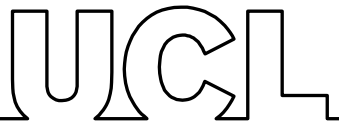
UCL SCHOOL OF PHARMACY

RESEARCH DEPARTMENT OF PRACTICE AND POLICY



Cardiovascular polypharmacy in patients with coronary heart disease and stroke

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Thesis submitted in accordance with the requirement of the University College London (UCL) for the degree of Doctor of Philosophy

Declaration

I, Tiantian Ma, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature _____

Date _____

Abstract

Background: There was limited evidence on the utilisation and effectiveness of cardiovascular (CV) polypharmacy (≥5 CV medications) in the secondary prevention of cardiovascular disease (CVD).

Aim: To investigate the patterns of CV polypharmacy and the impact of multiple CV medications on long-term survival in patients following the incident of myocardial infarction (MI) or stroke or CVD patients with diabetes and chronic obstructive pulmonary disease (COPD).

Methods: Firstly, a systematic review and meta-analysis was conducted to assess the effect of evidence-based combination pharmacotherapy on mortality and CV events in patients with CVD. Secondly, a cross-sectional study was conducted to investigate the patterns of CV medications initially prescribed after the incident CVD event. Thirdly, six retrospective cohort studies were conducted to assess the impact of multiple CV medications on long-term survival among patients with incident ischemic stroke or MI, and among those with comorbidity of type 2 diabetes or COPD.

Results: There were 40.6% of patients with CV polypharmacy. Male, younger age, current smoking, high BMI, hypertension, hyperlipidaemia, higher deprivation score and multiple comorbidities were associated with an increased likelihood of CV polypharmacy. Among patients with ischemic stroke, combination therapy with four or five CV medications was associated with around 40% reduction of all-cause mortality compared to monotherapy. Combinations containing antiplatelet agents (APAs), lipid-regulating medications (LRMs), angiotensin-converting enzyme inhibitors (ACEIs)/

angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) were associated with a significant 61% lower risk of mortality (95% CI: 53%-68%) compared with APAs alone. Among patients with MI, combination therapy with four CV medications was associated with the lowest risk of mortality compared to monotherapy (HR: 0.38, 0.32-0.45). The combination of APAs, LRMs, ACEIs/ARBs and BBs decreased the risk of mortality by 79% (70%-85%) compared with APAs alone.

Conclusions: This project suggested that combination therapy (more than two CV medications) is potentially beneficial and necessary to improve long-term survival among all individuals who have had an ischemic stroke or MI regardless of the further risk of CVD.

Impact statement

Multiple cardiovascular medications are commonly used in patients with CVD. Prior to my PhD work, there was a lack of convincing evidence on the patterns and effectiveness of cardiovascular polypharmacy (>=5 CVD drugs) in the secondary prevention of CVD. My PhD project aimed to fill this gap and highlighted that the combination use of cardiovascular medications is beneficial and necessary to improve long-term survival among patients who have had an incident ischemic stroke or MI or with coexisting diabetes and COPD. My PhD work has potential beneficial impacts on both inside and outside of academia.

Inside of academia, my PhD project adds new evidence in this area. My research comprehensively investigated the usage and impact of CV polypharmacy in patients with CVD. The systematic review has been published on PloS One; the drug utilisation study has been published on the British Journal of Clinical Pharmacology; the cohort study which assessed the impact of multiple CV medications on mortality in patients with stroke has been peer-reviewed by BMC Medicine with minor comments and a revision has been submitted. The findings in my research have been presented in several important academic conferences, including 34th-36th International Conference on Pharmacoepidemiology and Therapeutic Risk Management and 11th-12th ISPE's Asian Conference on Pharmacoepidemiology (ACPE). The oral presentations on 11th and 12th ACPE attracted the international counterparts' attention and interests. In addition, my project provides a good methodological example for future studies on polypharmacy, chronic diseases and long-term outcomes. My project applied some novel methodologies; for example,

marginal structure models were used to control for time-varying confounding and possible treatment switching during the long-term follow-up period; E-value was used to address unmeasured confounding. In the secondary prevention of CVD and CV polypharmacy, furthers studies in other populations could be undertaken based on the findings and limitations highlighted in my research.

Outside of academia, the findings of my PhD work could support optimal pharmacotherapy for CVD in clinical practice. My results highlighted the benefits and necessity of evidence-based combination pharmacotherapy in the secondary prevention of MI and stroke, but I also found under-prescribing of CV medications in CVD patients. The reason of under-prescribing is still unclear, but the findings could raise healthcare professionals' awareness about adherence to guideline-recommended pharmacotherapy. Further studies could further investigate the reasons of underuse of CV medications and take measures to improve the adherence to guidelines. My PhD project also filled gaps on CV polypharmacy in CVD patients with comorbidities (type 2 diabetes and COPD). There is still a lack of convincing evidence and recommendations in this area. Therefore, my findings could provide healthcare professionals with evidence and references on the therapy management in CVD patients with comorbidities. In addition, healthcare policies and guidelines could promote the management of combination therapy in CVD patients with comorbidities based on my findings. The implementation of these recommendations could lead to optimising the pharmacotherapy for the secondary prevention of CVD.

Publications and presentations resulting from this PhD work

Peer-reviewed research articles

Chapter 2.

Ma TT, Wong ICK, Man KKC, Chen Y, Crake T, Ozkor MA, Ding LQ, Wang ZX, Zhang L, Wei L. Effect of evidence-based therapy for secondary prevention of cardiovascular disease: Systematic review and meta-analysis. PLoS One. 2019 Jan 18;14(1):e0210988. doi: 10.1371/journal.pone.0210988. PMID: 30657781; PMCID: PMC6338367.

Chapter 5.

Ma TT, Wong ICK, Whittlesea C, Mackenzie IS, Man KKC, Lau W, Brauer R, Wei L. Initial cardiovascular treatment patterns during the first 90 days following an incident cardiovascular event. Br J Clin Pharmacol. 2020 Jul 9. doi: 10.1111/bcp.14463. Epub ahead of print. PMID: 32643191.

Chapter 6.

Ma TT, Wong ICK, Whittlesea C, Man KKC, Lau W, Wang Z, Brauer R, MacDonald TM, Mackenzie IS, Wei L. Impact of multiple cardiovascular medications on mortality after an incidence of ischemic stroke or transient ischemic attack. BMC Med. 2021 Feb 3;19(1):24. doi: 10.1186/s12916-021-01900-1. PMID: 33530992; PMCID: PMC7856718.

Chapter 9.

Ma TT, Wong ICK, Whittlesea C, Man KKC, Lau W, Wang ZX, Ju CS, Brauer

R, Wei L. Impact of multiple cardiovascular medications on mortality after an incidence of myocardial infarction.

Ready to submit to European Journal of Preventive Cardiology.

Conference abstracts

36th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Online Conference, Sep 2020

Poster presentation

Study title: Impact of multiple cardiovascular medications on mortality after an incidence of ischemic stroke or transient ischaemic attack: A 10-year cohort study

12th ISPE's Asian Conference on Pharmacoepidemiology, Kyoto, Japan, Oct 2019

Oral presentation

Study title: Impact of multiple cardiovascular medications on mortality after an incidence of stroke: A 10-year cohort study

35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

Philadelphia, the USA, Aug 2019

Poster presentation

Study title: The effects of initiation of secondary prevention pharmacotherapy on 1-year mortality after stroke

11th ISPE's Asian Conference on Pharmacoepidemiology

Xi'an, China, Oct 2018

Oral presentation

Study title: Polypharmacy and risk factors in patients with cardiovascular disease

34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

Prague, the Czech Republic, Aug 2018

Poster presentation

Study title: Effect of evidence-based therapy for secondary prevention of cardiovascular disease: systematic review and meta-analysis

Other publications during my PhD time

Wang Z, Man KKC, **Ma TT**, Howard LM, Wei L, Wong ICK, Brauer R. Association between antipsychotic use in pregnancy and the risk of gestational diabetes: Population-based cohort studies from the United Kingdom and Hong Kong and an updated meta-analysis. Schizophr Res. 2020 Nov 23:S0920-9964(20)30561-2. doi: 10.1016/j.schres.2020.11.021. Epub ahead of print. PMID: 33243714.

Brauer R, Wei L, **Ma TT**, Athauda D, Girges C, Vijiaratnam N, Auld G, Whittlesea C, Wong I, Foltynie T. Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes. Brain. 2020 Oct 1;143(10):3067-3076. doi: 10.1093/brain/awaa262. PMID: 33011770.

Alsharif AA, Wei L, **Ma TT**, Man KKC, Lau WCY, Brauer R, Almetwazi M, Howard R, Wong ICK. Prevalence and Incidence of Dementia in People with Diabetes Mellitus. J Alzheimers Dis. 2020;75(2):607-615. doi: 10.3233/JAD-191115. PMID: 32310163.

Mohsin-Shaikh S, Furniss D, Blandford A, McLeod M, **Ma TT**, Beykloo MY, Franklin BD. The impact of electronic prescribing systems on healthcare professionals' working practices in the hospital setting: a systematic review and narrative synthesis. BMC Health Serv Res. 2019 Oct 22;19(1):742. doi: 10.1186/s12913-019-4554-7. PMID: 31640689; PMCID: PMC6806498.

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List of Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
ANOVA	Analysis of variance
APA	Antiplatelet agents
ARB	Angiotensin receptor blocker
BB	Beta-blocker
BMI	Body mass index
BNF	British Heart Foundation
BP	Blood pressure
CCB	Calcium channel blockers
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DR	Diuretics
EBCP	Evidence-based combination pharmacotherapy
EBT	Evidence-based therapy
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HR	Hazard ratio
IPCWs	Inverse probability of censoring weights
IPTWs	Inverse probability of treatment weights
LDL-C	Low-density lipoprotein cholesterol
LRM	Lipid-regulating medications
MI	Myocardial infarction
NICE	National Institute for Health and Care Excellence
NSAIDs	Nonsteroidal anti-inflammatory medications
OMT	Optimal medical therapy
OR	Odds ratio

PCI	Percutaneous transluminal coronary intervention
RA	Rheumatoid arthritis
RCT	Randomised Controlled Trial
RR	Risk ratio
SD	Standard deviation
TC	Total cholesterol
TIA	Transient ischemic attack
UK	United Kingdom
WHO	World Health Organization

Chapter 1: General Background

1.1 Overview of cardiovascular disease

Cardiovascular disease (CVD) is a general term for disease affecting the heart or blood vessels caused by the process of atherosclerosis and an increased risk of blood clots(United Kingdom National Health Service, 2020b). CVD is the leading cause of morbidity and mortality worldwide, and its prevalence is increasing(Lozano et al., 2012; World Health Organization, 2020). Based on the statistics by the British Heart Foundation (BHF) in 2020, CVD was the main cause of death in the United Kingdom (UK), causing 27 per cent of all deaths(British Heart Foundation, 2020b). Coronary heart disease (CHD) and stroke are the principal manifestations of CVD. Adults aged ≥45 years old accounted for the majority of overall cardiovascular mortality (approximately 98.5%)(British Heart Foundation, 2020a). It is estimated that 7.4 million people are living in the UK with CVD; the number of inpatients episodes due to CVD increased by 143,975 between 2010/11 and 2018/19(British Heart Foundation, 2020a). The increase in the incidence and prevalence of CVD imposes a substantial burden on healthcare service. Healthcare costs relating to CVD are estimated at 9 billion pounds each year in the UK(World Health Organization, 2020). Therefore, prevention and control of CVD are priorities for global public health(World Health Organisation, 2020).

1.1.1 Coronary heart disease

CHD, also known as coronary artery disease or ischemic heart disease, happens when coronary arteries become narrowed by a gradual build-up of fatty substances(United Kingdom National Health Service, 2020d). These arteries supply the heart muscle with oxygen-rich blood. Fatty substances called atheroma can build up inside the walls of arteries. The process is known as atherosclerosis(United Kingdom National Health Service, 2020d). When coronary arteries become so narrow that they cannot deliver enough oxygen-rich blood to the heart, chest pain and discomfort known as angina will ensue(United Kingdom National Health Service, 2020a). If a piece of atheroma breaks off, it may cause a blood clot. If it blocks the coronary artery and the supply of oxygen-rich blood to the heart muscle, it may cause permanent damage to the heart. This is known as a myocardial infarction(MI) or a heart attack(United Kingdom National Health Service, 2020f).

CHD causes around 64000 deaths in the UK each year. In the UK, there are 2.3 million people living with CHD, with around 1.5 million men and 830,000 women(British Heart Foundation, 2020b). According to recent statistics, the survival rate for MIs in the UK improved since the 1960s, and more than 70% of MI patients survived in 2020(British Heart Foundation, 2020b).

1.1.2 Stroke

A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either blocked by a clot or bursts (ruptures), causing the blood supply

to part of the brain to be interrupted or reduced, so brain cells become damaged or die(United Kingdom National Health Service, n.d.). There are two main types of stroke. An ischemic stroke is caused by a clot obstructing the blood supply to the brain. A haemorrhagic stroke is caused by a blood vessel rupturing and bleeding inside the brain. A transient ischemic attack (TIA), or "mini-stroke", is caused by a temporary clot and the damage to the brain is reversible(United Kingdom National Health Service, n.d.). A blockage in the blood supply to the brain accounts for 80% to 85% of strokes, and haemorrhage for 15% to 20%(Intercollegiate Stroke Working party, 2016).

Stroke is the second most common cause of mortality worldwide and the fourth biggest killer in the UK(British Heart Foundation, 2020a; World Health Organization, 2020). It causes around 36,000 deaths in the UK each year. In the UK, there are approximately 1.3 million people living with a stroke or TIA until 2020(British Heart Foundation, 2020b). In England, Wales and Northern Ireland, the average age for men to have a stroke is 71 years old, and the average age for women to have a stroke is 75 years old(Stroke Association, 2018).

1.2 Modifiable risk factors for CVD

The risk factors that lead to an enhanced risk of developing CVD have been recognised for many years(Neaton, 1992). Modifiable risk factors for CVD are those that can be reduced or controlled, including cigarette smoking, obesity, physical inactivity, diabetes, hypertension and dyslipidaemia. Other risk factors,

such as advancing age, male gender and family history of CVD, are non-modifiable(Torpy et al., 2003).

1.2.1 Cigarette Smoking

Cigarette smoking (CS) is associated with a significant increase in the risk of cardiovascular morbidity and mortality. According to the WHO global report in 2012, smoking is responsible for 10% of death in all CVD(World Health Organisation, 2012). Cigarette smoke contains at least 4000 constituents(Burns, 1991; Zemann, 2011). A highly complex and changing mixture of compounds is responsible for disease initiation, progression and cardiovascular outcomes. Epidemiology studies strongly demonstrate that CS in both men and women increase the incidence of MI and fatal CHD(Goldenberg, 2003; Panagiotakos et al., 2007; Parish et al., 1995; Slone et al., 1978). A meta-analysis of 32 studies also showed an increased risk of stroke associated with CS (RR: 1.5, 1.4-1.6)(Shinton & Beevers, 1989).

1.2.2 Obesity

Overweight and obesity refer to an excess of body mass and usually relate to increased weight-for-height(United Kingdom National Health Service, 2020g). The most common measure of obesity is the Body Mass Index (BMI). In adults, overweight is defined as a BMI of 25.0 kg/m^2 to 29.9 kg/m^2, and obesity is defined as a BMI of ≥30.0 kg/m^2 (United Kingdom National Health Service, 2020g). Overweight and obesity have been increasing in epidemic proportions in adults in the UK. In 2018, 67% of men and 60% of women in England were

overweight or obese(United Kingdom National Health Service, 2020i). The proportion of adults who were obese was 28%. Obesity is an independent risk factor for CVD. It plays a major role in adversely affecting some major CVD risk factors, including hypertension, dyslipidaemia and diabetes(Van Gaal et al., 2006). A multinational case-control study based on patients in 52 countries showed that obesity (BMI ≥30.0 kg/m^2) was associated with an increased risk of MI (OR: 1.24, 1.16-1.33)(Yusuf et al., 2005). In the Physicians' Health Study, compared with men with BMIs < 23.0 kg/m^2, those with BMI ≥30.0 kg/m^2 had an increased risk of both ischemic stroke (RR: 1.96, 1.39-2.72) and haemorrhagic stroke (RR: 2.25, 1.01-5.01)(Kurth et al., 2002).

1.2.3 Physical activity

Insufficient physical activity (PA) is an important modifiable risk factor for CVD(S. S. Lim et al., 2012). Current recommendations for PA are to do at least 150 minutes of moderate-intensity activity per week or 75 minutes of vigorous-intensity activity per week. A systematic review of 36 studies found that achieving recommended PA levels (150 minutes of moderate-intensity activity per week) was associated with a 23% reduced risk of CVD mortality, 25% and 18% reduced risk of the incidence of MI and stroke, respectively(Wahid et al., 2016). The mechanisms underlying the protective effect of PA on CVD are still unclear. Potential mechanisms include effects on insulin sensitivity, lipoprotein metabolism, blood pressure, fibrinolytic activity and haemostatic function(Ahmed et al., 2012).

1.2.4 Hypertension

Hypertension is one of the most important individual risk factors for CVD(United Kingdom National Health Service, 2020b). Hypertension accelerates the development and progression of atherosclerosis, particularly of the coronary and cerebral vessels(Alexander, 1995; Hollander, 1976). In addition, the sustained elevation of blood pressure (BP) can increase the vulnerability of arteries to narrowing and plaque build-up associated with atherosclerosis(Alexander, 1995; Hollander, 1976). According to Heart and Circulatory Disease Statistics 2020, around 50% of heart attacks and strokes were associated with high BP in the UK(British Heart Foundation, 2020b). The INTERHEART study, a multinational study based on data from 52 countries, showed that hypertension was significantly associated with acute MI (OR: 1.91, 1.74-2.10)(Yusuf et al., 2004). The INTERSTROKE study found that hypertension was the most important risk factor for both ischemic stroke (OR: 2.64, 2.26-3.08) and intracerebral haemorrhagic stroke (OR: 3.80, 2.96-4.78)(O'Donnell et al., 2010).

1.2.5 Dyslipidaemia

Dyslipidaemia, including low levels of high-density lipoprotein cholesterol (HDL-C), high levels of non-high-density lipoprotein cholesterol (non-HDL-C), and elevated triglycerides, are associated with an increased risk of cardiovascular events(Cui et al., 2001; Sniderman et al., 2011). Low-density lipoprotein cholesterol (LDL-C) was previously used as the main measure of "bad"

cholesterol, but now other forms of non-HDL-C have also proved to be harmful. Non-HDL-C levels are currently determined to be a better predictor of CVD risk factor and mortality than LDL-C level(Cui et al., 2001; Sniderman et al., 2011). Too much non-HDL can adhere to the inside of walls of arteries, leading to the build-up of atherosclerosis(Cui et al., 2001; Sniderman et al., 2011). In addition, high cholesterol is also related to some other risk factors of CVD, including smoking, obesity and diabetes(Cui et al., 2001; Sniderman et al., 2011). A ten-year mortality study found that among patients with CVD, those with high total cholesterol levels (above 6.19 mmol/L), high LDL levels (above 4.13 mmol/L) or low HDL levels (below 0.9 mmol/L) had a higher risk of death compared with those with normal cholesterol levels. The hazard ratios were 3.45 (95% CI: 1.63-7.33), 5.92 (2.59-13.52) and 6.02 (2.73-13.28), respectively(Pekkanen et al., 1990).

1.2.6 Multiple risk factors

All of the risk factors of CVD are additive, acting to exaggerate the damage caused by each risk factor alone. The INTERHEART study showed that current smoking, hypertension and diabetes together increased the odds ratio (OR) for acute MI to 13.0 (99% CI: 10.7-15.8) versus those without these risk factors. The three factors accounted for 53% of the population attributable risks (PAR) of MI. Addition of apolipoprotein B (ApoB)/apolipoprotein A1 (ApoA1) ratio (top vs lowest quintile) increased the OR to 42.3 (33.2–54.0), and the PAR for these four risk factors together was 75.8%. Addition of abdominal obesity further increased the PAR to 80.2% (Figure 1) (Yusuf et al., 2004).

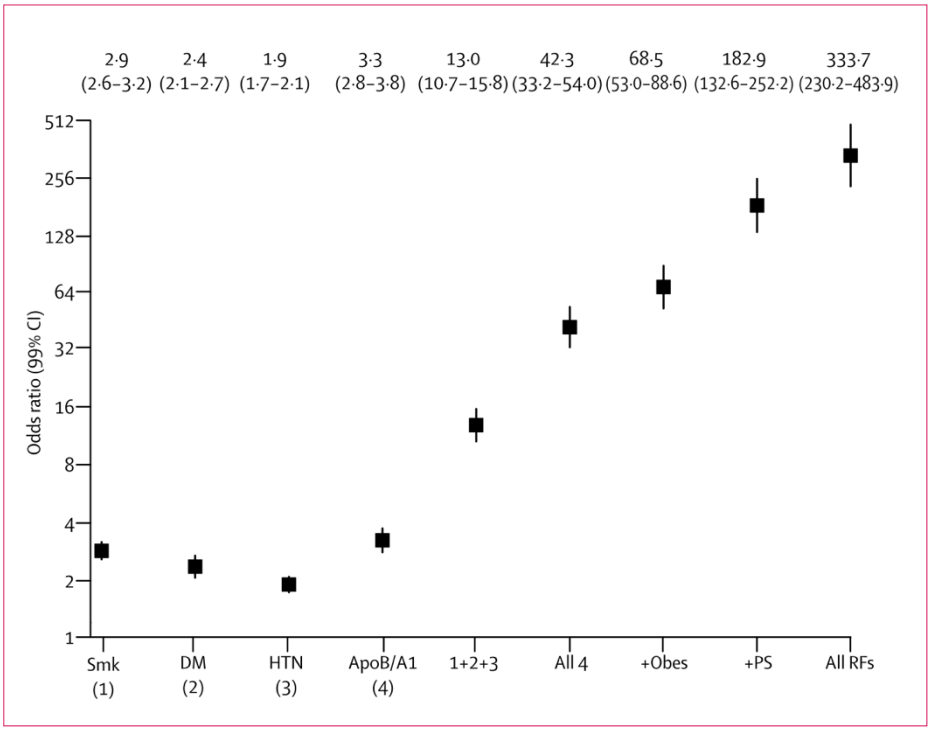

Figure 1-1 Risk of acute myocardial infarction associated with exposure to multiple risk factors

Smk=smoking. DM=diabetes mellitus. HTN=hypertension. Obes=abdominal obesity. PS=psychosocial. RF=risk factors. ApoB=apolipoprotein B. ApoA1= apolipoprotein A1. Note the doubling scale on the y axis. The odds ratios are based on current vs never smoking, top vs lowest tertile for abdominal obesity, and top vs lowest quintile for ApoB/ApoA1. If these three are substituted by current and former smoking, top two tertiles for abdominal obesity and top four quintiles for ApoB/ApoA1, then the odds ratio for the combined risk factor is 129.20 (99% CI 90.24–184.99). *Note*. Reprint from "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries in a case-control study based on the INTERHEART study", by Salim Yusuf *et al.*, 2004, Lancet, 364, 937-952.

1.3 Pharmaceutical therapy in secondary prevention of CVD

According to guidelines from the NICE, preventative strategies should be taken to attenuate risk in those patients with a high risk of developing CVD (primary prevention), and to prevent recurrence of events in those with established CVD (secondary prevention)(National Institute for Health and Care Excellence,

2020a). Secondary prevention of CVD comprises treating the risks of CVD before it causes permanent damage or creates critical medical consequences, and then conducting necessary interventions to reverse the effects of the disease. Optimal pharmacological therapy plays a key role in the secondary prevention of CVD. Pharmaceutical therapy of secondary prevention focuses on BP control, cholesterol-lowering treatment, and preventing platelet aggregation and inhibiting thrombus formation(National Institute for Health and Care Excellence, 2010; Piepoli et al., 2016). Antihypertensive agents(Fretheim et al., 2012; Thompson, 2011), cholesterol modifiers(Trialists, 2005) and antiplatelet agents(Antithrombotic Trialists' Collaboration, 2002; Collins et al., 2009; Karmali et al., 2016) as single treatment have been suggested to be relatively safe and beneficial in reducing the risk of mortality and further CV events.

1.3.1 Secondary prevention of MI

Guidelines from National Institute for Health and Care Excellence (NICE) recommend offering all people who have had MI with ACE inhibitor, dual antiplatelet therapy (aspirin plus a second antiplatelet agent), beta-blocker and statin(National Institute for Health and Care Excellence, 2020c).

1.3.1.1 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) work by interfering with the Renin-angiotensin-aldosterone system (RAAS). The RAAS is a hormone system within the body that is

essential for the regulation of blood pressure and fluid balance (Figure 1-2)(Atlas, 2007). The first stage of the RAAS is the release of the enzyme renin. In the liver, renin catalytically cleaves angiotensinogen and forms angiotensin I (A-I). Angiotensin-converting enzymes then convert angiotensin I to angiotensin II (A-II). A-II exerts its action by binding to various receptors throughout the body. A-II causes contraction of the muscles surrounding blood vessels, effectively narrowing vessels and increasing blood pressure. It also stimulates the release of aldosterone, which stimulates water and sodium reabsorption, thereby increasing blood volume and blood pressure. In addition, it increases the secretion of ADH, sympathetic activity and tubular water retention. Overactivity of the RAAS is associated with the development of atherosclerosis, hypertension, left ventricular hypertrophy, congestive heart failure, and nephrosclerosis(Ferrario & Strawn, 2006). ACEIs reduce RAAS activity by inhibiting the conversion of A-I into A-II, and ARBs inhibit the binding of A-II to A-II type 1 receptors. They decrease arteriolar resistance, arteriolar vasoconstriction, cardiac output and potassium excretion in the kidneys. Clinical trials have shown ACEIs/ARBs decrease the risk of death and cardiovascular events in patients after an acute MI(Domanski et al., 1999), and those with hypertension(Neal et al., 2000), preserved left ventricular function(Al-Mallah et al., 2006; Fu et al., 2012) and diabetes(Cheng et al., 2014).

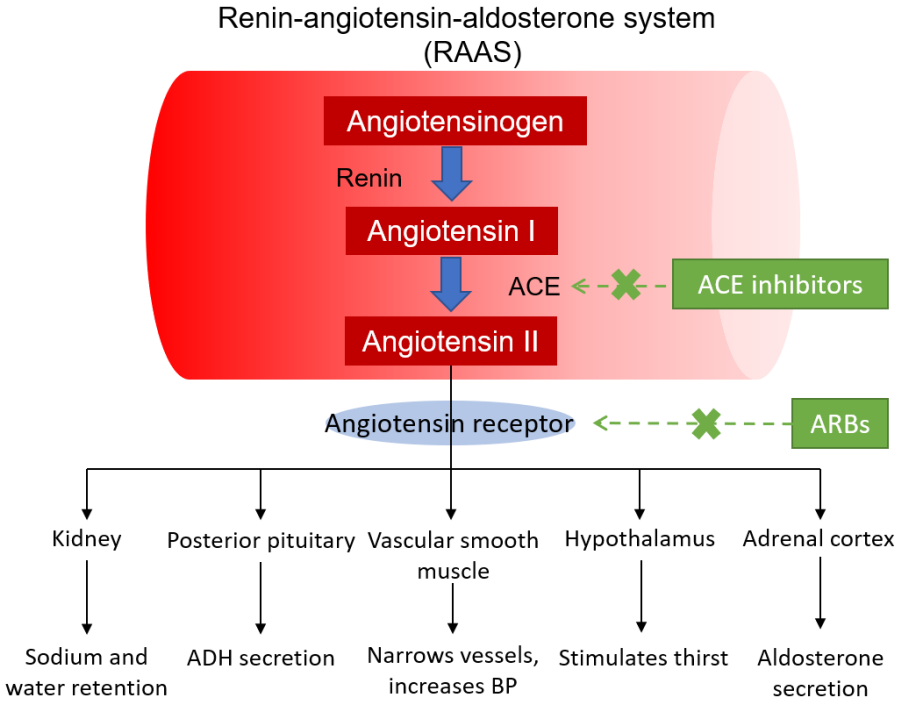

Figure 1-2 Renin-angiotensin-aldosterone system and the mechanism of ACEIs and ARB

The NICE guidelines suggest offering ACEIs, or ARBs if intolerant, to people after an acute MI and continuing it indefinitely. The combination of ACE inhibitors and ARBs is not recommended for patients after an MI(National Institute for Health and Care Excellence, 2020c).

1.3.1.2 Antiplatelet agents

The normal function of platelet within the circulation is to arrest the loss of blood when a blood vessel is damaged. Exaggerated platelet activation can lead to pathological thrombosis, which contributes to the pathogenesis of CVD(Willoughby et al., 2002). Antiplatelet agents can be classified based on the mechanism of action as follows (Figure 1-3): 1) platelet aggregation

inhibitors such as aspirin and related cyclooxygenase (COX) inhibitors; 2) platelet P2Y12 receptor blockers (e.g., clopidogrel, ticagrelor, ticlopidine, and prasugrel); 3) glycoprotein platelet inhibitors (e.g. abciximab, eptifibatide, tirofiban); 4) phosphodiesterase (PDE) inhibitors (e.g. dipyridamole, cilostazol)(Hashemzadeh et al., 2008; Kroetz, 2008).

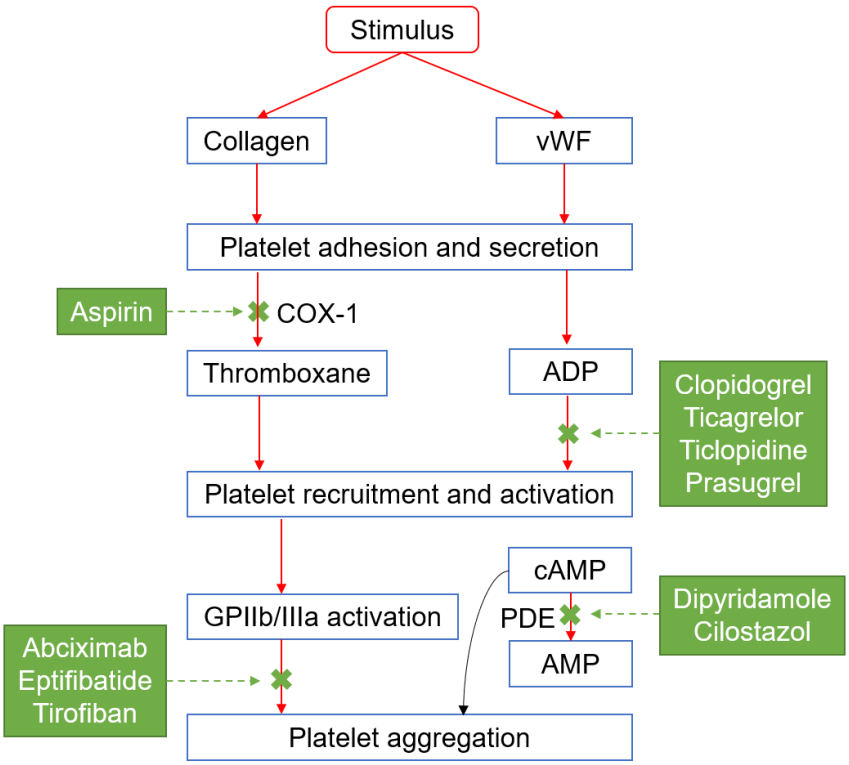

Figure 1-3 Mechanism of antiplatelet agents.

Aspirin inhibits thromboxane A2 (TXA2) synthesis by irreversibly acetylating cyclooxygenase-1 (COX-1). Reduced TXA2 release attenuates platelet activation and recruitment. Ticlopidine, clopidogrel, and prasugrel irreversibly block P2Y12, a key adenosine diphosphate (ADP) receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of P2Y12. Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor (vWF) binding to activated glycoprotein (GP) IIb/IIIa. Dipyridamole and cilostazol inhibit the phosphodiesterase enzyme (PDE), thus increasing the concentration of cyclic adenosine monophosphate (cAMP) in platelets, which in turn inhibits platelet aggregation.

Randomised clinical trials have shown that antiplatelet therapy prevents

vascular events in secondary prevention of CHD(Antithrombotic Trialists' Collaboration, 2002). The Antithrombotic Trialists' Collaboration demonstrated that antiplatelet therapy reduced the risk of having a serious vascular event by 36 (SE 5)/1000 treated for two years among patients with previous MI, and also an independently significant benefit among patients with unstable angina (46% reduction in serious vascular events)(Antithrombotic Trialists' Collaboration, 2002).

Guidelines from NICE recommend offering aspirin to all people after an MI and continue it indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. If aspirin is intolerant, clopidogrel is recommended. Dual antiplatelet therapy (aspirin plus a second antiplatelet agent, e.g. clopidogrel or ticagrelor) is indicated in all patients with MI(National Institute for Health and Care Excellence, 2020c).

1.3.1.3 Beta-blockers

Beta-blockers work by blocking the effects of the hormone adrenaline. This results in a slowing of the heart rate, a decreasing of myocardial contractility, cardiac output and heart oxygen demand. Beta-blockers also cause a decrease in renin secretion, which in turn decreases blood pressure(Gorre & Vandekerckhove, 2010). Beta-blockers have been shown to be beneficial in secondary prevention after MI. Meta-analyses of RCTs identified a 23% (95%CI: 15%-31%) reduction of the odds ratio of long-term mortality (Freemantle et al., 1999), and a reduction of MI (IRR: 0.72, 95% CI: 0.62-0.83) in patients after

MI(Bangalore et al., 2014).

The NICE guidelines recommend that to offer a beta-blocker to patients after an MI as soon as possible once haemodynamically stable. This should be continued for 12 months or lifelong if evidence of left ventricular systolic dysfunction(National Institute for Health and Care Excellence, 2020c).

1.3.1.4 Lipid-regulating agents

Lipid-regulating agents are targeted to decrease the production of lipoprotein or cholesterol, increase degradation of a lipoprotein, or increase the removal of cholesterol from the body(Pahan, 2006). Lipid-regulating agents can be classified based on the mechanism of action as follows: 1) HMG CoA reductase inhibitors (statins), inhibit cholesterol synthesis; 2) cholesterol absorption inhibitors (e.g. ezetimibe), reduce enterohepatic cholesterol cycling; 3) bile acid sequestrants (e.g. cholestyramine), divert cholesterol into bile acid synthesis; 4) fibrates, induce lipoprotein lipase and other genes; 5) nicotinic acids, inhibits lipolysis and fatty acid flux; 6) n-3 PUFA (fish oils), promotes intracellular catabolism of apolipoprotein(Gille et al., 2008; NAZIR et al., 1972; Pahan, 2006; Pizzini et al., 2017; Toth et al., 2012). RCTs have demonstrated that lowering blood cholesterol can prevent vascular events and mortality. Results of a meta-analysis of 26 RCTs indicated that a 10% (95% CI: 7%-13%) proportional reduction in all-cause mortality per mmol/L in LDL cholesterol reduction. There was a 21% (95% CI: 18%-24%) reduction in major coronary events per mmol/L in LDL cholesterol reduction in patients with post CHD(Baigent et al., 2010).

The NICE guidelines recommend that offering a statin for lipid modification in secondary prevention of CVD and in people with an acute coronary syndrome without delay(National Institute for Health and Care Excellence, 2016, 2020c).

1.3.1.5 Antihypertensive treatment

Antihypertensive medications can be classified based on the mechanism of action as follows: 1) centrally acting α agonists, stimulate α2 receptors in the brainstem, reduce sympathetic outflow; 2) β blockers, block cardiac β adrenergic receptors (refer to section 1.3.1.3); 3) ACEIs and ARBs, inhibit RAAS (refer to section 1.3.1.1); 4) calcium channel blockers, bind α1 subunit of L-type calcium channel in the muscle cell membrane, reduce vascular smooth muscle contractility; 5) direct-acting vasodilators (e.g. hydralazine and minoxidil), directly relax arteriolar smooth muscle; 6) thiazide diuretics, inhibit sodium-chloride cotransporter in the distal convoluted tubule of nephron, cause natriuresis; 7) loop diuretics, inhibit sodium-potassium-chloride cotransporter in the loop of Henle of the nephron, cause natriuresis; 8) mineralocorticoid receptor blockers, competitively inhibit aldosterone binding to the mineralocorticoid receptor, reduce sodium reabsorption in collecting duct of nephron(Abrams, 1969; Sica, 2015; Wile, 2012; Zsotér, 1983). Evidence from a meta-analysis of 147 RCTs has indicated a positive relationship between blood pressure reduction and decreased risk of vascular events in patients with CHD(Law et al., 2009). Another meta-analysis of 25 clinical trials showed that patients with a history of CHD but with blood pressures in the normal level also can obtain benefits in the reduced risk of CVD events (RR: 0.83, 0.75-0.93) and

all-cause mortality (RR: 0.89, 0.81-0.99) from antihypertensive treatments(Thompson, 2011).

According to the NICE guidelines, blood pressure should be monitored in patients who have had an MI. Antihypertensive drug treatment should be discussed to start in people aged under 80 with persistent stage 1 hypertension (Clinic blood pressure: 140/90 mmHg-159/99 mmHg) and established CVD(National Institute for Health and Care Excellence, 2019a). First-line antihypertensive drugs include ACE inhibitors, ARBs, CCBs and diuretics.

1.3.2 Secondary prevention of ischemic stroke and TIA

1.3.2.1 Antihypertensive treatment

Hypertension is estimated to cause about half of the ischemic strokes and is the principal risk factor for intracerebral haemorrhage(Intercollegiate Stroke Working party, 2016). Treatment of hypertension has been shown to significantly reduce subsequent vascular events and mortality. A meta-analysis of 147 RCTs showed that there was a 21% reduction in CHD events and a 34% reduction in stroke in people with a history of stroke, standardised to a blood pressure reduction of 10 (systolic)/5 (diastolic) mmHg(Law et al., 2009). Another meta-analysis of 61 prospective observational studies showed that a 20mmHg lower systolic blood pressure or 10mmHg lower diastolic blood pressure was associated with at least 50% reduction of risk of stroke death in patients aged under 80(Lewington et al., 2002).

The UK National Clinical Guidelines for Stroke recommend monitoring blood

pressure in people with stroke or TIA. Unless there is severe hypertension, acute intracerebral haemorrhage or to facilitate intravenous thrombolysis treatment, antihypertensive treatment should be initiated before discharge or at two weeks, whichever is the soonest, or at the first clinic visit for people not admitted(Intercollegiate Stroke Working party, 2016).

1.3.2.2 Lipid-regulating drugs

The benefit of lipid-lowering therapy with statins has been confirmed for people with cerebrovascular disease. Evidence from a systematic review and meta-analysis of 27 studies found that acute poststroke statin treatment was associated with a reduced risk of death at 90 days and 1-year mortality(Ní Chróinín et al., 2013). The SPARCL trial investigated the effect of atorvastatin 80 mg daily in patients with stroke or TIA and demonstrated a relative risk reduction of 16% in stroke and 35% in major coronary events with treatment(Amarenco et al., 2006).

The UK National Clinical Guidelines for Stroke recommend offering people with ischemic stroke or TIA with a statin drug unless contraindicated(Intercollegiate Stroke Working party, 2016).

1.3.2.3 Antiplatelet drugs

Antiplatelet treatment is one of the most important interventions for reducing the risk of recurrent vascular events after stroke. The Antithrombotic Trialists' Collaboration found that patients with previous stroke or TIA benefited from antiplatelet therapy (with an average of 29 months treatment) in the risk of a

serious vascular event (myocardial infarction, stroke or vascular death) (36 fewer events per 1000) (Antithrombotic Trialists' Collaboration, 2002).

According to the UK National Clinical Guidelines for Stroke, clopidogrel is recommended as the standard antithrombotic treatment for long-term prevention in people with ischemic stroke or TIA without paroxysmal or permanent atrial fibrillation. If clopidogrel is intolerant, then aspirin with/or modified-release dipyridamole is recommended if the two drugs are not contraindicated and tolerated. The combination of aspirin and clopidogrel is not recommended unless there is another indication (e.g. acute coronary syndrome, recent coronary stent)(Intercollegiate Stroke Working party, 2016).

1.3.2.4 Anticoagulation treatment

Anticoagulants are used to prevent the formation of a thrombus or the extension of an existing thrombus that is circulating in the bloodstream. Factor Xa and thrombin are recognised as indispensable components of the coagulation cascade, which catalyse the formation of fibrin and ultimately leads to the stabilisation of aggregated platelets to form a stable clot(Dahlbäck, 2000; Fenton et al., 1993). Anticoagulants can be classified based on the mechanism of action as follows (Figure 1-4): 1) vitamin K antagonists (e.g., warfarin), reduce the synthesis of coagulation factors II, VII, IX, and X; 2) direct thrombin inhibitors (e.g. dabigatran, argatroban and lepirudin), inhibit the intrinsic activity of the thrombin; 3) indirect thrombin inhibitors (e.g., heparin and fondaparinux), inhibit several of the activated clotting factors; 4) direct Xa inhibitors (e.g.,

rivaroxaban and apixaban), directly bind to the active site of factor Xa.

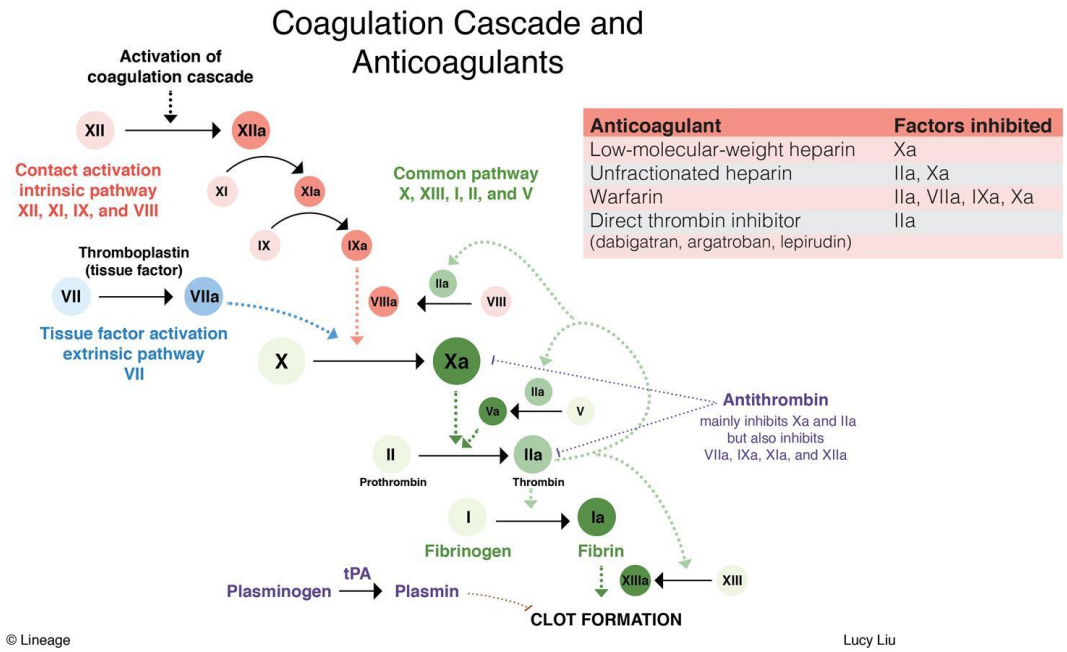

Figure 1-4 Mechanism of coagulation and anticoagulants

Note. Reprinted from "Anticoagulants" by Thomas Heineman. Accessed October 30, 2020. (https://step1.medbullets.com/hematology/111030/anticoagulants)

Anticoagulation treatment is restricted to long-term secondary prevention in patients with stroke(Intercollegiate Stroke Working party, 2016). Evidence from RCTs has suggested that long-term anticoagulant therapy is no more effective than antiplatelet agents in people with non-cardioembolic ischemic stroke or TIA but carries a greater risk of bleeding(Mohr et al., 2001; Sandercock et al., 2003). However, there is strong evidence for the more beneficial effects of anticoagulant therapy than antiplatelet therapy for long-term secondary prevention for people with paroxysmal, persistent or permanent atrial fibrillation (AF)(Koudstaal, 1996).

According to the UK National Clinical Guidelines for Stroke, anticoagulant drugs are initiated for secondary prevention for people with ischemic stroke or TIA and with paroxysmal, persistent or permanent AF or atrial flutter. Anticoagulation should not be given in people with intracranial bleeding or other contraindications (such as uncontrolled hypertension)(Intercollegiate Stroke Working party, 2016).

1.3.3 Secondary prevention of CVD in patients with comorbidities

The increase in life expectancy and the consequential ageing population has resulted in more patients developing multiple medical conditions. The 2019 BHF statistics showed that around 80% of people with CVD have at least one other health condition, and the proportion of patients with CVD and multimorbidity increased with age(British Heart Foundation, 2020b). Some conditions in the list of top 10 global causes of death, for example, chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM)(World Health Organization, 2020), also highly coexist with CVD(Tran et al., 2018). Comorbidity may influence cardiovascular prognosis. CVD patients with different comorbidities may have different responses to pharmacotherapy(Gurwitz, 2004; van Weel & Schellevis, 2006).

1.3.3.1 Patients with CVD and diabetes mellitus

Diabetes mellitus, commonly known as diabetes, is a chronic metabolic disease that causes high blood sugar level. Insulin is a hormone that regulates blood sugar(United Kingdom National Health Service, 2020e). There are two main

types of diabetes, type 1 diabetes and type 2 diabetes(United Kingdom National Health Service, 2020e). Type 1 diabetes occurs when the immune system attacks and destroys cells in the pancreas that produce insulin. Type 2 diabetes occurs when the body becomes resistant to insulin, or the body does not produce enough insulin. Type 2 diabetes is far more common than type 1. In the UK, around 90% of all adults with diabetes have type 2(DIABETES UK, 2020). Based on the statistics in 2020, there are around 25.9% of CHD patients and 20.4% of stroke patients living with diabetes in the UK(DIABETES UK, 2020). DM is a main risk factor for CVD(P. Wilson, 1998; P. W. F. Wilson et al., 1998). In the UK, compared to people without DM, patients with DM are 2.5 times more likely to have a MI and two times more likely to have a stroke(DIABETES UK, 2020). Patients with diabetes have a twice to a fivefold higher risk for cardiovascular mortality compared to non-diabetic patients(Fuller et al., 1983; Goldbourt et al., 1993; Stamler et al., 1993). Patients with DM are susceptible to accelerated atherosclerosis, the major cause of CVD. As shown in Figure 1-5, high risk of dyslipidaemia, hypertension, hyperglycaemia, and platelet activation in patients with diabetes, contribute to the accelerated atherosclerosis and poor prognosis of CVD(Bertoni et al., 2004; Creager et al., 2003; From et al., 2006; Grundy et al., 1999).

