10, S22.11, S22.2, S22.20, S22.21, S22.3, S22.30, S22.31, S22.4, S22.40, S22.41, S22.5, S22.50, S22.51, S22.8, S22.80, S22.81, S22.9, S22.90, S22.91, S32, S32.0, S32.00, S32.01, S32.1, S32.10, S32.11, S32.2, S32.20, S32.21, S32.3, S32.30, S32.31, S32.4, S32.40, S32.41, S32.5, S32.50, S32.51, S32.7, S32.70, S32.71, S32.8, S32.80, S32.81, S42, S42.0, S42.00, S42.01, S42.1, S42.10, S42.11, S42.2, S42.20, S42.21, S42.3, S42.30, S42.31, S42.4, S42.40, S42.41, S42.7, S42.70, S42.71, S42.8, S42.80, S42.81, S42.9, S42.90, S42.91, S52, S52.0, S52.00, S52.01, S52.1, S52.10, S52.11, S52.2, S52.20, S52.21, S52.3, S52.30, S52.31, S52.4, S52.40, S52.41, S52.5, S52.50, S52.51, S52.6, S52.60, S52.61, S52.7, S52.70, S52.71, S52.8, S52.80, S52.81, S52.9, S52.90, S52.91, S62, S62.0, S62.00, S62.01, S62.1,

Table A.2 continued from previous page

Outcome	ICD-10
Fracture	S62.10, S62.11, S62.2, S62.20, S62.21, S62.3, S62.30, S62.31, S62.4, S62.40, S62.41, S62.5, S62.50, S62.51, S62.6, S62.60, S62.61, S62.7, S62.70, S62.71, S62.8, S62.80, S62.81, S72, S72.0, S72.00, S72.01, S72.1, S72.10, S72.11, S72.2, S72.20, S72.21, S72.3, S72.30, S72.31, S72.4, S72.40, S72.41, S72.7, S72.70, S72.71, S72.8, S72.80, S72.81, S72.9, S72.90, S72.91, S82, S82.0, S82.00, S82.01, S82.1, S82.10, S82.11, S82.2, S82.20, S82.21, S82.3, S82.30, S82.31, S82.4, S82.40, S82.41, S82.5, S82.50, S82.51, S82.6, S82.60, S82.61, S82.7, S82.70, S82.71, S82.8, S82.80, S82.81, S82.9, S82.90, S82.91, S92, S92.0, S92.00, S92.01, S92.1, S92.10, S92.11, S92.2, S92.20, S92.21, S92.3, S92.30, S92.31, S92.4, S92.40, S92.41, S92.5, S92.50, S92.51, S92.7, S92.70, S92.71, S92.9, S92.90, S92.91
Cognitive Impairment	F02.3, F02.4, F02.8, F03, F05.1, F10.6, G30, G30.0, G30.1 G30.8, G30.9, G31.0, G31.1, G31.8, I67.3, A81.0, F00 F00.0, F00.1, F00.2, F00.9, F01, F01.0, F01.1, F01.2 F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2
Heart Failure	I11.0, I13.0, I13.2, I26.0, I50, I50.0, I50.1, I50.9
Stroke	G45.0, G45.1, G45.2, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9, I67, I67.0, I67.2, I67.3, I67.8, I67.9, I69, I69.8, I72.5, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I69.3, I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5,

Table A.2 continued from previous page

Outcome	ICD-10
Stroke	I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62, I62.0, I62.1, I62.9, I69.0, I69.1, I69.2, I64, I69.4, G45, G45.8, G45.9
Myocardial infarction	I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.1, I25.2
CVD Hospitalisation/ CVD Mortality	I11.0, I13.0, I13.2, I26.0, I50, I50.0, I50.1, I50.9 G45.0, G45.1, G45.2, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9, I67, I67.0, I67.2, I67.3, I67.8, I67.9, I69, I69.8, I72.5, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I69.3, I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62, I62.0, I62.1, I62.9, I69.0, I69.1, I69.2, I64, I69.4, G45, G45.8, G45.9 I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.1, I25.2
Electrolyte Abnormalities	E87.6, E87.5, E87.1
Hypotension	I95, I95.0, I95.1, I95.2, I95.8, I95.9
Syncope	R55