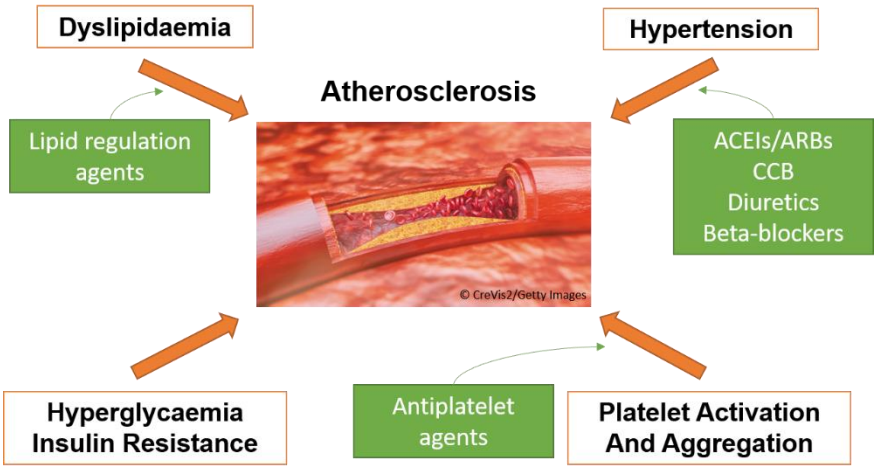

Figure 1-5 Association between atherosclerosis and diabetes, and related cardiovascular therapy

Patients with DM are at high risk of dyslipidaemia, hypertension, hyperglycaemia, and platelet activation. These factors contribute to the accelerated atherosclerosis. The process can be mitigated by using lipid regulation agents, antihypertensive agents, and antiplatelet agents in patients with DM.

It has been suggested that the effects of cardiovascular treatment on major cardiovascular events are different between individuals with and without DM(Blood Pressure Lowering Treatment Trialists' Collaboration, 2005; Patel et al., 2000). In patients with diabetes, platelets have been proven to be hyperreactive with intensified adhesion, activation and aggregation(Creager et al., 2003; Ferroni et al., 2004). In addition, there is an antiplatelet therapy resistance (diminished or lack of response to antiplatelet agents) in patients with diabetes(Angiolillo, 2009). These may partly explain why patients with DM, particularly those at the most advanced state (e.g., insulin-requiring DM), continue to have recurrent atherothrombotic events. Although the beneficial effects of antiplatelet therapy were impaired in patients with diabetes, antiplatelet therapy still plays a pivotal role in secondary prevention of CVD in

this group of patients(Balasubramaniam et al., 2012; Collaboration & Antiplatelet Trialists' Collaboration, 1994). Atherogenic dyslipidaemia is characterised by three lipoprotein abnormalities: elevated plasma triglyceride levels, low levels of high-density lipoprotein cholesterol, and high-level of low-density lipoprotein particles. Atherogenic dyslipidaemia in patients with diabetes often is called diabetic dyslipidaemia, which is also a cause of accelerated atherosclerosis in patients with diabetes(Schmieder et al., 2009). Cholesterol-lowering therapy has been well established through RCTs to be associated with a reduced risk of mortality and major vascular events in diabetic pateints(Cholesterol Treatment Trialists' (CTT) Collaborators; et al., 2008). Hypertension is highly prevalent in patients with DM. A systematic review found that hypertension has been reported to be present in greater than 50% of those with DM with rates in some studies exceeding 75%(Colosia et al., 2013). ACEIs/ARBs are the recommended first-line antihypertensive agent(H.-Y. Wu et al., 2013), and first-line therapy in secondary prevention of MI for patients with DM(National Institute for Health and Care Excellence, 2020c), because they have been well established to improve glycaemic control(Fogari et al., 1998) and protect renal function(Lewis et al., 1993) in patients with diabetes. Compared with patients without DM, CVD patients with DM treated with ACEIs/ARBs have been shown to have a greater reduced risk of mortality(Blood Pressure Lowering Treatment Trialists' Collaboration, 2005; Patel et al., 2000). The use of BBs is standard therapy in secondary prevention of MI. They were traditionally restricted in routine use for patients with DM,

because the first and second generation BBs were associated with increased insulin resistance, causing an increase in serum glucose and triglycerides, and a decrease in HDL levels(Bell, 2003). However, some studies also have shown the beneficial effect of BBs on survival after MI in patients with diabetes(J. Chen et al., 1999; MALMBERG et al., 1989). BBs can provide cardioprotection in post-MI patients with diabetes by lowering the myocardial workload and oxygen consumption, which may outweigh the theoretical risks(Landray et al., 2002).

1.3.3.2 Patients with CVD and chronic obstructive pulmonary disease

COPD is a lung disease characterised by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. It happens when the lungs become inflamed, damaged and narrowed(United Kingdom National Health Service, 2020c). The primary cause is tobacco smoking. COPD is the third leading cause of death based on statistics of mortality in 2019, developed by WHO(World Health Organization, 2020). A large population-based study in the UK reported that patients with COPD were nearly five times more likely to have CVD than those without COPD(Feary et al., 2010). CVD is a leading cause of death in people with COPD, with up to one-third dying of CVD(Sin et al., 2006). The association between COPD and CVD may be partly explained by COPD related systemic inflammation and pathophysiologic changes, which may affect cardiac function and increase the risk of CV events(Agustí et al., 2012; Barr et al., 2010). In addition, COPD and CVD share important risk factors, including tobacco smoking and older age(Divo et al., 2012; Mannino et al., 2008).

The effects of cardiovascular medication in secondary prevention of CVD patients may be influenced by coexisting of COPD. Some studies have reported that COPD-related systemic inflammatory status may affect platelet reactivity and responsiveness to antiplatelet agents(Campo et al., 2014; R. Wang et al., 2013). Lower drug responsiveness was observed in COPD patients on dual antiplatelet therapy (aspirin + clopidogrel) compared with patients without COPD(Campo et al., 2014). However, antiplatelet therapy still plays a key role in secondary prevention of CVD in COPD patients. A meta-analysis has suggested that antiplatelet therapy was associated with reduced all-cause mortality in COPD patients(Pavasini et al., 2016). Lipid regulating treatment has improved survival among COPD patients(Cao et al., 2015). Some studies also have reported that statins may be associated with an anti-inflammatory effect in the lungs and the airways(J.-H. Lee et al., 2005) and a lower incidence of exacerbations(Blamoun et al., 2008; M.-T. Wang et al., 2013) in COPD patients. ACEIs/ARBs may have a benefit against pneumonia in patients with COPD(Kim et al., 2016; Lai et al., 2018). Although the most common side effect of ACEIs is cough(Fletcher et al., 1994), they are not contraindicated in COPD patients and are still recommended as the first-line antihypertensive agents(National Institute for Health and Care Excellence, 2019a). Patients receiving ARBs were also less likely to have cough compared with those receiving ACEIs(Caldeira et al., 2012). In addition, several studies found that patients with ARBs had a lower risk of mortality compared with those with ACEIs in COPD patients(Mancini et al., 2006; Su et al., 2019). However, there is limited evidence to support ARBs

being superior to ACEIs in secondary prevention of CVD in COPD patients. BBs were historically considered to be strictly contraindicated in COPD because of concerns about bronchospasm and worsening of lung function(Chobanian, 2003; Tattersfield, 1991; Woolcock et al., 1991). Strong evidence from RCTs has suggested that cardioselective BBs do not produce a significant reduction in airway function or increase the incidence of COPD exacerbations in COPD patients(S.R Salpeter et al., 2003). BBs were also proved to be associated with improved survival in patients with COPD and CVD(Coiro et al., 2017; Gottlieb et al., 1998; Quint et al., 2013). However, underuse of BBs still exists in secondary prevention of CVD(K. P. Lim et al., 2017; Lipworth et al., 2016; Parkin et al., 2020).

1.4 Cardiovascular polypharmacy

Polypharmacy is widely considered to be the concurrent use of multiple medication items by one individual(Duerden et al., 2013). This term has been used for general medication use and multiple medications for specific conditions, e.g., antipsychotic polypharmacy and antihypertensive polypharmacy(Bromfield et al., 2017; Gallego et al., 2012; Junius-Walker et al., 2006; Payne et al., 2014; Veehof et al., 2000). My study is focused on cardiovascular polypharmacy.

The widespread advocacy on the comprehensive management of multiple risk factors gives rise to the combined use of an increased number of cardiovascular medications to reduce mortality and cardiovascular events. In addition,

advances in medical treatment have extended people's life expectancy; consequently, the ageing population is growing, with increasing chronic conditions, such as hypertension, diabetes mellitus and COPD coexisting with CVD. As a result, patients with CVD are associated with a high number of medications(Junius-Walker et al., 2006; Payne et al., 2014; Veehof et al., 2000). In the study by Payne *et al*., the mean number of medications for patients with only one condition of CHD was 3.7 and 8.0 for patients with CHD and other co-conditions(Payne et al., 2014). A UK study using primary health care data investigated the combination treatment for secondary prevention of CHD and found that approximately 50% patients received three-drug combination therapy, about 20% received four-drug combination therapy, and about 10% received five-drug combination in 2005(DeWilde et al., 2008). A Scottish study based on primary care data reported that 94.2% of patients with stroke had additional conditions, 22.9% received five or six medications, and 12.6% had 11 or more repeat prescriptions(Gallacher et al., 2014). It is common and necessary for some patients with chronic conditions (e.g. CVD) to receive multiple medications therapy in order to control the disease-related symptoms and prevent complications. Meanwhile, some associated negative consequences of polypharmacy such as adverse drug events, drug-drug interactions, inappropriate prescribing, reduced adherence, and increased healthcare costs are issues of concern and criticism(Maher et al., 2014).

To achieve optimal treatment for CVD, some treatment principles have been proposed, such as 1) polypill(Wald, 2003), 2) optimal medical therapy

(OMT)(Boden et al., 2007) and 3) evidence-based therapy (EBT)(Mukherjee et al., 2004). In 2003, Wald and Law quantified the efficacy and adverse effects of a fixed-dose combination from published trials and proposed that a fixed-dose combination pill, called polypill, consisting of a statin, BP-lowering agents, aspirin and folate could potentially reduce CVD by 80% in individuals from age 55(Wald, 2003). Both OMT and EBT also refer to a combination of antihypertensive agents, antiplatelet drugs and lipid modifiers. A recent systematic review and meta-analysis summarised 13 randomised trials (n=9059) on the fixed-dose combination, conducted in individuals with a prior MI or stroke or at a high risk of CV events(Bahiru et al., 2017). Compared with comparators (placebo, usual care, or active drug comparator), the benefits or risks for fixed-dose combination therapy in terms of all-cause mortality or CV events were uncertain. Fixed-dose combination therapy improved adherence; however, it was related to more adverse events(Bahiru et al., 2017). The probable advantages of compounding evidence-based drugs into one pill are that the strategy unites the effectiveness of each drug, meanwhile reducing cost and may improve adherence. However, convincing evidence of these benefits has not been achieved(Lonn et al., 2010). Regardless of dose modification, it is still unknown if an individual cardiovascular medication can provide additive benefits in combination therapy for secondary prevention of CVD. It is unclear how many drugs are required and what medications are the optimal constituents in combination therapy. Moreover, it is unknown if the combination therapy for secondary prevention has different effects on clinical outcomes in

CVD patients with different comorbidities.

Chapter 2: Effect of evidence-based therapy for secondary prevention of cardiovascular disease: systematic review and meta-analysis

Part of the review (data up to October 2018) has been published:

Ma TT, Wong ICK, Man KKC, Chen Y, Crake T, Ozkor MA, Ding LQ, Wang ZX, Zhang L, Wei L. Effect of evidence-based therapy for secondary prevention of cardiovascular disease: Systematic review and meta-analysis. PLoS One. 2019 Jan 18;14(1):e0210988. doi: 10.1371/journal.pone.0210988. PMID: 30657781; PMCID: PMC6338367.

2.1 Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide. Based on statistics from The World Health Organization (WHO), coronary heart disease (also known as ischemic heart disease) and stroke are the top two causes of death globally(World Health Organization, 2020). Pharmacological therapy plays a key role in secondary prevention of CVD. Large evidence supports medications conferring mortality benefit from several different classes: antiplatelet agents, ACEIs/ARBs, beta-blockers and lipid-lowering medications (Antithrombotic Trialists' Collaboration, 2002; Chou et al., 2016; Ettehad et al., 2016). These are recommended by the WHO (World Health Organisation, 2002) and guideline bodies including the National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care

Excellence, 2013, 2020c), the European Society of Cardiology (ECS) (Arslan et al., 2018), the American College of Cardiology/American Heart Association (ACC/AHA) (Amsterdam et al., 2014) and American Heart Association/American Stroke Association (AHACEIs/ARBsSA) (Kernan et al., 2014).

In 2001, a fix-dose combination pill was proposed by the WHO(World Health Organisation, 2002) and was specified as a combination of aspirin, a beta-blocker, an ACEIs and a statin. In 2003, Wald and Law proposed that a fixed-dose combination pill, called polypill, consisting of a statin, BP-lowering agents, aspirin and folic acid, could potentially reduce the risk of CVD by 80% in individuals from age 55 onward(Wald, 2003). Since the concept was presented, many research studies have investigated the efficacy of different medication combinations. A recent systematic review and meta-analysis summarised 13 RCTs of different polypills with a total of 9059 individuals, which were mainly conducted in individuals with pre-existing atherosclerotic cardiovascular disease(Bahiru et al., 2017). The relatively short duration of follow-up meant that there were no definitive conclusions possible supporting the mortality benefit of polypill from the RCT evidence(Bahiru et al., 2017). The current RCTs focus on a comparison between polypill and usual care. There is still a lack of RCT-level evidence on the effectiveness of individual medication combinations. The existing evidence on individual medication combinations is from some observational studies, which have examined the impact of the combination of antiplatelet agents, ACEIs/ARBs, beta-blockers and lipid-modifiers, called

evidence-based combination pharmacotherapy (EBCP) (Al-Zakwani et al., 2012; Amann et al., 2014; Bauer et al., 2010; Bezin et al., 2017; Bramlage et al., 2010), but there has been no systematic review to synthesise these together.

Uncertainties surrounding EBCP that have not yet been systematically assessed include: (i) whether there is conclusive statistical evidence suggesting multi-medication treatments do better than single-medication treatments for mortality benefit (ii) whether increasing the number of components will confer additional benefits; and (iii) the role of each component of combination therapy, and whether certain combinations have more potent mortality lowering effects. This systematic review was conducted with a meta-analysis of existing observational studies that investigated the impact of the EBCP on mortality and cardiovascular events in secondary prevention of CVD.

2.2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was used to guide the reporting of the methods and findings.(Higgins & Thomas, 2020; Moher et al., 2015). A completed PRISMA checklist is provided in Appendix A. The study protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42018078069).

2.2.1 Systematic literature search

I initially performed a systematic literature search without limitations of language on EMBASE (1980 to October 2018) and Medline (1946 to October

2018) in October 2018. In order to update the literature review for this thesis, I searched EMBASE and Medline for any articles published between October 2018 and January 2020. The search strategies were developed based on the PICO (population, intervention, comparator and outcome) principle(Stang, 2010b), search terms (Appendix B) covering CVD (CHD and stroke), cardiovascular medications (lipid-modifiers, antiplatelet agents and first-line antihypertensive medications) and terms for combination therapy. I also examined the bibliographies of some relevant reviews and articles to identify any additional studies.

2.2.2 Study selection

Two researchers (myself and another PhD student, ZiXuan Wang) independently screened studies to be included in the review using predetermined inclusion criteria. Studies were included in the systematic review if they: (i) included participants aged ≥18 years old with a history of coronary heart disease (MI, stable or unstable angina pectoris), stroke or TIA; (ii) clearly defined exposure to a combination pharmacotherapy including at least one antiplatelet agent, one lipid-modifier and one medication of ACEI/ARB, beta-blockers or other commonly used cardiovascular medications (diuretics, calcium channel blockers, α-adrenergic blockers, aldosterone antagonist, or renin inhibitor); (iii) clearly defined the outcome of all-cause mortality, major cardiovascular events (fatal or non-fatal MI, angina, stroke or TIA); (iv) reported relative risk/risk ratio (RR), hazard ratio (HR) or odds ratios (OR) or provided data for calculating the risk estimates.

There was no restriction on sample size or language. Conference proceedings and abstracts were excluded if there was insufficient data for determining the risk estimates and the 95% confidence intervals (CI); or if they were not cohort or case-control studies.

Antiplatelet agents included: acetylsalicylic acid, adenosine reuptake inhibitors, adenosine diphosphate receptor inhibitors, and P2Y12 antagonists. Lipid-modifiers consisted of all statins, bile acid sequestrants, ezetimibe, fibrates and nicotinic acid. Other commonly used cardiovascular medications included thiazide-type diuretics, loop diuretics, aldosterone antagonists, calcium channel blockers (CCBs), α-adrenergic blockers and renin inhibitors.

2.2.3 Assessment of study quality

Zixuan Wang and I assessed the methodological quality of included observational studies reviewing the study design, implementation, loss to follow-up, exposure and outcome determination. I adapted the Newcastle-Ottawa Scale (NOS)(Stang, 2010a) for assessing the quality of the included studies. Separate NOS criteria were used for case-control and cohort studies. Each version has eight items within three domains with a maximum of nine stars (*): selection (representativeness), comparability (due to design or analysis), and outcomes (assessment and follow-up). A study can receive one star for meeting each criterion, while a maximum of two stars can be given for comparability (design or analysis). Studies with one star for comparability only controlled for age and gender in the analysis whereas studies with two stars under comparability also controlled for other important variables such as body

mass index, comorbidity, laboratory tests or use of other relevant medications. A final score ≥ seven was considered as high quality(He et al., 2015).

2.2.4 Data extraction and management

Zixuan Wang and I completed the data extraction form, which was cross-matched to ensure consistency and accuracy. Details of the study duration and design, sample size and participant characteristics, study setting and data source, intervention(s) and outcome(s) definitions, covariates from each of the included studies were extracted. Risk estimates in the form of RR, OR or HR and their corresponding 95% CIs were used as a measure of the association between intervention and outcome. For each study, I extracted the risk estimates adjusted for the greatest number of confounding variables. For studies without an adjusted result, the crude results were used for analysis.

2.2.5 Data analysis

The risk estimates of each observational study were pooled in the meta-analysis to obtain the pooled RR. When a single study presented several risk estimates (i.e., separate estimates for the combination of four and three medications), I adjusted the pooled estimates for within-study correlation. The inverse variance method with random effects models was used to calculate the pooled RRs and 95% CIs(DerSimonian & Laird, 1986).

Heterogeneity was assessed using the Cochran Q test and Higgins' I^2 statistic(Higgins & Thomas, 2020). Galbraith plot and subgroup analyses were carried out to investigate potential sources of heterogeneity and conduct

sensitivity analyses. Galbraith plot evaluates the weight of each study on the meta-analysis by estimating the average RR and its contribution to the Q test(Galbraith, 1988). In sensitivity analyses, I excluded studies with the high weight shown by the Galbraith plot and repeated the random-effects meta-analysis. Subgroup analyses were conducted to identify study-level heterogeneous factors, which included design (prospective cohort study, retrospective cohort study and case-control study), diagnosis of CVD (CHD, acute coronary syndrome (ACS), MI and stroke), age (<65 years, 65-75 years and >75 years), length of follow-up (<1 year, 1 year and >1 year), study regions (Europe, Asia, North America, multi-regions) and different treatment groups. All statistical analyses were performed using STATA version 15.0 and Revman version 5.3.

2.3 Results

2.3.1 Results from systematic literature search

A total of 10,970 records up to October 2018 and 1733 updated records up to January 2020 were exported from the literature research. Titles and abstracts were screened, and the full texts of 91 articles were further reviewed. Twenty-seven studies met the inclusion criteria for this systematic review, involving 266,536 participants with CVD. Figure 2-1 shows the search and selection process.

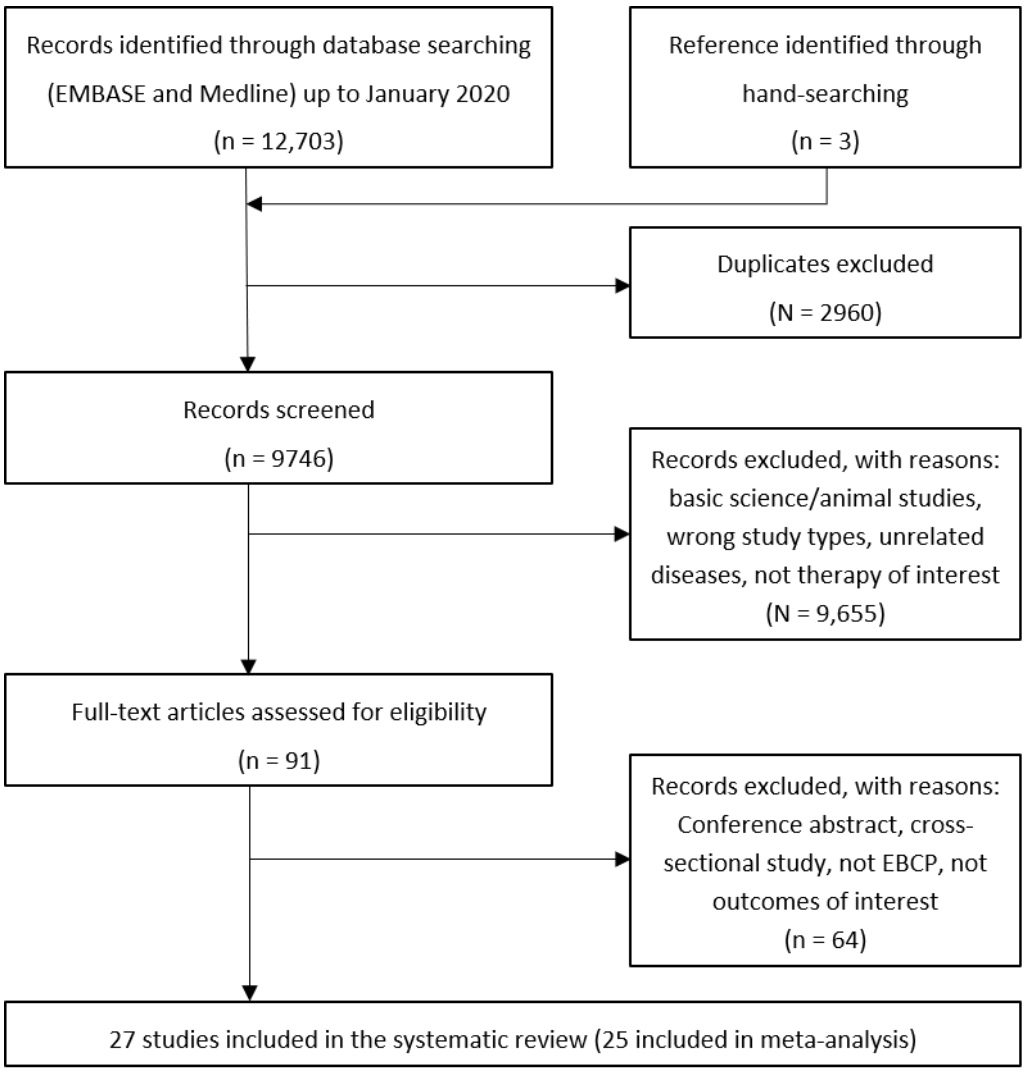

Figure 2-1 PRISMA flow chart summarising study identification and selection

2.3.2 Characteristics and quality of included studies

Table 2-1 summarise the characteristics of the included studies. All studies were published in English and from 2005 onwards: 14 were prospective cohort studies, 10 were retrospective cohort studies(Al-Zakwani et al., 2012, 2018; Amann et al., 2014; Bauer et al., 2010; Bezin et al., 2017, 2018; Bramlage et al., 2010; S. J. Chen et al., 2017; Cirillo et al., 2020; Danchin et al., 2005; Ge et al., 2019; Gouya et al., 2007; Gunnell et al., 2013; Kopel et al., 2014;

Kugathasan et al., 2018; Lafeber et al., 2013; Lahoud et al., 2012; J. H. Lee et al., 2010; Mukherjee et al., 2004; Park & Ovbiagele, 2015; Tay et al., 2008; Timóteo et al., 2006; Yan et al., 2007; Zeymer et al., 2011), and 3 were case-control studies(Hippisley-Cox & Coupland, 2005; Kirchmayer et al., 2013; van der Elst et al., 2007).

Two studies from Al-Zakwani were included. Both of the studies evaluated the impact of EBCP on 1-year all-cause mortality in patients with the acute coronary syndrome (ACS), but they used different registry designs. The study in 2012 used Gulf Race Registry II design that recruited 7,588 consecutive ACS patients from 6 Middle Eastern Gulf countries. The study in 2018 used Gulf COAST registry which recruited 4,055 consecutive citizens who were admitted to hospitals with a confirmed diagnosis of ACS from 4 Middle East Gulf countries. Two cohort studies from Bezin were included. The two studies assessed the long-term effectiveness of EBCP in secondary prevention of ACS using data from the French national health care insurance system database. The study in 2017 included 2874 patients, and the study in 2018 included 31,668 patients with an incident ACS. The summary of study design and results was shown in Appendix C.

Twenty-six observational studies included were considered as high quality according to their NOS score ≥ seven (Appendix D and E). The study of Timoteo *et al.* .(Timóteo et al., 2006) was not included in the meta-analysis due to the low quality with a NOS score of five.

Table 2-1 Characteristics of included studies

Author, year	Study design	Country and region	Inclusion Criteria	No. of Participants	Mean Age ± SD (Range)	Study duration	Medications	Exposure ascertainment	Outcome assessment
Al-Zakwani 2012	Prospective cohort study	6 Middle Eastern countries	Consecutive patients hospitalised with ACS	7567	56 ± 12	1 year	Combination of antiplatelet beta-blockers, ACEIs/ARBs and statin	Structured interview; discharge drugs	Telephone interviews
Al-Zakwani 2018	Prospective cohort study	4 Middle Eastern countries	Consecutive patients hospitalised with ACS; aged ≥18 years	3681	EBM:60 ± 12 No-EBM:60 ± 14	1 year	Combination of antiplatelet therapy, beta-blockers, ACEIs/ARBs and statin	Clinic visits or telephone interviews; discharge drugs	Clinic visits or telephone interviews
Amann 2014	Prospective cohort study	Germany	Consecutive patients hospitalised for an AMI	3844	62 (28-74)	6 years	Combination of antiplatelet agents, beta-blockers, ACEIs/ARBs and statin	Structured interview; discharge drugs	German population-based AMI registry; structured interview
Bauer 2010	Prospective cohort study	Germany	Consecutive hospital survivors of AMI	11823	Group 1: 71.1 (61.8-79) Group 2: 65.0 (56.0-73.4)	1 year	ASA, clopidogrel, bata-blocker, ACEIs/ARBs and statin	Structured interview; discharge drugs	Structured interview following determined criteria
Bezin 2017	Retrospective cohort study	France	Patients hospitalised for an ACS; aged ≥20 years	2874	67 (56-77)	3.6 years (2.2-5.3)	Bata-blockers, antiplatelet agents, statins and ACEIs/ARBs	EGB database; ATC code; exposure defined according to drug dispensing in the 3-month period following initial ACS	EGB database; ICD-10 codes
Bezin 2018	Retrospective cohort study	France	Patients hospitalised for an incident ACS; aged ≥20 years; treated with the full EBCM combination in the 90 days following ACS; affiliated with the general scheme of the French health insurance system; excluding if died during the first 90	31668	65 (55-76)	4.1 years (3.5-4.4)	Beta-blockers, antiplatelet agents, statins and ACEIs/ARBs	SNIIRAM database; ATC codes	SNIIRAM database; ICD-10 codes

Author, year	Study design	Country and region	Inclusion Criteria	No. of Participants	Mean Age ± SD (Range)	Study duration	Medications	Exposure ascertainment	Outcome assessment
			days						
Bramlage 2010	Prospective cohort study	Germany	Consecutive patients hospitalised for an AMI	5353	EBCP: 66.3 (56.9-75.1) Sub-EBCP: 70.5 (60.9-79.1)	1 year	Combination of ACEIs/ARBs, beta-blockers, statins, aspirin, clopidogrel unless contraindicated	Structured interview; secondary prevention at hospital discharge	SAMI registry; structured interview following determined criteria
Chen 2017	Retrospective cohort study	China	CAD patients	3176	EBCP: 64.4 Non-EBCP: 64.4	27.1 months	Combination of antiplatelet agents, statins, beta-blockers and ACEIs/ARBs	Medical records; discharge drugs	CAD database of West China hospital; identified with determined criteria; followed telephone or hospital-visits
Cirillo 2019	Prospective cohort study	Italy	ACS patients	770	OMT:66 ± 12 No-OMT:67 ± 13	1 year	DAPT (aspirin and a P2Y12 inhibitor), beta-blockers, statins, and ACEIs/ARBs	START ANTIPLATELET Registry; structured interview	Structured interview; validated by study physicians.
Danchin 2005	Prospective cohort study	France	Consecutive patients with AMI	2119	Triple therapy: 71 (58-79) Non-triple therapy: 62 (51-72)	1 year	Combination of antiplatelet agents, beta-blockers and statins	Structured interview; discharge drugs	Structured interview
Ge 2018	Retrospective cohort study	US	ACS patients undergoing PCI	4834	GDMT:62.4 ± 12.9 No-GDMT:65.6 ± 13.6	1 year	GDMT: combination of aspirin, a P2Y12 inhibitor, a statin, a beta-blocker and an ACEIs/ARBs	The National Cardiovascular Data Registry Catheterization PCI database	Database

Author, year	Study design	Country and region	Inclusion Criteria	No. of Participants	Mean Age ± SD (Range)	Study duration	Medications	Exposure ascertainment	Outcome assessment
Gouya 2007	Retrospective cohort study	Austria	Patients with AMI	250	70 ± 14 (34-93)	552±200 days	ACEI/ARB, beta-blockers, antiplatelet agents and lipid-lowering agents	BGKK database; ATC codes; discharge drugs	BGKK database; ICD-9 codes
Gunnel 2013	Retrospective cohort study	Australia	Patients hospitalised for a first AMI	9580	Hierarchy	11 years	Beta-blockers (BB), statins (ST) and ACEI/ARB	PBS register; PBS item codes; drugs received during the 29-day exposure period post-discharge for the primary AMI	Hospital morbidity data collection; Mortality Register; ICD-9 codes
Kopel 2014	Prospective national cohort study	USA	Hospital survivors of ACS	9107	1 drug: 67 ± 14 2 drugs: 65 ± 14 3 drugs: 63 ± 13 4 drugs: 63 ± 12	1 year	Antiplatelet, beta-blockers, statins, ACEIs/ARBs	Structured interview; discharge drugs	ACS Israeli Survey; National Population Registry; computerised audit checks and queries
Kugathasan 2019	Retrospective cohort study	Denmark	Patients admitted with first myocardial infarction; the cohort was dichotomously divided by a diagnosis of schizophrenia	105,018	Patients with schizophrenia: 57.3 General MI patients: 61.0	796,435 person-years	Antiplatelets, vitamin K antagonists, beta-blockers, ACEIs and statins	Danish National Patient Registry(NPR); ATC codes	Danish Causes of Death Registry
Lafeber 2013	Prospective cohort study	Netherlands	Patients with CAD	2706	60 ± 9	5.0 years (2.4-10.2)	Aspirin, statins, BP-lowering agents	Structured interview	Structured interview
Lahoud 2012	Retrospective cohort study	Michigan	ACS patients; aged ≥18 years; excluding if died before discharge or lost to follow-up at 2 years	2684	Men: 61.1±12.9 Women: 65.8±14.2	2 year	Aspirin, Beta-blockers, ACEIs/ARBs, and lipid-lowering agents	The University of Michigan Health System; telephone calls	Two year follow-up data were obtained via telephone calls and review of the

Author, year	Study design	Country and region	Inclusion Criteria	No. of Participants	Mean Age ± SD (Range)	Study duration	Medications	Exposure ascertainment	Outcome assessment
									National Death Index
Lee 2010	Prospective cohort study	Korea	Hospital survivors of AMI	9294	63.8 ± 12.5	180 ± 35 days	Combination of antiplatelet agents, statins, beta-blockers and ACEIs/ARBs	Structured interview; discharge drugs	KAMIR registry; medical records; telephone interview
Mukherjee 2004	Prospective cohort study	USA	Patients with ACS	1358	63.7 ± 13.3	6 months	Antiplatelet drugs, BB, ACEIs and lipid-lowering agents	Structured interview; discharge drugs	Health system record review or phone call interview
Park 2015	Retrospective cohort study	USA, Canada and Scotland	Non-cardioembolic stroke patients aged ≥ 35 years old	3680	Level 0: 63.3 ± 11.5 Level 1: 65.6 ± 12.5 Level 2: 67.2 ± 11.1 Level 3: 65.7 ± 10.2	2 years	Antihypertensive agents, lipid modifiers and antithrombotic agents. Composite appropriateness level: level 0, none of the indicated medications prescribed; level 1, 1 medication prescribed even though 3 medications indicated; level 2, 2 medications prescribed even though 2 medications indicated; and level 3, all indicated medications were prescribed.	Data from VISP trial; structured interview	Data from VISP trial; structured interview
Tay 2005	Prospective cohort study	Singapore	Consecutive patients with confirmed MI	5529	Young: 57 ± 10.7 Elderly: 81.42 ± 5.3	1 year	Antiplatelet agents, beta-blockers, ACEIs/ARBs, lipid-lowering agents	Structured interview; discharge drugs	Structured interview
Timoteo 2006	Retrospective cohort study	Portugal	Consecutive patients hospitalised for ACS	368	65 ± 13	30 days	Antiplatelet agents, beta-blockers, ACEIs, statins	Hospital clinical data; drugs at discharge or of and event, whichever	Hospital clinical data or telephone contact

Author, year	Study design	Country and region	Inclusion Criteria	No. of Participants	Mean Age ± SD (Range)	Study duration	Medications	Exposure ascertainment	Outcome assessment
								occurred first	
Yan 2007	Prospective cohort study	Canada	Patients with ACS	5833	65 (55, 74)	1 year	Combination of antiplatelet/anticoagulant, beta-blockers, ACEIs and lipid-modifying therapies	Structured interview; discharge drugs	Canadian ACS Registry; structured interview; telephone interview
Zeymer 2011	Prospective cohort study	Germany	Patients with AMI and treated with a beta-blocker at discharge	9998	0-1 drug: 70.1 (60.3, 78.0) 2 drugs: 67.6 (58.2, 76.3) 3 drugs: 64.7(55.5, 73.0)	396 days	Aspirin, ACEIs and statins	Structured interview; discharge drugs	ACOS registry; structured interview
Hippisley 2005	Nested case-control study	UK	Patients with a fist diagnosis of ischemic heart disease	13029	Cases: 80 (73, 86) Controls: 80 (73, 85)	Cases: 20.3 months; controls: 21.0 months	Different combinations of statins, aspirin, beta-blockers and ACEIs	Medical records	QRESEARCH database
Kirchmayer 2013	Nested case-control study	Italy	Patients with a diagnosis of AMI; aged 35-100 years	6880	Women: 72.5 Men: 63.7	994.5 days	Combination of antiplatelet agents, beta-blockers, statins and ACEIs/ARBs	Regional registry; ACT classification system	Data from the HIS; regional MIS database; ICD-9-CM codes
Van 2007	Nested case-control study	Netherlands	Patients with a history of MI	3513	Cases: 66.8 Controls: 66.0	Cases: 32.6 months; controls: 30.7 months	Different combinations of statins, antiplatelet agents, beta-blockers and ACEIs	Medical records	PHARMO record linkage system; ICD-9-CM codes

2.3.3 Mortality

I included nine cohort and two case-control studies that provided mortality results from combinations of EBCP and compared the risk of all-cause mortality with none or one component of EBCP in the primary meta-analysis (Fig 2-2). All the included studies presented a potential benefit of combination therapy with a lower risk of all-cause mortality. The pooled RRs of cohort and case-control studies were 0.30 (95% CI 0.24-0.36) and 0.41 (95% CI 0.36-0.51) respectively. Overall, the use of combination therapy reduced the risk of all-cause mortality by 67% (95% CI 61%-71%). In the study of Tay *et al*. (Tay et al., 2008), the outcomes were examined between younger patients (age < 75 years) and elderly patients separately. Younger patients benefited more from combination therapy than elderly individuals. The study of Lahoud *et al*. examined the effect of EBCP in male and female patients. The results showed a lower risk of mortality in male patients receiving EBCP than female patients(Lahoud et al., 2012).

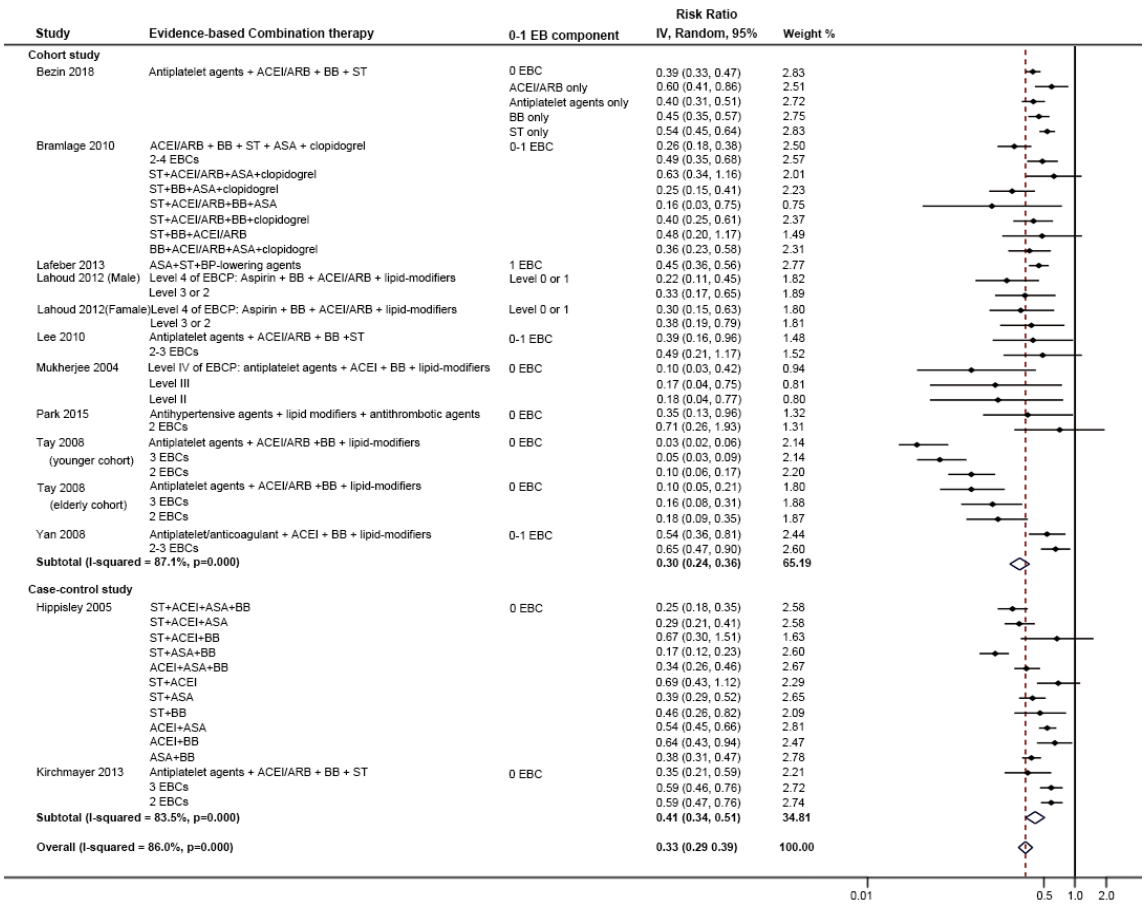

Figure 2-2 Comparison: EBCP versus 0-1 EB component, Outcome: all-cause mortality.

Compared with non-EBCP, the RRs of all-cause mortality improved with each additional component of EBCP added: 0.62 (95% CI 0.51-0.75), 0.39 (95% CI 0.29-0.52), 0.24 (95% CI 0.14-0.41) and 0.16 (0.07, 0.33) in patients with one, two, three and four components respectively. Overall, the use of evidence-based cardiovascular medications reduced the risk of all-cause mortality by 68% (95% CI 60%-74%) compared with none medication (Fig 2-3). Compared with suboptimal

EBCP (less than 4 components), optimal EBCP was associated with a lower risk of all-cause mortality by 37% (95% CI 31%-42%) (Fig 2-4). The effects were similar in all patients with CHD (RR: 0.56, 95% CI 0.46-0.66), and subgroups of: acute coronary syndromes 0.65 (95% CI 0.58-0.73), MI (RR: 0.63, 95% CI 0.57-0.69), and angina (RR: 0.59, 95% 0.37-0.92) (Fig 2-4).

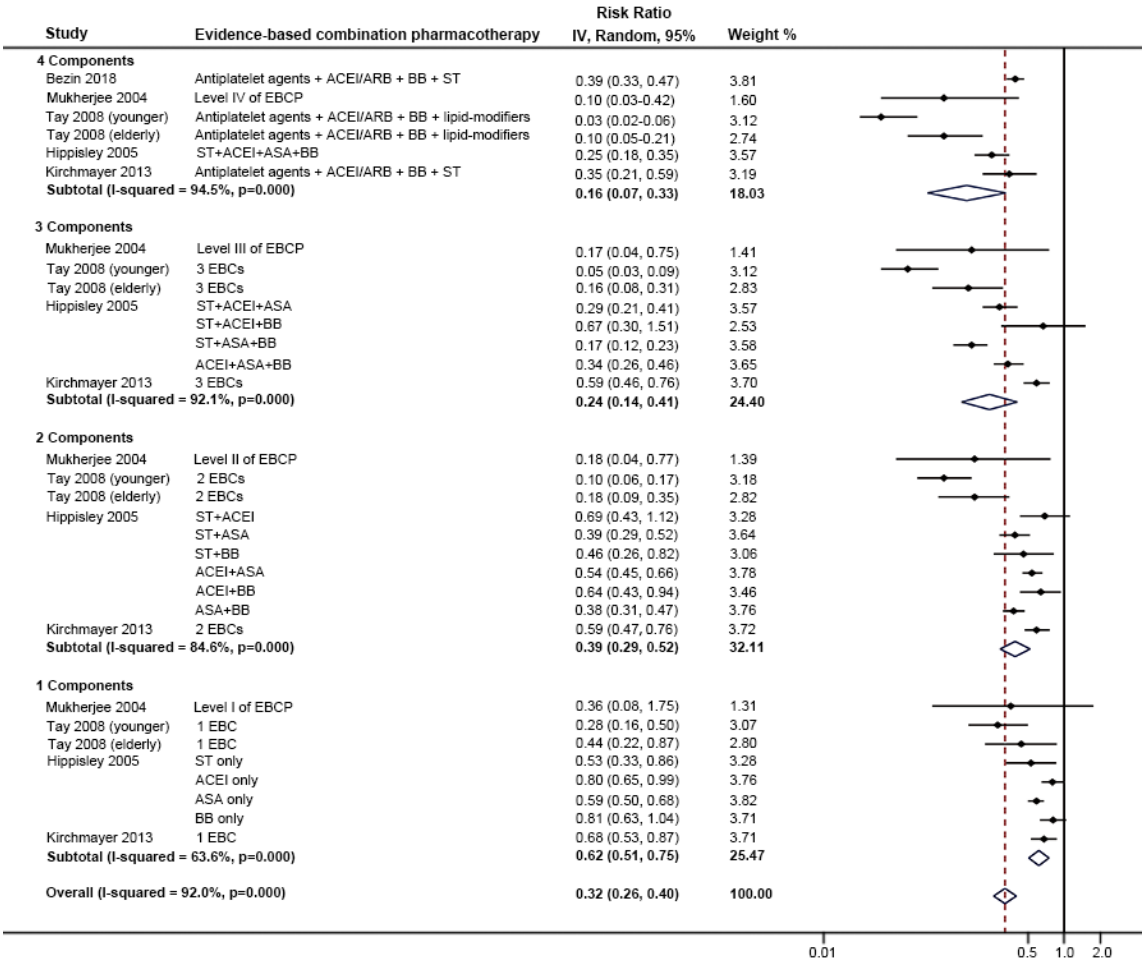

Figure 2-3 Comparison: combination therapy of different numbers of components versus 0 component, Outcome: all-cause mortality.

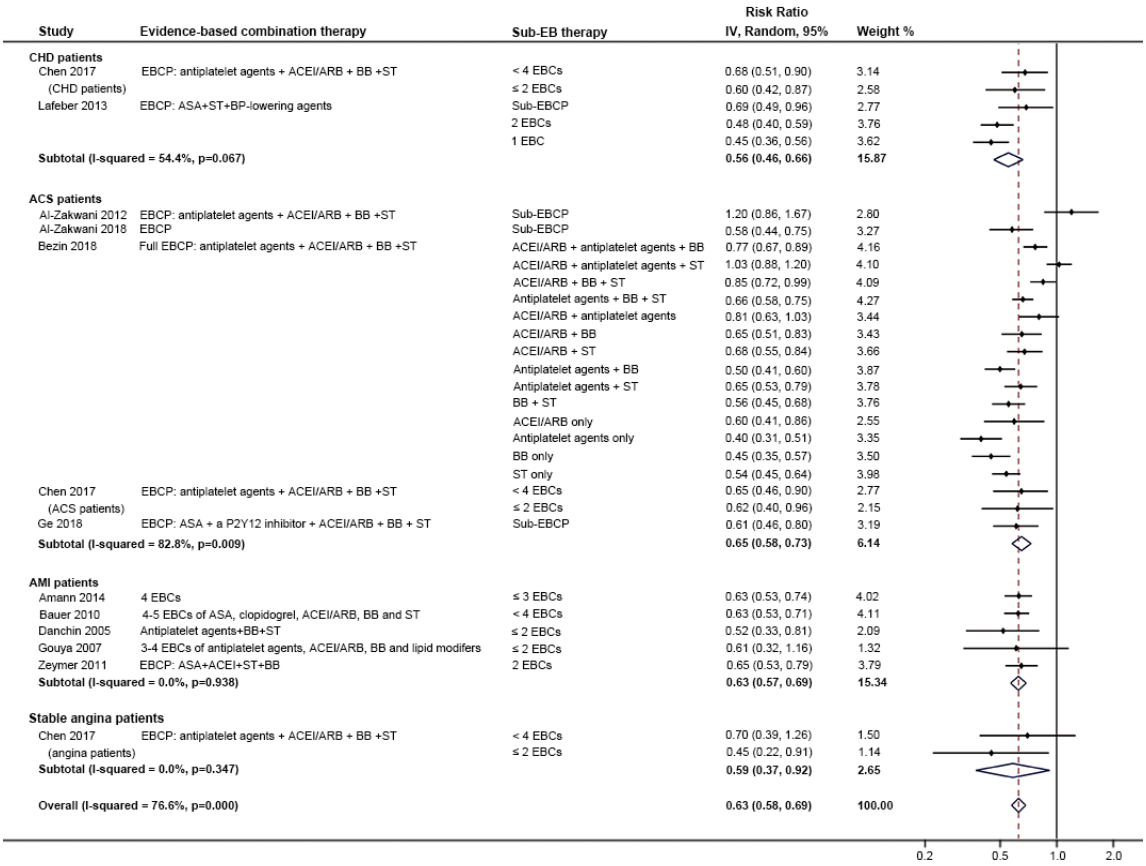

Figure 2-4 Comparison: EBCP versus sub-EBCP (< 4 components), Outcome: all-cause mortality.

To assess the weight of each component of EBCP on outcomes, I evaluated pooled estimate effects of combination therapy excluding any one component (Fig 2-5). The results show that omitting any one component would reduce the potential beneficial effects of optimal EBCP (RR: 0.22, 95% CI 0.14, 0.34). The changes were greatest when excluding antiplatelet agents (RR: 0.60, 95% CI 0.47, 0.77). The difference was modest when omitting beta-blocker (RR: 0.47, 95% CI 0.36, 0.63) and statins (RR: 0.44, 95% CI 0.35, 0.55). The change of pooled estimate of omitting ACEIs/ARBs is shown to be inconspicuous (RR 0.31, 95% CI 0.22, 0.44).

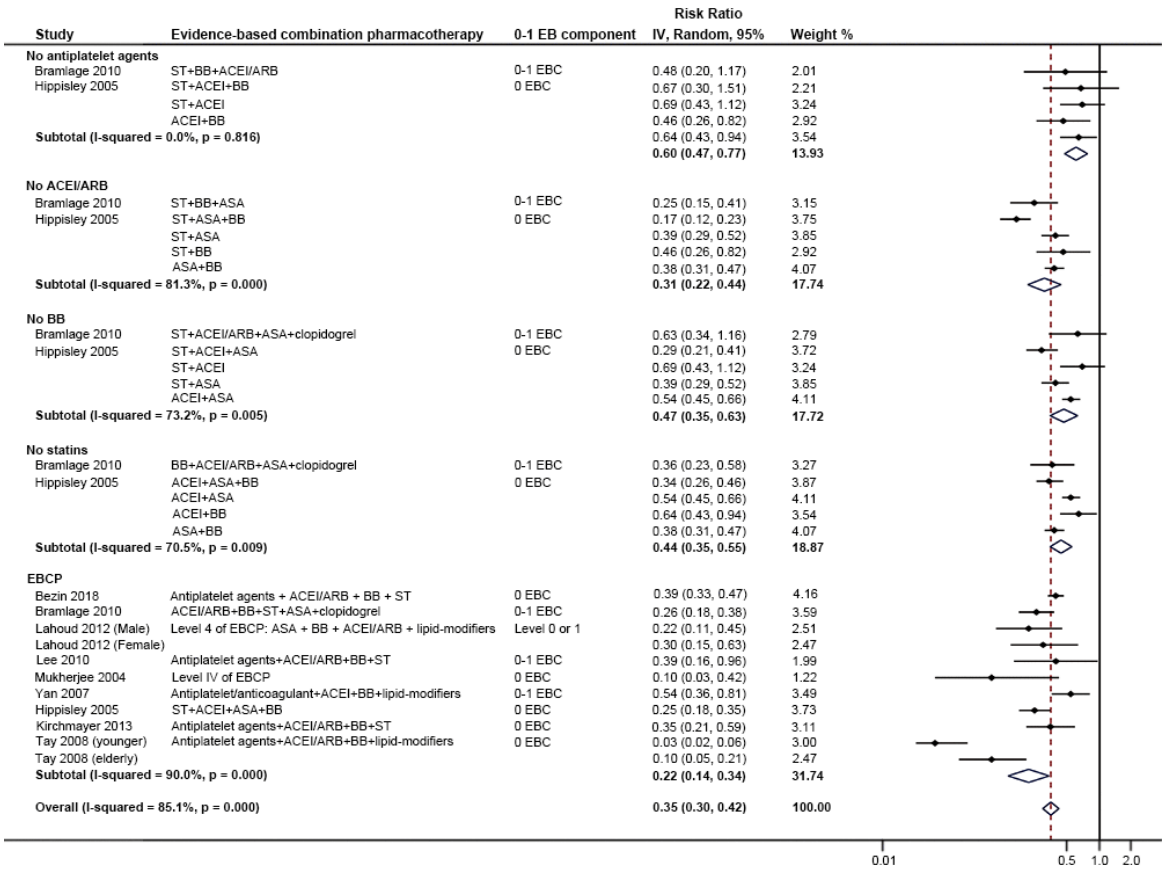

Figure 2-5 Comparison: combination excluding one component versus 0-1 EB component, Outcome: all-cause mortality.

2.3.4 Major cardiovascular events

Three studies reported a composite outcome of mortality and major non-fatal cardiovascular events (Bezin et al., 2017; Lafeber et al., 2013; Park & Ovbiagele, 2015). Compared with none or one component treatment, EBCP (>one medication) was associated with a lower risk of the composite outcome (RR: 0.55, 95% CI 0.50-0.62). Only Lafeber *et al.* reported the effect of combination therapy on the rate of vascular mortality, with an RR of 0.44 (95% CI 0.33, 0.58) (Lafeber et al., 2013). The pooled result of Lafeber *et al.* (Lafeber et al., 2013), Kirchmayer *et al.*

(Kirchmayer et al., 2013) and Van *et al.* (van der Elst et al., 2007) showed that combination treatment decreased the risk of MI by 52% (95% CI 35%-64%). Regarding cerebrovascular events, combination medication use also yielded a beneficial effect (RR: 0.58, 95% CI 0.42-0.81). In summary, compared with none or one EBCP component, the use of combination therapy reduced the relative risk of major cardiovascular events by 47% (95% CI 41%-52%) (Fig 2-6). Compared with suboptimal EBCP (less than 4 components), optimal EBCP was associated with a lower risk of cardiovascular events by 32% (95% CI 28%-37%) (Fig 2-7). The results present that optimal EBCP reduced the risk of the composite outcome by 30% (95% CI 25%-36%), vascular mortality by 52% (95% CI 43%-60%), MI by 31% (95% CI 20%-40%) and cerebrovascular events by 35% (95% CI 18%-49%).

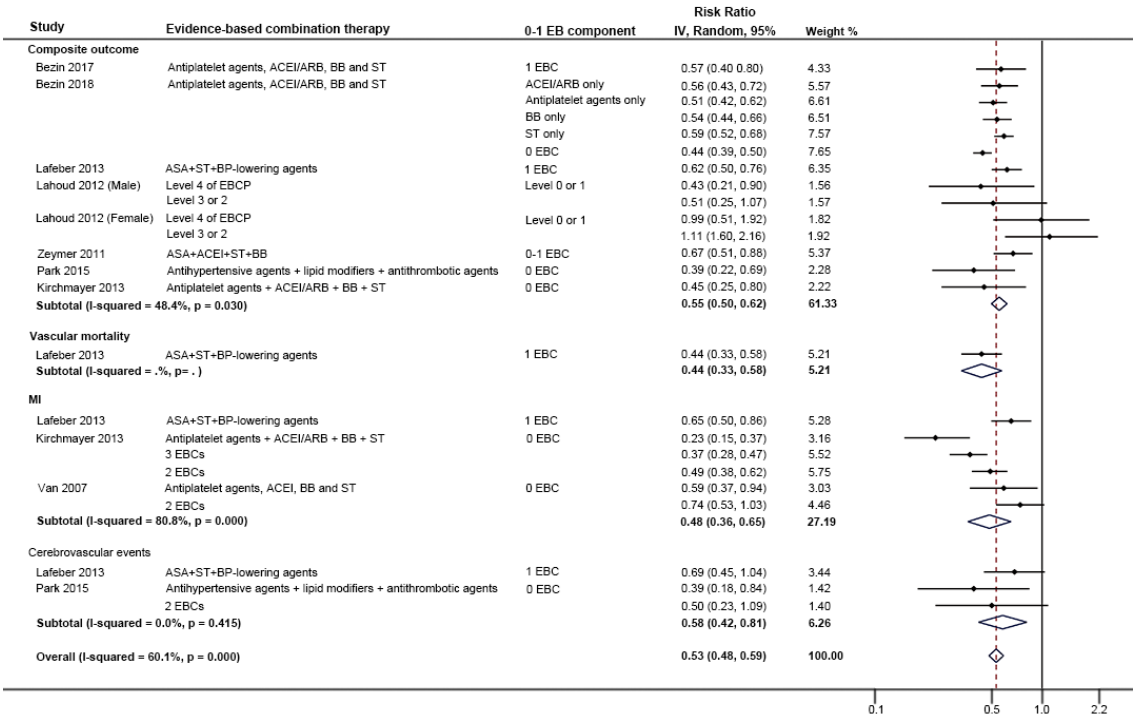

Figure 2-6 Comparison: EBCP versus 0-1 EB component, Outcome: major CV events.

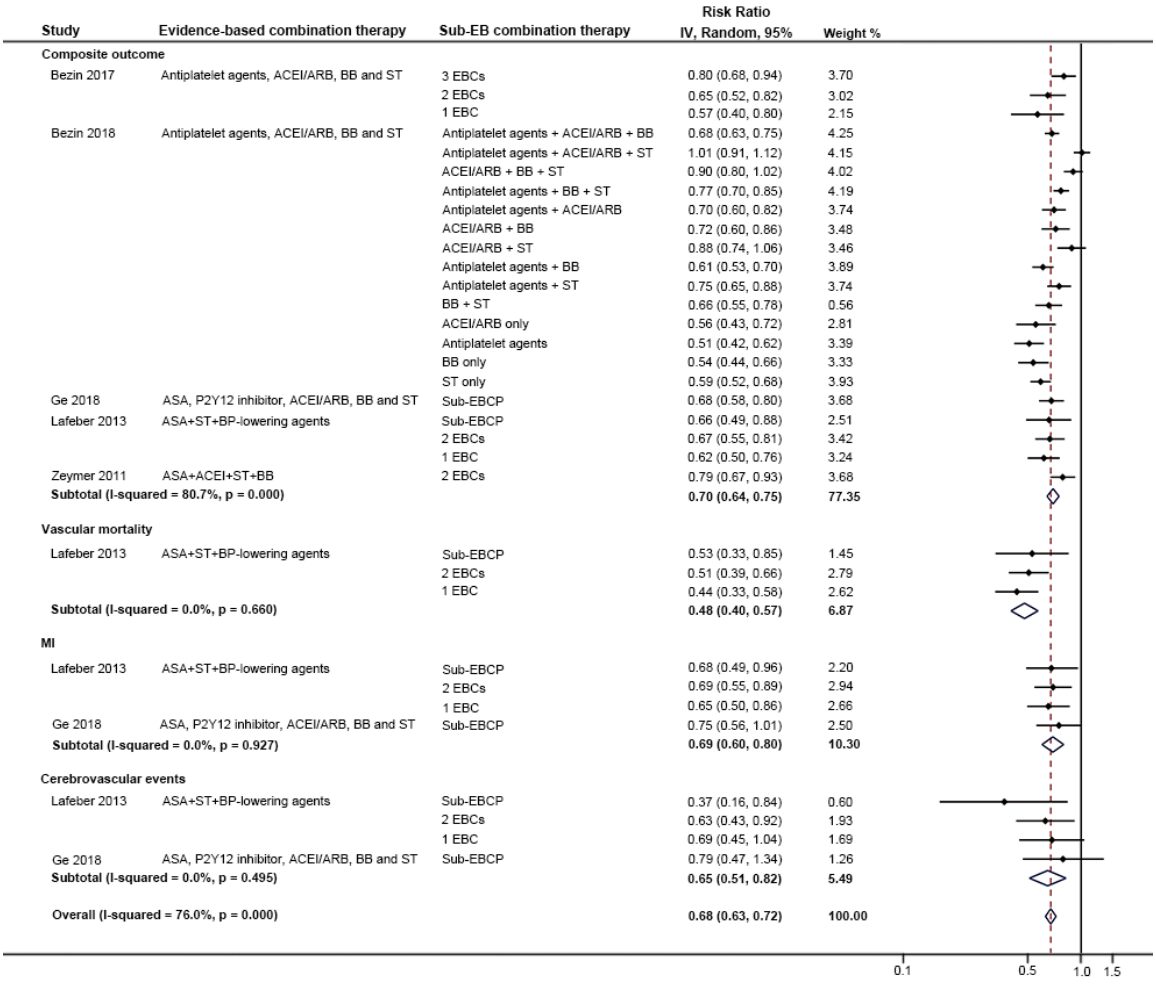

Figure 2-7 Comparison: EBCP versus sub-EBCP (< 4 components), Outcome: Subgroups of major CV events

2.4 Sensitivity analysis

The heterogeneity of the primary meta-analysis was high, with I^2 = 86.0% ($p < 0.001$) (Fig 2-2). In the Galbraith plot (Appendix F), the study of Bramlage *et al.* (Tay et al., 2008) induced the highest heterogeneity, followed by Hippisley *et al.*

(Hippisley-Cox & Coupland, 2005), Kirchmay *et al*. (Kirchmayer et al., 2013), Yan *et al*. (Yan et al., 2007) and Tay *et al*(Tay et al., 2008). I repeated the primary meta-analysis with the random-effects model after excluding each of the five studies (Appendix G). The study of Tay *et al.* was shown to be the largest contributor to heterogeneity. When omitting the study, I^2 decreased to 69.0% though the pooled RR did not change remarkably (0.40, 95% CI 0.35, 0.45).

I undertook subgroup analyses to examine the potential sources of heterogeneity related to age, study regions, different diagnoses, length of follow-up and study designs on the EBCP's effect on all-cause mortality (Appendix H). The results show significant differences between subgroups in age (P = 0.02) and region (P < 0.01) and different diagnoses (P = 0.05) indicating the three covariates were likely to be associated with heterogeneity. Conversely, length of follow-up (P = 0.99) and study designs (P = 0.08) did not affect the heterogeneity of the primary meta-analysis. The results of subgroups by age show that younger patients may benefit more from reductions in all-cause mortality from EBCP than elderly individuals, with RRs of 0.17 (95% CI 0.08, 0.33) in patients aged <65, and 0.44 (95% CI 0.37, 0.51) and 0.33 (95% CI 0.26, 0.43) for 65-75 and >75 years old respectively. In terms of the subgroup analyses between different regions, the relative risk of mortality was lower in Asian patients on EBCP (RR: 0.12, 96% CI 0.07, 0.23) than patients in Europe (RR 0.40, 95% CI 0.35, 0.46), Canada/USA (RR 0.34, 95% CI 0.24, 0.50) or multi-region of USA, Canada and Scotland (RR 0.50, 95% CI 0.25, 1.01). Besides, the differences between different diagnoses (RR: stroke: 0.50, ACS: 0.37,

CHD: 0.39 and AMI: 0.25) were also presented to be related to the heterogeneity. In addition, I performed another sensitivity analysis within studies which had the reference group of 0 EBCP medication (Appendix I). The results showed no significant difference from the primary meta-analysis (Fig 2-2).

2.5 Discussion

The meta-analysis of observational studies conducted in this chapter assessed the effects of EBCP with antiplatelet agents, ACEIs/ARBs, beta-blockers, and lipid-modifiers on mortality and major cardiovascular events in CVD patients. The results show a benefit for EBCP, suggesting an overall decrease in the risk of all-cause mortality (by 67%, 95% CI: 61%-71%) and cardiovascular events (by 47%, 95% CI: 41%-52%) compared to either monotherapy or no therapy.

In this systematic review, I examined the effects of increasing the number of components of EBCP. The results show that each additional component of EBCP could confer additive survival benefit of patients with CVD with a median follow-up of one year. When weighing the impact of each component, the results of the meta-analysis showed that antiplatelet agents made the greatest contribution to the beneficial effects of combination therapy on survival in patients with CHD. Excluding antiplatelet agents from optimal EBCP decreased the beneficial effects by 38%. Evidence from RCTs has demonstrated the benefit of antiplatelet therapy to major cardiovascular events (non-fatal MI, non-fatal stroke or vascular death). A

meta-analysis of 193 RCTs reported that antiplatelet therapy produced a significant 15% reduction in vascular deaths (P<0.0001) and about one-sixth of all-cause mortality (P<0.0001)(BERITIC, 1962). The evidence available from the literature for beta-blockers and statin therapy is equally as strong. A meta-analysis of 147 RCTs suggested that beta-blockers could reduce CHD events by 29% (RR 0.71, 95% CI 0.66, 0.78). Additional RCT studies have also shown that beta-blockers play an important role in reducing mortality and morbidity for up to a year after an MI (Finsterer & Stöllberger, 2008). A meta-analysis of 14 RCTs of statins also demonstrated that statins could reduce the risk of all-cause mortality by 12% and major vascular events by 21% (Trialists, 2005). Thus, beta-blockers and statins count as valuable components of the optimal EBCP for CVD. The results of the meta-analysis showed a more modest effect for ACEIs/ARBs as part of EBCP. The included two studies reported that the inclusion of ACEIs/ARBs in combination with statins, antiplatelet agents and beta-blockers was associated with a lower risk of mortality (Bramlage et al., 2010; Hippisley-Cox & Coupland, 2005). However, different results were found in the study of Bezin *et al.* in 2018(Bezin et al., 2018). The study compared the effect of 3-EBCP combinations and full EBCP on all-cause mortality, and found long-term use of ACEIs/ARBs made the greatest contribution to the beneficial effects of full EBCP, followed by statins and antiplatelet agents. Long-term use of beta-blockers appeared to have little effect on all-cause mortality in patients experienced an ACS. The present meta-analysis only included two studies. They mainly compared outcomes with individuals who exposed to none or

one component of EBCP. Different methodological choices among the three studies may partly explain the inconsistent results.

In this systematic review, I found some research gaps in terms of EBCP in secondary prevention of CVD.

Firstly, most studies included in the systematic review are based on CHD patients. Only the study of Park *et al.* (Park & Ovbiagele, 2015) was conducted in stroke patients. There is a paucity of evidence for the benefit of EBCP in reducing the mortality risk in stroke patients, even though stroke represents a significant proportion of all cardiovascular disease. Whilst co-morbidities and risk factors cluster together, and there is still a lack of data regarding any potential mortality benefit of ACEI and beta-blocker in post-stroke patients who otherwise do not have an indication for their prescription. This should be a priority area for further research.

Secondly, even though I did not limit any other conditions co-existing with CVD in the study population, I could not find any studies specifically evaluating the effects of EBCP for secondary prevention of CVD in patients with comorbidities. Only the study of Bezin *et al.* in 2018(Bezin et al., 2018) additionally investigated the effect of EBCP in patients with a history of heart failure. Most of the studies included in my review adjusted the risk estimates with comorbidities. Thus I was unable to identify if the results are applicable equally in the presence of other conditions. Comorbidities are highly prevalent in patients with CVD. A Dutch nationwide study

found the percentage of patients with comorbidity were 40% and 32% in coronary heart disease and cerebrovascular disease, respectively (Buddeke et al., 2017). In the context of clinical and functional heterogeneity, CVD patients with different co-conditions may have different responses to pharmacotherapy. In addition, interactions between cardiovascular medications and treatment for comorbidities also need attention. For example, some nonsteroidal anti-inflammatory medications like ibuprofen and naproxen are known to interfere with the antiplatelet effects of aspirin (Capone et al., 2005; Hudson et al., 2005) as well as affect renal function and hence handling of all components of EBCP, in particular ACEIs and ARBs.

Thirdly, most studies included in this systematic review only focused on the combination of aspirin, clopidogrel, beta-blockers, ACEIs/ARBs and statins, observational evidence for the combination of some other commonly used medications is lacking. This may in part be due to a lack of mortality benefit for many of these medications tested in randomized trials (e.g. diuretics, CCBs (Lv et al., 2012), and fibrates (D. Wang et al., 2015)), a lack of conclusive evidence of benefits for some medications on secondary prevention of CVD (e.g. spironolactone and eplerenone (Walker et al., 2014)), but may also be due to a lack of follow-up time for newer medications that have come to market, e.g. sacubitril/ valsartan combination.

Finally, the length of follow-up in most of the included studies was less than one

year, and only the effects of medications in discharge were examined without considering other important long-term effects. These include the possibility of sequential medication exchange or poor medication adherence. Only the study of Bezin *et al.* (Bezin et al., 2017) reported the cumulated use of cardiovascular medications, showing a persistent benefit of combination therapy and additionally reductive effects on the occurrence of major adverse cardiac events or mortality when increasing the number of components.

2.5.1 Strengths and limitations

In the absence of RCTs, I did the systematic review of observational studies. This review has several strengths. Firstly, I undertook extensive analysis in exploring potential variables that could affect the effects of secondary prevention for CVD, hence providing clinicians with an evidence base for their decision-making. Secondly, the results are robust and consistent, as shown by my extensive analyses by using influence analysis, subgroup analysis and sensitivity analysis.

There are some limitations to the current study. Firstly, the results of some subgroup analyses were not credible enough because only one study was included. Secondly, differences in study designs, exclusion criteria, control groups selection, duration of follow-up, exposure and outcome definitions, including covariates and analyses models can affect the accuracy of pooled estimates for both crude and adjusted RRs. Thirdly, several studies reported the estimated effect sizes with HRs and ORs instead of RRs, and the exact statistical method was not clearly described.

I was not able to exclude the influence on results by combining these three types of estimates in the meta-analysis. The variability between studies was unavoidable, and the study conclusions should be evaluated alongside the reported heterogeneity. Nevertheless, I conducted sensitivity analyses to examine the impact of heterogeneity between studies and assessed the potential causes of heterogeneity. In addition, as studies included in each meta-analysis were less than ten, I did not examine the publication bias (J. A. C. Sterne et al., 2011; Jonathan A.C. Sterne et al., 2000). Considering all included studies reported a positive effect of combination therapy only with a difference in the extent. Therefore I think that important publication bias due to a preferential publication of large studies with positive findings has not occurred.

Chapter 3: Research aims and objectives

3.1 Aims

The aim of this PhD project was to investigate the patterns of cardiovascular polypharmacy and to assess the impact of multiple cardiovascular medications on long-term survival in patients following the incident CHD or stroke.

3.2 Objectives

Specific objectives of this PhD project included:

1. To describe the patterns (numbers, classes and combinations) of cardiovascular medications initially prescribed in patients with the first diagnosis of CHD or stroke (Chapter 5).
2. To investigate the association between potential factors and cardiovascular polypharmacy (Chapter 5).
3. To examine the impact of increasing numbers and classes of cardiovascular medications and different combination regimens on long-term survival in overall patients who experienced an incident ischemic stroke (Chapter 6).
4. To examine the impact of increasing numbers and classes of cardiovascular medications and different combination regimens on long-term survival in overall patients who experienced an incident ischemic stroke and with a

history of type 2 diabetes mellitus (Chapter 7) or with a history of COPD (Chapter 8).

5. To examine the impact of increasing numbers and classes of cardiovascular medications and different combination regimens on long-term survival in patients following the incident MI (Chapter 9).
6. To examine the impact of increasing numbers and classes of cardiovascular medications and different combination regimens on long-term survival in patients following the incident MI and with a history of type 2 diabetes mellitus (Chapter 10) or with a history of COPD (Chapter 11).

Chapter 4: The Health Improvement Network database

The Health Improvement Network (THIN) database (now known as IQVIA Medical Research Data (IMRD)-UK database) is a primary care database which extracts anonymised data from general practices across the UK. It was set up in 2002 as a collaboration between two companies: EPIC (provider of the primary care patient data that is used for medical research) and In Practice Systems (INPS) (developer and supplier of the computer software Vision used by general practitioners in the UK)(Denburg et al., 2011). The THIN data collection began in September 2002; however, electronic records were used as early as 1987(Lo Re et al., 2009). In October 2017, a total of 17 million patients from over 800 general practices had contributed data. The active patients in THIN were over 3.1 million, representing approximately 6% of the UK population. The average length of follow-up over nine years (range 1-25 years)(The Health Improvement Network, n.d.). Figure 4-1 and 4-2 show that the THIN database is nationally representative of the UK population in different age levels and chronic conditions compared to national statistics in the UK. The THIN data reflects the “real-life” clinical practice, allowing rapid analyses in medical research on diseases and medication treatments. Over 1000 research articles have been published.

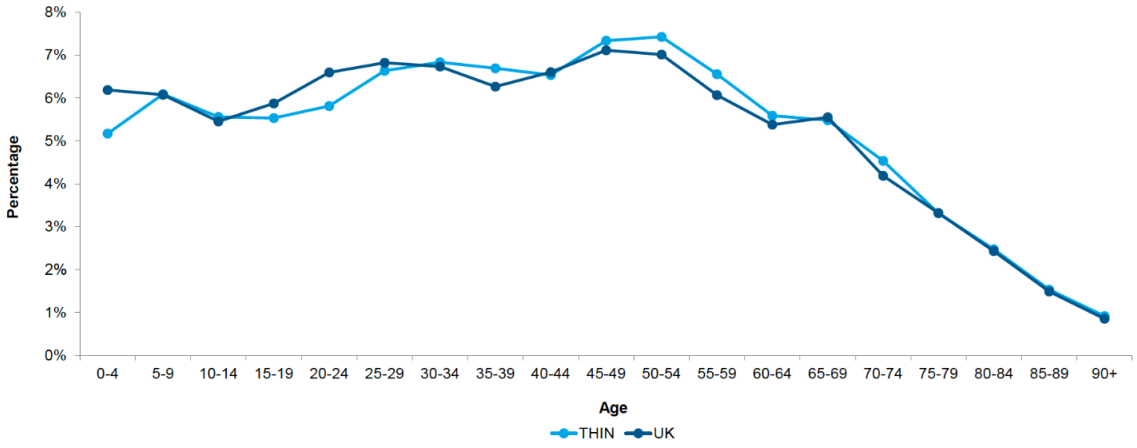

Figure 4-1 The population of THIN (THIN1701 version) compared to the UK (Office for National Statistics UK mid-year counts June 2015).

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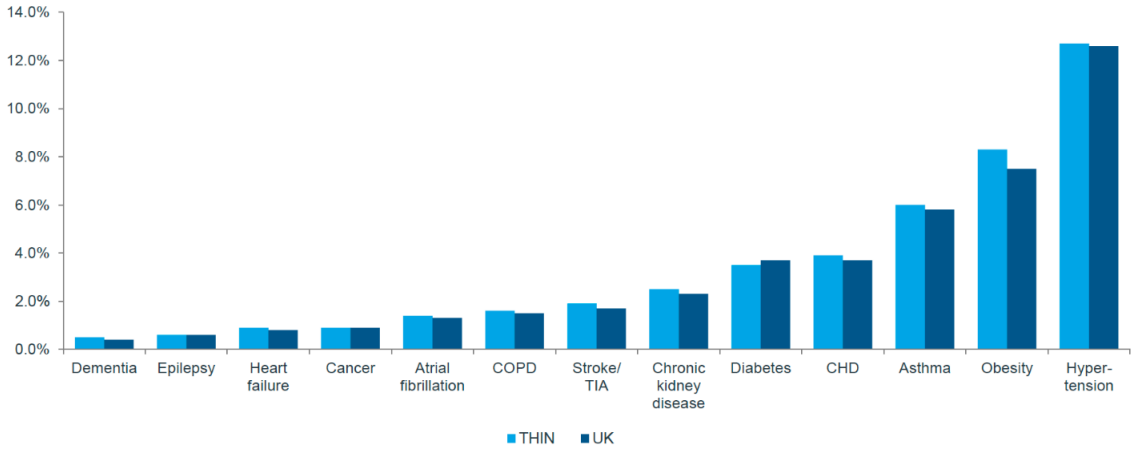

Figure 4-2 Database population representative of the national population (The Quality and Outcomes Framework 2006/2007)

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4.1 Primary care and general practitioner practice

The UK National Health Service (NHS) is organised according to levels of care, depending on how specialised service is. Primary care service provides the first point of contact in the healthcare system, acting as the 'front door' of the NHS. Primary care includes general practitioner (GP) practice, community pharmacy, dentists, and eye health services(United Kingdom National Health Service, 2020h). A GP is always the first doctor if a person has a health problem. All UK residents are entitled to the services of a GP near their home. Patients can register with only one GP at a time. Primary care is based on caring for the person rather than specific conditions, so GPs are generalists rather than specialists in any particular disease area. GP practices can provide a wide range of services including advice on health problems, treatment of common illnesses, prescriptions for medication, management of chronic conditions, examinations and vaccinations. All GP practices in the UK are operated using one type of electronic systems. The GP is informed of medical treatment provided elsewhere, from which significant details are entered on the practice computer. GP practices keep medical records for all their patients, which includes information about any medical conditions, tests, prescribed medications and treatment, referral information, hospital admission and discharge information(Royal Gollege of General Practitioners, 2011).

4.2 Strengths and limitations of THIN data

4.2.1 Strengths

1. THIN is broadly representative of the UK population in general. The data is collected from each GP practice and therefore reflects “real-life” clinical practice as the GP is the first point of contact for all sections of healthcare in the UK. The use of standardised coding systems, and GPs working within guidelines, enables researchers to develop methodologies for database research using pre-collected data. This strength minimises selection bias and improves the validity of epidemiologic studies.
2. THIN represents a defined population. It allows investigators to study all patients with a given disease and control patients from the same source. The well-defined population of the THIN also allows researchers to study families and to link health information in mothers to their children.
3. THIN has a large size of the population which allows studying rare outcomes.
4. THIN provides longitudinal and frequently updated medical records for each patient since the early 1990s in some practices.
5. THIN provides access to original medical records. It allows researchers to verify information captured on death certificates and letters from specialists, without breach of confidentiality.

6. THIN allows a linkage to secondary care information in Hospital Episode Statistics (HES) database. HES data involves details of all admissions, outpatients, accident and emergency attendances, maternity care and critical care at NHS hospitals in England.

4.2.2 Limitations

1. Prescription data in THIN only reflect what was prescribed by GPs. THIN data do not capture data for hospital treatment, treatment in some care homes or nursing homes, and over the counter (OTC) medications.
2. The THIN database is not able to determine if medications were actually dispensed, taken or used by patients in line with the administration directions.
3. THIN still has limited data on non-NHS care, lifestyles, diet. For example, information on occupation, employment and individual socioeconomic status is not available electronically. Some important confounding variables (smoking, alcohol use, weight, and height) are only available for some patients.
4. Minor medical events are more likely to be missed than medically significant diagnoses or events.
5. Some medical data (e.g., communication from specialists, discharge summaries from hospitals and test results from pathology laboratories) are often received in hard copy and must be manually entered into the

computer. Type errors are inevitable, which can affect the accuracy of data. In addition, due to a time-consuming process, some practices will only enter abnormal medical information onto the computer. These are now more likely to be received and recorded electronically, so the bias is removed in more recent data.

4.3 Data structure

In the THIN database, the raw data from each practice have been organised in different files: patient file, medical file, therapy file, additional health data (AHD) file and other linked files (e.g., consult, practice, demography, staff and postcode variable indicators (PVI))(IQVIA, 2017). The THIN data files also provided with a series of dictionaries (e.g., medical dictionary and drug dictionary) and look-up tables (e.g., pack size, dosage and AHD codes) which allow the coded information to be interpreted. Researchers can use the unique patient ID, to link a patient's information on demographics, diagnoses, prescriptions, referrals, laboratory tests, immunisations. The local area deprivation score can be linked via postcode. (Figure 4-3).

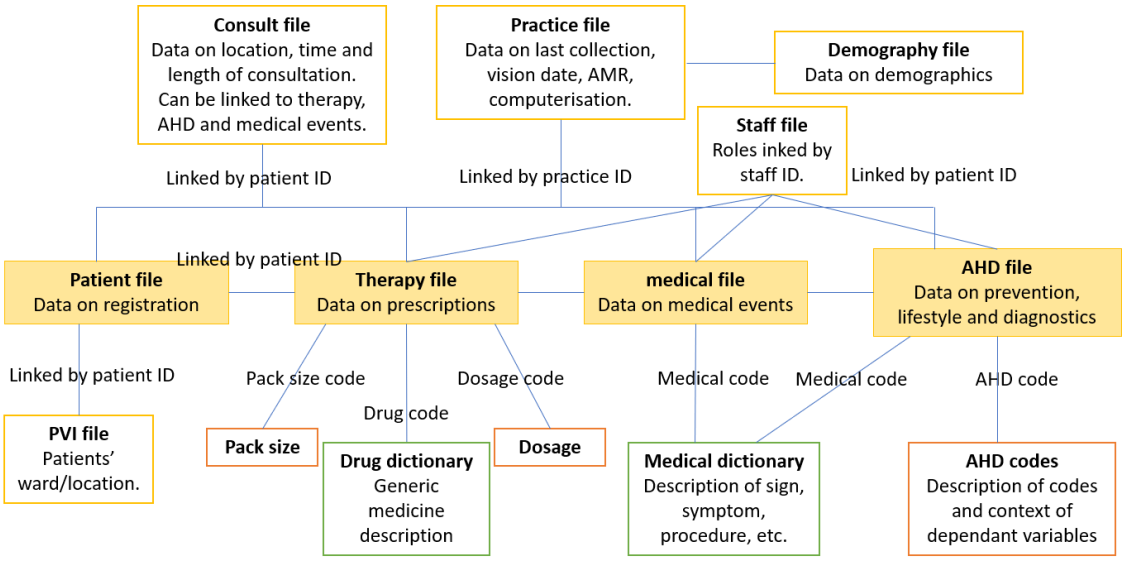

Figure 4-3 THIN research format data structure.

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4.3.1 Patient file

The patient file contains information on patients' basic characteristics (e.g. sex and year of birth) and registration details. Figure 4-4 shows an example of two patients' records. THIN provides researchers with a "THIN bible" (THIN Research Format Data Guide) which contains lookup tables and detailed interpretation to interpret information in each file. For example, Table 4-1 is the interpretation of each field value. Table 4-2 interprets different values in the filed "sex".

	Patid	patflag	famnum	sex	regstat	regrea	deathinf	accept	institut	married	dispens	prscxmpt	sysdate	xferdate	deathdte	pracid	regdate	dob
1	0001	A	008347	2	02	00		0	N	01		00	20130512	.	.	a6641	06/07/1983	01/07/1983
2	0002	A	005582	2	02	00		3	N	01		00	20170120	.	.	a6641	27/04/2016	01/07/1980

Figure 4-4 Example of patient records in THIN data (SAS 9.4 version)

Table 4-1 Interpretation of field values in patient file

Field	Character type	Max number of characters	Description
patid	Any ASCII	4	Patient identifier - case sensitive and unique within practice
patflag	A	1	Flag which indicates the integrity of the data for that patient
yob	YYYYMM00 Or YYYY0000	8	Year of birth (month also included for children)
famnum	999999	6	Identifier shared by patients living at same address
sex	9	1	Sex of patient
regdate	YYYYMMDD	8	Patients registration date with the practice
regstat	99	2	Registration status
xferdate	YYYYMMDD	8	Date of transfer out of practice (if applicable) 00000000 if not transferred out
regrea	99	2	Extended registration information
deathdate	YYYYMMDD	8	Patients date of death (derived by IQVIA) 00000000 if no death date
deathinfo	A	1	Death information – cause of death (linked from death certificate or comment)
accept	9	1	Registration acceptance type
institute	Y	1	Residential Institute Y = yes N = unknown
marital	99	2	Marital status
dispensing	Y	1	Y indicates they are a dispensing patient, whose prescriptions can be dispensed by the practice. Blank if not a dispensing patient.
prscexempt	99	2	Prescription exemption
sysdate	YYYYMMDD	8	System date

Table 4-2 Lookup table for sex

sex	description
1	Male
2	Female
3	Not Specified
4	Unknown
0	Null record

4.3.2 Therapy file

The therapy file contains details of prescriptions issued to patients by primary care. Each record is generated with one prescription, including information on formulation, strength, dose, quantity and prescribed date (Figure 4-5). Prescription data are recorded via drug codes, and these can be identified by their generic name or by the British National Formulary (BNF) chapter in drug dictionary(Davé & Petersen, 2009) (Table 4-3). Researchers always develop a code list which contains a set of drug codes to identify the drugs of interest.

	patid	drugcode	therflag	doscode	prscqty	prscdays	private	staffid	prsctype	opno	bnf	seqnoiss	maxnoiss	packsize	dosgval	locate	drugsrce	inprac	therid	cnsultid	modified	pracid	prscdate
1	0001	00000000	B	0000683	2.000000	000	N	0009	1	00000.00		0000	0000	0000001	-1.00	0	5	Y	0@rN	1ZUY	N	a6641	24/01/2006
2	0001	82446998	Y	0000008	60.00000	000	N	000@	1	00000.00	01060100	0000	0000	0000001	-1.00	0	5	Y	0@r0	1ZUa	Y	a6641	01/02/2006

Figure 4-5 Example of therapy records in THIN data (SAS 9.4 version)

Table 4-3 Example of drug information in drug dictionary

Drugcode	Bnfcode1	Bnfcode2	Bnfcode3	generic name	formulation	strength	unit	status	hospitalonly	nhsflag	ATC
94513998	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 100mg effervescent tablets	effervescent tablets	100	mg	D	1	0	B01A C06
94589998	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 100mg effervescent tablets	effervescent tablets	100	mg	D	1	0	B01A C06
93099998	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 100mg modified release tablets	modified release tablets	100	mg	D	1	0	B01A C06
96877992	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 100mg modified release tablets	modified release tablets	100	mg	D	1	0	B01A C06
98776996	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 100mg modified-release tablets	modified release tablets	100	mg	D	1	0	B01A C06
94709996	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 162.5mg capsules	modified release capsules	162.5	mg	D	1	0	B01A C06
83013998	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 162.5mg modified release capsules	modified release capsules	162.5	mg	D	1	0	B01A C06
83014998	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 162.5mg modified-release capsules	modified release capsules	162.5	mg	D	1	0	B01A C06

94513997	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 300mg effervescent tablets	effervescent tablets	300	mg	D	1	0	B01A C06
94589997	02.09.00.00	04.07.01.00	00.00.00.00	Aspirin 300mg effervescent tablets	effervescent tablets	300	mg	D	1	0	B01A C06

4.3.3 Medical file

The medical file contains records of symptoms, diagnoses and interventions recorded by primary care system (Figure 4-6). There are numerous records per patient as a record is generated for each new event related to the patient. Primary care physicians and practice staff use a Read Code system to input and distinguish diagnoses, symptoms, investigations and lifestyle information in the electronic clinical notes. In medical file, the filed “medcode” indicates Read codes which consist of seven characters. To identify records of a disease of interest (e.g., MI), researchers always develop a code list which involves a comprehensive set of Read codes for the disease (Table 4-3).

	patid	enddate	datatype	medcode	medflag	staffid	source	episode	nhsspec	locate	textid	category	priority	medinfo	inprac	private	medid	consultid	modified	evntdate
1	0001	00000000	01	1Z...00	R	0024	0	0	000	0	0000001	1	3		Y	N	2T1b	1ZUB	N	13/06/1983
2	0001	00000000	01	9122.00	R	0024	0	0	000	0	0000001	6	3		Y	N	2T1a	1ZUB	N	13/06/1983

Figure 4-6 Example of medical records in THIN data (SAS 9.4 version)

Table 4-4 Example of code list for MI

Read Code	Read term
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction

4.3.4 AHD file

The AHD file contains information on lifestyle data, preventative healthcare, immunisations, test results and death details (Figure 4-7). AHD codes are used to find this type of information (Figure 4-8). Each AHD record includes AHD code, AHD flag, event date and may have following recorded: data1 to data6 and medcode. Data1 to data6 may include the detailed values of the AHD information of interest. For example, the first record in Figure 4-7 shows a record of smoking as the ahdcode is “100304000” which indicates smoking in Figure 4-8. Based on the interpretation of smoking information in Figure 4-8, Data 1 presents “Y” which indicates the patient is a current smoker; Data 2 presents “5” which indicates five cigarettes per day.

	patid	ahdcode	ahdflag	data1	data2	data3	data4	data5	data6	medcode	source	nhsspec	locate	staffid	textid	category	ahdinfo	inprac	private	ahdid	cnsultid	modified	evntdate
15	0001	1003040000	Y	Y	5					137R.00	0	0	0	0005	069A	2		Y	N	069A	1ZUV	N	21/02/2005
16	0001	1003050000	Y	Y	0					1362.00	0	0	0	0005	02ED	2		Y	N	02ED	1ZUV	N	21/02/2005
17	0001	1005010100	Y	1.57000						229..00	0	0	0	000@	0000001	2		Y	N	05sZ	1ZUa	N	01/02/2006
18	0001	1005010200	Y	56.0000		22.7000				22A..00	0	0	0	000@	0000001	2		Y	N	06EU	1ZUa	N	01/02/2006

Figure 4-7 Example of AHD records in THIN data (SAS 9.4 version)

	datafile	ahdcode	description	data1	data2	data3	data4	data5	data6
1	CLINICAL	1001400147	Fundoscopy	QUALIFIER					
2	CLINICAL	1001400287	Scoring test result	NUM_RESULT	READ_CODE	TEST_METHOD			
3	CLINICAL	1002337002	Immunisations contraindicated	CONTRAINDICATED(Y/N)					
4	CLINICAL	1002371112	Parental consent for immunisation	PARENTAL_CONSENT					
5	CLINICAL	1002550000	Contraception	CONTRACEPTIVE_SERVICE_TYPE	IUCDDATE	DRUG_CODE	CLAIM_EXPIRY(DATE)		
6	CLINICAL	1002600000	Immunisation status	IMMS_STATUS					
7	CLINICAL	1003040000	Smoking	SMOKER	CIGARETTES(DAY)	CIGARS(DAY)	TOBACCO_OUNCES(DAY)	STARTSMOKE(DATE)	STOPSMOKE(DATE)
8	CLINICAL	1003040003	Passive smoking	PASSIVE_SMOKE(Y/N)					
9	CLINICAL	1003050000	Alcohol	DRINKER	UNITS(WEEK)	STARTDRINK(DATE)	STOPDRINK(DATE)		
10	CLINICAL	1005010100	Height	HEIGHT(M)	CENTILE				
11	CLINICAL	1005010200	Weight	WEIGHT(KG)	CENTILE	BMI			
12	CLINICAL	1005010500	Blood pressure	DIASTOLIC	SYSTOLIC	KOROTKOFF	EVENT_TIME	LATERALITY	POSTURE

Figure 4-8 Example of the interpretation of AHD codes

4.4 Ethical/Scientific Approval for THIN Data

In the UK, all research involving data collected from NHS patients must be approved by a Research Ethics Committee (REC). The South East Multicentre REC has approved The THIN data collection scheme and has permitted the establishment of Scientific Review Committees (SRC) to review research protocols. Researchers who plan to use THIN data will require approval by the SRC. The SRC application includes the submission of a study protocol and an application form.

Ethics approval for my PHD project was obtained in 2017 from the SRC, protocol reference: SRC 17THIN100.

Chapter 5: Initial usage of cardiovascular medications and factors associated with cardiovascular polypharmacy in patients with cardiovascular diseases

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5.1 Introduction

CVD is the leading cause of morbidity and mortality worldwide, and its prevalence is increasing in line with the ageing population. CHD and stroke are the most common CVD conditions and are the top two causes of death globally(World Health Organization, 2020). According to the UK Heart and Circulatory Disease Statistics 2020, adults aged 45 years and above accounted for the majority of overall cardiovascular mortality (approximately 98.5%)(British Heart Foundation, 2020a). Polypharmacy refers to the current use of multiple medications by one individual(Duerden et al., 2013). Cardiovascular conditions always appear to be the main contributions to polypharmacy. A Scottish study on polypharmacy found that the mean number of medications for patients with only one condition of ischaemic heart disease is 3.7, and 8.0 for patients with ischaemic heart disease

and other co-conditions(Payne et al., 2014). Historically, polypharmacy has been considered negatively, but it is now increasingly recognised to be necessary and beneficial in patients with some chronic disease (e.g. cardiovascular disease) if polypharmacy is well managed. Currently, only a few studies have reported the prescribing patterns of cardiovascular medications(DeWilde et al., 2008; Gunnell et al., 2016; Yusuf et al., 2011). These studies only investigated limited classes of cardiovascular medications, rather than providing a comprehensive overview of utilisation pattern. A UK study indicated that cardiovascular risk factors influenced general practitioners' decision to prescribe statins and antihypertensive medications(Mohammed et al., 2012). However, it is unclear whether these factors are associated with the prescribing of multiple medications. This study aimed to investigate the initial prescription patterns of cardiovascular medications in UK primary care, and the association between potential risk factors and cardiovascular polypharmacy in patients aged 45 years old and above following their first records of coronary heart disease or stroke.

5.2 Methods

5.2.1 Data source

The detailed data source are presented in chapter 4. In brief, The THIN database is a primary care clinical database which includes anonymised data from general practices across the UK. The database includes over 16 million patients from over 744 general practices. In 2013, the active patients in THIN represented

approximately 6% of the UK population[9]. THIN includes information for each individual on demographics, diagnoses, prescriptions, referrals, laboratory tests, immunisations, and local area deprivation (Townsend score)[10]. THIN data have previously been used to study acute cardiovascular events[11].

Ethics approval was obtained from the THIN Scientific Review Committee (SRC), protocol reference: SRC 17THIN100.

5.2.2 Study Participants

The study included patients with the first general practitioner (GP) record of CVD between January 2007 and December 2016. CVD was defined based on Read Codes for CHD (MI and angina) and stroke (haemorrhagic stroke, ischaemic stroke and TIA). Patients were divided into groups (CHD and stroke groups) according to their first record of CVD. Other inclusion criteria were patients aged 45 or above at their first diagnosis of CVD and patients had been registered for at least three years in THIN before their first diagnosis of CVD. I excluded patients who died within the first 90 days following the initial cardiovascular event, because their clinical data and prescription information may not be recorded between the first diagnosis and death.

5.2.3 Initial treatment

In this study, initial pharmacotherapy with cardiovascular medications in each patient was defined according to the cardiovascular medications prescribed during

the first 90-day window after the first recorded CVD diagnosis. In the UK, repeat prescriptions are usually issued by primary care physicians for chronic conditions. The prescription interval is usually 28 or 56 days. This study included CV medications with a prescription duration ≥ 28 days or with at least two prescriptions during the 90-day exposure window. This was to make sure medications were prescribed for long-term use. Patients were also categorised into groups according to the specific number or combination of medications prescribed. Cardiovascular medications were identified from the BNF Chapter two (cardiovascular system). Compound medicines are separated into individual medication constituents.

5.2.4 Data extraction and missing data

Information on demographics, clinical characteristics and cardiovascular prescriptions were extracted from the THIN database. Baseline characteristics included age, gender, smoking status, alcohol consumption, body mass index (BMI), blood pressure (BP), total cholesterol (TC), Townsend score, and comorbidities during the one year window prior to the first cardiovascular event.

Missing data for each baseline characteristic were coded as a separate category.

5.2.5 Statistical Analysis

All analyses were performed using SAS software version 9.4. Data were presented as mean (standard deviation [SD]) for continuous variables and as frequency (%) for categorical variables. Comparisons were performed using student's t-test for

continuous variables, and the chi-squared test for categorical variables between the CHD and stroke patients.

The study examined the percentage of CVD medications prescribed by the numbers of medications (0, 1, 2, 3, 4, 5, 6, ≥7) issued during the first 90 days following the diagnosis of CVD stratified by age (10-year age groups up to ≥85 years), gender, smoking status (never smoked, current smoker, ex-smoker), BMI (mean, normal, overweight, obesity and underweight), blood pressure (normal, stage 1, 2 and 3 hypertension and hypotension), total cholesterol (optimal, intermediate and high), Charlson comorbidity index (excluding myocardial infarction and cerebrovascular disease), history of percutaneous transluminal coronary intervention (PCI), hypertension, hyperlipidaemia, arrhythmia, heart failure (HF), dementia, diabetes, chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis (RA) or chronic kidney disease (CKD) and area deprivation status (Townsend score 1-5).

The average number and the percentage of patients with different numbers of CVD medications in each calendar year were calculated. The proportion of patients prescribed with the most commonly used classes and combinations of CV medications during the study period was also investigated.

ORs and the corresponding 95% CIs were evaluated by logistic regression model to examine the association between baseline characteristics and CV polypharmacy (defined as ≥5 CV medications). All two-sided p-values less than

0.05 were considered to be statistically significant.

5.3 Results

5.3.1 Characteristics

From 2007 to 2016, 121,600 patients aged 45 years and above were diagnosed with CVD. The study included 59,843 patients with CHD (25,266 with angina and 34,577 with MI) and 61,757 patients with stroke. Patient characteristics at their first CVD are presented in Table 5-1. The mean patient age at CV events was 69.3 ± 11.7 years (67.0 ± 11.4 years for CHD patients and 71.7 ± 11.5 years for stroke patients). The proportion of male patients with CVD was 55.5% (62.0% with CHD and 48.6 % with stroke).

Table 5-1 Characteristics of the study population at their first CV event

Characteristics	Total (n=121 600)	CHD (n = 59 843)	Stroke (n = 61 757)	P value
Male (%)	67 073 (55.2)	36 894 (61.7)	30 179 (48.9)	<0.01
Age, mean ± SD, years	69.5 ± 11.9	67.2 ± 11.5	71.8 ± 11.7	<0.01
Age groups, years (%)				
45-54	15 370 (12.6)	9540 (15.9)	5830 (9.4)	<0.01
55-64	27 427 (22.6)	16 235 (27.1)	11 192 (18.1)	
65-74	34 262 (28.2)	17 119 (28.6)	17 143 (27.8)	
75-84	31 134 (25.6)	12 517 (20.9)	18 617 (30.2)	
85 and older	13 407 (11.0)	4432 (7.4)	8975 (14.5)	
Smoking status (%)				
Non-smoker	53 094 (43.7)	24 438 (40.8)	28656 (46.4)	<0.01
Current smoker	24 679 (20.3)	13 195 (22.1)	11 483 (18.6)	

Ex-smoker	41 025 (33.7)	21 287 (35.6)	19 737 (32.0)	
Missing	2803 (2.3)	923 (1.5)	1880 (3.1)	
Alcohol consumption (%)				
Non-drinker	18 767 (15.4)	9143 (15.3)	9624 (15.6)	<0.01
Current drinker	66 108 (54.4)	34 390 (57.5)	31 718 (51.4)	
Ex-drinker	4280 (3.5)	2136 (3.6)	2144 (3.5)	
Missing	32 445 (26.7)	14 174 (23.7)	18 271 (29.6)	
BMI, mean ± SD	27.9 ± 5.3	28.2 ± 5.2	27.5 ± 5.3	<0.01
BMI groups (%)				
Normal (18.5-24.9 kg/m^2)	29 160 (24.0)	13 151 (22.0)	16 009 (25.9)	<0.01
Overweight (25.0-29.9 kg/m^2)	41 148 (33.8)	21 517 (36.0)	19 631 (31.8)	
Obesity (≥ 30.0 kg/m^2)	31 061 (25.5)	16 885 (28.2)	14 176 (23.0)	
Underweight (< 18.5 kg/m^2)	1932 (1.6)	739 (1.2)	1193 (1.9)	
Missing	18 299 (15.1)	7551 (12.6)	10 748 (17.4)	
BP status (%)				
Normal (BP < 140/90 mmHg)	40 689 (39.0)	21 539 (39.8)	19150 (38.2)	<0.01
Stage 1 hypertension (BP ≥ 140/90 mmHg)	31 458 (30.2)	15 944 (29.5)	15 514 (30.9)	
Stage 2 hypertension (BP ≥ 160/100 mmHg)	10 371 (10.0)	4900 (9.1)	5471 (10.9)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	4312 (4.1)	1713 (3.2)	2599 (5.2)	
Hypotension (BP < 90/60 mmHg)	157 (0.2)	101 (0.2)	56 (0.1)	
Missing	17 276 (16.6)	9878 (18.3)	7398 (14.7)	
TC status (%)				
Optimal (<5.2 mmol/L)	48 685 (40.0)	23 624 (39.5)	25 061 (40.6)	<0.01
Intermediate (5.3-6.2 mmol/L)	30 403 (25.0)	14 983 (25.0)	15 420 (25.0)	

High (>6.2 mmol/L)	19 460 (16.0)	10 342 (17.3)	9118 (14.8)	
Missing	23 052 (19.0)	10 894 (18.2)	12 158 (19.7)	
Townsend score (%)				
1 (least deprived)	25 088 (20.6)	11 958 (20.0)	13 130 (21.3)	<0.01
2	24 957 (20.5)	12 245 (20.5)	12 712 (20.6)	
3	23 234 (19.1)	11 438 (19.1)	11 796 (19.1)	
4	20 126 (16.6)	10 024 (16.8)	10 102 (16.4)	
5 (most deprived)	14 240 (11.7)	7310 (12.2)	6930 (11.2)	
Missing	13 955 (11.5)	6868 (11.5)	7087 (11.5)	
Charlson comorbidity index				
0	59 272 (48.7)	29 492 (49.3)	29 780 (48.2)	<0.01
1	29 763 (24.5)	14 740 (24.6)	15 023 (24.3)	
2	13 481 (11.1)	6263 (10.5)	7218 (11.7)	
3	10 953 (9.0)	5383 (9.0)	5570 (9.0)	
4	4785 (3.9)	2372 (4.0)	2413 (3.9)	
≥5	3346 (2.8)	1593 (2.7)	1753 (2.8)	
History or PCI	6426 (6.2)	6182 (11.4)	237 (0.5)	<0.01
Comorbidity (%)				
Hypertension	64 631 (53.2)	29 798 (49.8)	34 833 (56.4)	<0.01
Hyperlipidaemia	19 242 (15.8)	10 164 (17.0)	9078 (14.7)	<0.01
Arrhythmia	14 847 (12.2)	5430 (9.1)	9417 (15.3)	<0.01
Heart Failure	6992 (5.8)	4379 (7.3)	2613 (4.2)	<0.01
Dementia	2869 (2.4)	664 (1.1)	2205 (3.6)	<0.01
Diabetes	20 734 (17.1)	10 423 (17.4)	10 311 (16.7)	<0.01
COPD	10 417 (8.6)	5175 (8.7)	5242 (8.5)	0.32
Asthma	16 705 (13.7)	8469 (14.2)	8236 (13.3)	<0.01
RA	2540 (2.1)	1265 (2.1)	1275 (2.1)	0.55
CKD	21 258 (17.5)	9428 (15.8)	11 830 (19.2)	<0.01

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; PCI, percutaneous transluminal coronary intervention; RA, rheumatoid arthritis; TC, total cholesterol.

5.3.2 Usage of cardiovascular medications

Figure 5-1 shows the percentage of patients receiving different numbers of CV medications after their first CVD events. Overall, 11.0% of CVD patients had prescriptions for 0 or 1 long-term used CV medication, 29.8% were receiving 2 or 3 regular medications, 38.6% were receiving 4 or 5 medications, and 20.5% were receiving ≥6 CV medications. There was 40.6% of patients receiving cardiovascular polypharmacy (defined as ≥5 CV medications). The average number of CV medications was 3.9 (SD:1.9) in the overall patients with CVD, 4.8 (SD:1.8) in patients with CHD, and 3.1 (SD:1.7) in patients with stroke, respectively. The majority of patients with CHD were prescribed with five or more medications (61.1%). By contrast, patients with stroke were prescribed with fewer CV medications; 62.5 % were receiving two to four medications.

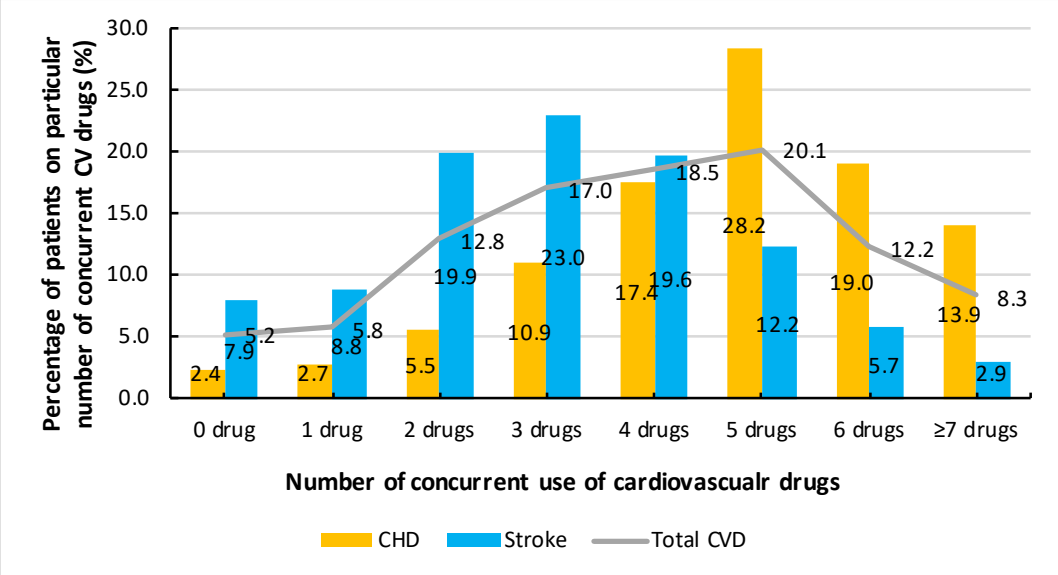


Figure 5-1 Percentage of patients receiving different numbers of CV medications.

Overall, in CVD patients, the most commonly prescribed CV medications were aspirin (59.9%), simvastatin (48.0%), clopidogrel (39.8%), bisoprolol (34.5%), ramipril (30.5%) and atorvastatin (28.3%) (Figure 5-2). In CHD patients, aspirin (79.0%), bisoprolol (59.6%), clopidogrel (45.6%), ramipril (45.0%), simvastatin (44.2%) and atorvastatin (38.6%) were frequently issued. In stroke patients, simvastatin (51.8%), aspirin (41.4%), clopidogrel (34.3%), amlodipine (18.4%), atorvastatin (18.4%) and ramipril (16.6%) were commonly prescribed medications.

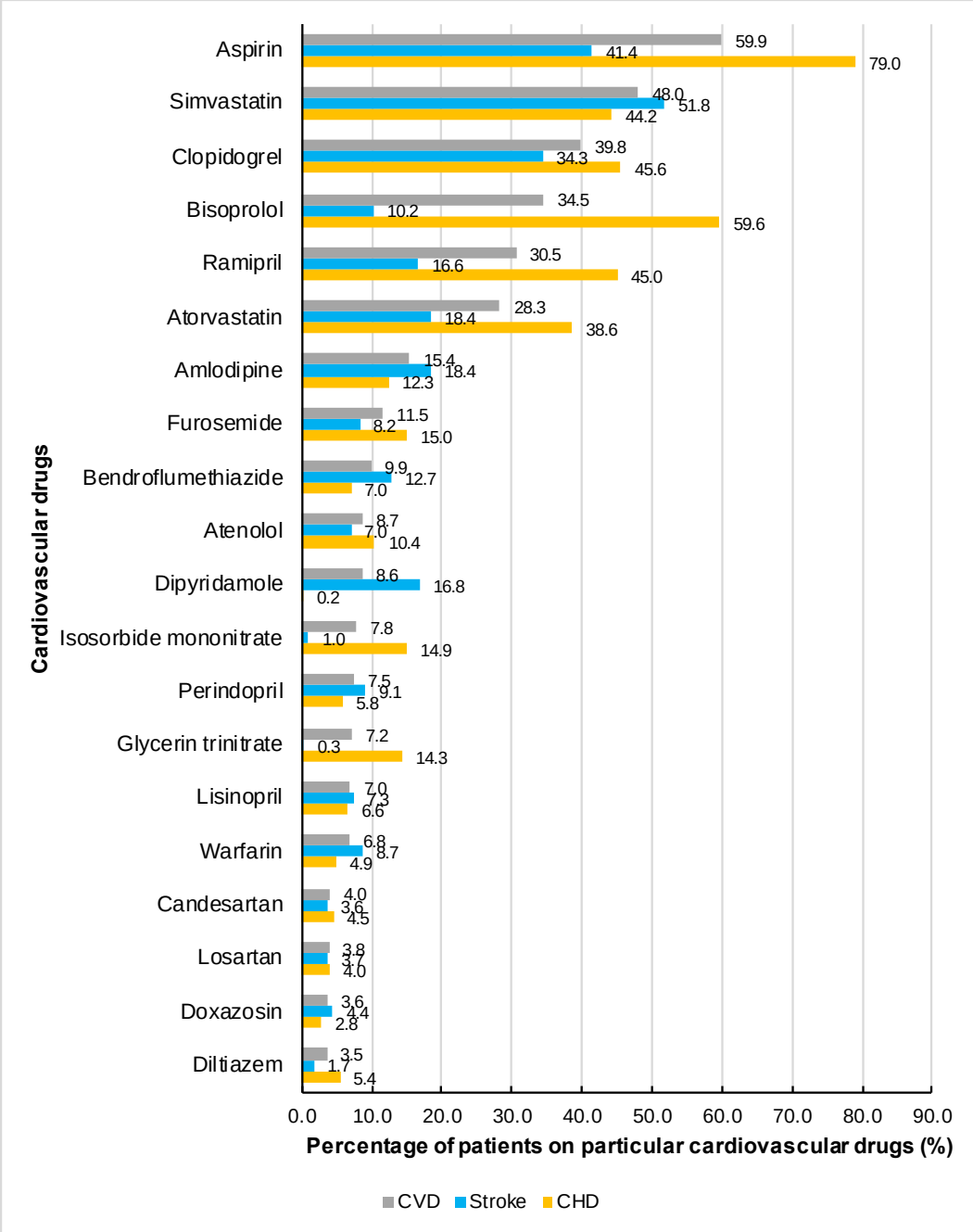


Figure 5-2 Percentage of patients with CVD receiving particular cardiovascular medications during 2007 and 2016

Among patients with CHD, the most commonly used classes of CV medications were antiplatelet agents (84.9%), lipid-regulating medications (85.3%), β-blockers (73.1%), ACEIs/ ARBs (67.7%) and antianginal medications (30.2%). Dual antiplatelet therapy was prescribed to 48.2% of CHD patients. However, the proportions of dual antiplatelet therapy and ACEIs/ARBs were 72.0% and 82.1% in patients with MI. In patients with stroke or TIA, the most frequently prescribed CV medications were antiplatelet agents (72.3%), lipid-regulating medications (72.3%), ACEIs/ARBs (43.8%), calcium-channel blockers (CCBs) (27.5%) and diuretics (26.4%) (Figure 5-3). Prescribing for patients with MI and angina are shown separately in online supplementary data Figure 5-4.

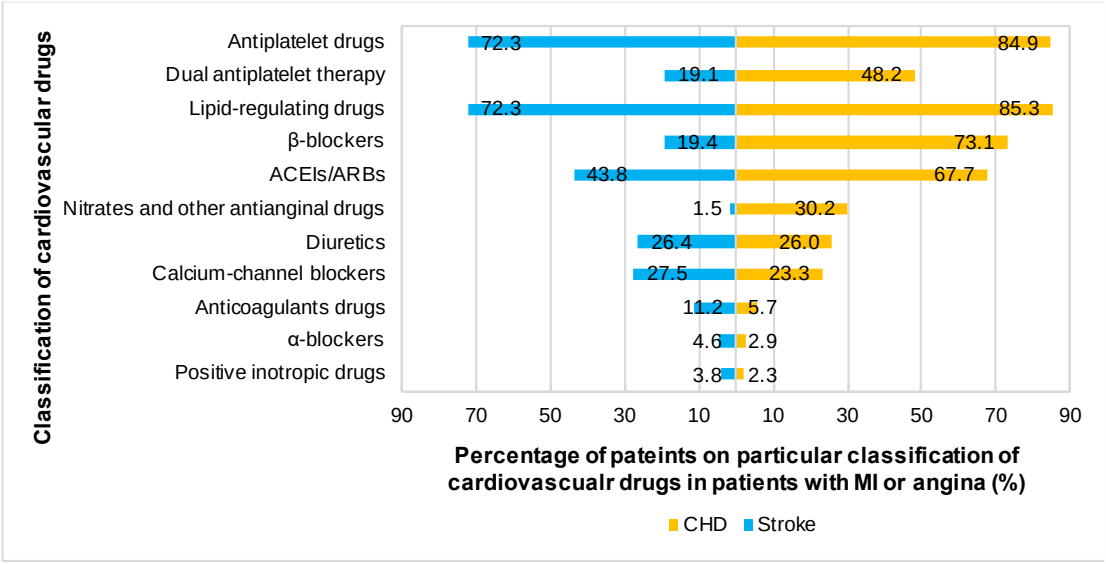


Figure 5-3 Percentage of patients receiving particular classification of cardiovascular medications in separate disease groups during 2007 and 2016

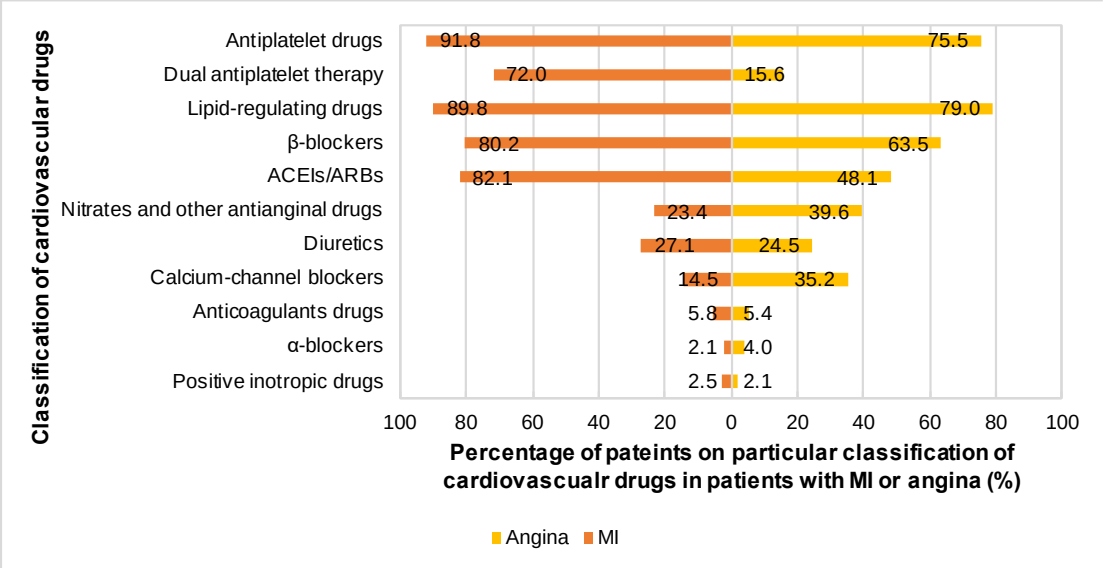


Figure 5-4 Percentage of patients receiving particular classification of cardiovascular medications in patients with MI or angina during 2007 and 2016

Details of specific combinations of the top five commonly used classes of cardiovascular medications in CHD and stroke patients are presented in Table 5-2. Of the 59,843 patients with CHD, 4896 (8.2%) were prescribed with none or one prescription of antiplatelet agents, lipid-regulating medications, β-blockers, ACEIs/ARBs or antianginal medications. The majority of CHD patients were prescribed with a combination of three (23.2%) or four (44.1%) medication classes. The combined use of antiplatelet agents, lipid-regulating medications, β-blockers and ACEIs/ARBs (34.3%) was most frequently prescribed in CHD patients. In 61,757 patients with stroke, 5841 (9.5%) patients were prescribed with none of antiplatelet agents, lipid-regulating medications, ACEIs/ARBs, CCBs or diuretics. 13.0%, 29.0% and 27.4% of stroke patients were prescribed with one, two and three of the five classes of CV medications. The combinations of antiplatelet agents

and lipid-regulating medications (18.6%), and the combination of antiplatelet agents, lipid-regulating medications and ACEIs/ARBs (12.4%) were frequently prescribed to patients with stroke.

Table 5-2 The combinations of the top five commonly issued classes of CV medications in patients with CHD and stroke/TIA.

CHD (n = 59 843)			**Stroke (n = 61 757)**		
CV medications	**Frequency**	**%**	**CV medications**	**Frequency**	**%**
None of the five class medications	1927	3.2	**None of the five class medications**	5841	9.5
One class	2969	5	**One class**	8043	13
APDs	844	1.4	APAs	3515	5.7
LRMs	800	1.3	LRMs	2560	4.2
BBs	563	0.9	ACEIs/ARBs	843	1.4
ACEIs/ARBs	466	0.8	CCBs	562	0.9
AADs	296	0.5	DRs	563	0.9
Two combination	6444	10.8	**Two combination**	17911	29.0
APAs + LRMs	2100	3.5	APAs + LRMs	11487	18.6
APAs + BBs	898	1.5	APAs + ACEIs/ARBs	1053	1.7
APAs + ACEIs/ARBs	543	0.9	APAs + CCBs	692	1.1
APAs + AADs	372	0.6	APAs + DRs	744	1.2
LRMs + BBs	855	1.4	LRMs + ACEIs/ARBs	1528	2.5
LRMs + ACEIs/ARBs	684	1.1	LRMs + CCBs	714	1.2
LRMs + AADs	257	0.4	LRMs + DRs	559	0.9
BBs + ACEIs/ARBs	423	0.7	ACEIs/ARBs + CCBs	446	0.7
BBs + AADs	164	0.3	ACEIs/ARBs + DRs	487	0.8
ACEIs/ARBs + AADs	148	0.3	CCBs + DRs	201	0.3
Three combination	13894	23.2	**Three combination**	16905	27.4
APAs + LRMs + BBs	5262	8.8	APAs + LRMs + ACEIs/ARBs	7667	12.4
APAs + LRMs + ACEIs/ARBs	3728	6.2	APAs + LRMs + CCBs	3397	5.5
APAs + LRMs + AADs	1284	2.2	APAs + LRMs + DRs	2076	3.4
APAs + BBs + ACEIs/ARBs	996	1.7	APAs + ACEIs/ARBs + CCBs	507	0.8
APAs + ACEIs/ARBs +AADs	413	0.7	APAs + ACEIs/ARBs + DRs	776	1.3
APAs + BBs + AADs	236	0.4	APAs + CCBs +DRs	285	0.5
LRMs + BBs + ACEIs/ARBs	1180	2.0	LRMs + ACEIs/ARBs + CCBs	747	1.2

LRMs + BBs + AADs	368	0.6	LRMs + ACEIs/ARBs + DRs	942	1.5
LRMs + ACEIs/ARBs + AADs	288	0.5	LRMs + CCBs + DRs	275	0.5
BBs + ACEIs/ARBs + AADs	139	0.2	ACEIs/ARBs + CCBs + DRs	233	0.4
Four combination	26382	44.1	**Four combination**	10264	16.6
APAs + LRMs + BBs + ACEIs/ARBs	20495	34.3	APAs + LRMs + ACEIs/ARBs + CCBs	3912	6.3
APAs + LRMs + BBs + AADs	2906	4.9	APAs + LRMs + ACEIs/ARBs + DRs	4131	6.7
APAs + LRMs + ACEIs/ARBs + AADs	2115	3.5	APAs + LRMs + CCBs + DRs	1261	2.0
APAs + BBs + ACEIs/ARBs + AADs	400	0.7	APAs + ACEIs/ARBs + CCBs + DRs	351	0.6
LRMs + BBs + ACEIs/ARBs + AADs	466	0.8	LRMs + ACEIs/ARBs + CCBs + DRs	609	1.0
Five combination	8227	13.8	**Five combination**	2793	4.5
APAs + LRMs + BBs + ACEIs/ARBs + AADs	8227	13.8	APAs + LRMs + ACEIs/ARBs + CCBs + DRs	2793	4.5

ACEIs, angiotensin-converting enzyme inhibitors; AADs, antianginal medications; APAs, antiplatelet agents; ARBs, angiotensin receptor blockers; BBs, β-blockers; CCBs, calcium channel blockers; CHD, coronary heart disease; CV, cardiovascular; DRs, diuretics; LRMs, lipid-regulating medications.

5.3.3 Trends in initial secondary prevention 2007-2016

Figure 5-5 shows the trends in the number of cardiovascular medications issued to CVD patients from 2007 to 2016. From 2010 the percentage of patients receiving two medications increased from 10.9% in 2010 to 15.8% in 2016. Conversely, the percentage of patients receiving six medications (from 13.0% to 10.8%) and seven or more medications (from 8.9% to 7.0%) showed a declining trend from 2010 to 2016.

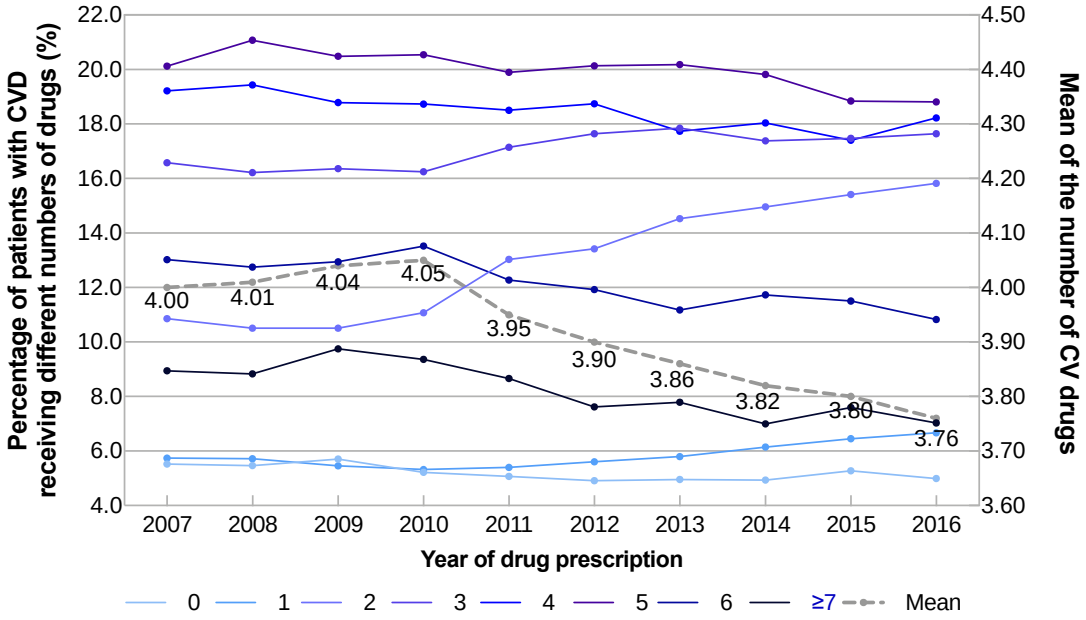


Figure 5-5 Trends in different numbers and mean of the number of CV medications prescribed in patients with CVD between 2007 and 2016.

When investigating the trends in CHD and stroke separately, the CV medication usage remained stable. In patients with CHD, there was a slight increase of the use of β-blockers (from 68.7% to 73.8%) and the combination of antiplatelet agents, lipid-regulating medications, β-blockers and ACEIs/ARBs (from 29.8% to 34.2%) from 2007 to 2016. The percentages of patients receiving antiplatelet agents, lipid-regulating medications, ACEIs/ARBs, anti-anginal medications and the combination of the most commonly prescribed five medications stayed

stably (Figure 5-6). In patients with stroke, the trends of the use of antiplatelet agents, lipid-regulating medications and the combination of antiplatelet agents, lipid-regulating medications and ACEIs/ARBs unchanged considerably. The percentages of patients receiving ACEIs/ARBs and diuretics declined 6.0% and 10.1% through the decade, respectively from 2007 to 2016. On the contrary, there were increase trends in the percentages of patients issued with calcium channel blockers (6.2%) and the combination of antiplatelet agents and lipid-regulating medications (4.0%) during 2007 and 2016 (Figure 5-7).

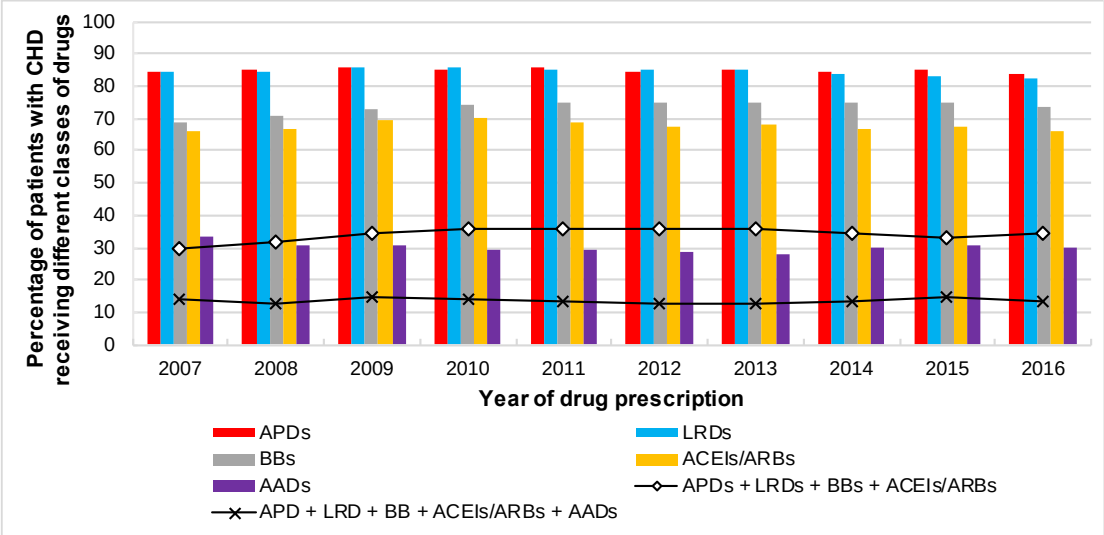


Figure 5-6 Most commonly prescribed classes of CV medications in patients with CHD between 2007 and 2016.

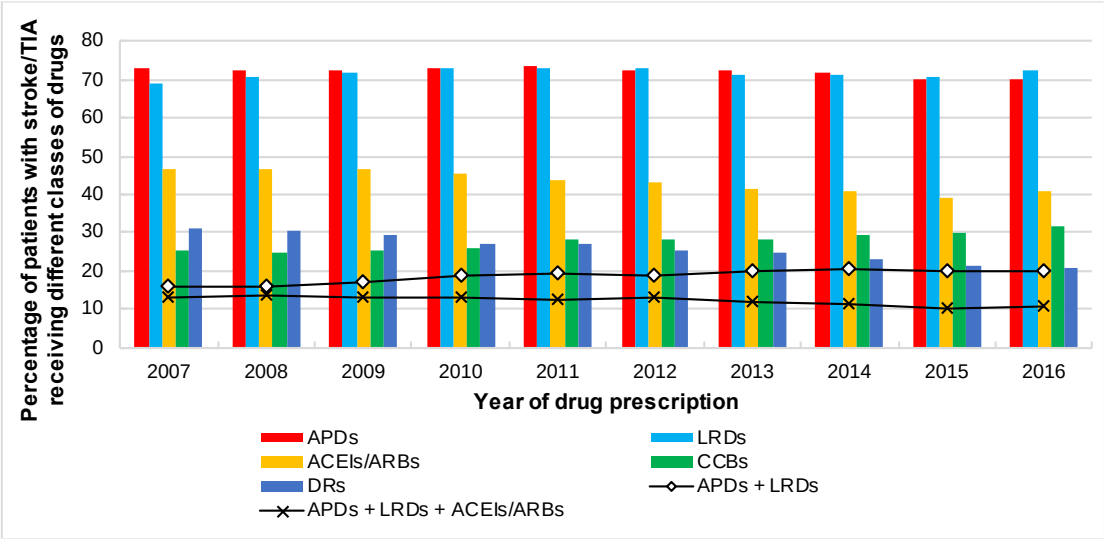


Figure 5-7 Most commonly prescribed classes of CV medications in patients with stroke between 2007 and 2016.

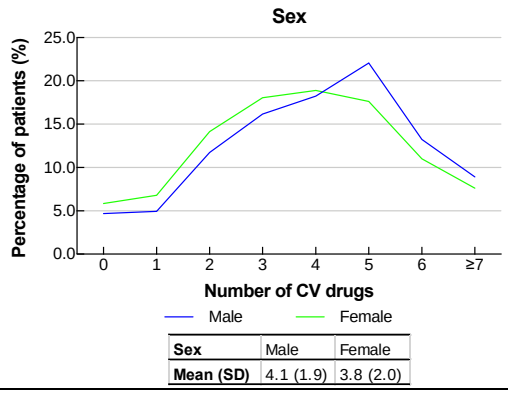
5.3.4 Factors associated with cardiovascular polypharmacy

Figure 5-8 shows the proportion of patients receiving different numbers of cardiovascular medications and means of the number of cardiovascular medications by stratified in groups of the potential factors. The means of the number of cardiovascular medication in patients with CHD and stroke are separately showed in Appendix J. Table 5-3 summarises the potential factors predicting the probability of cardiovascular polypharmacy. The mean number of cardiovascular medications were 4.1 (SD: 1.9) in men and 3.8 (SD: 2.0) in women. Women were less likely to be issued with five or more cardiovascular medications (OR: 0.74, 95% CI: 0.72-0.76). The mean number of cardiovascular medications were 3.9 (SD: 2.0), 4.1(SD: 1.9), 4.0 (SD: 1.9), 3.9 (SD: 2.0) and 3.5 (SD: 2.0) in patients aged 45-54, 55-64, 65-74, 75-84 and 85+ years old, respectively. Patients receiving cardiovascular polypharmacy decreased with increasing age (OR = 0.94, 0.81, 0.69 and 0.50 in patients aged 55-64, 65-74, 75-84 and 85+ years old vs patients aged 45-54 years old). The mean number of cardiovascular medications were 3.9 (SD: 1.9), 4.0 (SD: 1.9) and 4.0 (SD: 1.9) in non-smokers, ex-smokers and current smokers, respectively. Current smokers were more likely to be receiving cardiovascular polypharmacy with an OR of 1.19 (95% CI: 1.15-1.24). The mean number of cardiovascular medications were 3.7 (SD: 1.9), 4.0 (SD: 1.9) and 4.3 (SD: 2.0) in patients with normal BMI, overweight and obese individuals, respectively. High BMI was shown to be associated with cardiovascular polypharmacy as overweight patients (OR = 1.23, 95% CI: 1.19-1.27) and obese patients (OR =

1.38, 95% CI: 1.34-1.43) were significantly more likely to be prescribed five or more cardiovascular medications. The mean number of cardiovascular medications were 3.9 (SD: 2.0), 4.0 (SD: 1.9), 4.1 (SD:1.9) and 4.2 (2.1) in patients with normal blood pressure status, stage 1, stage 2 and stage 3 hypertension status, respectively. Compared to patients with normal blood pressure, the ORs were 1.06 (95% CI: 1.03-1.09), 1.08 (95% CI: 1.04-1.13) and 1.24 (95% CI: 1.17-1.32) for patients with stage 1, stage 2 and stage 3 hypertension. The area deprivation status was associated with polypharmacy. Compared with patients living in the least deprived area, the ORs of cardiovascular polypharmacy increased with higher deprived areas (OR = 1.05 and 1.06 in patients assigned a Townsend score of four and five, respectively). The probability of receiving cardiovascular polypharmacy in patients with a history of PCI was 5.26 times (95% CI: 4.96-5.58) compared to patients with no history. The mean number of cardiovascular medications were 3.8 (SD: 1.9), 3.9 (SD: 2.0), 3.9 (SD: 2.0), 4.2 (SD: 2.0), 4.4 (SD: 2.1) and 4.3 (SD: 2.1) in patients with CCIs of zero, one, two, three, four and five or more. High Charlson comorbidity index (CCI) was also a predictive factor of cardiovascular polypharmacy with ORs of 1.22 (95% CI: 1.17-1.28), 1.31 (95% CI: 1.23-1.40) and 1.25 (95% CI: 1.16-1.35) in CCIs of three, four and five or more, respectively. CVD patients with hypertension (OR: 2.03, 95% CI: 1.97-2.08), hyperlipidaemia (OR: 1.16, 95% CI: 1.12-1.20), heart failure (OR: 2.57, 95% CI: 2.43-2.71), diabetes (OR: 1.25, 95% CI: 1.21-1.29), chronic kidney disease (OR: 1.19, 95% CI: 1.16-1.24) and arrhythmia (OR: 1.05, 95% CI: 1.01-1.10) were more likely to be issued with five or more CV medications. Conversely, having a history of dementia (OR: 0.44, 95% CI: 0.40-0.49), COPD (OR: 0.92, 95% CI:

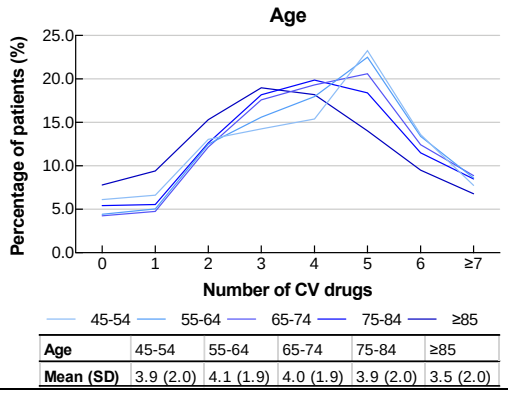
0.88-0.97) or asthma (OR: 0.90, 95% CI: 0.87-0.93) decreased the probability of CV polypharmacy.

(a)



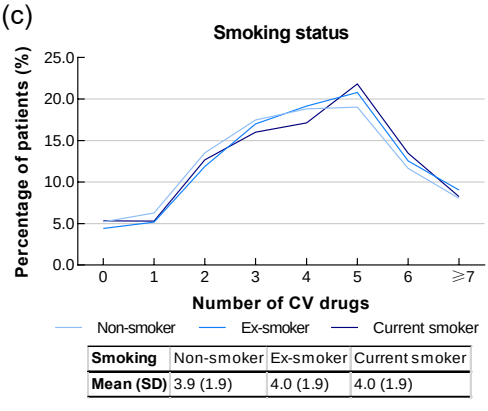
Sex	Male	Female
Mean (SD)	4.1 (1.9)	3.8 (2.0)

(b)



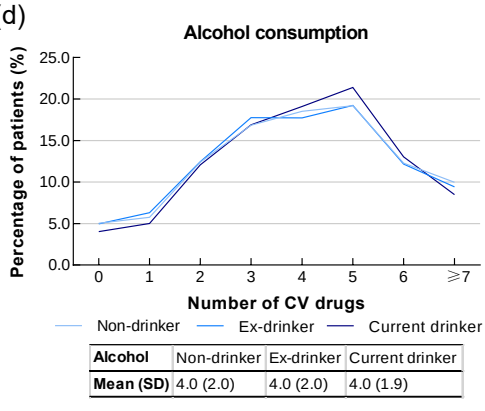
Age	45-54	55-64	65-74	75-84	≥85
Mean (SD)	3.9 (2.0)	4.1 (1.9)	4.0 (1.9)	3.9 (2.0)	3.5 (2.0)

(c)



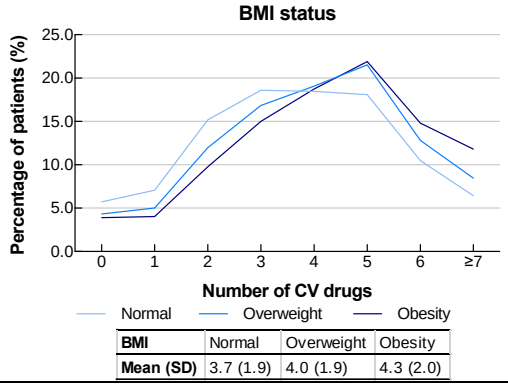
Smoking	Non-smoker	Ex-smoker	Current smoker
Mean (SD)	3.9 (1.9)	4.0 (1.9)	4.0 (1.9)

(d)



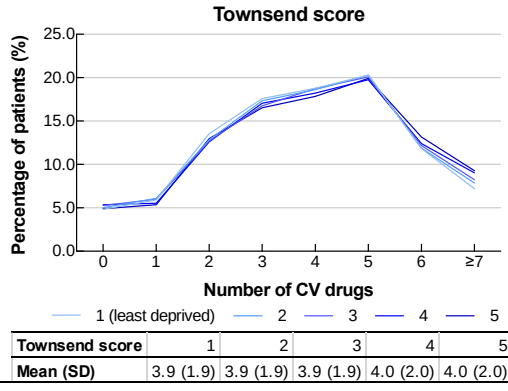
Alcohol	Non-drinker	Ex-drinker	Current drinker
Mean (SD)	4.0 (2.0)	4.0 (2.0)	4.0 (1.9)

(e)



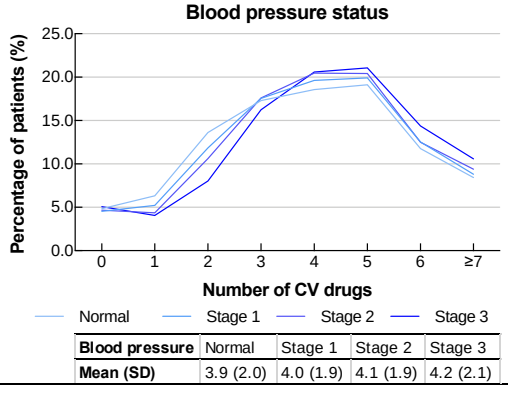
BMI	Normal	Overweight	Obesity
Mean (SD)	3.7 (1.9)	4.0 (1.9)	4.3 (2.0)

(f)



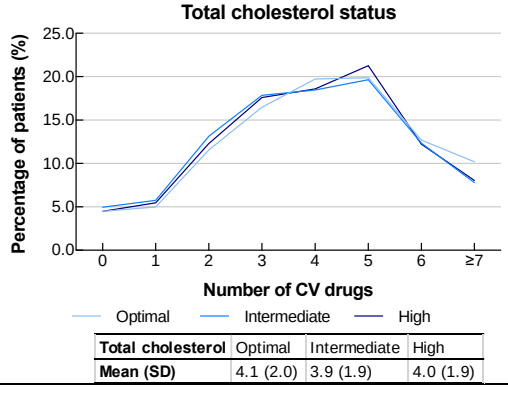
Townsend score	1	2	3	4	5
Mean (SD)	3.9 (1.9)	3.9 (1.9)	3.9 (1.9)	4.0 (2.0)	4.0 (2.0)

(g)



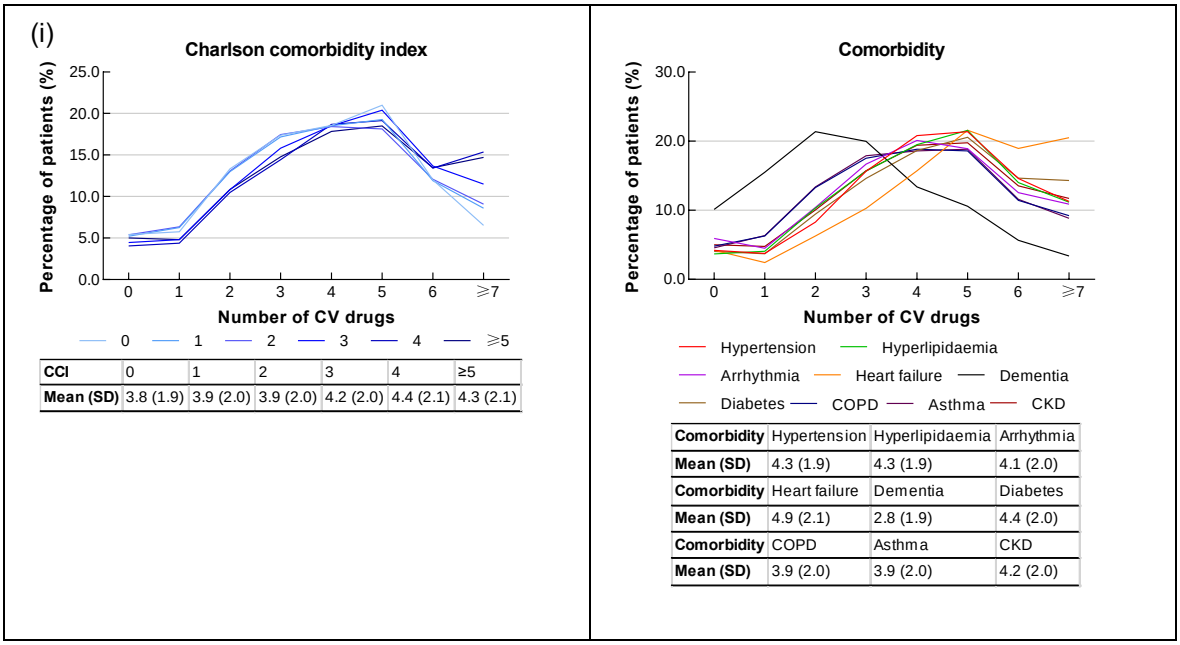
Blood pressure	Normal	Stage 1	Stage 2	Stage 3
Mean (SD)	3.9 (2.0)	4.0 (1.9)	4.1 (1.9)	4.2 (2.1)

(h)



Total cholesterol	Optimal	Intermediate	High
Mean (SD)	4.1 (2.0)	3.9 (1.9)	4.0 (1.9)

(j)



CCI	0	1	2	3	4	≥5
Mean (SD)	3.8 (1.9)	3.9 (2.0)	3.9 (2.0)	4.2 (2.0)	4.4 (2.1)	4.3 (2.1)

Comorbidity	Hypertension	Hyperlipidaemia	Arrhythmia
Mean (SD)	4.3 (1.9)	4.3 (1.9)	4.1 (2.0)
Comorbidity	Heart failure	Dementia	Diabetes
Mean (SD)	4.9 (2.1)	2.8 (1.9)	4.4 (2.0)
Comorbidity	COPD	Asthma	CKD
Mean (SD)	3.9 (2.0)	3.9 (2.0)	4.2 (2.0)

Figure 5-8 Percentage of patients receiving different numbers of CV medications and by (a) sex, (b) age, (c)smoking status, (d) alcohol assumption, (e) BMI status, (f) Townsend score, (g) blood pressure status, (h) total cholesterol status, (i) Charlson comorbidity index and (j) comorbidities.

Table 5-3 Odds ratios for risk factors of cardiovascular polypharmacy.

Variables	Univariable OR (95% CI)	Multivariable OR (95% CI)
Gender		
Male	1 (reference)	1 (reference)
Female	0.72 (0.70-0.74)	0.74 (0.72-0.76)
Age group (years)		
45-54	1 (reference)	1 (reference)
55-64	1.00 (0.96-1.04)	0.94 (0.90-0.98)
65-74	0.90(0.86-0.93)	0.81 (0.78-0.85)
75-84	0.77 (0.75-0.81)	0.69 (0.66-0.72)
85 and over	0.54 (0.52-0.57)	0.50 (0.47-0.53)
Smoking status		
Non-smoker	1 (reference)	1 (reference)
Ex-smoker	1.17 (1.14-1.20)	1.09 (1.06-1.12)
Current smoker	1.22 (1.18-1.26)	1.19 (1.15-1.24)
Alcohol status		
Non-drinker	1 (reference)	1 (reference)
Ex-drinker	0.98 (0.91-1.04)	0.88 (0.82-0.94)
Current drinker	1.06 (1.03-1.10)	0.98 (0.94-1.01)
BMI group		
Normal	1 (reference)	1 (reference)
Overweight	1.39 (1.35-1.43)	1.23 (1.19-1.27)
Obesity	1.75 (1.70-1.81)	1.38 (1.34-1.43)
Underweight	0.63 (0.57-0.70)	0.73 (0.66-0.82)
BP status		
Normal	1 (reference)	1 (reference)
Stage 1 hypertension	1.08 (1.05-1.11)	1.06 (1.03-1.09)
Stage 2 hypertension	1.13 (1.09-1.18)	1.08 (1.04-1.13)
Stage 3 hypertension	1.32 (1.24-1.40)	1.24 (1.17-2.05)
TC status		
Optimal	1 (reference)	1 (reference)
Intermediate	0.89 (0.86-0.91)	1.02 (0.99-1.05)
High	0.95 (0.92-0.98)	1.13 (1.09-1.17)
Townsend score		
1 (least deprived)	1 (reference)	1 (reference)
2	1.03 (0.99-1.07)	1.03 (0.99-1.06)
3	1.05 (1.01-1.09)	1.03 (0.99-1.07)
4	1.08 (1.04-1.12)	1.05 (1.00-1.09)
5 (most deprived)	1.13 (1.09-1.18)	1.06 (1.04-1.14)

Charlson Comorbidity index		
0	1 (reference)	1 (reference)
1	1.01 (0.98-1.04)	1.01 (0.98-1.04)
2	0.99 (0.95-1.03)	1.05 (1.01-1.09)
3	1.28 (1.23-1.33)	1.22 (1.17-1.28)
4	1.41 (1.33-1.49)	1.31 (1.23-1.40)
≥5	1.34 (1.25-1.44)	1.25 (1.16-1.35)
History of PCI	4.73 (4.47-5.00)	5.26 (4.96-5.58)
Comorbidity		
Hypertension	1.41 (1.38-1.45)	2.03 (1.97-2.08)
Hyperlipidaemia	1.16 (1.12-1.20)	1.16 (1.12-1.20)
Arrhythmia	1.09 (1.05-1.12)	1.05 (1.01-1.10)
Heart failure	2.41 (2.29-2.53)	2.57 (2.43-2.71)
Dementia	0.35 (0.32-0.38)	0.44 (0.40-0.49)
Diabetes	1.55 (1.50-1.59)	1.25 (1.21-1.29)
COPD	0.94 (0.90-0.98)	0.92 (0.88-0.97)
Asthma	0.94 (0.90-0.97)	0.90 (0.87-0.93)
Chronic kidney disease	1.24 (1.21-1.28)	1.19 (1.16-1.24)
RA	0.98 (0.90-1.07)	1.08 (0.99-1.17)

5.4 Discussion

Although there were studies on medication utilisation of cardiovascular disease, this is the first UK study to provide a comprehensive overview of initial prescription patterns of cardiovascular medications and investigate potential factors associated with the occurance of cardiovascular polypharmacy in patients with new diagnoses of coronary heart disease or stroke. The results showed that 40.6% of patients with CVD were prescribed with cardiovascular polypharmacy. The average number of cardiovascular medications was 4.8 in patients with CHD and 3.1 in patients with stroke. Male, younger age, current smoking, high BMI, hypertension, hyperlipidaemia, higher deprivation score

and multiple comorbidities were associated with an increased likelihood of receiving cardiovascular polypharmacy.

Antiplatelet therapy, statins, ACEIs and beta-blockers are recommended offering all patients for secondary prevention of MI(Amsterdam et al., 2014; Arslan et al., 2018; National Institute for Health and Care Excellence, 2013, 2020c). I observed high rates of antiplatelet agents (91.8%), lipid-regulating medications (89.8%), ACEIs/ARBs (82.1%) and β-blockers (80.2%) in patients with MI. The proportion of patients prescribed with dual antiplatelet (72.0%) therapy was relatively lower. In patients with stroke, over 75% of stroke patients initially were prescribed with at least one of antiplatelet agents and lipid-regulating medications. ACEIs/ARBs (43.8%), CCBs (27.5%) and diuretics (26.4%) were also frequently issued. Guidelines state that blood pressure therapy is indicated for secondary prevention of stroke in patients who have a sustained BP ≥140 mmHg systolic or ≥90 mmHg diastolic, and ACEIs/ARBs, CCBs and diuretics are the first-line antihypertensive medications(Kernan et al., 2014). The results indicated that the usage of cardiovascular medications in 'real-world' patients may be sub-optimally adhered to the guideline recommendations.

Between 2007 and 2016, the initial use of cardiovascular medications for secondary prevention of CVD remained stable. This trend is not surprising because ACEI, aspirin, β-blocker and statin were advocated to reduce mortality after acute MI in the NICE guidelines published in 2001(Skinner et al., 2007), which was consistent with the latest version(National Institute for Health and Care Excellence, 2020c). Similarly, the first-line pharmacotherapy for stroke and TIA recommended in the latest NICE guidelines was in accordance with

the guidelines published in 2008(National Institute for Health and Care Excellence, 2013, 2019b).

I further estimated the association between prescribing of cardiovascular polypharmacy and potential risk factors at baseline. In my analysis, women were less likely to have cardiovascular polypharmacy. Several studies have reported underuse of cardiovascular medications in women after their first diagnosis of CVD(DeWilde et al., 2008; Gunnell et al., 2016; Turnbull et al., 2011; Yusuf et al., 2011). The AusHEART study(Turnbull et al., 2011) reported that women were more likely to be underestimated by physicians on the true risk of cardiovascular disease. A previous study conducted in the UK has also suggested that women were less likely to be systematically screened for cardiovascular disease than men(Bartys et al., 2005). These might partially explain the gender difference in cardiovascular medication prescribing.

In accordance with current evidence, the results of this study found a lower rate of cardiovascular polypharmacy in older patients(DeWilde et al., 2008; Ramsay et al., 2005; Simpson, 2005). One potential reason could be that combination therapy may be a less cost-effective regimen for older patients because of a longer recovery period and shorter life-expectancy(Bowling, 1999). In addition, for older patients, multiple factors like drug-interactions and potential adverse effects have to be considered, which may lead to an underuse of drug therapies(Rowe et al., 1976; Tan et al., 2015). Current smoking, high body mass index, high blood pressure and hyperlipidaemia were shown to be considerably and positively associated with initiating cardiovascular polypharmacy, which might be attributable to awareness of the increased risk of cardiovascular disease. CVD patients with a history of PCI were more likely to be treated with

five or more cardiovascular medications, which might be related to higher severity of disease condition or additional medications prescribed as a result of intervention, e.g. stenting.

Multi-comorbidities were also presented as a risk factor for cardiovascular polypharmacy. CVD patients with a history of heart failure, diabetes or chronic kidney disease often receive combination therapy more frequently. In addition to the medications for secondary prevention of CHD or stroke, guidelines recommend that those patients with HF should be prescribed some other cardiovascular medications. For example, mineralocorticoid receptor antagonists are indicated for patients who have HF with reduced ejection fraction and continue to have symptoms of HF. Anticoagulant medications combined with antiplatelet agents may be recommended for patients with stroke and HF(National Institute for Health and Care Excellence, 2018a). Diabetes is a significant risk factor for cardiovascular disease, so it would be expected that doctors may prescribe additional cardiovascular medications for those CVD patients with diabetes. Many significant CVD risk factors including diabetes, hypertension and dyslipidaemia are highly prevalent in patients with CKD(Sarnak et al., 2003). The guidelines indicate that CKD patients should aim to control their blood pressure below 140/90mmHg and lower than 130/80mmHg if they also have diabetes(National Institute for Health and Care Excellence, 2014). Therefore, CVD patients with CKD may be prescribed more cardiovascular medications. In contrast, patients with a history of dementia were less likely to be prescribed more than five cardiovascular medications. The reason for the underuse of cardiovascular medications in dementia is uncertain. NICE guidelines suggest that some commonly used medications

may cause cognitive impairment, which might be a concern for doctors prescribing for patients who have CVD and dementia(National Institute for Health and Care Excellence, 2018b). The results showed that patients with asthma also were prescribed with cardiovascular polypharmacy less frequently, which might due to concerns of drug interactions as β-blockers have been debated for many years to be contraindicated in asthma patients(Shelley R. Salpeter et al., 2002). In addition, this study showed that high social deprivation status was associated with cardiovascular polypharmacy. This is probably attributed to a poorer level of health associated with social deprivation. This finding is similar to the result of a Scottish study(Appleton et al., 2014).

Polypharmacy has historically been considered negatively because of the associated risk of adverse events and decreased adherence (Mukete & Ferdinand, 2016; Sørensen et al., 2009). It is now accepted that in many chronic conditions, polypharmacy is also therapeutically beneficial. Patients who have had a CHD or stroke are at high risk of recurrent CV events and mortality. The prescribing of appropriate multiple cardiovascular medications is necessary for these high-risk patients. My systematic review and meta-analysis study (Chapter 2) assessed the effectiveness of evidence-based combination pharmacotherapy (EBCP) and found that EBCP is associated with a decreased risk of all-cause mortality and cardiovascular events in patients with cardiovascular disease. However, the results showed that the underuse of evidence-based pharmacotherapy still existed in patients with cardiovascular disease, and this finding was consistent with the previous studies(Sheppard et al., 2014; J. Wu et al., 2013). The relative lower risk of CVD (e.g., non-smokers and patients without comorbidities) may partially explain the phenomenon of

underuse of CVD medications. The result indicated that cardiovascular risk factors may influence general practitioners' decision to prescribe cardiovascular medications[8]. Evidence-based recommendations on personalised medicine are still limited. Further studies are required to evaluate the risk and benefit of cardiovascular polypharmacy when prescribing for the prevention and treatment of cardiovascular disease.

5.4.1 Strengths and limitations

This study has several strengths. It used a large UK primary care data source which is representative of the UK general population. The analysis has provided comprehensive details about the patterns of initial cardiovascular pharmacotherapy prescribing by primary physicians in patients with coronary heart disease and stroke.

The current study also has limitations. Firstly, the dataset only provides records of prescriptions; therefore, it was not possible to determine if medications were actually dispensed, taken or adequately used by patients. However, the current study aimed to describe the utilisation patterns of CV medications after a CV event, this will not affect the results. Secondly, because the THIN database does not capture data from hospital treatment and over-the-counter (OTC) medications (e.g., aspirin available OTC), the study was not able to address drug usage outside the records from general practice which may lead to an underestimation in the results. This may be important, especially for patients under the age of 60 years who may be liable to pay prescription charges in England. Thirdly, THIN dataset has incomplete records on some of the important confounding variables (i.e. smoking, alcohol use, BMI and laboratory tests) for some patients.

In conclusion, multiple cardiovascular medications treatment was common in CVD patients in the UK. High-risk factors of CVD were associated with cardiovascular polypharmacy. Further studies are warranted to assess the impact of cardiovascular polypharmacy and its interaction on CVD recurrence and mortality.

Chapter 6: Impact of multiple cardiovascular medications on mortality after an incidence of stroke or transient ischemic attack

This chapter has been peer-reviewed by BMC Medicine with minor comments and a revision has been submitted.

6.1 Introduction

Stroke is the second most common cause of death worldwide, and the third most common cause of death in the UK(British Heart Foundation, 2020a; World Health Organization, 2020). According to Heart and Circulatory Disease Statistics 2019, over 1.3 million people in the UK have survived a stroke or TIA(British Heart Foundation, 2020a). Optimal pharmacological therapy plays a key role in preventing recurrence of stroke, cardiovascular events and reducing the risk of mortality. To manage the risk factors and to improve clinical outcomes, patients with stroke commonly receive multiple cardiovascular medications. Guidelines recommend antihypertensive, lipid modification and antiplatelet agents for secondary prevention of stroke (Kernan et al., 2014; National Institute for Health and Care Excellence, 2013). The findings from the INTERSTROKE study identified hypertension as the most important risk factor for stroke with a population-attributable risk of 51.8%(O'Donnell et al., 2010). Evidence from a systematic review of RCTs suggested that antihypertensive treatment reduced recurrent vascular events by 21% in patients after stroke(Rashid et al., 2003). A large systematic review of observational studies and RCTs supported a short-term outcome benefit from statins(Ní Chróinín et

al., 2013). Antiplatelet agents have been shown to prevent death and vascular events in patients with high-risk of cardiovascular disease(Thijs et al., 2008). Although in routine practice, most patients are on combination therapy of multiple cardiovascular medications, the existing evidence from clinical trials has mostly focused on a single cardiovascular medication. The effect of combined antiplatelet agents and combined antihypertensive medications was only assessed in clinical trials for the prevention of stroke(Arima et al., 2006; Geeganage et al., 2012).

A knowledge gap remains in identifying the optimal combination of medication therapy after ischemic stroke. It is unclear whether increasing the numbers or the classes of cardiovascular medications would have additional benefits on long-term survival. Further, the optimal constituents of combination therapy have not been comprehensively identified. This study aimed to investigate the effect of multiple cardiovascular medications on long-term survival after an initial ischemic stroke or TIA event.

6.2 Methods

6.2.1 Study design

A retrospective cohort study was conducted using the THIN database.

6.2.2 Database

The detailed data source are presented in chapter 4. In brief, the THIN database is a primary care clinical database which includes anonymised data from general practices across the UK. The database includes over 16 million patients from over 744 general practices. In 2013, the active patients in THIN

represented approximately 6% of the UK population[9]. THIN includes information for each individual on demographics, diagnoses, prescriptions, referrals, laboratory tests, immunisations, and local area deprivation (Townsend score)[10].

Ethics approval for this study was obtained in 2017 from the SRC, protocol reference: SRC 17THIN100.

6.2.3 Study population

This study included patients with their first diagnosis of ischemic stroke or TIA between January 2007 and December 2016. The records of disease diagnosis were identified using the Read Codes. Patients who were aged 45 or above and who had been registered for at least three years in the THIN database before the first stroke event were included in this study. I excluded patients who had a history of myocardial infarction (MI) before the first stroke or TIA event, who had died of all causes or who had an occurrence of a further cardiovascular event within the first 90 days after the first event of stroke or TIA. Follow-up of the included patients commenced at the date of the incident stroke/TIA event, and ended until the earliest of 31st of December 2016, date of registered death, and the date of leaving the general practice during the study period. For each patient, the follow-up was divided into contiguous periods of 1 year, each defined with specific entry and exit points. For example, one patient was followed for three years then died (Figure 6-1). The follow-up of this patient was divided into three one-year periods. I defined an entry point at the start of each separate period. Cardiovascular medications were identified during the first 90-day window at each entry point.

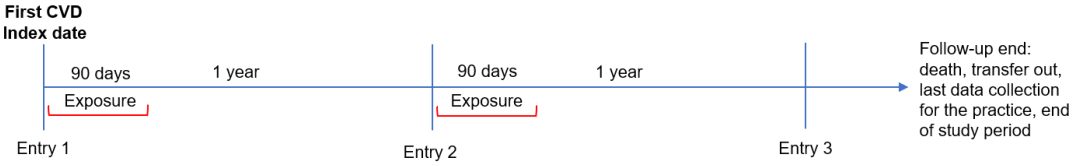


Figure 6-1 Study cohort

6.2.4 Exposure and control groups

Cardiovascular prescriptions were identified using drug codes in the THIN database. Each patient could contribute to several therapy categories, according to the cardiovascular medications issued at each entry point. In the UK repeat prescriptions are usually issued by primary care physicians for chronic conditions. The prescription interval is usually 28 or 56 days. I included cardiovascular medications with a 28+ day prescription or with at least two prescriptions during the 90-day exposure window to make sure medications were prescribed for long-term use. Cardiovascular medications were identified based on all medications classified in the BNF Chapter two (cardiovascular system). Combination preparations were separated into their individual drug constituents.

I investigated the effect of combination therapy based on different numbers, classes, and combination regimens on all-cause mortality. According to the numbers of cardiovascular medications (any medications identified based on BNF) prescribed in each 90-day exposure window, patients were stratified into groups of 0, 1, 2, 3, 4, 5, and ≥6 cardiovascular medications at each entry point. I then selected six evidence-based classes of cardiovascular medications commonly used for secondary prevention of cardiovascular disease. The six classes of cardiovascular medications were antiplatelet agents (APAs), lipid-

regulating medications (LRMs), ACEIs/ ARBs, beta-blockers (BBs), diuretics (DRs), and calcium channel blockers (CCBs). Patients were stratified into groups of 0 (none of any cardiovascular medication) to 6 classes. Six classes of cardiovascular medications are APAs, LRMs, ACEIs/ARBs, CCBs, DRs and BBs exclusively. Patients who were on other class treatment were excluded from the study due to the complexity of the drug combination and few patients. Finally, I selected 20 most commonly prescribed combinations (≥2 classes) exclusively containing the six classes of medications. Patients with one medication treatment or one class medication treatment were considered as the control group.

6.2.5 Outcomes

The outcome of the study was all-cause mortality.

6.2.6 Data extraction and confounders

Patient demographics, clinical characteristics within one year prior to each entry point, and prescriptions within three months prior to each entry point were extracted from the THIN database. Confounding variables included age, gender, smoking status (never smoked, former smoker), alcohol consumption (never drank, current drinker, former drinker), BMI (mean, normal, overweight, obese and underweight), BP status (normal, stage 1, 2 and 3 hypertension and hypotension), TC status (optimal, intermediate and high), Townsend scores, history of hypertension, hyperlipidaemia, arrhythmia, heart failure, peripheral vascular disease, percutaneous transluminal coronary intervention, dementia, chronic obstructive pulmonary disease, asthma, chronic kidney disease and rheumatoid arthritis. Previous use of cardiovascular medications and

nonsteroidal anti-inflammatory medications (NSAIDs) were also included. Read codes were used to identify previous medical conditions from the THIN database.

6.2.7 Statistical analysis

Data are summarised as mean (SD) for continuous variables and as frequencies (%) for categorical variables. Comparisons were performed using analysis of variance (ANOVA) for continuous variables, and the chi-squared test for categorical variables. Multiple imputation was applied in addressing missing values for smoking status, alcohol consumption, BMI status, BP status, TC status, and Townsend scores. We used multiple imputation by chained equations (MICE) (also called fully conditional specification (FCS)) in SAS software to create 25 imputed datasets(Azur et al., 2011). The factors used in the multiple imputation included all confounders mentioned in “6.2.6 data extraction and confounders”, outcome (death), exposure to different numbers of cardiovascular medications. Rubin’s rules were applied to combine the results from analyses on each of the imputed datasets to produce estimates and confidence intervals(Rubin, 1987).

We estimated the risk of mortality presented as HRs in relation to the number of medications, medication classes prescribed and different combinations using a marginal structural Cox proportional hazards model, as described by Hernán *et al.* (Hernán et al., 2000).

In some longitudinal studies, both treatment and confounder can change over time (time-varying). Figure 6-2 illustrates the theoretical foundation of the type of time-varying confounding. Let BP be a time-varying confounder, T is the time-

varying treatment (e.g., antihypertensive treatment) and death is the outcome, with subscripts 0 and 1 denoting two time points during follow-up. In this situation, BP is associated with (i) previous antihypertensive treatment, (ii) subsequent antihypertensive treatment and (iii) death. Marginal structural models (MSMs) are a multi-step estimation procedure designed to control for the effects of time-varying confounder, and are affected by previous treatment.

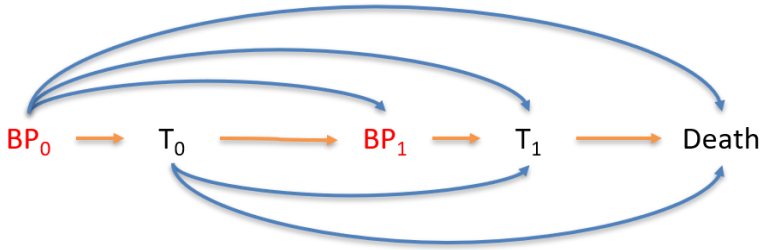


Figure 6-2 Time-varying confounding.

Abbreviations: →, causal effect; BP_0, blood pressure at time 0; BP_1, blood pressure at time 1, T_0, antihypertensive treatment at time 0; T_1, antihypertensive treatment at time 1.

MSMs use inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCWs) to create a pseudo-population in which the probabilities of treatment and censoring are not a function of the time-varying covariates but the effect of treatment on time to outcomes is the same as in the original population(Hernán et al., 2000). MSMs are fitted in a two-stage process:

1. Estimate the individual IPTWs and IPCWs;
2. Use the IPTWs and IPCWs as weights in a regression model of the effect of the treatment on the outcome.

In the first stage, the IPTWs are calculated based on each subject's probability

of the treatment they actually receiving at each time point given the covariates (including time-varying covariates). The IPCWs are similarly estimated based on each subject's probability at each time point to be censored based on covariates. Final weight is calculated by simply multiplying the two weights. In the secondary stage, previous studies always used a weighted pooled logistic regression model to estimate the effect of treatment on a survival outcome(Cook et al., 2002; Gerhard et al., 2012; Havercroft & Didelez, 2012; Hernán et al., 2000). MSMs assume no unmeasured confounding.

For my study, an MSM was used to estimate the association between cardiovascular treatment on all-cause mortality. In the estimation of IPTWs and IPCWs at each entry point, the numerator included the time-dependent intercept and the baseline covariates: sex, baseline age, Townsend score, history of comorbidities and previous cardiovascular medications. The denominator included the time-dependent intercept, the baseline covariates and the following time-varying covariates: age at each entry point, most recently available smoking status, alcohol consumption, BMI status, BP status, TC status, comorbidities and previous occurrence of cardiovascular events (nonfatal MI, angina, stroke or TIA) one year prior to each entry point, and time-varying variables of previous cardiovascular medications and NSAIDs use three months prior to each entry point. Hazard ratios were finally estimated by fitting a weighted logistic regression model. All analyses were performed using SAS version 9.4. SAS code of MSMs was provided by Hernan *et al*. (Hernán et al., 2000) and Douglas *et al*(Faries et al., 2010).

6.2.8 Sensitivity analysis

I conducted six sensitivity analyses: (1) using a 60-day screening period instead of a 90-day window; (2) dividing the one-year follow-up time frame into intervals of 6 months; (3) including patients who had a history of MI before the first stroke/TIA event; (4) repeating the analyses in patients with completed characteristics data (complete-case analyses); (5) categorising missing data for each covariate as a separate group; and (6) repeating the analyses separately for patients with TIA and patients with ischemic stroke; and (7) an additional sensitivity analysis was conducted to assess the robustness of my findings to unmeasured confounding by computing the E-Value (Haneuse et al., 2019).

The E-Value is defined as “the minimum strength of association, on the risk ratio scale, that an unmeasured confounder must have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates”(Haneuse et al., 2019). The E-value analysis considers how strong the unmeasured confounding has to be to negate the observed results.

The calculation formulas of E-Value for risk ratios (RR) are shown in table 6-1. The formulas in Table 6-1 can be used for the calculation of E-value for HR for rare outcomes (e.g., <15%)(VanderWeele & Ding, 2017). An online calculator for the E-value can be applied via: https://www.evalue-calculator.com.

Table 6-1 Calculating the E-value for Risk Ratios

Estimate or CI, by Direction of Risk Ratio	Computation of the E-Value
RR > 1	
Estimate	E-value = RR + sqrt {RR × (RR − 1)}
CI	If LL ≤ 1, then E-value = 1 If LL > 1, then E-value = LL + sqrt {LL × (LL − 1)}
RR < 1	
Estimate	Let RR*=1/RR E-value = RR* + sqrt {RR* × (RR* − 1)}
CI	If UL ≥ 1, then E-value = 1 If UL < 1, then let UL*=1/UL and E-value = UL* + sqrt {UL* × (UL* − 1)}

LL = lower limit of the CI; RR = risk ratio; RR* = inverse of RR; UL = upper limit of the CI; UL* = inverse of UL. *Note*. Reprint from "Sensitivity Analysis in Observational Research: Introducing the E-Value", by Tyler J. *et al.*, 2017, Annals of Internal Medicine, 167(4): 271.

The interpretation of an E-value can be explained by an example, the study from Fisher and colleagues(Fisher et al., 2018). The study found that bariatric surgery was associated with a lower composite incidence of macrovascular events at 5 years (HR: 0.60, 95% CI: 0.42-0.86). The E-value for this result was 2.72, meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association at least as large as 2.72 with both macrovascular events and with bariatric surgery. In this study, the HRs for some powerful macrovascular disease risk factors were 1.09 (95% CI, 0.85-1.41) for hypertension, 1.88 (95% CI, 1.34-2.63) for dyslipidaemia, and 1.48 (95% CI, 1.17-1.87) for being a current smoker. It is not likely that an unmeasured or unknown confounder would have a substantially greater effect on macrovascular disease development than these known risk factors by having a relative risk exceeding 2.72. The magnitude of an E-value in a particular study may be large or small depending on the magnitude of the associations of other risk factors. For

example, if most other risk factors have an HR lower than the E-value (like the previous example), the unmeasured confounding would have to have much larger effects than most risk factors to explain away the reported association. In contrast, if many risk factors have an HR larger than the E-value, the unmeasured confounding would have a stronger power to negate the observed results.

6.3 Results

The study cohort consisted of 25,200 men (47.9%) and 27,419 women (52.1%) who experienced an initial ischemic stroke or TIA event from 1 January 2007 to 31 December 2016. Overall, 8.1% of patients did not receive any cardiovascular medications, 9.2% received 1, 20.3% received 2, 23.0% received 3, 19.4% received 4, 11.7% received 5, and 8.2% of patients received 6+ cardiovascular medications during the 90 days following their initial ischemic stroke or TIA event. The mean age at the start of follow-up was 72.0 (SD, 11.9) years, and the mean follow-up time was 3.6 (SD, 2.6) years. In total, the study recorded 9,230 deaths during follow-up, and the crude death rate was 46.3/1000 person-years. Table 1 shows the baseline characteristics of the patients at their initial ischemic stroke or TIA events based on the number of cardiovascular medications received during the first 90 days. There were significant differences in all characteristics except peptic ulcer disease between the groups.

Table 6-2 Baseline characteristics of study patients at their initial stroke events, 2007-2016.

		Cardiovascular treatment groups							
No. of CV medications	**Total**	**0**	**1**	**2**	**3**	**4**	**5**	**≥6**	**P value**
	n = 52,619	n = 4259 (8.1%)	n = 4837 (9.2%)	n = 10,705 (20.3%)	n = 12,112 (23.0%)	n = 10,197 (19.4%)	n = 6177 (11.7%)	n = 4332 (8.2%)	
Sex, % women	27,419 (52.1)	2256 (53.0)	2654 (54.9)	5507 (51.4)	6096 (50.3)	5283 (51.8)	3294 (53.3)	2329 (53.8)	<0.01
Age, (years) mean ± SD	72.0 ± 11.9	71.7 ± 13.3	71.9 ± 13.6	70.7± 12.5	71.8 ± 11.7	72.6 ± 11.1	72.9 ± 10.7	73.1 ± 10.6	<0.01
Smoking (%)									
Current	9847 (18.7)	877 (20.6)	911 (18.8)	2252 (21.0)	2401 (19.8)	1822 (17.9)	948 (15.4)	636 (14.7)	
Former	16,458 (31.3)	1186 (27.9)	1349 (27.9)	3144 (29.4)	3855 (31.8)	3304 (32.4)	2121 (34.3)	1499 (34.6)	
Never	24,507 (46.6)	1997 (46.9)	2364 (48.9)	4930 (46.1)	5442 (44.9)	4767 (46.8)	2929 (47.4)	2078 (48.0)	
Missing	1807 (3.4)	199 (4.7)	213 (4.4)	379 (3.5)	414 (3.4)	304 (3.0)	179 (2.9)	119 (2.8)	
Alcohol (%)									
Current	26,023 (49.5)	1923 (45.2)	2132 (44.1)	5152 (48.1)	6133 (50.6)	5216 (51.2)	3222 (52.2)	2245 (51.8)	
Former	1728 (3.3)	116 (2.7)	189 (3.9)	355 (3.3)	410 (3.4)	318 (3.1)	213 (3.5)	127 (2.9)	
Never	8658 (16.5)	712 (16.7)	788 (16.3)	1700 (15.9)	1920 (15.9)	1659 (16.3)	1070 (17.3)	809 (18.7)	
Missing	16,210 (30.8)	1508 (35.4)	1728 (35.7)	3498 (32.7)	3649 (30.1)	3004 (29.5)	1672 (27.1)	1151 (26.6)	
BMI status (%)									
Normal (18.5-24.9 kg/m2)	12,506 (23.8)	1052 (24.7)	1327 (27.4)	2786 (26.0)	2922 (24.1)	2350 (23.1)	1299 (21.0)	770 (17.8)	
Overweight (25.0-29.9 kg/m2)	14,897 (28.3)	1080 (25.4)	1229 (25.4)	2879 (26.9)	3408 (28.1)	3062 (30.0)	1933 (31.3)	1306 (30.2)	
Obesity (≥ 30.0 kg/m2)	11,131 (21.2)	715 (16.8)	670 (13.9)	1748 (16.3)	2410 (19.9)	2382 (23.4)	1727 (28.0)	1479 (34.1)	
Underweight (< 18.5 kg/m2)	1075 (2.0)	109 (2.6)	182 (3.8)	268 (2.5)	272 (2.3)	151 (1.5)	58 (0.9)	35 (0.8)	
Missing	13,010 (24.7)	1303 (30.6)	1429 (29.5)	3024 (28.3)	3100 (25.6)	2252 (22.1)	1160 (18.8)	742 (17.1)	
BP status (%)									
Normal (BP < 140/90 mmHg)	21,263 (40.4)	1608 (37.8)	2191 (45.3)	4537 (42.4)	4780 (39.5)	3966 (38.9)	2432 (39.4)	1749 (40.4)	

Stage 1 hypertension (BP ≥ 140/90 mmHg)	15,626 (29.7)	1066 (25.0)	1221 (25.2)	2841 (26.5)	3658 (30.2)	3293 (32.3)	2109 (34.1)	1438 (33.2)	
Stage 2 hypertension (BP ≥ 160/100 mmHg)	5166 (9.8)	355 (8.3)	332 (6.9)	766 (7.2)	1198 (9.9)	1184 (11.6)	765 (12.4)	566 (13.1)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	2413 (4.6)	154 (3.6)	129 (2.7)	284 (2.7)	508 (4.2)	578 (5.7)	406 (6.6)	354 (8.2)	
Missing	8078 (15.4)	1070 (25.1)	958 (19.8)	2263 (21.1)	1953 (16.1)	1159 (11.4)	454 (7.4)	221 (5.1)	
TC status (%)									
Optimal (<5.2 mmol/L)	16,562 (31.5)	995 (23.4)	1092 (22.6)	2648 (24.7)	3560 (29.4)	3636 (35.7)	2571 (41.6)	2060 (47.6)	
Intermediate (5.3-6.2 mmol/L)	7898 (15.0)	519 (12.2)	626 (12.9)	1596 (14.9)	1929 (15.9)	1598 (15.7)	974 (15.8)	656 (15.1)	
High (>6.2 mmol/L)	4510 (8.6)	314 (7.4)	386 (8.0)	921 (8.6)	1111 (9.2)	902 (8.9)	551 (8.9)	325 (7.5)	
Missing	23,649 (44.9)	2431 (57.1)	2733 (56.5)	5540 (51.8)	5512 (45.5)	4061 (39.8)	2081 (33.7)	1291 (29.8)	
Townsend score (%)									
1 (least deprived)	10,959 (20.8)	809 (19.0)	1037 (21.4)	2256 (21.1)	2627 (21.7)	2155 (21.1)	1248 (20.2)	827 (19.1)	
2	10,833 (20.6)	851 (20.0)	1058 (21.9)	2216 (20.7)	2496 (20.6)	2083 (20.4)	1306 (21.1)	823 (19.0)	
3	9949 (18.9)	827 (19.4)	952 (19.7)	2051 (19.2)	2168 (17.9)	1932 (19.0)	1173 (19.0)	846 (19.5)	
4	8613 (16.4)	745 (17.5)	734 (15.2)	1716 (16.0)	2011 (16.6)	1639 (16.1)	1004 (16.3)	764 (17.6)	
5 (most deprived)	5995 (11.4)	494 (11.6)	515 (10.7)	1255 (11.7)	1400 (11.6)	1113 (10.9)	724 (11.7)	494 (11.4)	
Missing	6270 (11.9)	533 (12.5)	541 (11.2)	1211 (11.3)	1410 (11.6)	1275 (12.5)	722 (11.7)	578 (13.3)	
History of PCI (%)	262 (0.5)	13 (0.3)	6 (0.1)	26 (0.2)	42 (0.4)	51 (0.5)	43 (0.7)	81 (1.9)	
Comorbidity (%)									
Hypertension	29,382 (55.8)	1802 (42.3)	1604 (33.2)	3547 (33.1)	6353 (52.5)	7208 (70.7)	5058 (81.9)	3810 (88.0)	<0.01
Hyperlipidaemia	7510 (14.3)	433 (10.2)	463 (9.6)	1257 (11.7)	1644 (13.6)	1629 (16.0)	1187 (19.2)	897 (20.7)	<0.01
Arrhythmia	8159 (15.5)	645 (15.1)	449 (9.3)	1095 (10.2)	1611 (13.3)	1851 (18.2)	1331 (21.6)	1177 (27.2)	<0.01
Heart Failure	2235 (4.3)	154 (3.6)	98 (2.0)	233 (2.2)	373 (3.1)	446 (4.4)	415 (6.7)	516 (11.9)	<0.01
PVD	2752 (5.2)	209 (4.9)	178 (3.7)	450 (4.2)	557 (4.6)	583 (5.7)	427 (6.9)	348 (8.0)	<0.01

Diabetes	8921 (17.0)	568 (13.3)	511 (10.6)	1313 (12.3)	1845 (15.2)	1933 (19.0)	1442 (23.3)	1309 (30.2)	<0.01
Dementia	2549 (4.8)	271 (6.4)	518 (10.7)	653 (6.1)	518 (4.3)	324 (3.2)	170 (2.8)	95 (2.2)	<0.01
COPD	4424 (8.4)	297 (7.0)	412 (8.5)	881 (8.2)	1058 (8.7)	892 (8.8)	517 (8.4)	367 (8.5)	0.02
Asthma	6888 (13.1)	494 (11.6)	679 (14.0)	1418 (13.3)	1642 (13.6)	1292 (12.7)	789 (12.8)	574 (13.3)	<0.01
Liver disease	338 (0.6)	45 (1.1)	45 (0.9)	59 (0.6)	79 (0.7)	61 (0.6)	29 (0.5)	20 (0.5)	<0.01
Peptic ulcer disease	2974 (5.7)	240 (5.6)	282 (5.8)	594 (5.6)	689 (5.7)	587 (5.8)	346 (5.6)	236 (5.5)	0.98
RA	1094 (2.1)	96 (2.3)	113 (2.3)	199 (1.9)	259 (2.1)	206 (2.0)	132 (2.1)	89 (2.1)	0.51
CKD	9366 (17.8)	666 (15.6)	597 (12.4)	1346 (12.7)	1922 (16.0)	2045 (20.1)	1495 (24.2)	1259 (29.2)	<0.01

BMI = body mass index; BP = blood pressure; TC = total cholesterol; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PCI = percutaneous transluminal coronary intervention; PVD = peripheral vascular disease; RA = rheumatoid arthritis;

Figure 6-3 shows the risk of all-cause mortality in patients prescribed with different numbers of cardiovascular medications. Compared with monotherapy, the risk of all-cause mortality was lower in patients with combination therapy: 18% (95% CI: 11%-24%) lower with two medications, 36% (95% CI: 31%-41%) lower with three medications, 39% (95% CI: 33%-44%) lower with four medications, 42% (95% CI: 36%-48%) lower with five medications and 35% (95% CI: 27%-42%) lower with six or more medications. Conversely, no use of cardiovascular medications was associated with an increased risk of all-cause mortality (adjusted HR: 1.67, 95% CI: 1.53-1.82) compared with monotherapy. Similar results were found for the different numbers of cardiovascular medication classes. Figure 6-4 shows decreased risks of mortality in patients with two (adjusted HR: 0.79, 95% CI: 0.73-0.86), three (adjusted HR: 0.60, 95% CI: 0.55-0.66), four (adjusted HR: 0.51, 95% CI: 0.46-0.57), five (adjusted HR: 0.54, 95% CI: 0.46-0.63), and six (adjusted HR: 0.53, 95% CI: 0.36-0.77) specific classes of cardiovascular medications compared with patients prescribed one class. Patients with a four-class combination had the lowest risk of mortality.

Number of CV medications	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥6	621	13702	45.3	0.70 (0.63-0.77)	0.66 (0.59-0.74)
5	847	22124	38.3	0.59 (0.54-0.65)	0.60 (0.54-0.66)
4	1429	37572	38.0	0.58 (0.54-0.63)	0.61 (0.56-0.67)
3	1724	44459	38.8	0.58 (0.54-0.63)	0.65 (0.59-0.70)
2	1802	37784	47.7	0.71 (0.66-0.77)	0.82 (0.75-0.89)
1	1212	18166	66.7	1	1
0	1595	15258	104.5	1.44 (1.33-1.55)	1.67 (1.53-1.83)

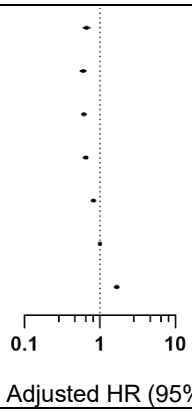


Figure 6-3 Risk of all-cause mortality in patients prescribed with various numbers of cardiovascular medications

Number of CV classes	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
6	35	952	36.8	0.64 (0.45-0.90)	0.53 (0.36-0.77)
5	251	7382	34.0	0.59 (0.51-0.68)	0.54 (0.46-0.63)
4	675	21948	30.8	0.53 (0.48-0.58)	0.51 (0.46-0.57)
3	1260	35848	35.1	0.60 (0.55-0.65)	0.60 (0.55-0.66)
2	1660	39186	42.4	0.72 (0.67-0.77)	0.79 (0.73-0.86)
1	1309	22144	59.1	1	1
0	1595	15258	104.5	1.62 (1.50-1.75)	1.58 (1.45-1.73)

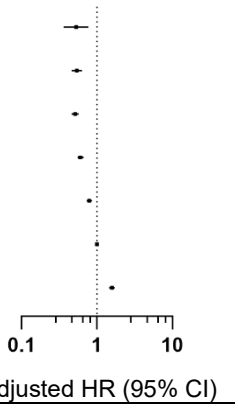


Figure 6-4 Risk of all-cause mortality in patients prescribed with various numbers of specific six classes of cardiovascular medications

Combination	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR	Adjusted HR
APAs+LRMs+ACEIs/ARBs+CCBs	159	7632	20.8	0.27 (0.23-0.32)	0.39 (0.32-0.47)
APAs+LRMs+ACEIs/ARBs+CCBs+BBs	46	1763	26.1	0.35 (0.26-0.46)	0.40 (0.28-0.57)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs	97	4097	23.7	0.32 (0.26-0.40)	0.41 (0.32-0.52)
APAs+LRMs+CCBs+DRs	68	2081	32.7	0.41 (0.32-0.53)	0.42 (0.32-0.56)
APAs+LRMs+ACEIs/ARBs	365	17244	21.2	0.28 (0.25-0.32)	0.44 (0.38-0.51)
APAs+LRMs+CCBs	187	6647	28.1	0.35 (0.30-0.42)	0.45 (0.38-0.55)
APAs+LRMs+ACEIs/ARBs+DRs	189	7384	25.6	0.34 (0.29-0.40)	0.47 (0.37-0.59)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs+BBs	41	1257	32.6	0.42 (0.30-0.58)	0.49 (0.34-0.71)
APAs+LRMs+ACEIs/ARBs+BBs	91	2970	30.6	0.47 (0.38-0.57)	0.50 (0.38-0.67)
LRMs+ACEIs/ARBs	65	2178	29.8	0.36 (0.28-0.47)	0.57 (0.42-0.76)
APAs+LRMs	765	25726	29.7	0.38 (0.34-0.42)	0.59 (0.52-0.67)
APAs+ACEIs/ARBs	139	3014	46.1	0.61 (0.51-0.73)	0.63 (0.52-0.78)
APAs+ACEIs/ARBs+DRs	81	1410	57.5	0.78 (0.62-0.98)	0.64 (0.49-0.84)
APAs+LRMs+DRs	218	4285	50.9	0.66 (0.56-0.77)	0.65 (0.54-0.78)
LRMs alone	190	5989	31.7	0.42 (0.36-0.49)	0.66 (0.55-0.81)
APAs+LRMs+DRs+BBs	75	1173	63.9	0.84 (0.66-1.08)	0.69 (0.51-0.95)
APAs+LRMs+BBs	116	2638	44.0	0.58 (0.47-0.70)	0.72 (0.57-0.91)
APAs+LRMs+ACEIs/ARBs+DRs+BBs	109	2024	53.9	0.74 (0.61-0.90)	0.73 (0.56-0.96)
ACEIs/ARBs alone	107	2628	40.7	0.49 (0.40-0.60)	0.76 (0.57-1.01)
APAs+CCBs	124	1679	73.9	0.97 (0.80-1.18)	0.92 (0.73-1.15)
APAs alone	753	9731	77.4	1	1

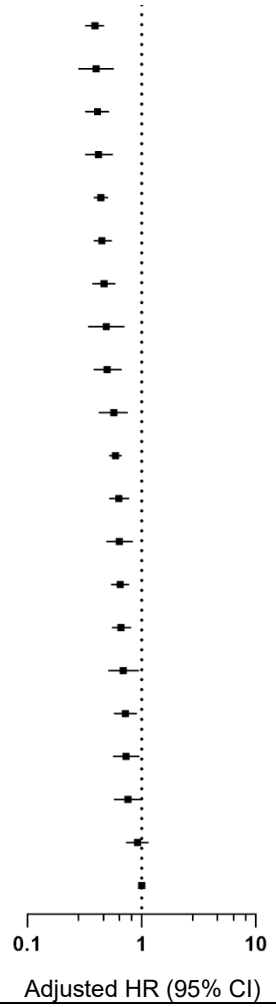


Figure 6-5 Risk of all-cause mortality in the 20 most commonly used regimens of the specific six classes of cardiovascular medications compared with antiplatelet agents alone

Among 20 most commonly used therapy regimens containing APA, LRM, ACEIs/ARBs, CCBs, diuretics, and beta-blockers, I found a significantly lower risk of mortality in combinations containing APA, LRM, ACEIs/ARBs and CCB (Figure 6-5) when compared with APA alone, the risk of mortality was lowered by 65% (95% CI: 56%-72%). When adding DR or BBs to the four-medication combination, the risk of mortality was lowered further by 62% (95% CI: 51%-71%) and 61% (95% CI: 44%-73%) respectively when compared to APA alone. The combination of only three classes of APA, LRM and ACEIs/ARBs also showed a significantly lower risk of mortality with an HR of 0.43 (95% CI: 0.36-0.50).

6.3.1 Sensitivity analysis

The primary results of the risk of mortality in patients with different numbers of CV medications and different numbers of classes of CV medications are similar to the results in the analysis using a 60-day exposure window. The analyses in patients with a history of MI, patients with competing risk characteristic , when categorising missing data as a separate group, and in separate analyses among patients with TIA only and patients with ischemic stroke only were consistent with the results of primary analyses. The results showed an even lower risk of mortality in patients with combination therapy when the follow-up duration was divided into 6-month intervals. The risk ratios of E-values for the three main analyses of all-cause mortality ranged from 1.74 to 4.57.

Table 6-3 Risk of all-cause mortality in patients prescribed with various numbers of cardiovascular medications in sensitivity analyses

	Adjusted HR (95% CI)							
Number of CV medications	**Primary analysis**	**60-day exposure window[a]**	**6-month interval[b]**	**With history of MI[c]**	**Complete data[d]**	**Categorised missing data[e]**	**Patients with TIA[f]**	**Patients with stroke[g]**
≥6	0.66 (0.59-0.74)	0.73 (0.64-0.82)	0.48 (0.42-0.54)	0.63 (0.56-0.71)	0.64 (0.52-0.79)	0.68 (0.61-0.76)	0.65 (0.54-0.79)	0.64 (0.56-0.75)
5	0.60 (0.54-0.66)	0.62 (0.56-0.70)	0.46 (0.41-0.51)	0.57 (0.51-0.64)	0.64 (0.52-0.78)	0.60 (0.54-0.66)	0.54 (0.46-0.64)	0.58 (0.51-1.67)
4	0.61 (0.56-0.67)	0.63 (0.58-0.68)	0.48 (0.44-0.53)	0.59 (0.53-0.64)	0.59 (0.49-0.71)	0.62 (0.57-0.68)	0.56 (0.48-0.64)	0.63 (0.56-0.71)
3	0.65 (0.59-0.70)	0.66 (0.60-0.72)	0.53 (0.48-0.57)	0.62 (0.56-0.68)	0.62 (0.52-0.74)	0.65 (0.60-0.70)	0.64 (0.56-0.73)	0.63 (0.56-0.70)
2	0.82 (0.75-0.89)	0.82 (0.75-0.89)	0.69 (0.64-0.75)	0.78 (0.71-0.85)	0.82 (0.69-0.98)	0.82 (0.76-0.89)	0.78 (0.69-0.89)	0.84 (0.75-0.93)
1	1	1	1	1	1	1	1	1
0	1.67 (1.53-1.83)	1.60 (1.45-1.76)	2.16 (1.99-2.34)	1.65 (1.50-1.81)	1.88 (1.56-2.26)	1.58 (1.45-1.73)	1.58 (1.37-1.82)	1.64 (1.46-1.84)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted in patients who had a history of MI before the first stroke or TIA event; [d]A sensitivity analysis conducted in patients with complete charateristics data; [e]A sensitivity analysis conducted by categorising missing data as a separate group; [f]A sensitivity analysis conducted in patients with the first TIA event; [g]A sensitivity analysis conducted in patients with the first ischemic stroke event

Table 6-4 Risk of all-cause mortality in patients prescribed with various numbers of specific six classes of cardiovascular medications in sensitivity analyses

	Adjusted HR (95% CI)							
Number of classes	Primary analysis	60-day exposure window[a]	6-month interval[b]	With history of MI[c]	Complete data[d]	Categorised missing data[e]	Patients with TIA[f]	Patients with stroke[g]
6	0.53 (0.36-0.77)	0.66 (0.59-0.74)	0.47 (0.27-0.81)	0.61 (0.38-0.97)	0.58 (0.31-1.08)	0.73 (0.48-1.09)	0.82 (0.41-1.63)	1.07 (0.55-2.08)
5	0.54 (0.46-0.63)	0.60 (0.54-0.66)	0.40 (0.33-0.47)	0.56 (0.47-0.65)	0.67 (0.51-0.86)	0.73 (0.61-0.86)	0.62 (0.46-0.83)	0.77 (0.57-1.04)
4	0.51 (0.46-0.57)	0.61 (0.56-0.67)	0.42 (0.38-0.47)	0.51 (0.45-0.58)	0.59 (0.49-0.72)	0.63 (0.56-0.71)	0.52 (0.44-0.63)	0.64 (0.53-0.78)
3	0.60 (0.55-0.66)	0.65 (0.59-0.70)	0.50 (0.45-0.54)	0.58 (0.52-0.65)	0.62 (0.53-0.74)	0.69 (0.62-0.76)	0.62 (0.53-0.72)	0.67 (0.58-0.78)
2	0.79 (0.73-0.86)	0.82 (0.75-0.89)	0.67 (0.61-0.72)	0.76 (0.69-0.84)	0.80 (0.68-0.94)	0.76 (0.68-0.85)	0.77 (0.68-0.88)	0.86 (0.75-0.98)
1	1	1	1	1	1	1	1	1
0	1.58 (1.45-1.73)	1.67 (1.53-1.83)	2.12 (1.96-2.29)	1.59 (1.41-1.79)	1.97 (0.66-2.34)	1.17 (0.92-1.47)	1.58 (0.31-1.92)	1.56 (1.34-1.81)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted in patients who had a history of MI before the first stroke or TIA event;[d]A sensitivity analysis conducted in patients with complete charateristics data; [e]A sensitivity analysis conducted by categorising missing data as a separate group; [f]A sensitivity analysis conducted in patients with the first TIA event; [g]A sensitivity analysis conducted in patients with the first ischemic stroke event

Table 6-5 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
All combinations with ≥ two classes	0.63 (0.59-0.67)	0.70 (0.65-0.75)
Without APAs	0.85 (0.76-0.94)	0.87 (0.77-0.98)
Without LRMS	1.32 (1.22-1.44)	1.03 (0.94-1.14)
Without ACEIs/ARBs	0.75 (0.70-0.80)	0.78 (0.72-0.84)
Without CCBs	0.66 (0.62-0.71)	0.73 (0.68-0.79)
Without DRs	0.54 (0.50-0.58)	0.65 (0.60-0.70)
Without BBs	0.57 (0.53-0.61)	0.49 (0.31-0.79)

Table 6-5 shows the results of the effect of combination therapy omitting one of the specific six classes on all-cause mortality compared to one class therapy. All combination therapy with two or more of the specific six classes appeared to reduce the risk of all-cause mortality by 30% (95% CI: 25%-35%). When removing LRMs, combination therapy showed no significant effect on all-cause mortality compared with one class (HR: 1.03; 95% CI: 0.94-1.14). When removing APAs, ACEIs/ARBs or CCBs, combination therapy reduced the risk of all-cause mortality by 13% (95%CI: 2%-23%), 22% (16%-28%) or 27% (21%-32%), respectively.

6.4 Discussion

This cohort study is the first large, long-term follow-up database study to report the effectiveness of increasing numbers, classes, and combinations of cardiovascular medications in secondary prevention of all-cause mortality in patients who experienced an incident ischemic stroke or TIA. The results showed that increasing the numbers and classes of cardiovascular medications appeared to produce additional benefits on long-term survival. APAs, LRMs, ACEIs/ARBs, and CCBs appeared to be the optimal constituents of combination therapy associated with reduced risk of mortality after stroke or TIA.

Previous studies have suggested the benefit of the management of single risk factors such as hypertension, high cholesterol, and thrombus formation in secondary prevention of stroke(Collaboration & Antiplatelet Trialists' Collaboration, 1994; Law, 2003; Rashid et al., 2003). The findings from this study strongly suggest that multiple pharmacological interventions can provide potentially greater benefits

on long-term survival for stroke patients. The results showed that HR of mortality reached a plateau in patients with four (0.61, 95% CI: 0.56-0.67) or five medications (0.60, 95% CI: 0.54-0.66). Contrary to combination therapy, patients with no use of cardiovascular medications had a higher risk of mortality. In summary, the combined use of four or five cardiovascular medications in the present study appeared optimal to improve long-term survival after stroke.

Evidence-based guidelines recommend APAs, LRMs and antihypertension medications for secondary prevention of stroke and TIA(National Institute for Health and Care Excellence, 2020b). Diuretics, ACEIs/ARBs, and CCBs are the first-line antihypertensive medications(National Institute for Health and Care Excellence, 2019a). The present study identified the priority of APAs, LRMs, ACEIs/ARBs and CCBs in secondary prevention of stroke, which is consistent with the current guideline recommendations. This four-medication combination was associated with a 61% reduction in mortality compared with APAs alone. I furtherly estimated the role of the six classes medications in combination therapy. The results showed omitting LRMs, ACEIs/ARBs, APAs or CCBs from combination therapy would reduce the beneficial effect of combination therapy (Table 6-4). The changes were greatest when excluding LRMs, followed by APAs, ACEIs/ARBs and CCBs. The 2-year retrospective cohort study of Park *et al.* (Park & Ovbiagele, 2015) suggested that the combination of antihypertensive medications, anti-thrombotic medications, and lipid modifiers was associated with a significant reduction of death following an occurrence of stroke. The study classified several classes of cardiovascular medications such as ACEIs/ARBs, CCBs, DRs and BBs as

antihypertensive medications. However, the present study did not find a significant additional benefit when beta-blockers were added to combination therapy on long-term survival. This is in line with a systematic review of RCTs(De Lima et al., 2014), in which no clear evidence supported a beneficial effect of beta-blockers for secondary prevention of stroke or TIA.

In addition, the results highlighted an issue that the use of cardiovascular medications for secondary prevention of stroke and TIA remained sub-optimal. In this study, 8.1% of patients did not receive long-term use of cardiovascular medications, and 9.2% received only monotherapy following their first stroke or TIA event. Other studies in the UK population have also indicated the underuse of evidence-based pharmacotherapy for cardiovascular disease in the secondary prevention(DeForge et al., 2006; Sheppard et al., 2014). I investigated demographics and clinical characteristics at each entry point during the follow-up period. Patients with no or one cardiovascular medication were mostly at a relatively lower risk of cardiovascular disease (e.g. younger age, normal BMI status, with fewer comorbidities) compared with patients with three or more drugs (Appendix K). However, I could not rule out the missing data issue here as aspirin is widely available over-the-counter and there may be some patients who had been admitted to hospitals; therefore the cardiovascular medication during that period would not be available in the GP record. Previous studies also have demonstrated that cardiovascular risk levels(Thijs et al., 2008), concerns on treatment risk (e.g., side-effects)(Hobbs, 2000) and patients preferences(Bryan et al., 2006; Montgomery et al., 2001) may explain the discrepancy between guidelines and

real-world clinical practice. My results have strengthened the evidence for the long-term beneficial effects of combined guideline-recommended cardiovascular medications. I demonstrated that pharmacotherapy in secondary prevention is necessary and beneficial for individuals who have had a stroke regardless of the risk level of cardiovascular disease. This study suggests that guideline compliance deserves better attention to improve survival in patients with stroke or TIA.

6.4.1 Strengths and limitations

This study has several strengths. Firstly, it was based on a large population-based primary care practice database. As such, it is likely to reflect the usual healthcare in the UK. Secondly, this study compared different numbers, classes and combinations of cardiovascular medications which comprehensively demonstrated the effect of combination therapy on long-term survival. Thirdly, when assessing the effect of different combinations, I defined exposure groups as patients who were exclusively using the selected cardiovascular medications of interest and this was to remove potential effects of other cardiovascular medications which were not of interest on the outcome. In addition, I used MSMs to control for confounding due to both time-invariant and time-varying confounders that may lead to treatment switching or informative censoring. I demonstrated the robustness of my findings to unmeasured confounding using the E-Value estimate. Most HRs of all-cause mortality for known, strong risk factors of cardiovascular disease were below 1.74, the minimum E-Value estimate in this study. For example, the HRs of mortality was 1.61 (95% CI:1.49-1.74) for current smokers, 1.27 (95% CI:1.19-1.36) for patients with diabetes and 1.14 (95% CI:1.07-1.20) for patients with hypertension. It is not

likely that an unmeasured or unknown confounder would have a substantially larger effect on cardiovascular disease development or mortality than these known risk factors by having a relative risk exceeding 1.74. Finally, most compellingly, I used all-cause mortality as my outcome measure. Despite the influence of non-cardiovascular mortality on the outcome, this study produced very clear results. Had I measured cause-specific cardiovascular mortality, I suspect that the findings would have been more pronounced.

This study has limitations. Firstly, the THIN database only provides records of prescriptions; therefore, my study was not able to determine if medications were actually dispensed, taken or used in line with the administration directions by patients. Secondly, because the THIN database does not capture data for hospital treatment, care homes or nursing homes, and over the counter (OTC) medications (e.g., aspirin available OTC), the study was not able to address any medication usage not included in records from general practice. Thirdly, I had no information on the severity of stroke. Due to shorter life-expectancy, health interventions may be less cost-effective in patients with more severe cardiovascular conditions(Murray et al., 2003; National Institute for Health and Care Excellence, 2009). In this case, patients with severe stroke may be more likely to be undertreated and thus more likely to die. However, I adopted measures to balance heterogeneity between different exposure groups to some extent: (1) I excluded patients who had a history of MI before the first stroke event, (2) excluded patients who died or had a nonfatal cardiovascular event during the first 90 days, and (3) I adjusted for risk factors of cardiovascular disease when estimating mortality

hazard ratios. Fourthly, this study only focused on the six most commonly prescribed classes of CV medications, APAs, LRMs, ACEIs/ARBs, CCBs, DRs and BBs, due to the complexity of the drug combination. The effect of other CV medications (e.g., anticoagulants) in combination therapy on long-term survival was not estimated. Further study can explore this area. Fifthly, I only estimated the effect of cardiovascular medications by their major classification so the study cannot tell the effect of sub-classes of these cardiovascular medications on long-term outcomes. For instance, I did not compare the effect of dual-antiplatelet therapy and monotherapy on long-term mortality. Further research is required to explore this area. In addition, the clinical guidelines of pharmacotherapy for secondary prevention of stroke had no major changes over the period of 2007-2016 (refer to guidelines from AHA/ASA 2006(Sacco et al., 2006), 2010(Furie et al., 2011), 2014(Kernan et al., 2014), National clinical guideline for stroke 2008(Intercollegiate Stroke Working party, 2008), 2012(Intercollegiate Stroke Working party, 2012), 2016(Intercollegiate Stroke Working party, 2016)). There are some changes of recommendations on dosage and individual drug. For example, in terms of lipid-lowering therapy in secondary prevention, the National Clinical Guideline 2008 recommended using statins according to a recommended cholesterol level. Guideline 2012 recommended high-intensity statin use such as atorvastatin 20-80mg daily and Guideline 2016 recommended initiated using a statin with low acquisition cost such as simvastatin 40mg daily. This study only focused on the numbers and classes of CV drugs and did not address the dosage issue in the study due to the complexity of the research question and analysis.

There may be some residual confounding impact on the mortality outcome in this study. But I would expect this impact is minimal. Future studies on drug dosage are encouraged.

6.5 Conclusion

This study suggests that combination therapy of four or five cardiovascular medications may improve long-term survival in patients with stroke or TIA. APAs, LRMs, ACEIs/ARBs and CCBs were the optimal constituents of combination therapy in the present study.

Chapter 7: Impact of multiple cardiovascular medications on mortality in patients with ischemic stroke and type 2 diabetes mellitus

7.1 Introduction

Type 2 diabetes mellitus is a well-established risk factor for ischemic stroke(Banerjee et al., 2012). Epidemiological studies have shown that the risk of stroke is at least the twice greater in patients with diabetes than non-diabetic patients(Almdal et al., 2004; Kissela et al., 2005). Patients with diabetes are more likely to die and to have a poorer prognosis after stroke than nondiabetic patients(Cakir et al., 2003; Megherbi et al., 2003; Weir et al., 1997). The management of type 2 diabetes and ischemic stroke share many characteristics, primarily due to the fact that diabetes is associated with abnormalities in the blood vessel and stroke is a vascular disease(R. Chen et al., 2016). In addition, individuals with diabetes are more likely to suffer from hypertension and dyslipidaemia, which are major risk factors for ischemic stroke(R. Chen et al., 2016). Consequently, aggressive management of cardiovascular risk factors and optimal pharmacotherapy are paramount for secondary prevention in patients with diabetes after ischemic stroke. For example, some studies have suggested that intensive anti-hypertensive treatment is more likely to reduce the risk of stroke and mortality than the standard-therapy group in patients with diabetes(Group U K P D S, 1898; Zanchetti et al., 2003). Diabetic patients commonly receive more

cardiovascular medications compared to nondiabetic patients. In my drug utilization study, the average number of cardiovascular medications was 3.6 (SD: 1.9) in patients with diabetes and 3.0 (SD:1.7) in nondiabetic patients following their incident stroke events. However, it is unclear whether different single cardiovascular medications in combination therapy produce additive benefit on long-term survival in type 2 diabetic patients suffering an ischemic stroke. Further, the optimal constituents of combination therapy have not been well recognised. This study, therefore, aimed to investigate the effect of multiple cardiovascular medications on long-term survival in stroke patients with a co-existing disease of type 2 diabetes.

7.2 Method

The study cohort design, exposure definition, and statistical analysis were the same as those described in **Chapter 6**, 6.2 Methods.

7.2.1 Study population

This study included patients with a first diagnosis of ischemic stroke or TIA between January 2007 and December 2016, and with a history of type 2 diabetes before their first stroke event. Inclusion criteria included patients who were aged 45 or above and who had been registered for at least three years in the THIN database before the first stroke event. I excluded patients who died or who had an occurrence of a further cardiovascular event within the first 90 days following their incident stroke event. Patients were followed from the initial event until the end of December 2016 and were censored if they left their general practice during the

study period. The outcome was all-cause mortality. For each patient, the follow-up was divided into contiguous periods of six months, each defined with specific entry and exit points.

7.2.2 Data extraction and confounders

The data of demographic and clinical characteristics six months prior to each entry point and prescriptions three months prior to each entry point were extracted from the THIN database. In addition to the variables mentioned in "**Chapter 6**, 6.2.6 Data extraction and confounders", Hemoglobin A1c (HbA1c) value at baseline, duration of diabetes (years since the first diagnosis of diabetes), previous use of diabetes medications were also included as confounders. Diabetes medications were identified based on medications classified in the BNF, Chapter 6.1: Drugs used in diabetes.

7.2.3 Sensitivity analysis

Five sensitivity analyses were conducted: (1) using a 60-day exposure period to assess the impact of the duration of the exposure window; (2) dividing the 6-month follow-up time frame into intervals of 3 months; (3) categorising the missing data for each covariate as a separate group; (4) using E-value methodology to assess the robustness of findings to unmeasured confounding; (5) conducting an analysis to evaluate the effect of combination therapy ($\geqslant$2 classes) omitting one class versus the use of one class only. In addition, to assess the role of thiazide-type diuretics in the combination therapy, I repeated the fifth sensitivity analysis by only keeping thiazide-type DRs from the overall DRs.

7.3 Results

The study consisted of 3955 men (51.3%) and 3760 women (48.7%) who had experienced the initial ischemic stroke or TIA event from 1 January 2007 to 31 December 2016 and who had a history of type 2 diabetes before the initial stroke event. Overall, 6.9% of patients did not receive long-term used cardiovascular medications, 5.4% received one, 13.9% received two, 20.3% received three, 21.7% received four, 16.7% received five, and 9.2% of patients received six, and 6.4% received seven or more cardiovascular medications during the 90 days following their initial ischemic stroke or TIA event.

The mean age at the start of follow-up was 73.1 (SD, 10.9) years, and the mean follow-up time was 3.5 (SD, 2.6) years. In total, 1589 patients died during the follow-up, and the crude death rate was 64.4/1000 person-years. Table 1 shows the baseline characteristics of the patients by the number of cardiovascular medications received during the first 90 days.

Table 7-1 Baseline characteristics of the study patients, 2007-2016.

		Cardiovascular treatment groups								
No. of CV medications	**Total**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**≥7**	**P value**
	n = 7715	n = 535 (6.9%)	n = 414 (5.4%)	n = 1071 (13.9%)	n = 1562 (20.3%)	n = 1673 (21.7%)	n = 1285 (16.7%)	n = 708 (9.2%)	n = 467 (6.1%)	
Sex, % women	3760 (48.7)	270 (50.5)	194 (46.9)	525 (49.0)	748 (47.9)	820 (49.0)	636 (49.5)	357 (50.4)	210 (45.0)	<0.01
Age, (years) mean ± SD	73.1 ± 10.9	74.7 ± 11.7	74.4 ± 11.8	72.9± 11.7	72.6 ± 11.3	73.4 ± 10.7	73.0 ± 10.2	73.0 ± 10.2	71.9± 9.6	<0.01
Smoking (%)										
Current	1170 (15.2)	88 (16.5)	64 (15.5)	188 (17.6)	257 (16.5)	259 (15.5)	180 (14.0)	78 (11.0)	56 (12.0)	0.03
Former	2825 (36.6)	175 (32.7)	142 (34.3)	371 (34.6)	581 (37.2)	597 (35.7)	505 (39.3)	269 (38.0)	185 (39.6)	
Never	3622 (47.0)	264 (49.4)	204 (49.3)	497 (46.4)	701 (44.9)	794 (47.5)	587 (45.7)	355 (50.1)	220 (47.1)	
Missing	98 (1.3)	8 (1.5)	4 (1.0)	15 (1.4)	23 (1.5)	23 (1.4)	13 (1.0)	6 (0.9)	6 (1.3)	
Alcohol (%)										
Current	3931 (51.0)	248 (46.4)	199 (48.1)	525 (49.0)	834 (53.4)	863 (51.6)	672 (52.3)	363 (51.3)	227 (48.6)	0.51
Former	354 (4.6)	27 (5.1)	22 (5.3)	44 (4.1)	71 (4.6)	75 (4.5)	62 (4.8)	31 (4.4)	22 (4.7)	
Never	1884 (24.4)	151 (28.2)	107 (25.9)	281 (26.2)	354 (22.7)	390 (23.3)	300 (23.4)	171 (24.2)	130 (27.8)	
Missing	1546 (20.0)	109 (20.4)	86 (20.8)	221 (20.6)	303 (19.4)	345 (20.6)	251 (19.5)	143 (20.2)	88 (18.8)	
BMI status (%)										
Normal (18.5-24.9 kg/m2)	1399 (18.1)	118 (22.1)	100 (24.2)	241 (22.5)	292 (18.7)	307 (18.4)	201 (15.6)	94 (13.3)	46 (9.9)	<0.01
Overweight (25.0-29.9 kg/m2)	2617 (33.9)	177 (33.1)	137 (33.1)	381 (35.6)	547 (35.0)	562 (33.6)	443 (34.5)	220 (31.1)	150 (32.1)	
Obesity (≥ 30.0 kg/m2)	3278 (42.5)	197 (36.8)	139 (33.6)	363 (33.9)	641 (41.0)	714 (42.7)	597 (46.5)	371 (52.4)	256 (54.8)	
Underweight (< 18.5 kg/m2)	80 (1.0)	8 (1.5)	8 (1.9)	19 (1.8)	12 (0.8)	22 (1.3)	5 (0.4)	5 (0.7)	1 (0.2)	
Missing	341 (4.4)	35 (6.5)	30 (7.3)	67 (6.3)	70 (4.5)	68 (4.1)	39 (3.0)	18 (2.5)	14 (3.0)	
BP status (%)										
Normal (BP < 140/90 mmHg)	3991 (51.7)	271 (50.7)	246 (59.4)	632 (59.0)	859 (55.0)	841 (50.3)	613 (47.7)	346 (48.9)	183 (39.2)	<0.01
Stage 1 hypertension (BP ≥ 140/90 mmHg)	2462 (31.9)	164 (30.7)	116 (28.0)	313 (29.2)	485 (31.1)	553 (33.1)	430 (33.5)	231 (32.6)	170 (36.4)	

Stage 2 hypertension (BP ≥ 160/100 mmHg)	793 (10.3)	61 (11.4)	35 (8.5)	74 (6.9)	147 (9.4)	172 (10.3)	159 (12.4)	80 (11.3)	65 (13.9)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	377 (4.9)	29 (5.4)	12 (2.9)	34 (3.2)	52 (3.3)	86 (5.1)	73 (5.7)	46 (6.5)	45 (9.6)	
Missing	80 (1.0)	9 (1.7)	4 (1.0)	16 (1.5)	16 (1.0)	19 (1.1)	9 (0.7)	5 (0.7)	2 (0.4)	
TC status (%)										
Optimal (<5.2 mmol/L)	5785 (75.0)	370 (69.2)	295 (71.3)	750 (70.0)	1152 (73.8)	1275 (76.2)	1005 (78.2)	557 (78.7)	381 (81.6)	<0.01
Intermediate (5.3-6.2 mmol/L)	1113 (14.4)	92 (17.2)	64 (15.5)	179 (16.7)	241 (15.4)	238 (14.2)	172 (13.4)	79 (11.2)	48 (10.3)	
High (>6.2 mmol/L)	569 (7.4)	53 (9.9)	33 (8.0)	90 (8.4)	122 (7.8)	111 (6.6)	77 (6.0)	56 (7.9)	27 (5.8)	
Missing	248 (3.2)	20 (3.7)	22 (5.3)	52 (4.9)	47 (3.0)	49 (2.9)	31 (2.4)	16 (2.3)	11 (2.4)	
Hba1c level (%)										
< 6.0%	667 (8.7)	48 (9.0)	37 (8.9)	80 (7.5)	130 (8.3)	172 (10.3)	110 (8.6)	58 (8.2)	32 (6.9)	<0.01
6.0%-6.4%	1109 (14.4)	64 (12.0)	60 (14.5)	140 (13.1)	227 (14.5)	259 (15.5)	191 (14.9)	98 (13.8)	70 (15.0)	
≥ 6.5%	4924 (63.8)	334 (62.4)	245 (59.2)	689 (64.3)	1008 (64.5)	1027 (61.4)	837 (65.1)	472 (66.7)	312 (66.8)	
Missing	1015 (13.2)	89 (16.6)	72 (17.4)	162 (15.1)	197 (12.6)	215 (12.9)	147 (11.4)	80 (11.3)	53 (11.4)	
Townsend score (%)										
1 (least deprived)	1349 (17.5)	73 (13.6)	75 (18.1)	178 (16.6)	278 (17.8)	329 (19.7)	217 (16.9)	126 (17.8)	73 (15.6)	0.11
2	1422 (18.4)	104 (19.4)	79 (19.1)	188 (17.6)	325 (20.8)	303 (18.1)	234 (18.2)	113 (16.0)	76 (16.3)	
3	1456 (18.9)	110 (20.6)	76 (18.4)	233 (21.8)	278 (17.8)	311 (18.6)	231 (18.0)	138 (19.5)	79 (16.9)	
4	1433 (18.6)	108 (20.2)	82 (19.8)	179 (16.7)	292 (18.7)	292 (17.5)	244 (19.0)	134 (18.9)	102 (21.8)	
5 (most deprived)	1057 (13.7)	62 (11.6)	51 (12.3)	156 (14.6)	203 (13.0)	218 (13.0)	190 (14.8)	107 (15.1)	70 (15.0)	
Missing	998 (12.9)	78 (14.6)	51 (12.3)	137 (12.8)	186 (11.9)	220 (13.2)	169 (13.2)	90 (12.7)	67 (14.4)	
Comorbidity (%)										
Hypertension	5813 (75.4)	382 (71.4)	227 (54.8)	560 (52.3)	1046 (67.0)	1375 (82.2)	1142 (88.9)	647 (91.4)	434 (92.9)	<0.01
Hyperlipidaemia	1700 (22.0)	106 (19.8)	67 (16.2)	213 (19.9)	304 (19.5)	375 (22.4)	329 (25.6)	187 (26.4)	119 (25.5)	<0.01
Arrhythmia	1312 (17.0)	121 (22.6)	52 (12.6)	130 (12.1)	181 (11.6)	272 (16.3)	269 (20.9)	163 (23.0)	124 (26.6)	<0.01
Heart Failure	546 (7.1)	45 (8.4)	11 (2.7)	50 (4.7)	73 (4.7)	90 (5.4)	107 (8.3)	93 (13.1)	77 (16.5)	<0.01

PVD	647 (8.4)	54 (10.1)	27 (6.5)	71 (6.6)	109 (7.0)	152 (9.1)	123 (9.6)	61 (8.6)	50 (10.7)	<0.01
Dementia	396 (5.1)	28 (5.2)	45 (10.9)	83 (7.8)	84 (5.4)	76 (4.5)	50 (3.9)	26 (3.7)	4 (0.9)	<0.01
COPD	732 (9.5)	40 (7.5)	44 (10.6)	101 (9.4)	154 (9.9)	175 (10.5)	109 (8.5)	63 (8.9)	46 (9.9)	0.42
Asthma	1204 (15.6)	71 (13.3)	71 (17.2)	184 (17.2)	237 (15.2)	256 (15.3)	213 (16.6)	116 (16.4)	56 (12.0)	0.13
Liver disease	80 (1.0)	12 (2.2)	9 (2.2)	13 (1.2)	20 (1.3)	9 (0.5)	12 (0.9)	3 (0.4)	2 (0.4)	<0.01
Peptic ulcer disease	472 (6.1)	41 (7.7)	30 (7.3)	57 (5.3)	85 (5.4)	102 (6.1)	86 (6.7)	42 (5.9)	29 (6.2)	0.50
RA	157 (2.0)	13 (2.4)	7 (1.7)	16 (1.5)	35 (2.2)	42 (2.5)	18 (1.4)	17 (2.4)	9 (1.9)	0.37
CKD	2349 (30.5)	170 (6.9)	113 (5.4)	294 (13.9)	409 (20.3)	523 (21.7)	402 (16.7)	268 (9.2)	170 (6.1)	<0.01

BMI = body mass index; BP = blood pressure; TC = total cholesterol; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PCI = percutaneous transluminal coronary intervention; PVD = peripheral vascular disease; RA = rheumatoid arthritis.

Figure 7-1 shows the risk of all-cause mortality in patients prescribed different numbers of cardiovascular medications. Compared with monotherapy, the risk of all-cause mortality was lower in patients with combination therapy: 25% (95% CI: 2%-43%) lower with two medications, 45% (95% CI: 28%-58%) lower with three medications, 48% (95% CI: 32%-61%) lower with four medications, 59% (95% CI: 45%-69%) lower with five medications, 56% (95% CI: 38%-69%) lower with six medications and 51% (95% CI: 26%-67%) lower with seven or more medications. Conversely, patients with no use of cardiovascular medications were associated with an increased risk of all-cause mortality (adjusted HR: 2.14, 95% CI: 1.63-2.81) compared with monotherapy. Similar results were found for the different numbers of cardiovascular medication classes. Figure 7-2 shows the decreased risks of mortality in patients with two (adjusted HR: 0.74, 95% CI: 0.56-0.98), three (adjusted HR: 0.55, 95% CI: 0.41-0.72), four (adjusted HR: 0.53, 95% CI: 0.39-0.74) and five (adjusted HR: 0.36, 95% CI: 0.24-0.55) specific classes of cardiovascular medications compared with patients prescribed one class. Patients with a five-class combination had the lowest risk of mortality.

Number of CV medications	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥7	52	1329	39.1	0.39 (0.29-0.53)	0.49 (0.33-0.74)
6	95	2242	42.4	0.42 (0.33-0.54)	0.44 (0.31-0.62)
5	163	4130	39.5	0.38 (0.31-0.48)	0.41 (0.31-0.55)
4	254	5367	47.3	0.44 (0.36-0.54)	0.52 (0.39-0.68)
3	249	5069	49.1	0.46 (0.38-0.57)	0.55 (0.42-0.72)
2	244	3514	69.4	0.63 (0.51-0.77)	0.75 (0.57-0.98)
1	148	1441	102.7	1	1
0	384	1585	242.3	2.27 (1.87-2.76)	2.14(1.63-2.81)

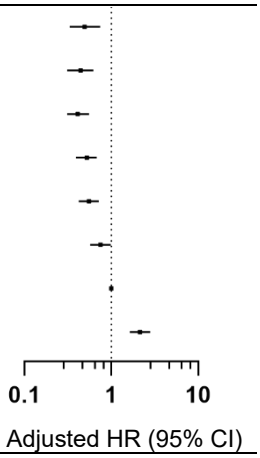


Figure 7-1 Risk of all-cause mortality in patients prescribed cardiovascular medications

Number of CV classes	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
6	17	456	37.3	0.38 (0.23-0.62)	0.59 (0.31-1.14)
5	63	2033	31.0	0.32 (0.24-0.42)	0.36 (0.24-0.55)
4	151	4205	35.9	0.36 (0.29-0.45)	0.53 (0.39-0.74)
3	205	4821	42.5	0.41 (0.33-0.51)	0.55 (0.41-0.72)
2	225	3545	63.5	0.60 (0.48-0.74)	0.74 (0.56-0.98)
1	141	1414	99.7	1	1
0	384	1585	242.3	2.34 (1.92-2.85)	2.16 (1.60-2.90)

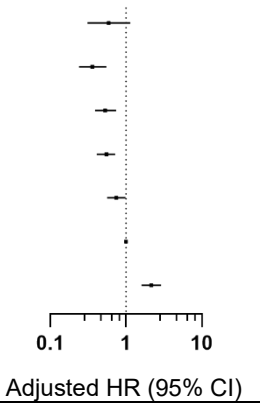


Figure 7-2 Risk of all-cause mortality in patients prescribed six specific classes of cardiovascular medications

Combination	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR	Adjusted HR
APAs+LRMs+ACEIs/ARBs+CCBs+DRs	21	925	22.7	0.18 (0.11-0.29)	0.31 (0.16-0.59)
APAs+LRMs+ACEIs/ARBs+CCBs+BBs	9	473	19.0	0.15 (0.07-0.30)	0.32 (0.12-0.83)
APAs+LRMs+ACEIs/ARBs	59	2469	23.9	0.29 (0.17-0.52)	0.33 (0.21-0.51)
APAs+LRMs+ACEIs/ARBs+CCBs	33	1583	20.8	0.28 (0.14-0.58)	0.36 (0.21-0.60)
APAs+LRMs+CCBs	20	577	34.7	0.18 (0.13-0.27)	0.36 (0.19-0.69)
LRMs+ACEIs/ARBs+CCBs	9	245	36.7	0.47 (0.25-0.87)	0.40 (0.16-0.95)
APAs+LRMs+ACEIs/ARBs+DRs	33	1012	32.6	0.17 (0.11-0.25)	0.45 (0.25-0.83)
APAs+LRMs+ACEIs/ARBs+BBs	24	583	41.1	0.25 (0.17-0.39)	0.49 (0.26-0.92)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs+BBs	17	456	37.3	0.31 (0.18-0.53)	0.49 (0.25-0.98)
APAs+ACEIs/ARBs+DRs	13	222	58.5	0.74 (0.43-1.27)	0.50 (0.28-0.90)
APAs+LRMs+ACEIs/ARBs+DRs+BBs	21	429	48.9	0.38 (0.23-0.64)	0.55 (0.37-0.83)
APAs+LRMs	97	1972	49.2	0.38 (0.28-0.53)	0.56 (0.31-0.99)
APAs+LRMs+DRs	26	324	80.2	0.28 (0.17-0.47)	0.59 (0.29-1.20)
LRMs+ACEIs/ARBs	15	407	36.8	0.66 (0.35-1.25)	0.61 (0.35-1.06)
LRMs alone	24	399	60.2	0.46 (0.28-0.75)	0.71 (0.33-1.51)
APAs+ACEIs/ARBs	26	353	73.7	0.56 (0.36-0.89)	0.73 (0.34-1.54)
ACEIs/ARBs alone	13	208	62.5	0.51 (0.27-0.94)	0.83 (0.43-1.63)
APAs+LRMs+BBs	17	230	74.0	0.61 (0.38-0.98)	0.89 (0.41-1.94)
APAs+LRMs+CCBs+DRs	13	183	70.9	0.33 (0.21-0.54)	1.06 (0.53-2.12)
APAs+ACEIs/ARBs+CCBs	17	182	93.2	0.61 (0.35-1.06)	2.05 (1.45-2.91)
APAs alone	69	579	119.2	1	1

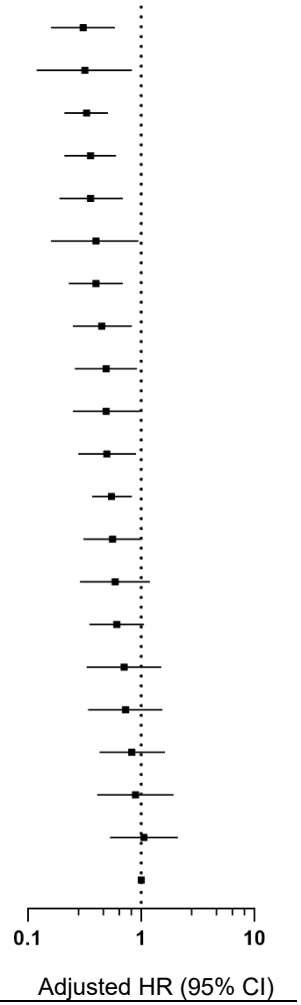


Figure 7-3 Risk of all-cause mortality in the 20 most commonly used regimens containing the six specific classes of cardiovascular medications compared with antiplatelet agents alone

In the analysis of the effect of the 20 most commonly used regimens containing APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs versus APAs alone, I found a significantly lower risk of mortality in combinations containing APAs, LRMs, ACEIs/ARBs and CCBs (Figure 7-3). In patients with the combination treatment of APAs, LRMs and ACEIs/ARBs, the risk of mortality was lowered by 67% (95% CI: 49%-79%) compared with APAs alone. When adding CCB, DRs or BBs to the three-medication treatment, the HRs of mortality was 0.36 (95% CI: 0.21-0.60), 0.45 (95% CI: 0.25-0.83) and 0.49 (95% CI: 0.26-0.92), respectively. The five-medication combination containing APAs, LRMs, ACEIs/ARBs, CCBs and DRs appeared to be associated with the lowest risk of mortality (adjusted HR: 0.31, 95% CI: 0.16-0.59). The combination of APAs, LRMs, ACEIs/ARBs, CCBs and BBs also showed a lower HR of mortality but with wide confidence intervals (adjusted HR: 0.32, 95% CI: 0.12-0.83).

7.3.1 Sensitivity analyses

Results of sensitivity analyses are provided in Table 7-2 and Table 7-3. The primary results of the risk of mortality in patients with different numbers of CV medications and different numbers of classes of CV medications were similar to the results in the sensitivity analyses. The E-values for the three main analyses of all-cause mortality ranged from 2.00 to 5.00.

Table 7-2 Risk of all-cause mortality in patients prescribed with various numbers of cardiovascular medications in sensitivity analyses.

	Adjusted HR (95% CI)			
Number of CV medications	**Primary analysis**	**60-day exposure window[a]**	**3-month interval[b]**	**Categorised missing data[c]**
≥7	0.49 (0.33-0.74)	0.68 (0.45-1.03)	0.34 (0.21-0.55)	0.35 (0.22-0.56)
6	0.44 (0.31-0.62)	0.54 (0.39-0.75)	0.43 (0.30-0.62)	0.44 (0.32-0.61)
5	0.41 (0.31-0.55)	0.47 (0.35-0.61)	0.34 (0.25-0.46)	0.40 (0.30-0.53)
4	0.52 (0.39-0.68)	0.63 (0.49-0.80)	0.42 (0.32-0.56)	0.49 (0.38-0.63)
3	0.55 (0.42-0.72)	0.64 (0.50-0.81)	0.43 (0.33-0.56)	0.55 (0.43-0.71)
2	0.75 (0.57-0.98)	0.79 (0.62-1.00)	0.73 (0.56-0.94)	0.73 (0.57-0.93)
1	1	1	1	1
0	2.14(1.63-2.81)	1.81 (1.44-2.28)	2.63 (2.05-3.37)	2.06 (1.60-2.65)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted by categorising missing data as a separate group.

Table 7-3 Risk of all-cause mortality in patients prescribed with various numbers of specific six classes of cardiovascular medications in sensitivity analyses.

	Adjusted HR (95% CI)			
Number of CV medications	**Primary analysis**	**60-day exposure window[a]**	**3-month interval[b]**	**Categorised missing data[d]**
6	0.59 (0.31-1.14)	0.55 (0.29-1.05)	0.29 (0.08-1.06)	0.35 (0.18-0.68)
5	0.36 (0.24-0.55)	0.37 (0.25-0.54)	0.33 (0.18-0.60)	0.30 (0.20-0.44)
4	0.53 (0.39-0.74)	0.51 (0.37-0.70)	0.38 (0.25-0.58)	0.43 (0.31-0.59)
3	0.55 (0.41-0.72)	0.52 (0.39-0.69)	0.45 (0.31-0.66)	0.47 (0.36-0.63)
2	0.74 (0.56-0.98)	0.71 (0.54-0.93)	0.58 (0.41-0.83)	0.65 (0.49-0.85)
1	1	1	1	1
0	2.16 (1.60-2.90)	1.47 (1.13-1.92)	2.46 (1.76-3.44)	1.79 (1.36-2.35)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted by categorising missing data as a separate group.

Figure 7-4 shows the results of the effect of combination therapy omitting one of the specific six classes (APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs) on all-cause mortality compared to one class therapy. All combination therapy with two

or more of the specific six classes appeared to reduce the risk of all-cause mortality by 50% (95% CI: 39%-59%). When removing LRMs, APAs, ACEIs/ARBs or CCBs, combination therapy reduced the risk of all-cause mortality by 26% (95%CI: 6%-42%), 44% (28%-56%), 35% (19%-47%) or 46% (34%-56%), respectively. Combination therapy without DRs (adjusted HR: 0.47, 95% CI: 0.38-0.59) or BBs (adjusted HR: 0.46, 95% CI: 0.37-0.57) showed lower HRs for mortality. Figure 9-5 shows the results of the effect of combination therapy omitting one of the specific six classes (APAs, LRMs, ACEIs/ARBs, CCBs, thiazide-type DRs, and BBs) on all-cause mortality compared to one class therapy. Difference from the results is shown in Table 7-4, the HR for all-cause mortality of the combination without thiazide-type DRs (adjusted HR: 0.51, 95% CI: 0.40-0.64) was higher than the HR of all combination therapy (adjusted HR: 0.46, 95% CI: 0.38-0.58). The result was similar to the combination without CCBs (adjusted HR: 0.50, 95% CI: 0.40-0.63).

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.61 (0.47-0.78)	0.58 (0.43-0.78)
Without LRMS	0.88 (0.70-1.12)	0.78 (0.59-1.01)
Without ACEIs/ARBs	0.63 (0.51-0.78)	0.66 (0.53-0.83)
Without CCB	0.48 (0.39-0.58)	0.53 (0.43-0.65)
Without **DRs**	0.38 (0.31-0.47)	0.47 (0.38-0.59)
Without BBs	0.39 (0.32-0.48)	0.46 (0.37-0.57)
All combinations (≥ classes)	0.43 (0.35-0.52)	0.50 (0.41-0.61)

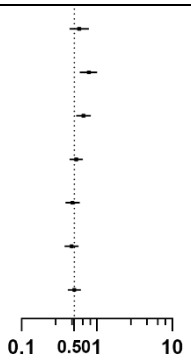


Figure 7-4 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.49 (0.36-0.67)	0.54 (0.37-0.78)
Without LRMS	0.80 (0.61-1.06)	0.75 (0.55-1.03)
Without ACEIs/ARBs	0.52 (0.41-0.65)	0.57 (0.45-0.73)
Without CCB	0.41 (0.33-0.51)	0.49 (0.39-0.62)
Without **thiazide-type DRs**	0.40 (0.32-0.49)	0.48 (0.38-0.60)
Without BBs	0.34 (0.28-0.42)	0.41 (0.32-0.51)
All combinations (≥ classes)	0.38 (0.31-0.46)	0.45 (0.36-0.56)

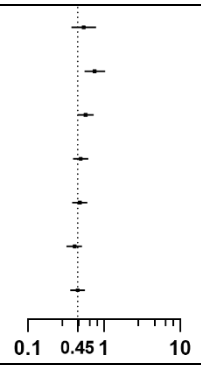


Figure 7-5 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

7.4 Discussion

This cohort study estimated the effectiveness of increasing numbers, classes and combinations of cardiovascular medications on all-cause mortality in stroke patients with a history of type 2 diabetes. The results showed that increasing the numbers and classes of cardiovascular medications appeared to produce additional benefits on long-term survival. APAs, LRMs, ACEIs/ARBs, CCBs and DRs appeared to be the optimal constituents of combination therapy associated

with reduced risk of mortality after stroke or TIA.

Similar to the results in the study for patients with incident stroke (Chapter 7), this study found that compared with monotherapy, multiple pharmacological interventions can provide potentially greater benefits on long-term survival for type 2 diabetic patients after their incident stroke events. The present study showed that five-medication combination was associated with the lowest risk of mortality compared with one cardiovascular medication. Six or more mediations showed no additional benefit on long-term survival compared with monotherapy. The results indicated that for medicine optimisation, the number of medications used in combination therapy should be managed with care.

APAs, LRMs and antihypertension medications are recommended by evidence-based guidelines for secondary prevention of stroke and TIA(National Institute for Health and Care Excellence, 2020b). Platelets play a key role in the build-up of atherosclerosis. In type 2 diabetic patients, platelets have been proven to be hyperreactive with intensified adhesion, activation and aggregation(Creager et al., 2003; Ferroni et al., 2004). Besides, diabetes-related dyslipidemia is also a key factor related to the increased risk of atherosclerosis. Therefore, antiplatelet therapy and lipid management are essential for secondary prevention following a stroke in patients with diabetes. In the present study, APAs and LRMs have been proven to produce significantly additive benefit on long-term survival in combination therapy for type 2 diabetic patients with stroke. Hypertension is the single most important risk factor for ischemic stroke(O'Donnell et al., 2010). Hypertension is highly prevalent in patients with diabetes(Colosia et al., 2013). In

the present study, the prevalence of hypertension is 74.5%. In patients with diabetes and hypertension, renin-angiotensin system blockers have been shown to improve cardiovascular outcomes, both alone and in comparison to other antihypertensive agents, and have long been considered as first-line hypertensive agent(H.-Y. Wu et al., 2013). My results supported that ACEIs/ARBs may play a key role in combination therapy to improve long-term survival in patients with diabetes following stroke. In addition, some studies have shown that ACEIs had the ability to improve glycemic control(Fogari et al., 1998) and protect renal function(Lewis et al., 1993) in type 2 diabetic patients. Thiazide-type DRs and CCBs have been proven to be acceptable initial antihypertensive agents for patients with diabetes. In ALLHAT trial, although results for CHD and mortality did not differ between various hypertensive agents, chlorthalidone was superior to amlodipine and lisinopril in new-onset heart failure and superior to lisinopril in the secondary outcome of stroke(The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002). In a meta-analysis of RCTs, CCBs were shown to be the preferred treatment in combination with ACEIs if blood pressure cannot be adequately controlled by ACEIs alone(H.-Y. Wu et al., 2013). My results showed both classes had additional beneficial effects on long-term survival in combination therapy; CCBs were shown to have an advantage over thiazide-type DRs but not apparent (Table 7-5). Similar to the results in the study of patients with incident stroke (Chapter 7), BBs showed no additive benefit on long-term survival in combination therapy for patients with diabetes after stroke in the present study. Some studies also suggested that beta-blockers may be

associated with worsening glycemic control and increased diabetes(Gress et al., 2000; UK Prospective Diabetes Study Group, 1998). In summary, APAs, LRMs and ACEIs/ARBs were proven to be central components in combination therapy associated with reduced risk of mortality after stroke or TIA in type 2 diabetic patients. CCBs and thiazide-type DRs can provide additive benefits in combined with the previous three components.

7.4.1 Strengths and limitations

In addition to the strengths presented in “Chapter 6**,** 6.4.1”, this study has the following strengths. Firstly, this study firstly comprehensively assessed the effect of different combinations among stroke patients with a co-current type 2 DM. Secondly, this study controlled for key diabetic-related time-invariant and time-varying confounders, including HbA1c value, duration of diabetes, previous use of diabetes medications. Thirdly, this study conducted a sensitivity analysis to evaluate the effect of combination therapy omitting one class, in order to assess the weight of each component of combination therapy on the outcome.

This study has some limitations besides that presented in “Chapter 6**,** 6.4.1”. Firstly, this study did not investigate the individual effect of ACEIs and ARBs in combination therapy on long-term survival. Secondly, this study only focused on cardiovascular medications; thus, the study cannot determine the effect of different antidiabetic medications or their potential interaction with cardiovascular medications on long-term survival in patients with ischemic stroke and DM. Further studies are required in this area. Finally, the power of this study was still limited. Some results had a wide CI due to relatively small sample size. However, the main

results still had a clear direction to show the effect of the exposure of interest on the outcome. Further studies in a large population are encouraged to confirm the study findings.

7.5 Conclusion

This study suggests that combination therapy of five cardiovascular medications may improve long-term survival in patients with stroke or TIA and type 2 diabetes. APAs, LRMs, ACEIs/ARBs, CCBs and DRs were probably the optimal constituents of combination therapy in the present study.

Chapter 8: Impact of multiple cardiovascular medications on mortality in patients with ischemic stroke and chronic obstructive pulmonary disease

8.1 Introduction

Stroke and chronic obstructive pulmonary disease (COPD), the second and third leading cause of death in the world(World Health Organization, 2020), are closely interrelated. It has been suggested COPD is significantly more prevalent among patients with stroke and that the co-existence of both is associated with poor clinical outcomes and mortality(Lekoubou & Ovbiagele, 2017; Söderholm et al., 2016). Stroke and COPD share two important risk factors, smoking and ageing. Some traditional stroke risk factors are also common in patients with COPD, including hypertension, hypercholesterolemia and diabetes(Lahousse et al., 2015). Moreover, some evidence has shown that COPD-specific systemic inflammation and oxidative stress might independently worsen prognosis after stroke(Austin et al., 2016). Patients with COPD after stroke should be treated according to the guidelines for secondary prevention after stroke regardless of COPD because there is no evidence to support an alternative management strategy(National Institute for Health and Care Excellence, 2020b). There is little evidence that patients with stroke should be treated differently in the presence of COPD. It is unclear whether different single cardiovascular medications in combination therapy produces an additive benefit on long-term survival in COPD patients suffering an

ischemic stroke. Further, the optimal constituents of combination therapy have not been well recognised. Therefore, this study aimed to investigate the effect of multiple cardiovascular medications on long-term survival in patients with COPD after their incident ischemic stroke or TIA event.

8.2 Method

The study cohort design, exposure definition, data extraction and statistical analysis refer to **Chapter 6**, 6.2 Methods.

8.2.1 Study population

This study included patients with a first diagnosis of ischemic stroke or TIA between January 2007 and December 2016, and with a history of COPD before their first stroke event. Inclusion criteria included patients who were aged 45 or above who had been registered for at least three years in the THIN database before the first stroke event. I excluded patients who died or who had an occurrence of a further cardiovascular event within the first 90 days following their incident stroke event. Patients were followed from the initial event until the end of December 2016 and were censored if they had left their general practice during the study period. The outcome was all-cause mortality. For each patient, the follow-up was divided into contiguous periods of six months, each defined with specific entry and exit points.

8.2.2 Data extraction and confounders

The data of demographic and clinical characteristics six months prior to each entry point and prescriptions three months prior to each entry point were extracted from the THIN database. In addition to variables mentioned in "**Chapter 6**, 6.2.6 Data

extraction and confounders", the forced expiratory volume in 1s (FEV1), duration of COPD (years since the first diagnosis of COPD), records of exacerbations, previous use of medications for COPD were also included as confounders. COPD medications were identified based on medications classified in the BNF Chapter 3: Obstructive airway disease.

8.2.3 Sensitivity analysis

The E-value methodology was used to assess the robustness of findings to unmeasured confounding. A sensitivity analysis was conducted to evaluate the effect of combination therapy (⩾2 classes) omitting one class compared with one class. In addition, to assess the role of thiazide-type diuretics in the combination therapy, I repeated the fifth sensitivity analysis by only keeping thiazide-type DRs from the overall DRs.

8.3 Results

The study consisted of 2405 men (51.2%) and 2295 women (48.8%) who had experienced the initial stroke event from 1 January 2007 to 31 December 2016 and who had a history of COPD before the initial stroke event. Overall, 8.3% of patients did not receive long-term cardiovascular medications, 9.7% received one, 19.5% received two, 23.0% received three, 19.5% received four, 11.5% received five, 8.5% of patients received six or more cardiovascular medications during the 90 days following their initial stroke event.

The mean age of the cohort at the start of follow-up was 69.8 (SD, 11.5) years, and the mean follow-up time was 3.2 (SD, 2.4) years. In total, the study recorded 1225

deaths during the follow-up, and the crude death rate was 82.0/1000 person-years. Table 10-1 shows the baseline characteristics of the patients at their initial stroke events based on the number of cardiovascular medications received during the first 90 days.

Table 8-1 Baseline characteristics of study patients at their initial stroke events, 2007-2016.

	Cardiovascular treatment groups								
No. of CV medications	**Total**	**0**	**1**	**2**	**3**	**4**	**5**	**≥6**	**P value**
	n = 4700	n = 392 (8.3)	n = 456 (9.7)	n = 915 (19.5)	n = 1080 (23.0)	n = 918 (19.5)	n = 542 (11.5)	n = 397 (8.5)	
Sex, % women	2295 (48.8)	208 (53.1)	230 (50.4)	432 (47.2)	519 (48.1)	428 (46.6)	275 (50.7)	203 (51.1)	0.24
Age, (years) mean ± SD	75.5 ± 10.0	73.2 ± 10.5	73.1 ± 11.0	73.0± 10.5	73.5 ± 9.7	74.1 ± 9.8	74.0 ± 9.2	74.0 ± 9.2	<0.01
Smoking (%)									
Current	1588 (33.8)	164 (41.8)	157 (34.4)	324 (35.4)	402 (37.2)	272 (29.6)	157 (29.0)	112 (28.2)	0.15
Former	2389 (50.8)	172 (43.9)	221 (48.5)	457 (50.0)	534 (49.4)	495 (53.9)	301 (55.5)	209 (52.6)	
Never	696 (14.8)	54 (13.8)	73 (16.0)	129 (14.1)	137 (12.7)	144 (15.7)	83 (15.3)	76 (19.1)	
Missing	27 (0.6)	<5	<5	7 (0.7)	7 (0.8)	<5	0	6 (0.6)	
Alcohol (%)									
Current	2464 (52.4)	189 (48.2)	216 (47.4)	471 (51.5)	563 (52.1)	514 (56.0)	279 (51.5)	232 (58.4)	<0.01
Former	258 (5.5)	18 (5.7)	26 (5.3)	48 (6.5)	70 (6.5)	41 (4.5)	41 (7.6)	14 (3.5)	
Never	773 (16.5)	73 (18.6)	65 (14.3)	163 (17.8)	171 (15.8)	138 (15.0)	90 (16.6)	73 (18.4)	
Missing	1205 (25.6)	112 (28.6)	149 (32.7)	233 (25.5)	276 (25.6)	225 (24.5)	132 (24.4)	78 (19.7)	
BMI status (%)									
Normal (18.5-24.9 kg/m2)	1476 (31.4)	139 (35.5)	156 (34.2)	330 (36.1)	368 (34.1)	254 (27.7)	140 (25.8)	89 (22.4)	<0.01
Overweight (25.0-29.9 kg/m2)	1453 (30.9)	112 (28.6)	127 (27.9)	271 (29.6)	335 (31.0)	300 (32.7)	193 (35.6)	115 (29.0)	
Obesity (≥ 30.0 kg/m2)	1102 (23.5)	75 (19.1)	73 (16.0)	179 (19.6)	213 (19.7)	260 (28.3)	145 (26.8)	157 (39.6)	
Underweright (<18.5kg/m2)	214 (4.6)	19 (4.6)	47 (10.3)	40 (4.4)	56 (5.2)	33 (3.6)	15 (2.8)	<5	
Missing	455 (9.7)	47 (12.0)	53 (11.6)	95 (10.4)	108 (10.0)	71 (7.7)	49 (9.0)	32 (8.1)	
BP status (%)									
Normal (BP < 140/90 mmHg)	2447 (52.1)	207 (52.8)	251 (55.0)	524 (57.3)	561 (51.9)	448 (48.8)	269 (49.6)	187 (47.1)	<0.01
Stage 1 hypertension (BP ≥ 140/90 mmHg)	1577 (33.6)	127 (32.4)	144 (31.6)	302 (33.0)	377 (34.9)	310 (33.8)	180 (33.2)	137 (34.5)	

Stage 2 hypertension (BP ≥ 160/100 mmHg)	437 (9.3)	36 (9.2)	40 (8.8)	59 (6.5)	99 (9.2)	101 (11.0)	60 (11.1)	42 (10.6)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	171 (3.6)	13 (3.3)	14 (3.1)	18 (2.0)	31 (2.9)	46 (5.0)	22 (4.1)	27 (6.8)	
Missing	59 (1.3)	7 (1.8)	7 (1.5)	11 (1.2)	11 (1.0)	11 (1.2)	10 (1.9)	<5	
TC status (%)									
Optimal (<5.2 mmol/L)	2263 (48.2)	153 (39.0)	191 (41.9)	375 (41.0)	494 (45.7)	501 (54.6)	299 (55.2)	250 (63.0)	<0.01
Intermediate (5.3-6.2 mmol/L)	1045 (22.2)	86 (21.9)	99 (21.7)	218 (23.8)	261 (24.2)	195 (21.2)	112 (20.7)	74 (18.6)	
High (>6.2 mmol/L)	523 (11.1)	53 (13.5)	47 (10.3)	104 (11.4)	124 (11.5)	104 (11.3)	58 (10.7)	33 (8.3)	
Missing	869 (18.5)	100 (25.5)	119 (26.1)	218 (23.8)	201 (18.6)	118 (12.9)	73 (13.5)	40 (10.1)	
Townsend score (%)									
1 (least deprived)	703 (15.0)	68 (17.4)	69 (15.1)	131 (14.3)	145 (13.4)	133 (14.5)	91 (16.8)	66 (16.6)	0.53
2	717 (15.3)	56 (14.3)	70 (15.4)	135 (14.8)	167 (15.5)	156 (17.0)	85 (15.7)	48 (12.1)	
3	888 (18.9)	71 (18.1)	90 (19.7)	197 (21.5)	185 (17.1)	167 (18.2)	104 (19.2)	74 (18.6)	
4	955 (20.3)	77 (19.6)	88 (20.2)	185 (20.2)	242 (22.4)	179 (19.5)	106 (19.6)	78 (19.7)	
5 (most deprived)	813 (17.3)	59 (15.1)	88 (19.3)	156 (17.1)	196 (18.2)	157 (17.1)	89 (16.4)	68 (17.1)	
Missing	624 (13.3)	61 (15.6)	51 (11.2)	111 (12.1)	145 (13.4)	126 (13.7)	67 (12.4)	63 (15.9)	
Comorbidity									
Hypertension	2624 (55.8)	162 (41.3)	156 (34.2)	340 (37.2)	579 (53.6)	647 (70.5)	411 (75.8)	329 (82.9)	<0.01
Hyperlipidaemia	703 (15.0)	40 (10.2)	45 (9.9)	131 (14.3)	150 (13.9)	167 (18.2)	107 (19.7)	63 (15.9)	0.15
Arrhythmia	823 (17.6)	74 (18.9)	48 (10.5)	89 (9.7)	143 (13.2)	176 (19.2)	158 (29.2)	137 (34.5)	<0.01
Heart Failure	368 (7.8)	22 (5.6)	18 (4.0)	44 (4.8)	49 (4.5)	77 (8.4)	74 (13.7)	84 (21.2)	<0.01
PVD	500 (10.6)	41 (10.5)	35 (7.7)	78 (8.5)	96 (8.9)	107 (11.7)	79 (14.6)	64 (16.1)	<0.01
Diabetes	877 (18.7)	50 (12.8)	58 (12.7)	130 (14.2)	187 (17.3)	199 (21.7)	128 (23.6)	125 (31.5)	<0.01
Dementia	160 (3.4)	13 (3.3)	32 (7.0)	43 (4.7)	37 (3.4)	18 (2.0)	8 (1.5)	9 (2.3)	<0.01
Asthma	2137 (45.5)	183 (46.7)	208 (45.6)	391 (42.7)	508 (47.0)	385 (41.9)	256 (47.2)	206 (51.9)	0.01
Liver disease	56 (1.2)	5 (1.3)	8 (1.8)	13 (1.4)	11 (1.0)	12 (1.3)	5 (0.9)	<5	0.68

Peptic ulcer disease	441 (9.4)	35 (8.9)	46 (10.1)	71 (7.8)	109 (10.1)	94 (10.2)	57 (10.5)	29 (7.3)	0.28
RA	136 (2.9)	13 (3.3)	18 (4.0)	27 (3.0)	40 (3.7)	18 (2.0)	13 (2.4)	7 (1.8)	0.14
CKD	927 (19.7)	68 (8.3)	55 (9.7)	141 (19.5)	199 (23.0)	205 (19.5)	142 (11.5)	117 (8.5)	<0.01

BMI = body mass index; BP = blood pressure; TC = total cholesterol; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PCI = percutaneous transluminal coronary intervention; PVD = peripheral vascular disease; RA = rheumatoid arthritis.

Figure 8-1 shows the risk of all-cause mortality in patients prescribed with different numbers of cardiovascular medications. Compared with monotherapy, the risk of all-cause mortality was lower in patients with combination therapy: 24% (95% CI: 04%-40%) lower with two medications, 34% (95% CI: 16%-48%) lower with three medications, 33% (95% CI: 14%-48%) lower with four medications, 36% (95% CI: 15%-52%) lower with five medications and 38% (95% CI: 22%-57%) lower with six or more medications. Conversely, no use of cardiovascular medications was associated with an increased risk of all-cause mortality (adjusted HR: 2.78, 95% CI: 2.19-3.52) compared with monotherapy. Figure 8-2 shows decreased risks of mortality in patients with two (adjusted HR: 0.75, 95% CI: 0.57-0.99), three (adjusted HR: 0.58, 95% CI: 0.43-0.79) and four (adjusted HR: 0.59, 95% CI: 0.43-0.82) specific classes of cardiovascular medications compared with patients prescribed one class.

Number of CV medications	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥6	62	1022	60.6	0.63 (0.47-0.86)	0.62 (0.43-0.88)
5	107	1712	62.5	0.64 (0.50-0.83)	0.64 (0.48-0.85)
4	175	2935	59.6	0.62 (0.49-0.78)	0.67 (0.52-0.86)
3	205	3477	59.0	0.61 (0.49-0.76)	0.66 (0.52-0.84)
2	208	3041	68.4	0.70 (0.56-0.87)	0.76 (0.60-0.96)
1	144	1481	97.2	1	1
0	324	1269	255.3	2.72 (2.20 -3.36)	2.78 (2.19-3.52)

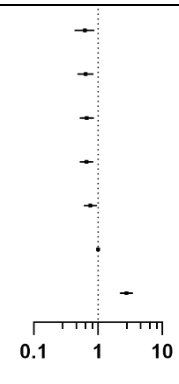


Figure 8-1 Risk of all-cause mortality in patients prescribed cardiovascular medications

Number of CV classes	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
6	17	456	37.3	0.17 (0.09-0.33)	0.20 (0.02-1.17)
5	63	2033	31.0	0.25 (0.18-0.36)	0.63 (0.34-0.82)
4	151	4205	35.9	0.17 (0.12-0.24)	0.59 (0.43-0.79)
3	205	4821	42.5	0.40 (0.28-0.57)	0.58 (0.43-0.79)
2	225	3545	63.5	0.55 (0.37-0.81)	0.75 (0.57-0.99)
1	141	1414	99.7	1	1
0	384	1585	242.3	2.02 (1.45-2.81)	3.01 (2.21-4.09)

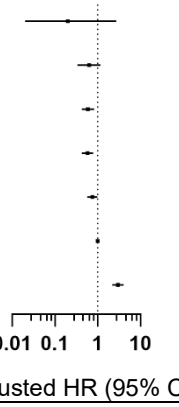


Figure 8-2 Risk of all-cause mortality in patients prescribed six specific classes of cardiovascular medications

Combination	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR	Adjusted HR
APAs+LRMs+ACEIs/ARBs+CCBs+DRs	11	382	28.8	0.27 (0.14-0.51)	0.24 (0.12-0.48)
APAs+LRMs+ACEIs/ARBs+CCBs	24	591	40.6	0.29 (0.11-0.80)	0.35 (0.15-0.82)
APAs+LRMs+ACEIs/ARBs+BBs	4	139	28.9	0.29 (0.20-0.43)	0.37 (0.03-4.82)
APAs+LRMs+ACEIs/ARBs	39	1241	31.4	0.30 (0.18-0.50)	0.38 (0.24-0.60)
LRMs+ACEIs/ARBs	40	735	54.4	0.37 (0.24-0.59)	0.39 (0.17-0.90)
APAs+LRMs+BBs	7	166	42.1	0.40 (0.18-0.90)	0.40 (0.16-0.99)
APAs+LRMs+CCBs	14	206	67.9	0.42 (0.31-0.58)	0.40 (0.24-0.66)
APAs+CCBs	93	2054	45.3	0.45 (0.21-0.97)	0.48 (0.22-1.04)
APAs+LRMs	17	272	62.4	0.47 (0.22-1.03)	0.51 (0.34-0.76)
APAs+LRMs+ACEIs/ARBs+DRs	19	594	32.0	0.50 (0.24-1.06)	0.56 (0.19-0.90)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs+BBs	8	154	52.0	0.51 (0.34-0.76)	0.60 (0.20-1.84)
CCBs alone	7	152	45.9	0.60 (0.27-1.33)	0.64 (0.38-2.06)
APAs+ACEIs/ARBs	4	56	71.3	0.62 (0.36-1.06)	0.72 (0.38-1.37)
APAs+LRMs+CCBs+DRs	41	458	89.6	0.65 (0.39-1.06)	0.77 (0.24-1.54)
ACEIs/ARBs	7	132	53.1	0.65 (0.24-1.79)	0.82 (0.48-2.76)
LRMs alone	22	310	71.0	0.66 (0.36-1.20)	0.89 (0.62-1.63)
APAs+LRMs+DRs	15	132	113.3	0.85 (0.57-1.26)	1.00 (0.46-1.62)
APAs+ACEIs/ARBs+DRs	26	158	164.6	1.16 (0.66-2.06)	1.06 (0.55-2.44)
APAs+DRs	7	127	55.3	1.61 (0.99-2.62)	1.15 (0.39-2.41)
DRs alone	23	107	215.7	2.02 (1.94-3.40)	2.77 (1.57-7.59)
APAs alone	76	720	105.5	1	1

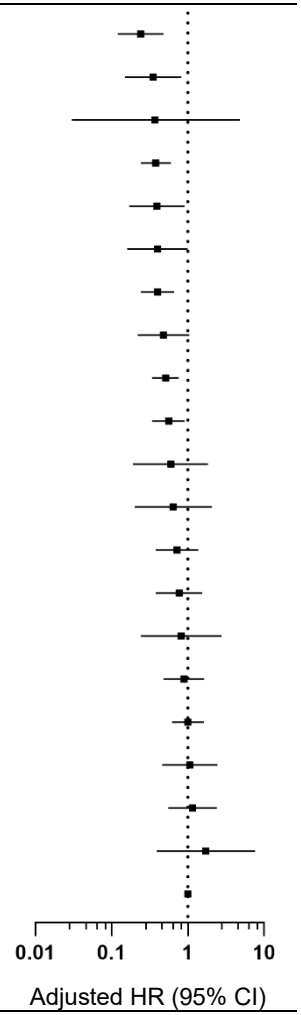


Figure 8-3 Risk of all-cause mortality in the 20 most commonly used regimens containing the six specific classes of cardiovascular medications compared with antiplatelet agents alone

In the analysis of the effect of the 20 most commonly used regimens containing APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs versus APAs alone, I found a significantly lower risk of mortality in combinations containing APAs, LRMs, ACEIs/ARBs, CCBs and DRs(Figure 8-3). In patients with the combination treatment of APAs, LRMs, ACEIs/ARBs and CCBs, the risk of mortality was lowered by 65% (95% CI: 18%-85%) compared with APAs alone. When adding DRs to the four-combination therapy, the combination appeared to be associated with the lowest risk of mortality (adjusted HR: 0.24, 95% CI: 0.12-0.48). The combination only containing APAs, LRMs and ACEIs/ARBs also showed a lower HR of mortality (adjusted HR: 0.38, 95% CI: 0.24-0.60).

8.3.1 Sensitivity analyses

Figure 8-4 shows the results of the effect of combination therapy omitting one of the specific six classes(APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs) on all-cause mortality compared to one class therapy. All combination therapy with two or more of the specific six classes appeared to reduce the risk of all-cause mortality by 41% (95% CI: 25%-53%). When removing LRMs, combination therapy showed no significant effect on all-cause mortality compared with one class (HR: 0.96; 95% CI: 0.73-1.26). When removing APAs, ACEIs/ARBs or CCBs, combination therapy reduced the risk of all-cause mortality by 33% (95%CI: 6%-53%), 38% (22%-50%) or 38% (23%-51%), respectively. Combination therapy without DRs (adjusted HR: 0.47, 95% CI: 0.37-0.59) or BBs (adjusted HR: 0.53, 95% CI: 0.43-0.66) showed lower HRs for mortality. Figure 8-5 shows the results of the effect of combination

therapy omitting one of the specific six classes (APAs, LRMs, ACEIs/ARBs, CCBs, thiazide-type DRs, and BBs) on all-cause mortality compared to one class therapy. The results showed the HRs for mortality in combinations omitting LRMs (HR: 0.80; 95% CI: 0.55-1.14), APAs (HR: 0.53; 95% CI: 0.34-0.83) and ACEIs/ARBs (HR: 0.53; 95% CI: 0.40-0.68) were higher than the HR for mortality in all combination therapy (HR: 0.52; 95% CI: 0.40-0.67). The E-values for the three main analyses of all-cause mortality ranged from 3.15 to 24.49.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.76 (0.56-1.04)	0.67 (0.47-0.94)
Without LRMS	1.09 (0.85-1.40)	0.96 (0.73-1.26)
Without ACEIs/ARBs	0.65 (0.52-0.80)	0.62 (0.50-0.78)
Without CCB	0.62 (0.50-0.75)	0.62 (0.49-0.77)
Without **DRs**	0.46 (0.37-0.56)	0.47 (0.37-0.59)
Without BBs	0.53 (0.44-0.65)	0.53 (0.43-0.66)
All combinations (≥ 2 classes)	0.57 (0.47-0.70)	0.59 (0.47-0.75)

Figure 8-4 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.47 (0.27-0.82)	0.53 (0.34-0.83)
Without LRMS	0.70 (0.46-1.06)	0.80 (0.55-1.14)
Without ACEIs/ARBs	0.46 (0.34-0.64)	0.53 (0.40-0.68)
Without CCB	0.41 (0.30-0.56)	0.51 (0.39-0.65)
Without **thiazide-type DRs**	0.44 (0.33-0.59)	0.52 (0.41-0.66)
Without BBs	0.39 (0.29-0.52)	0.47 (0.37-0.60)
All combinations (≥ 2 classes)	0.41 (0.31-0.55)	0.52 (0.40-0.67)

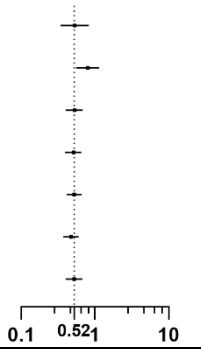


Figure 8-5 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

8.4 Discussion

This cohort study estimated the effectiveness of multiple cardiovascular medications in secondary prevention of all-cause mortality in patients who experienced an incident ischemic stroke or TIA and with a history of COPD. The results showed that increasing the numbers and classes of cardiovascular medications appeared to produce additional benefits on long-term survival. APAs, LRMs and ACEIs/ARBs appeared to be the central constituents of combination therapy associated with reduced risk of mortality after a stroke or TIA in patients with a history of COPD.

Previous studies have suggested the benefit of the management of single risk factors such as hypertension, high cholesterol, and thrombus formation in secondary prevention of stroke(Collaboration & Antiplatelet Trialists' Collaboration, 1994; Law, 2003; Rashid et al., 2003). This study found that compared with monotherapy, multiple pharmacological interventions can provide potentially greater benefits on long-term survival for patients with incident stroke event and a history of COPD. Contrary to combination therapy, patients with no use of cardiovascular medications had two to four times higher risk of mortality than monotherapy.

Evidence-based guidelines recommend APAs, LRMs and antihypertension medications for secondary prevention of ischemic stroke and TIA(National Institute for Health and Care Excellence, 2020b). In the present study, APAs appeared to confer an additive survival benefit in combination therapy on reduced risk of all-cause mortality in COPD patients after stroke. Patients with COPD have been

identified to have an increased platelet activation(Maclay et al., 2011). A meta-analysis also suggested that antiplatelet therapy might significantly contribute to reduced all-cause mortality in COPD patients(Pavasini et al., 2016). My results found that LRMs played a key role in combination therapy to reduce the risk of all-cause mortality. Several previous studies have also suggested that statin treatment can reduce mortality among COPD patients(Mancini et al., 2006; Søyseth et al., 2006). In addition, some studies have reported that statins may be associated with an anti-inflammatory effect in the lungs and the airways(J.-H. Lee et al., 2005) and a lower incidence of exacerbations in COPD patients(Blamoun et al., 2008). Hypertension is a well-established risk factor for stroke. Diuretics, ACEIs/ARBs, and CCBs are recommended as the first-line antihypertensive medications(National Institute for Health and Care Excellence, 2019a). In the present study, ACEIs/ARBs also appeared to have an additional effect on reducing the risk of mortality in combination therapy. Studies have found that the use of ACEIs/ARBs had a benefit on reduced risk of pneumonia in patients with COPD(Kim et al., 2016; Lai et al., 2018).

A study reported that ARBs were associated with lower rates of pneumonia and mortality than ACEIs in patients with COPD(Lai et al., 2018). Patients receiving ARBs were also less likely to have a cough compared with those receiving ACEIs(Caldeira et al., 2012). There is little evidence of whether ARBs were superior to ACEIs on long-term survival in COPD patients suffering a stroke. Further research is required in this area. In this study, diuretics and CCBs didn't show clearly additive benefits in combination therapy on long-term survival in

COPD patients suffering a stroke. There is still a lack of outcome data from RCTs designed to evaluate the effects of diuretics and CCBs in the treatment of hypertension in patients with COPD(Dart et al., 2003). However, there are theoretical benefits derived from using these two classes of medications adhered to guideline recommendations for hypertension treatment. In line with evidence from RCTs(De Lima et al., 2014), my results didn't find an additive benefit of BBs in secondary prevention of stroke or TIA.

8.4.1 Strengths and limitations

In addition to the strengths presented in "Chapter 6**,** 6.4.1", this study has some more strengths. Firstly, this study firstly comprehensively assessed the effect of different combinations among stroke patients with a comorbid COPD. Secondly, this study controlled for some COPD-related time-invariant and time-varying confounders, including FEV1, duration of COPD, records of exacerbations, previous use of medications for COPD. Thirdly, this study conducted a sensitivity analysis to evaluate the effect of combination therapy omitting one class, in order to assess the weight of each component of combination therapy on the outcome.

This study has some limitations besides that presented in "Chapter 6**,** 6.4.1". Firstly, this study did not estimate the individual effect of ACEIs and ARBs in combination therapy on long-term survival. It is still unknown if ARBs were superior to ACEIs on long-term survival in stroke patients with COPD. Secondly, this study did not investigate the effect of cardioselective BBs on long-term outcomes. Further studies are required to explore this area. Thirdly, this study only focuses on cardiovascular medications; thus, the study cannot determine the effect of different

medications for COPD or their potential interaction with cardiovascular medications on long-term survival in patients with ischemic stroke and COPD. Further studies are required in this area.

8.5 Conclusion

This study suggests that combination therapy of cardiovascular medications may improve long-term survival in patients with stroke or TIA and COPD. APAs, LRMs and ACEIs/ARBs appeared to be the central constituents of combination therapy in the present study.

Chapter 9: Impact of multiple cardiovascular medications on mortality after an incidence of myocardial infarction

9.1 Introduction

Coronary heart disease (CHD) consists of angina and myocardial infarction (MI) and is the leading cause of mortality worldwide and in the UK(British Heart Foundation, 2020a; World Health Organization, 2020). According to the Heart and Circulatory Disease Statistics 2019, CHD is responsible for around 64,000 deaths in the UK each year(British Heart Foundation, 2020a). MI, also known as heart attack, is the main type of CHD. In the UK, more than 100,000 hospital admissions each year are due to MIs(British Heart Foundation, 2020a). Pharmacological therapy is recommended by guidelines to lower mortality and morbidity after MI(Ibanez et al., 2018; National Institute for Health and Care Excellence, 2020c). In particular, antithrombotic therapy (i.e., antiplatelet agents and oral anticoagulants), beta-blockers, lipid-regulating medications (i.e., statins) and ACEIs proved to be beneficial in randomised clinical trials(Baigent et al., 2010; Collins et al., 2009; European, 2004; Freemantle et al., 1999). Hypertension is a highly prevalent risk factor in patients with CHD(British Heart Foundation, 2020a); consequently, antihypertensive agents (i.e., calcium channel blockers and diuretics) are suggested to control for blood pressure after MI(Ibanez et al., 2018; National Institute for Health and Care Excellence, 2020c). Nearly all the current evidence from clinical trials have only estimated the benefits of individual medications; however, most of the real-life patients use a large variety of combination therapy.

In 2003, Wald and Law proposed that a fixed-dose combination pill, called polypill, consisting of a statin, three antihypertensive agents (i.e., a thiazide, a beta-blocker and an AECI), aspirin and folic acid, could potentially reduce the risk of CHD and stroke by 80% in individuals from age 55(Wald, 2003). The previous systematic review and meta-analysis of observational studies (Chapter 2) assessed the effect of evidence-based combination pharmacotherapy (EBCP) and found EBCP is associated with a decreased risk of all-cause mortality and cardiovascular events in patients with cardiovascular disease(Ma et al., 2019).

However, there are some research gaps in the combination therapy after MI. It is unclear whether different single cardiovascular medications in combination therapy produce additive effects on long-term survival after MI. Further, the optimal constituents of combination therapy have not been well recognised. This study, therefore, aimed to investigate the effect of multiple cardiovascular medications on long-term survival after an initial MI event.

9.2 Methods

The study cohort design, CV medication exposure definition, data extraction and statistical analysis can be found in **Chapter 6**, 6.2 Methods.

9.2.1 Study population

This study included patients with their first diagnosis of MI between January 2007 and December 2016. The records of disease diagnosis were identified based on Read Code from the clinical dataset. Patients who were aged 45 or above and who had been registered for at least three years in the THIN

database before the first MI event were included in this study. I excluded patients who had a history of stroke or TIA before the first MI event, who had died or who had an occurrence of a further cardiovascular event within the first 90 days after the first event of MI.

9.2.2 Sensitivity analysis

Seven sensitivity analyses were conducted: (1) in a 60-day exposure period to assess the impact of the duration of the exposure window; (2) by dividing the one-year follow-up time frame into intervals of 6 months; (3) including patients who had a history of stroke or TIA before the MI event; (4) in patients with completed characteristics data; (5) by categorising the missing data for each covariate as a separate group; (6) an additional sensitivity analysis was conducted to assess the robustness of the findings to unmeasured confounding using E-value methodology of Van der Weele and Ding(Haneuse et al., 2019). In addition, (7) to assess the weight of the effect of APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs in combination therapy on all-cause mortality, I evaluated the effect of combination therapy (⩾2 classes) omitting one class compared with one class (e.g., combination therapy without APAs compared with one class).

9.3 Results

The study consisted of 20,095 men (64.1%) and 11,253 women (35.9%) who experienced their initial MI event between 1 January 2007 and 31 December 2016. Overall, 823 (2.6%) patients did not receive repeat cardiovascular medications, 530 (1.7%) received one, 974 (3.1%) received two, 1,940 (6.2%)

received three, 4,286 (13.7) received four, 10,414 (33.2%) received five, 7,232 (23.1%) received six and 5,149 (16.4%) patients received seven or more repeat cardiovascular medications at their initial MI event. The mean age of the patients at the start of follow-up was 67.4 (SD, 12.3) years and the mean follow-up time was 3.9 (SD: 2.7) years. In total, 4,375 patients died during the follow-up period, and the crude death rate was 40.0/1000 population. Table 9-1 shows the baseline characteristics of the patients at their initial MI events by the number of cardiovascular medications received during the first 90 days. There was a significant difference in all characteristics between patients with different numbers of CV medications.

Table 9-1 Baseline characteristics of study patients at their initial myocardial infarction events, 2007-2016.

		Cardiovascular treatment groups								
No. of CV medications	**Total**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**≥7**	**P value**
	n = 31348	n = 823 (2.6%)	n = 530 (1.7%)	n = 974 (3.1%)	n = 1940 (6.2%)	n = 4286 (13.7%)	n = 10414 (33.2%)	n = 7232 (23.1%)	n = 5149 (16.4%)	
Sex, % women	11253 (35.9)	379 (46.1)	265 (50.0)	470 (48.3)	867 (44.7)	1632 (38.1)	3200 (30.7)	2462 (34.0)	1978 (38.4)	<0.01
Age, (years) mean ± SD	67.4 ± 12.3	71.2 ± 13.7	72.5 ± 14.0	73.2± 13.3	71.1 ± 13.0	68.1 ± 12.5	65.3 ± 11.6	66.4 ± 12.0	68.7± 11.7	<0.01
Smoking										
Current	8582 (27.4)	205 (24.9)	113 (21.3)	204 (20.9)	451 (23.3)	1181 (27.6)	3050 (29.3)	2099 (29.0)	1279 (24.8)	<0.01
Former	10251 (32.7)	229 (27.8)	173 (32.6)	331 (34.0)	628 (32.4)	1439 (33.6)	3359 (32.3)	2347 (32.5)	1745 (33.9)	
Never	11778 (37.6)	334 (40.6)	230 (43.4)	402 (41.3)	801 (41.3)	1559 (36.4)	3791 (36.4)	2633 (36.4)	2028 (39.4)	
Missing	737 (2.4)	55 (6.7)	14 (2.6)	37 (3.8)	60 (3.1)	107 (2.5)	214 (2.1)	153 (2.1)	97 (1.9)	
Alcohol										
Current	16417 (52.4)	339 (41.2)	225 (42.5)	412 (42.3)	931 (48.0)	2197 (51.3)	5750 (55.2)	3902 (54.0)	2661 (51.7)	<0.01
Former	1089 (3.5)	33 (4.0)	16 (3.0)	48 (4.9)	64 (3.3)	172 (4.0)	295 (2.8)	256 (3.5)	205 (4.0)	
Never	4924 (15.7)	161 (19.6)	108 (20.4)	179 (18.4)	365 (18.8)	676 (15.8)	1410 (13.5)	1077 (14.9)	948 (18.4)	
Missing	8918 (28.5)	290 (35.2)	181 (34.2)	335 (34.4)	580 (29.9)	1241 (29.0)	2959 (28.4)	1997 (27.6)	1335 (25.9)	
BMI status										
Normal (18.5-24.9 kg/m2)	6310 (20.1)	199 (24.2)	141 (26.6)	250 (25.7)	479 (27.6)	997 (28.0)	2031 (29.3)	1331 (29.9)	882 (29.2)	<0.01
Overweight (25.0-29.9 kg/m2)	9054 (28.9)	177 (21.5)	159 (30.0)	272 (27.9)	535 (27.6)	1200 (28.0)	3047 (29.3)	2160 (29.9)	1504 (29.2)	
Obesity (≥ 30.0 kg/m2)	7220 (23.0)	153 (18.6)	91 (17.2)	164 (16.8)	388 (20.0)	880 (20.5)	2173 (20.9)	1797 (24.9)	1574 (30.6)	
Underweight (< 18.5 kg/m2)	484 (1.5)	29 (3.5)	22 (4.2)	40 (4.1)	52 (2.7)	88 (2.1)	111 (1.1)	86 (1.2)	56 (1.1)	
Normal (18.5-24.9 kg/m2)	8280 (26.4)	265 (32.2)	117 (22.1)	248 (25.5)	486 (25.1)	1121 (26.2)	3052 (29.3)	1858 (25.7)	1133 (22.0)	

BP status										
Normal (BP < 140/90 mmHg)	12134 (38.7)	304 (36.9)	226 (42.6)	417 (42.8)	803 (41.4)	1734 (40.5)	3819 (36.7)	2680 (37.1)	2151 (41.8)	<0.01
Stage 1 hypertension (BP ≥ 140/90 mmHg)	8044 (25.7)	189 (23.0)	149 (28.1)	266 (27.3)	519 (26.8)	1039 (24.2)	2514 (24.1)	1937 (26.8)	1431 (27.8)	
Stage 2 hypertension (BP ≥ 160/100 mmHg)	2267 (7.2)	74 (9.0)	31 (5.9)	62 (6.4)	149 (7.7)	306 (7.1)	705 (6.8)	514 (7.1)	426 (8.3)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	878 (2.8)	24 (2.9)	15 (2.8)	19 (2.0)	49 (2.5)	103 (2.4)	246 (2.4)	227 (3.1)	195 (3.8)	
Missing	7942 (25.3)	228 (27.7)	107 (20.2)	206 (21.2)	415 (21.4)	1098 (25.6)	3103 (29.8)	1855 (25.7)	930 (18.1)	
TC status (%)										
Optimal (<5.2 mmol/L)	8054 (25.7)	186 (22.6)	129 (24.3)	259 (26.6)	488 (25.2)	1071 (25.0)	2269 (21.8)	1863 (25.8)	1789 (34.7)	<0.01
Intermediate (5.3-6.2 mmol/L)	4260 (13.6)	80 (9.7)	67 (12.6)	117 (12.0)	245 (12.6)	550 (12.8)	1451 (13.9)	1053 (14.6)	697 (13.5)	
High (>6.2 mmol/L)	2769 (8.8)	51 (6.2)	38 (7.2)	70 (7.2)	160 (8.3)	360 (8.4)	1010 (9.7)	665 (9.2)	415 (8.1)	
Missing	16265 (51.9)	506 (61.5)	296 (55.9)	528 (54.2)	1047 (54.0)	2305 (53.8)	5684 (54.6)	3651 (50.5)	2248 (43.7)	
Townsend score										
1 (least deprived)	6100 (19.5)	135 (16.4)	102 (19.3)	179 (18.4)	346 (17.8)	839 (19.6)	2171 (20.9)	1430 (19.8)	898 (17.4)	<0.01
2	6190 (19.4)	160 (21.5)	114 (18.8)	183 (18.8)	365 (20.1)	862 (20.1)	2107 (2.02)	1420 (19.6)	979 (19.0)	
3	5916 (18.9)	143 (17.4)	107 (20.2)	163 (16.7)	388 (20.0)	816 (19.0)	1987 (19.1)	1362 (18.8)	950 (18.5)	
4	5457 (17.4)	148 (18.0)	82 (15.5)	194 (19.9)	377 (19.4)	741 (17.3)	1728 (16.6)	1245 (17.2)	942 (18.3)	
5 (most deprived)	3845 (12.3)	89 (10.8)	69 (13.0)	146 (15.0)	238 (12.3)	549 (12.8)	1138 (10.9)	925 (12.8)	691 (13.4)	
Missing	3840 (12.3)	148 (18.0)	56 (10.6)	109 (11.2)	226 (11.7)	479 (11.2)	1283 (12.3)	850 (11.8)	689 (13.4)	
Comorbidity										
Hypertension	14640 (46.7)	380 (46.2)	253 (47.7)	443 (45.5	912 (47.0)	1821 (3968)	3968 (38.1)	3588 (49.6)	3275 (63.6)	<0.01
Hyperlipidaemia	4420 (14.1)	105 (12.8)	77 (14.5)	118 (12.1)	256 (13.2)	576 (13.4)	1352 (13.0)	1028 (14.2)	908 (17.6)	<0.01

Arrhythmia	2817 (9.0)	94 (11.4)	68 (12.8)	119 (12.2)	273 (14.1)	353 (8.2)	669 (6.4)	554 (7.7)	687 (13.3)	<0.01
Heart Failure	2807 (9.0)	76 (9.2)	40 (7.6)	101 (10.4)	167 (8.6)	324 (7.6)	626 (6.0)	641 (8.9)	832 (16.2)	<0.01
PVD	1927 (6.2)	75 (9.1)	36 (6.8)	94 (9.7)	141 (7.3)	265 (6.2)	429 (4.1)	423 (5.9)	464 (9.0)	<0.01
Diabetes	5366 (17.1)	134 (16.3)	101 (19.1)	172 (17.7)	328 (16.9)	667 (15.6)	1367 (13.1)	1226 (17.0)	1371 (26.6)	<0.01
Dementia	538 (1.7)	40 (4.9)	24 (4.5)	57 (5.9)	74 (3.8)	84 (2.0)	125 (1.2)	72 (1.0)	62 (1.2)	<0.01
COPD	2846 (9.1)	88 (10.7)	63 (11.9)	138 (14.2)	215 (11.1)	444 (10.4)	780 (7.5)	580 (8.0)	538 (10.5)	<0.01
Asthma	4052 (12.9)	116 (14.1)	78 (14.7)	170 (17.5)	307 (15.8)	609 (14.2)	1187 (11.4)	852 (11.8)	733 (14.2)	<0.01
Liver disease	155 (0.5)	6 (0.7)	6 (1.1)	13 (1.3)	11 (0.6)	31 (0.7)	40 (0.4)	25 (0.4)	23 (0.5)	<0.01
Peptic ulcer disease	1719 (5.5)	44 (5.4)	35 (6.6)	61 (6.3)	125 (6.4)	277 (6.5)	544 (5.2)	349 (4.8)	284 (5.5)	<0.01
RA	746 (2.4)	21 (2.6)	29 (5.5)	25 (2.6)	58 (3.0)	114 (2.7)	222 (2.1)	164 (2.3)	113 (2.2)	<0.01
CKD	4589 (14.6)	154 (2.6)	94 (1.7)	213 (3.1)	360 (6.2)	660 (13.7)	1084 (33.2)	988 (23.1)	1036 (16.4)	<0.01

BMI = body mass index; BP = blood pressure; TC = total cholesterol; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PCI = percutaneous transluminal coronary intervention; PVD = peripheral vascular disease; RA = rheumatoid arthritis;

Figure 9-1 shows the risk of all-cause mortality in patients prescribed with different numbers of cardiovascular medications. Compared with monotherapy, the risk reduction of all-cause mortality in patients with combination therapy was: 25% (95% CI: 7%-36%) for two medications, 39% (95% CI: 28%-49%) for three medications, 62% (95% CI: 55%-68%) for four medications, 57% (95% CI: 49%-64%) for five medications, 53% (95% CI: 44%-61%) for six medications and 43% (95% CI: 31%-53%) for seven or more medications. Conversely, patients with no long-term used cardiovascular medications were associated with an increased risk of all-cause mortality (adjusted HR: 1.53, 95% CI: 1.27-1.84). Figure 9-2 shows decreased hazard ratios of mortality in patients with two classes (adjusted HR: 0.64, 95% CI: 0.51-0.80), three classes (adjusted HR: 0.46 95% CI: 0.38-0.56), four classes (adjusted HR: 0.29, 95% CI: 0.24-0.35), five classes (adjusted HR: 0.37, 95% CI: 0.30-0.45) and six classes combination (adjusted HR: 0.28, 95% CI: 0.19-0.42) of APAs, LRMs, ACEIs/ARBs, BBs, DRs and CCBs compared with one class. Conversely, patients with none repeated CV medications were associated with an increased risk of all-cause mortality (adjusted HR: 1.27, 95% CI: 1.04-1.56) compared with one class.

In the analysis of the effect of the 20 most commonly used regimens containing APAs, LRMs, ACEI/ARB, CCBs, diuretics and BBs, I found a significantly lower risk of mortality in combinations containing APAs, LRMs, ACEIs/ARBs and BBs when compared with APAs alone (Figure 9-3). The combination of APAs, LRMs, ACEIs/ARBs and BBs decreased the risk of mortality by 79% (95% CI: 70%-85%) compared with APAs alone. When adding CCBs to the four-medication

combination, the risk of mortality was reduced by 77% (95% CI: 61%-86%) versus APAs alone. The combination of only three classes of LRMs, ACEIs/ARBs and BBs also showed a significant reduction in mortality with an HR of 0.29 (95% CI: 0.17-0.50).

Number of medications	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥7	515	9253	55.7	0.52 (0.44-0.61)	0.57 (0.47-0.69)
6	549	14604	37.6	0.35 (0.30-0.41)	0.47 (0.39-0.56)
5	779	26939	28.9	0.28 (0.24-0.32)	0.43 (0.36-0.51)
4	700	30895	22.7	0.25 (0.21-0.29)	0.38 (0.32-0.45)
3	646	14475	44.6	0.49 (0.42-0.58)	0.61 (0.51-0.72)
2	412	6231	66.1	0.73 (0.62-0.86)	0.77 (0.64-0.93)
1	270	2883	93.7	1	1
0	504	3968	127.0	1.25 (1.07-1.46)	1.53 (1.27-1.84)

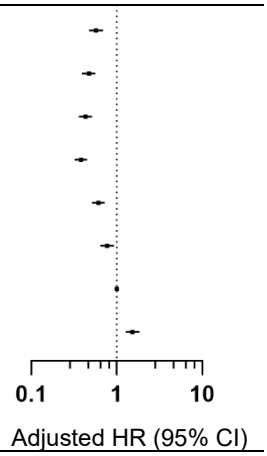


Figure 9-1 Risk of all-cause mortality in patients prescribed with various numbers of cardiovascular medications

Number of classes	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
6	38	1140	33.3	0.51 (0.35-0.73)	0.39 (0.26-0.59)
5	323	10133	31.9	0.51 (0.43-0.60)	0.37 (0.30-0.46)
4	604	38950	15.5	0.24 (0.21-0.28)	0.29 (0.24-0.34)
3	566	19674	28.8	0.47 (0.41-0.54)	0.47 (0.39-0.57)
2	404	9458	42.7	0.72 (0.62-0.84)	0.67 (0.54-0.82)
1	327	5416	60.4	1	1
0	504	4379	115.1	1.76 (1.52-2.05)	1.27 (1.04-1.56)

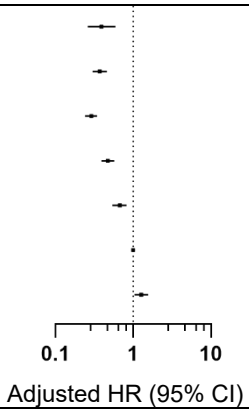


Figure 9-2 Risk of all-cause mortality in patients prescribed with various numbers of specific six classes of cardiovascular medications

Combination	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR	Adjusted HR
APAs+LRMs+ACEIs/ARBs+BBs	304	35814	8.5	0.09 (0.07-0.11)	0.21 (0.15-0.30)
APAs+LRMs+ACEIs/ARBs+CCBs+BBs	43	4046	10.6	0.12 (0.08-0.17)	0.23 (0.14-0.39)
LRMs+ACEIs/ARBs+BBs	26	2162	12.0	0.15 (0.09-0.22)	0.29 (0.17-0.50)
APAs+LRMs+ACEIs/ARBs+CCBs	37	1886	19.6	0.23 (0.16-0.34)	0.33 (0.20-0.56)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs+BBs	42	1406	29.9	0.34 (0.24-0.49)	0.37 (0.23-0.60)
ACEIs/ARBs+BBs	21	660	31.8	0.38 (0.24-0.62)	0.38 (0.20-0.69)
APAs+LRMs+ACEIs/ARBs	105	5789	18.1	0.22 (0.16-0.28)	0.41 (0.29-0.58)
APAs+LRMs+ACEIs/ARBs+DRs+BBs	257	702	366.3	0.43 (0.34-0.53)	0.46 (0.30-0.71)
APAs+ACEIs/ARBs+BBs	57	2174	26.2	0.30 (0.22-0.42)	0.51 (0.30-0.85)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs	33	702	47.0	0.59 (0.40-0.89)	0.51 (0.26-1.01)
LRMs+ACEIs/ARBs	17	784	21.7	0.26 (0.16-0.44)	0.51 (0.35-0.76)
APAs+LRMs+BBs	129	4639	27.8	0.31 (0.24-0.40)	0.52 (0.23-1.15)
LRMs+BBs	13	690	18.8	0.23 (0.13-0.41)	0.53 (0.35-0.80)
APAs+LRMs	78	2171	35.9	0.44 (0.33-0.59)	0.54 (0.35-0.84)
APAs+LRMs+ACEIs/ARBs+DRs	75	1338	56.0	0.67 (0.49-0.90)	0.54 (0.32-0.92)
APAs+ACEIs/ARBs	33	800	41.2	0.51 (0.35-0.75)	0.66 (0.44-0.99)
APAs+LRMs+DRs+BBs	89	964	92.4	1.03 (0.77-1.38)	0.79 (0.50-1.27)
APAs+BBs	57	892	63.9	0.75 (0.54-1.04)	0.90 (0.48-1.69)
ACEIs/ARBs alone	71	1584	44.8	0.49 (0.36-0.67)	1.08 (0.65-2.08)
LRMs alone	62	1495	41.5	0.49 (0.36-0.68)	1.32 (0.94-1.84)
APAs alone	118	1345	87.8	1	1

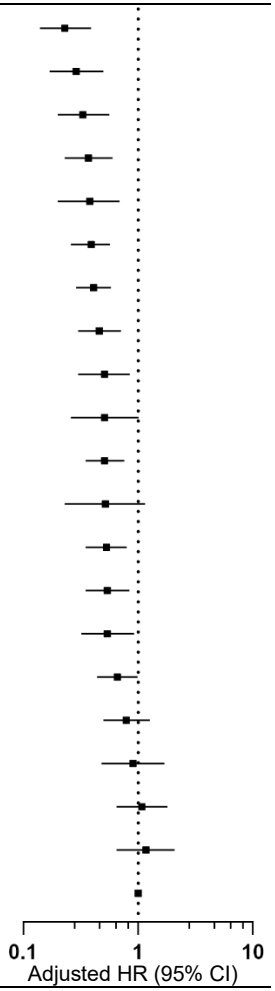


Figure 9-3 Risk of all-cause mortality in the 20 most commonly used regimens containing the six specific classes of cardiovascular medications compared with antiplatelet agents alone

9.3.1 Sensitivity analyses

Results of sensitivity analyses are provided in Table 9-2 and Table 9-3. The results of the risk of mortality in patients with different numbers of CV medications and different numbers of classes of CV medications were similar to the results in the sensitivity analyses. The E-values estimates for the three main analyses of all-cause mortality ranged from 1.86 to 8.99.

To assess the weight of each component of EBCP on outcomes, I assessed effects of combination therapy excluding any one component. Table 9-4 shows the results of the effect of combination therapy omitting one of the specific six classes on all-cause mortality compared to one class therapy. All combination therapy with two or more of the specific six classes appeared to reduce the risk of all-cause mortality by 43% (95% CI: 36%-50%). When removing LRMs, combination therapy showed no significant effect on all-cause mortality compared with one class (HR: 0.93; 95% CI: 0.81-1.07). When removing ACEIs/ARBs, APAs or BBs, combination therapy reduced the risk of all-cause mortality by 14% (95%CI: 2%-25%), 21% (8%-32%) or 27% (17%-36%), respectively.

Table 9-2 Risk of all-cause mortality in patients prescribed with different numbers of cardiovascular medications in sensitivity analyses.

	Adjusted HR (95% CI)				
Number of CV medications	**Primary analysis**	**60-day exposure window[a]**	**6-month interval[b]**	**With history of stroke/TIA[c]**	**Categorised missing data[d]**
≥7	0.57 (0.47-0.69)	0.68 (0.57-0.82)	0.62 (0.34-1.15)	0.57 (0.47-0.69)	0.56 (0.46-0.68)
6	0.47 (0.39-0.56)	0.58 (0.49-0.69)	0.37 (0.30-0.46)	0.45 (0.38-0.54)	0.47 (0.39-0.56)
5	0.43 (0.36-0.51)	0.52 (0.45-0.61)	0.33 (0.27-0.41)	0.41 (0.34-0.48)	0.42 (0.35-0.50)
4	0.38 (0.32-0.45)	0.47 (0.41-0.55)	0.33 (0.28-0.40)	0.36 (0.30-0.43)	0.38 (0.32-0.46)
3	0.61 (0.51-0.72)	0.64 (0.55-0.75)	0.50 (0.42-0.61)	0.59 (0.50-0.70)	0.63 (0.53-0.76)
2	0.77 (0.64-0.93)	0.80 (0.67-0.94)	0.92 (0.54-1.56)	0.66 (0.55-0.80)	0.78 (0.64-0.95)
1	1	1	1	1	1
0	1.53 (1.27-1.84)	1.30 (1.11-1.53)	1.90 (1.57-2.30)	1.45 (1.20-1.75)	1.47 (1.21-1.78)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted in patients who had a history of ischemic stroke/TIA before the first MI event; [d]A sensitivity analysis conducted by categorising missing data as separate group.

Table 9-3 Risk of all-cause mortality in patients prescribed with different numbers of specific six classes of cardiovascular medications in sensitivity analyses.

	Adjusted HR (95% CI)				
Number of CV medications	**Primary analysis**	**60-day exposure window[a]**	**6-month interval[b]**	**With history of stroke/TIA[c]**	**Categorised missing data[d]**
6	0.39 (0.26-0.59)	0.54 (0.34-0.85)	0.17 (0.11-0.26)	0.34 (0.23-0.49)	0.45 (0.29-0.70)
5	0.37 (0.30-0.46)	0.51 (0.42-0.63)	0.30 (0.24-0.36)	0.39 (0.32-0.47)	0.41 (0.31-0.53)
4	0.29 (0.24-0.34)	0.38 (0.32-0.45)	0.26 (0.22-0.30)	0.30 (0.25-0.35)	0.34 (0.25-0.46)
3	0.47 (0.39-0.57)	0.57 (0.48-0.67)	0.42 (0.36-0.50)	0.51 (0.43-0.60)	0.55 (0.42-0.71)
2	0.67 (0.54-0.82)	0.72 (0.61-0.86)	0.59 (0.49-0.70)	0.62 (0.51-0.75)	0.62 (0.48-0.81)
1	1	1	1	1	1
0	1.27 (1.04-1.56)	1.57 (1.31-1.88)	1.85 (1.58-2.17)	1.42 (1.18-1.70)	1.58 (1.45-1.73)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted in patients who had a history of ischemic stroke/TIA before the first MI event; [d]A sensitivity analysis conducted by categorising missing data as separate group.

Table 9-4 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
All combinations with ≥ two classes	0.51 (0.45-0.57)	0.57 (0.50-0.64)
Without APAs	0.96 (0.84-1.11)	0.79 (0.68-0.92)
Without LRMS	1.32 (1.15-1.51)	0.93 (0.81-1.07)
Without ACEIs/ARBs	1.12 (0.98-1.27)	0.86 (0.75-0.98)
Without BBs	0.89 (0.78-1.01)	0.73 (0.64-0.83)
Without CCBs	0.50 (0.45-0.57)	0.58 (0.51-0.66)
Without DRs	0.31 (0.27-0.35)	0.45 (0.39-0.52)

9.4 Discussion

This study is the first long-term and large database study to report the effectiveness of numbers, classes and different combinations of cardiovascular medications on all-cause mortality in patients after their incident MI event. The results showed that increasing the numbers and classes of cardiovascular medications appeared to produce additional benefit on long-term survival. APAs, LRMs, ACEIs/ARBs and BBs are the optimal constituents of combination therapy to reduce the risk of mortality after MI.

Random control trials have shown the benefits of the modification of individual risk factors such as thrombus formation, high cholesterol and hypertension(Collins et al., 2009; European, 2004; Freemantle et al., 1999; Trialists, 2005) on the reduction of mortality and morbidity after MI. In my systematic review and mate-analysis of observational studies (Chapter 2), I found that each component of evidence-based combination pharmacotherapy (EBCP, containing one antiplatelet agent, one lipid-modifier one ACEI/ARB and one BB) conferred an additive benefit

on the survival in patients with MI(Ma et al., 2019). The results in the present study also determined that multiple pharmacological interventions can provide cumulative benefits on long-term survival for MI patients. Four CV medications appeared to have the best of mortality outcome in MI patients (adjusted HR, 0.38, 95% CI: 0.32-0.45). However, the mortality benefit decreased in patients with five medications (0.43, 95% CI: 0.36-0.51). Therefore, for medicine optimization, the number of combined medications should be managed with care.

To further investigate the additive effects of evidence recommended medications in secondary prevention of MI, I compared the mortality risks in patients with different numbers of combined use of APAs, LRMs, ACEIs/ARBs, BBs, and two commonly used antihypertensive agents, CCBs and diuretics. The results showed that the hazard ratio of mortality was lowest in patients with four classes (0.29, 95% CI: 0.24-0.34) compared with patients prescribed one class. The results of different regimens suggested that APAs, LRMs, ACEIs/ARBs and BBs maybe the optimal components in the combination therapy. The four medications combination was shown to reduce the all-cause mortality by 79% (95% CI: 70%-85%) compared with the use of APAs alone. This result is consistent with the finding from my meta-analysis that compared with none or one component, the all-cause mortality was reduced by 78% (RR: 0.22, 95% CI:14-0.34) in patients with optimal EBCP (Figure 2-5). The optimal EBCP contains an APA, an ACEI/ARB, a BB and an LRM. In addition, I also found that CCBs are also an effective component in the combination therapy but did not show a significant additive benefit compared to BBs. When BBs were replaced by CCBs in combined with APAs, LRMs, ACEIs/ARBs, the risk of

mortality increased from 0.21 (0.15-0.30) to 0.33 (0.20-0.56). According to guidelines, CCBs (e.g. diltiazem or verapamil) are not routinely offered for secondary prevention of myocardial infarction but are considered to use if BBs are not appropriate(National Institute for Health and Care Excellence, 2020c).

The study furtherly estimated the role of the six class medications in combination therapy. The results showed omitting LRMs, ACEIs/ARBs, APAs or BBs from combination therapy would reduce the beneficial effect of combination therapy (Table 8-4). The results indicate that the four medications played key roles in combination therapy to reduce the risk of all-cause mortality. The changes were greatest when excluding LRMs, followed by ACEIs/ARBs, APAs and BBs. My results were similar to another large-database study(Bezin et al., 2018). The study compared the effect of 3-EBCP combinations and full EBCP on all-cause mortality, and showed that ACEIs/ARBs and statins made the greatest contribution to the beneficial effects of EBCP, followed by antiplatelet agents. However, different results were found in a meta-analysis of my systematic review (Figure 2-5). In the meta-analysis, ACEIs/ARBs appeared to have little effect on the reduction of mortality in patients with acute coronary syndrome (ACS). The two studies included in the meta-analysis compared outcomes with individuals who were exposed to none or one component of EBCP. To choose non-exposure as the reference category is open to criticism, as it is prone to exposing the study to a confounding and immeasurable time bias.

In addition, this study found that underuse of cardiovascular medications still existed in patients with MI. The results showed 823 (2.6%) patients did not receive

long-term used cardiovascular medications and 530 (1.7%) received only one medication following their incident MI. The results of this study have determined the potential long-term beneficial effects of the combined use of guideline-recommended cardiovascular medications, which indicates that guideline compliance deserves attention for improving survival in patients with MI.

9.4.1 Strengths and limitations

In my systematic review (Chapter 2), some previous studies also have estimated the effect of multiple cardiovascular medications in patients with CHD or MI. Compared with these previous researches, my study has several strengths. Firstly, it was based on a large population-based primary care practice database. As such, it is likely to reflect “real-life” healthcare in the UK. Secondly, this study compared different numbers, classes and combinations of cardiovascular medications which comprehensively demonstrated the effect of combination therapy on long-term survival. Thirdly, when assessing the effect of different combinations, I defined exposure groups as patients who were exclusively using the selected cardiovascular medications of interest and this was to remove potential effects of other cardiovascular medications which were not of interest on the outcome. In addition, I used MSMs to control for confounding due to both time-invariant and time-varying confounders that may lead to treatment switching or informative censoring. I demonstrated the robustness of my findings to unmeasured confounding using the E-Value estimate. Most HRs of all-cause mortality for known, strong risk factors of cardiovascular disease were below 1.86, the minimum E-Value estimate in this study. For example, the HRs of mortality was 1.65 (95%

CI:1.45-1.88) for current smokers, 1.49 (95% CI:1.36-1.63) for patients with diabetes and 1.16 (95% CI:1.07-1.26) for patients with hypertension. It is not likely that an unmeasured or unknown confounder would have a substantially larger effect on cardiovascular disease development or mortality than these known risk factors by having a relative risk exceeding 1.74. Finally, most compellingly, I used all-cause mortality as my outcome measure. Despite the influence of non-cardiovascular mortality on the outcome, this study produced very clear results. Had I measured cause-specific cardiovascular mortality; I suspect that the findings would have been more pronounced.

This study has limitations. Firstly, the THIN database only provides records of prescriptions; therefore, my study was not able to determine if medications were actually dispensed, taken or used in line with the administration directions by patients. Secondly, because the THIN database does not capture data for hospital treatment, care homes or nursing homes, and over the counter (OTC) medications (e.g., aspirin available OTC), the study was not able to address any medication usage not included in records from general practice. Thirdly, I had no information on the severity of MI. Due to shorter life-expectancy, health interventions may be less cost-effective in patients with more severe cardiovascular conditions(Murray et al., 2003; National Institute for Health and Care Excellence, 2009). In this case, patients with the severe condition may be more likely to be undertreated and thus more likely to die. However, I adopted measures to balance heterogeneity between different exposure groups to some extent: (1) I excluded patients who had a history of stroke before the first MI event, (2) excluded patients who died or had a nonfatal

cardiovascular event during the first 90 days, and (3) I adjusted for risk factors of cardiovascular disease when estimating mortality hazard ratios. Fourthly, I only estimated the effect of cardiovascular medications by their major classification so the study cannot tell the effect of sub-classes of these cardiovascular medications on long-term outcomes. For instance, I did not compare the effect of dual-antiplatelet therapy and monotherapy on long-term mortality. Further research is required to explore this area.

9.5 Conclusion

My study suggests that combination therapy of four cardiovascular medications may improve long-term survival in patients with MI. APAs, LRMs, ACEIs/ARBs and BBs were probably the optimal constituents of combination therapy in the present study.

Chapter 10: Impact of multiple cardiovascular medications on mortality in patients with myocardial infarction and type 2 diabetes mellitus

10.1 Introduction

It has been well established that diabetes is a major risk factor for CHD(Grundy et al., 1999). There is strong evidence that the mortality rate after MI is higher in patients with diabetes than in nondiabetic patients(Haffner et al., 1998; Miettinen et al., 1998). CHD is a major cause of death in people with diabetes, accounting for over half in people with Type 2 diabetes(Morrish et al., 2001). Several factors, such as chronic hyperglycaemia, severe coronary atherosclerosis, heart failure, hypertension and dyslipidaemia, are related to poor prognosis in patients with both diabetes and MI(Bertoni et al., 2004; Creager et al., 2003; From et al., 2006). Thus, aggressive management of cardiovascular risk factors and optimal pharmacotherapy play key roles in secondary prevention of MI in patients with diabetes. These patients commonly receive more cardiovascular medications compared to nondiabetic patients. In my drug utilisation study (Chapter 5), the average number of cardiovascular medications was 5.2 (SD: 1.9) in patients with diabetes and 4.7 (SD:1.8) in nondiabetic patients following their incident CHD events. My systematic review and meta-analysis of observational studies (Chapter 2) have suggested that EBCP (containing one antiplatelet agent, one lipid-modifier, one ACEI/ARB and one BB) can reduce the risk of mortality in patients with MI(Ma

et al., 2019). However, there was still no study specifically evaluating the effects of EBCP for secondary prevention of CVD in patients with diabetes. In addition, some other cardiovascular medications are also commonly prescribed in patients with diabetes with CVD. For example, hypertension is highly prevalent in type 2 diabetic patients (above 70% among European patients)(Colosia et al., 2013). It is unclear whether CCBs and diuretics (two commonly used first-line antihypertensive agents) also produce an additive benefit in combination therapy on long-term survival in type 2 diabetic patients after MI. Furthermore, the optimal constituents of combination therapy for secondary prevention in patients with diabetes has not been well recognised. This study, therefore, aimed to investigate the effect of multiple cardiovascular medications on long-term survival in patients with both MI and type 2 diabetes.

10.2 Methods

The study cohort design, exposure definition, data extraction and statistical analysis refer to **Chapter 6**, 6.2 Methods.

10.2.1 Study population

This study included patients with a first diagnosis of MI between January 2007 and December 2016, and with a history of type 2 diabetes before their first MI event. Inclusion criteria included patients who were aged 45 or above and who had been registered for at least three years in the THIN database before the first MI event. I excluded patients who died or who had an occurrence of a further cardiovascular event within the first 90 days following their incident MI event. Patients were

followed from the initial event until the end of December 2016 and were censored if they left their general practice during the study period. The outcome was all-cause mortality. For each patient, the follow-up was divided into contiguous periods of six months, each defined with specific entry and exit points.

10.2.2 Data extraction and confounders

The data of demographic and clinical characteristics six months prior to each entry point and prescriptions three months prior to each entry point were extracted from the THIN database. In addition to the variables mentioned in "**Chapter 6**, 6.2.6 Data extraction and confounders", Haemoglobin A1c (HbA1c) value at baseline, duration of diabetes, previous use of diabetes medications were also included as confounders. Diabetes medications were identified based on medications classified in the BNF Chapter 6.1: Drugs used in diabetes.

10.2.3 Sensitivity analysis

Sensitivity analyses were conducted: (1) in a 60-day exposure period to assess the impact of the duration of the exposure window; (2) by dividing the 6-month follow-up time frame into intervals of 3 months; (3) by categorising the missing data for each covariate as a separate group; (4) using E-value methodology to assess the robustness of findings to unmeasured confounding; (5) an sensitivity analysis was conducted to evaluate the effect of combination therapy ($\geqslant$2 classes) omitting one class compared with one class. In addition, to assess the role of thiazide-type diuretics in the combination therapy, I repeated the fifth sensitivity analysis by only keeping thiazide-type DRs from the overall DRs.

10.3 Results

The study consisted of 2893 men (62.8%) and 1711 women (37.2%) who had experienced the initial MI event from 1 January 2007 to 31 December 2016 and had a history of type 2 diabetes before the initial MI event. Overall, 3.2% of patients did not receive long-term cardiovascular medications, 1.9% received one, 3.5% received two, 5.9% received three, 12.2% received four, 24.8% received five, 22.6% of patients received six, and 26.0% received seven or more cardiovascular medications during the 90 days following their initial MI event.

The mean age at the start of follow-up was 69.8 (SD, 11.5) years, and the mean follow-up time was 3.4 (SD, 2.5) years. In total, the study recorded 926 deaths during the follow-up, and the crude death rate was 59.6/1000 person-years. Table 9-1 shows the baseline characteristics of the patients at their initial MI events based on the number of cardiovascular medications received during the first 90 days.

Table 10-1 Baseline characteristics of study patients at their initial MI events, 2007-2016.

	Cardiovascular treatment groups									
No. of CV medications	**Total**	**0**	**1**	**3**	**3**	**4**	**5**	**6**	**≥7**	**P value**
	n = 4604	n = 146 (3.2%)	n = 89 (1.9%)	n = 159 (3.5%)	n = 270 (5.9%)	n = 561 (12.2%)	n = 1141 (24.8%)	n = 1041 (22.6%)	n = 1197 (26.0%)	
Sex, % women	1711 (37.2)	54 (3.2)	37 (1.9)	58 (3.5)	112 (5.9)	215 (12.2)	372 (24.8)	399 (22.6)	464 (26.0)	0.03
Age, (years) mean ± SD	69.8 ± 11.5	71.1 ± 12.4	73.6 ± 12.4	72.8± 11.8	72.5 ± 11.3	70.1 ± 11.4	68.3 ± 11.5	69.2 ± 11.9	70.2± 10.9	<0.01
Smoking (%)										
Current	961 (20.9)	25 (17.1)	16 (18.0)	20 (12.6)	58 (21.5)	114 (20.3)	264 (23.1)	239 (23.0)	225 (18.8)	0.15
Former	1669 (36.3)	57 (39.0)	30 (33.7)	64 (40.3)	88 (32.6)	220 (39.2)	399 (35.0)	372 (35.7)	439 (36.7)	
Never	1934 (42.0)	62 (42.5)	41 (46.1)	72 (45.3)	122 (45.2)	221 (39.4)	469 (41.1)	424 (40.7)	523 (43.7)	
Missing	40 (0.9)	<5	<5	<5	<5	6 (1.1)	9 (0.8)	6 (0.6)	10 (0.8)	
Alcohol (%)										
Current	2333 (50.7)	67 (45.9)	34 (38.2)	65 (40.9)	131 (48.5)	276 (49.2)	616 (54.0)	543 (52.2)	601 (50.2)	<0.01
Former	237 (5.2)	<5	<5	12 (7.6)	13 (4.8)	40 (7.1)	53 (4.7)	52 (5.0)	62 (5.2)	
Never	1125 (24.4)	45 (30.8)	26 (29.2)	46 (28.9)	78 (28.9)	126 (22.5)	232 (20.3)	254 (24.4)	318 (26.6)	
Missing	909 (19.7)	31 (21.2)	27 (30.3)	36 (22.6)	48 (17.8)	119 (21.2)	240 (21.0)	192 (18.4)	216 (18.1)	
BMI status (%)										
Normal (18.5-24.9 kg/m2)	729 (15.8)	34 (23.3)	16 (18.0)	31 (19.5)	53 (19.6)	104 (18.5)	185 (16.2)	149 (14.3)	157 (13.1)	<0.01
Overweight (25.0-29.9 kg/m2)	1578 (34.3)	49 (33.6)	36 (40.5)	58 (36.5)	102 (37.8)	201 (35.8)	400 (35.1)	349 (33.5)	383 (32.0)	
Obesity (≥ 30.0 kg/m2)	2057 (44.7)	49 (33.6)	30 (33.7)	61 (38.4)	104 (38.5)	232 (41.4)	491 (43.0)	499 (47.9)	591 (49.4)	
Missing	210 (4.6)	10 (6.9)	7 (7.9)	6 (3.8)	8 (3.0)	22 (3.9)	56 (4.9)	40 (3.8)	61 (5.1)	
BP status (%)										
Normal	2528 (54.9)	80 (54.8)	42 (47.2)	91 (57.2)	162 (60.0)	321 (57.2)	629 (55.1)	558 (53.6)	645 (53.9)	0.07

(BP < 140/90 mmHg)										
Stage 1 hypertension (BP ≥ 140/90 mmHg)	1436 (31.2)	39 (26.7)	37 (41.6)	44 (27.7)	72 (26.7)	172 (30.7)	366 (32.1)	339 (32.6)	367 (30.7)	
Stage 2 hypertension (BP ≥ 160/100 mmHg)	371 (8.1)	15 (10.3)	7 (7.9)	11 (6.9)	25 (9.3)	42 (7.5)	86 (7.5)	85 (8.2)	100 (8.4)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	181 (3.9)	6 (4.1)	<5	10 (6.3)	10 (3.7)	18 (3.2)	34 (3.0)	41 (3.9)	59 (4.9)	
Missing	72 (1.6)	5 (3.4)	<5	<5	<5	7 (1.6)	22 (1.9)	14 (1.3)	23 (1.9)	
TC status (%)										
Optimal (<5.2 mmol/L)	3232 (70.2)	106 (72.6)	56 (62.9)	116 (73.0)	192 (71.1)	402 (71.7)	782 (68.5)	703 (67.5)	875 (73.1)	0.29
Intermediate (5.3-6.2 mmol/L)	740 (16.1)	20 (13.7)	20 (22.5)	25 (15.7)	47 (17.4)	91 (16.2)	184 (16.1)	183 (17.6)	170 (14.2)	
High (>6.2 mmol/L)	438 (9.5)	11 (7.5)	8 (9.0)	13 (8.2)	24 (8.9)	52 (9.3)	117 (10.3)	111 (10.7)	102 (8.5)	
Missing	194 (4.2)	9 (6.2)	5 (5.6)	5 (3.1)	7 (2.6)	16 (2.9)	58 (5.1)	44 (4.2)	50 (4.2)	
Townsend score (%)										
1 (least deprived)	763 (16.6)	21 (14.4)	19 (21.4)	27 (17.0)	48 (17.8)	99 (17.7)	203 (17.8)	170 (16.3)	176 (14.7)	0.64
2	816 (17.7)	20 (13.7)	13 (14.6)	28 (17.6)	52 (19.3)	114 (20.3)	223 (19.5)	179 (17.2)	187 (15.6)	
3	893 (19.4)	31 (21.2)	16 (18.0)	30 (18.9)	49 (18.2)	107 (19.1)	209 (18.3)	211 (20.3)	240 (20.1)	
4	917 (19.9)	30 (20.6)	23 (25.8)	34 (21.4)	51 (18.9)	101 (18.0)	216 (18.9)	200 (19.2)	262 (21.9)	
5 (most deprived)	655 (14.2)	24 (16.4)	12 (13.5)	19 (12.0)	41 (15.2)	74 (13.2)	147 (12.9)	157 (15.1)	181 (15.1)	
Missing	560 (12.2)	20 (13.7)	6 (6.7)	21 (13.2)	29 (10.7)	66 (11.8)	143 (12.5)	124 (11.9)	151 (12.6)	
History of PCI (%)	18 (12.2)	8 (12.3)	5 (9.0)	13 (3.1)	52 (4.8)	152 (9.3)	146 (13.3)	168 (14.0)	18 (14.0)	
Comorbidity										
Hypertension	3303 (71.7)	106 (72.6)	61 (68.5)	112 (70.4)	191 (70.7)	380 (67.7)	727 (63.7)	759 (72.9)	967 (80.8)	<0.01
Hyperlipidaemia	1072 (23.3)	41 (28.1)	16 (18.0)	32 (20.1)	58 (21.5)	141 (25.1)	246 (21.6)	235 (22.6)	303 (25.3)	0.15
Arrhythmia	557 (12.1)	17 (11.6)	18 (20.2)	18 (11.3)	30 (11.1)	62 (11.1)	107 (9.4)	112 (10.8)	193 (16.1)	<0.01

Heart Failure	669 (14.5)	22 (15.1)	9 (10.1)	23 (14.5)	29 (10.7)	76 (13.6)	126 (11.0)	131 (12.6)	253 (21.1)	<0.01
PVD	517 (11.2)	24 (16.4)	16 (18.0)	22 (13.8)	33 (12.2)	54 (9.6)	90 (7.9)	115 (11.1)	163 (13.6)	<0.01
Dementia	79 (1.7)	5 (3.4)	<5	6 (3.8)	4 (1.5)	15 (2.7)	21 (1.8)	9 (0.9)	17 (1.4)	0.04
COPD	412 (9.0)	8 (5.5)	7 (7.9)	18 (11.3)	32 (11.9)	49 (8.7)	93 (8.2)	85 (8.2)	120 (10.0)	0.21
Asthma	651 (14.1)	16 (11.0)	11 (12.4)	28 (17.6)	47 (17.4)	86 (15.3)	149 (13.1)	129 (12.4)	185 (15.5)	0.12
Liver disease	46 (1.0)	<5	<5	5 (3.1)	6 (2.2)	7 (1.3)	11 (1.0)	5 (0.5)	8 (0.7)	0.02
Peptic ulcer disease	251 (5.5)	8 (5.5)	6 (6.7)	7 (4.4)	27 (10.0)	34 (6.1)	57 (5.0)	54 (5.2)	58 (4.9)	0.06
RA	110 (2.4)	<5	<5	<5	7 (2.6)	16 (2.9)	29 (2.5)	28 (2.7)	22 (1.8)	0.82
CKD	1321 (28.7)	48 (32.9)	23 (25.8)	57 (35.9)	92 (34.1)	174 (31.0)	270 (23.7)	272 (26.1)	385 (32.2)	<0.01

BMI = body mass index; BP = blood pressure; TC = total cholesterol; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PCI = percutaneous transluminal coronary intervention; PVD = peripheral vascular disease; RA = rheumatoid arthritis;

Figure 10-1 shows the risk of all-cause mortality in patients prescribed different numbers of cardiovascular medications. Compared with monotherapy, the risk of all-cause mortality was lower in patients with combination therapy: 53% (95% CI: 25%-71%) lower with two medications, 53% (95% CI: 29%-69%) lower with three medications, 71% (95% CI: 56%-81%) lower with four medications, 72% (95% CI: 58%-81%) lower with five medications, 62% (95% CI: 42%-75%) lower with six medications and 73% (95% CI: 59%-82%) lower with seven or more medications. Conversely, patients with no use of cardiovascular medications were associated with an increased risk of all-cause mortality (adjusted HR: 1.87, 95% CI: 1.24-2.82) compared with monotherapy. Figure 10-2 shows decreased risks of mortality in patients with two (adjusted HR: 0.52, 95% CI: 0.33-0.82), three (adjusted HR: 0.50, 95% CI: 0.32-0.76), four (adjusted HR: 0.25, 95% CI: 0.17-0.38), five (adjusted HR: 0.35, 95% CI: 0.23-0.54) and six (adjusted HR: 0.17, 95% CI: 0.08-0.37) specific classes of cardiovascular medications compared with patients prescribed one class. Patients with a six-class combination had the lowest risk of mortality but with wider CI.

Number of CV medications	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥7	107	2235	47.9	0.28 (0.20-0.40)	0.27 (0.18-0.41)
6	122	2508	48.6	0.30 (0.21-0.41)	0.38 (0.25-0.58)
5	141	3768	37.4	0.24 (0.17-0.33)	0.28 (0.19-0.42)
4	121	3394	35.6	0.24 (0.17-0.34)	0.29 (0.19-0.44)
3	110	1638	67.1	0.46 (0.33-0.65)	0.47 (0.31-0.71)
2	71	835	85.0	0.60 (0.42-0.87)	0.47 (0.29-0.75)
1	59	440	134.0	1	1
0	195	729	267.3	1.87 (1.37-2.56)	1.87(1.24-2.82)

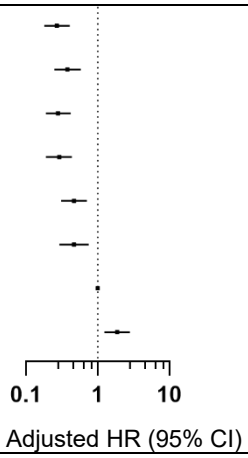


Figure 10-1 Risk of all-cause mortality in patients prescribed cardiovascular medications

Number of CV classes	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
6	17	456	37.3	0.17 (0.09-0.33)	0.17 (0.08-0.37)
5	63	2033	31.0	0.25 (0.18-0.36)	0.35 (0.23-0.54)
4	151	4205	35.9	0.17 (0.12-0.24)	0.25 (0.17-0.38)
3	205	4821	42.5	0.40 (0.28-0.57)	0.50 (0.32-0.76)
2	225	3545	63.5	0.55 (0.37-0.81)	0.52 (0.33-0.82)
1	141	1414	99.7	1	1
0	384	1585	242.3	2.02 (1.45-2.81)	2.05 (1.38-3.06)

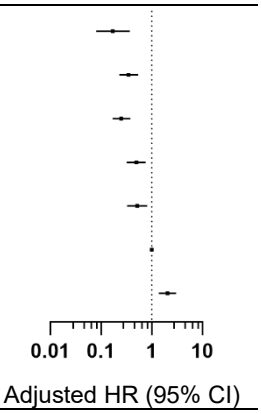


Figure 10-2 Risk of all-cause mortality in patients prescribed six specific classes of cardiovascular medications

Combination	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR	Adjusted HR
APAs+LRMs+ACEIs/ARBs+CCBs+BBs	21	925	22.7	0.06 (0.03-0.14)	0.08 (0.02-0.37)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs+BBs	9	473	19.0	0.12 (0.05-0.27)	0.11 (0.02-0.52)
APAs+LRMs+ACEIs/ARBs+BBs	59	2469	23.9	0.05 (0.02-0.09)	0.12 (0.04-0.40)
APAs+LRMs+ACEIs/ARBs+DRs	33	1583	20.8	0.21 (0.09-0.49)	0.13 (0.03-0.63)
APAs+LRMs+ACEIs/ARBs	20	577	34.7	0.09 (0.04-0.22)	0.18 (0.05-0.73)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs	9	245	36.7	0.22 (0.09-0.56)	0.22 (0.04-1.28)
APAs+ACEIs/ARBs+BBs	33	1012	32.6	0.19 (0.08-0.44)	0.23 (0.05-0.97)
APAs+LRMs+DRs+BBs	24	583	41.1	0.47 (0.23-0.96)	0.29 (0.08-1.05)
APAs+LRMs+CCBs+BBs	17	456	37.3	0.18 (0.05-0.62)	0.31 (0.05-1.92)
LRMs+ACEIs/ARBs+DRs+BBs	13	222	58.5	0.26 (0.09-0.73)	0.34 (0.06-1.97)
APAs+LRMs+ACEIs/ARBs+CCBs	21	429	48.9	0.21 (0.09-0.47)	0.35 (0.09-1.38)
APAs+LRMs+ACEIs/ARBs+DRs+BBs	97	1972	49.2	0.24 (0.13-0.43)	0.35 (0.11-1.09)
APAs+ACEIs/ARBs+DRs+BBs	26	324	80.2	0.45 (0.20-1.02)	0.37 (0.09-1.49)
APAs+ACEIs/ARBs+BBs	15	407	36.8	0.30 (0.15-0.60)	0.39 (0.11-1.37)
APAs+LRMs	24	399	60.2	0.37 (0.17-0.81)	0.39 (0.10-1.47)
LRMs+ACEIs/ARBs+BBs	26	353	73.7	0.13 (0.05-0.37)	0.41 (0.08-2.06)
APAs+BBs	13	208	62.5	0.33 (0.13-0.84)	0.44 (0.10-1.88)
LRMs+ACEIs/ARBs	17	230	74.0	0.23 (0.08-0.71)	0.45 (0.05-3.96)
APAs+LRMs+DRs	13	183	70.9	1.04 (0.49-2.21)	0.67 (0.19-2.44)
LRMs alone	17	182	93.2	0.52 (0.22-1.25)	0.89 (0.20-3.93)
APAs alone	69	579	119.2	1	1

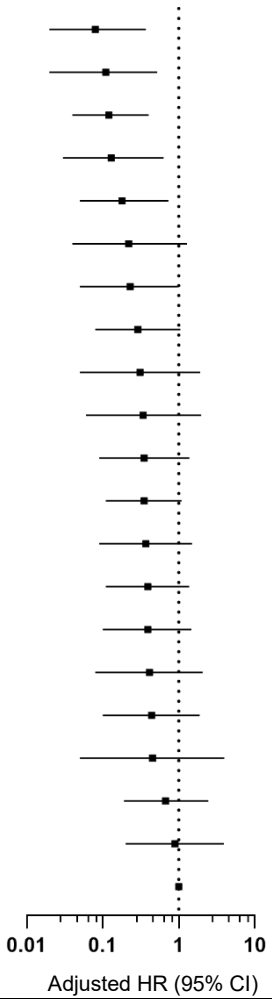


Figure 10-3 Risk of all-cause mortality in the 20 most commonly used regimens containing the six specific classes of cardiovascular medications compared with antiplatelet agents alone

In the analysis of the effect of the 20 most commonly used regimens containing APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs versus APAs alone, I found a lower risk of mortality in combinations containing APAs, LRMs, ACEIs/ARBs, BBs and CCBs(Figure 10-3). In patients with the combination treatment of APAs, LRMs, ACEIs/ARBs and BBs, the risk of mortality was lowered by 88% (95% CI: 60%-96%) compared with APAs alone. When adding CCB to the four-combination therapy, the combination was shown to be associated with the lowest risk of mortality (adjusted HR: 0.08, 95% CI: 0.02-0.37). The combination of the six classes medications also showed a lower HR of mortality but with wider confidence intervals (adjusted HR: 0.11, 95% CI: 0.02-0.52). Similarly, the combination containing APAs, LRMs, ACEIs/ARBs and DRs showed a lower HR of mortality but with wider confidence intervals (adjusted HR: 0.13, 95% CI: 0.03-0.63).

10.3.1 Sensitivity analyses

Results of sensitivity analyses are provided in Table 10-2 and Table 10-3. The primary results of the risk of mortality in patients with different numbers of CV medications and different numbers of classes of CV medications are similar to the results in the analysis using 60-day exposure window and the analysis categorising missing data as separate groups. The results showed an even lower risk of mortality in patients with combination therapy when the follow-up duration was divided into 3-month intervals. The E-values for the three main analyses of all-cause mortality ranged from 3.15 to 24.49.

Table 10-2 Risk of all-cause mortality in patients prescribed with various numbers of cardiovascular medications in sensitivity analyses.

	Adjusted HR (95% CI)			
Number of CV medications	**Primary analysis**	**60-day exposure window[a]**	**3-month interval[b]**	**Categorised missing data[d]**
≥7	0.27 (0.18-0.41)	0.33 (0.22-0.50)	0.19 (0.11-0.32)	0.27 (0.17-0.43)
6	0.38 (0.25-0.58)	0.45 (0.31-0.66)	0.23 (0.14-0.37)	0.38 (0.25-0.59)
5	0.28 (0.19-0.42)	0.38 (0.27-0.55)	0.16 (0.10-0.25)	0.31 (0.20-0.46)
4	0.29 (0.19-0.44)	0.29 (0.20-0.42)	0.17 (0.10-0.28)	0.29 (0.19-0.45)
3	0.47 (0.31-0.71)	0.56 (0.39-0.81)	0.35 (0.20-0.60)	0.53 (0.34-0.82)
2	0.47 (0.29-0.75)	0.42 (0.28-0.64)	0.35 (0.20-0.60)	0.49 (0.31-0.79)
1	1	1	1	1
0	1.87(1.24-2.82)	1.56 (1.11-2.20)	2.27 (1.47-3.51)	1.62 (1.06-2.46)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted in patients who had a history of ischemic stroke/TIA before the first MI event; [d]A sensitivity analysis conducted by categorising missing data as separate group.

Table 10-3 Risk of all-cause mortality in patients prescribed with various numbers of specific six classes of cardiovascular medications in sensitivity analyses.

	Adjusted HR (95% CI)			
Number of CV medications	**Primary analysis**	**60-day exposure window[a]**	**3-month interval[b]**	**Categorised missing data[d]**
6	0.17 (0.08-0.37)	0.17 (0.08-0.36)	0.04 (0.01-0.27)	0.14 (0.06-0.32)
5	0.35 (0.23-0.54)	0.35 (0.22-0.54)	0.20 (0.12-0.35)	0.31 (0.19-0.49)
4	0.25 (0.17-0.38)	0.25 (0.16-0.38)	0.12 (0.07-0.19)	0.23 (0.15-0.36)
3	0.50 (0.32-0.76)	0.48 (0.31-0.75)	0.33 (0.20-0.54)	0.50 (0.32-0.79)
2	0.52 (0.33-0.82)	0.52 (0.31-0.86)	0.31 (0.18-0.52)	0.53 (0.32-0.88)
1	1	1	1	1
0	2.05 (1.38-3.06)	1.35 (0.91-2.00)	2.28 (1.48-3.52)	1.69 (1.11-2.59)

[a]A sensitivity analysis conducted in a 60-day exposure period; [b]A sensitivity analysis conducted in 6-month intervals; [c]A sensitivity analysis conducted in patients who had a history of ischemic stroke/TIA before the first MI event; [d]A sensitivity analysis conducted by categorising missing data as separate group.

Figure 10-4 shows the results of the effect of combination therapy omitting one of the specific six classes(APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs) on all-

cause mortality compared to one class therapy. All combination therapy with two or more of the specific six classes appeared to reduce the risk of all-cause mortality by 69% (95% CI: 57%-78%). When removing LRMs, APAs, ACEIs/ARBs, CCBs or BBs combination therapy reduced the risk of all-cause mortality by 26% (95%CI: 6%-42%), 44% (28%-56%), 35% (19%-47%), 46% (34%-56%) or 59% (40%-72%), respectively. Combination therapy without DRs (adjusted HR: 0.24, 95% CI: 0.16-0.35) showed lower HRs for mortality. Figure 10-5 shows the results of the effect of combination therapy omitting one of the specific six classes (APAs, LRMs, ACEIs/ARBs, CCBs, thiazide-type DRs, and BBs) on all-cause mortality compared to one class therapy. The HR for all-cause mortality of the combination without LRMs (0.46, 95% CI: 0.26-0.81), ACEIs/ARBs (0.55, 95% CI: 0.34-0.88), or BBs (0.31, 95% CI: 0.17-0.57) still show significantly higher HRs than the HR for all combination therapy (0.27, 95% CI: 0.18-0.41).

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.40 (0.27-0.59)	0.37 (0.22-0.43)
Without LRMS	0.58 (0.40-0.83)	0.64 (0.42-0.97)
Without ACEIs/ARBs	0.65 (0.46-0.91)	0.55 (0.38-0.81)
Without CCB	0.28 (0.21-0.39)	0.36 (0.25-0.51)
Without **DRs**	0.27 (0.20-0.38)	0.24 (0.16-0.35)
Without BBs	0.42 (0.29-0.59)	0.41 (0.28-0.60)
All combinations (≥ 2 classes)	0.27 (0.20-0.36)	0.31 (0.22-0.43)

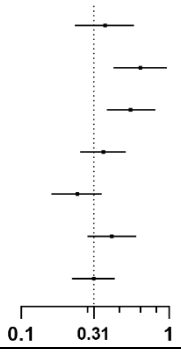


Figure 10-4 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.28 (0.16-0.49)	0.26 (0.14-0.49)
Without LRMS	0.39 (0.24-0.64)	0.46 (0.26-0.81)
Without ACEIs/ARBs	0.54 (0.35-0.83)	0.55 (0.34-0.88)
Without CCB	0.19 (0.13-0.28)	0.28 (0.18-0.43)
Without **thiazide-type DRs**	0.20 (0.14-0.29)	0.27 (0.18-0.41)
Without BBs	0.34 (0.22-0.53)	0.31 (0.17-0.57)
All combinations (≥ 2 classes)	0.20 (0.14-0.29)	0.27 (0.18-0.41)

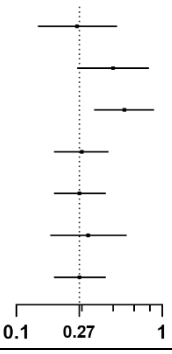


Figure 10-5 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

10.4 Discussion

This cohort study estimated the effectiveness of increasing numbers, classes and combinations of cardiovascular medications on all-cause mortality in patients with a history of type 2 diabetes after their incident MI event. The results showed that increasing the numbers and classes of cardiovascular medications appeared to produce additional benefits on long-term survival. APAs, LRMs, ACEIs/ARBs, CCBs and BBs appeared to be the optimal constituents of combination therapy associated with reduced risk of mortality after MI.

Similar to the results in the study for patients with incident MI (Chapter 8), this study found that compared with monotherapy, multiple pharmacological interventions can provide potentially greater benefits on long-term survival for type 2 diabetic patients after their incident MI events.

APAs, LRMs, ACEIs and BBs are recommended by international guidelines and the combination of the four medication is normally considered as evidence-based pharmacotherapy for secondary prevention after MI(Skinner et al., 2007; World Health Organisation, 2002). In my systematic review, APAs have been suggested to be an important constituent in the EBCP. However, the present study assessed the weight of each class in combination therapy and found that APAs made a moderate contribution in combination therapy on the reduced risk of all-cause mortality in patients with diabetes after MI (Figure 10-4 and 10-5). Platelets play a key role in the development of atherosclerosis and its atherothrombotic complications. In type 2 diabetic patients, platelets have been proven to be hyperreactive with intensified adhesion, activation and aggregation(Creager et al.,

2003; Ferroni et al., 2004). Besides, there is a reduced clinical efficacy ("resistance") of antiplatelet therapy in patients with diabetes, which is well established to be associated with a poor prognosis of CVD(Angiolillo, 2009). Although impaired beneficial effects on outcomes, antiplatelet therapy still plays a pivotal role in secondary prevention of MI with diabetes. Treatment strategies to optimise platelet inhibitory effects are specially required in this group of patients. Accelerated atherosclerosis in patients with diabetes is also attributable to worsening of dyslipidemia, especially the development of atherogenic dyslipidemia (elevated plasma triglyceride levels, low levels of high-density lipoprotein cholesterol, and small, dense low-density lipoprotein particles)(Schmieder et al., 2009). Strong evidence from RCTs has suggested that cholesterol-lowering therapy was associated with reduced risk of vascular mortality and major vascular events in patients with diabetes compared with individuals without diabetes(Cholesterol Treatment Trialists' (CTT) Collaborators; et al., 2008). Consistently, my results have shown that LRMs played a key role in combination therapy to improve the long-term survival in patients with diabetes after their incident MI events. The present study also suggested that ACEIs/ARBs were possibly one of the most important constituents in combination therapy. ACEIs have been well established to decrease the risk of death and cardiovascular events after MI(Domanski et al., 1999) and patients with diabetes(Cheng et al., 2014). In addition, some studies have shown that ACEIs had the ability to improve glycemic control(Fogari et al., 1998) and protect renal function(Lewis et al., 1993) in type 2 diabetic patients. BBs are one of the evidence-based medications and are

recommended by guidelines for the secondary prevention of MI. It has traditionally applied with cautions for patients with diabetes, because the first and second generation BBs are associated with increased insulin resistance, causing an increase in serum glucose and triglycerides, and a decrease in HDL levels(Bell, 2003). Even though the third generation BBs circumvent these problems(Giugliano, 1997), the second generation BBs are still the most commonly used BBs in "real-world" practice based on the results from my drug utilization study (Chapter 5). In the present study, BBs appeared to confer additive benefit in combination therapy on the decreased risk of mortality. Hypertension is an important risk factor for MI, and is highly prevalent in patients with diabetes(Colosia et al., 2013). In the present study, 71.7% of study patients had hypertension at their first MI events. Thiazide-type DRs and CCBs have been proven to be acceptable initial antihypertensive agents for patients with diabetes. In a meta-analysis of RCTs, CCBs were shown to be the preferred treatment in combination with ACEIs if blood pressure cannot be adequately control by ACEIs alone(H.-Y. Wu et al., 2013). The present study found that CCBs conferred additive survival benefit in combination therapy, but unclear effects with DRs. In summary, APAs, LRMs, ACEIs/ARBs, CCBs and BBs were proven to be optimal components in combination therapy associated with reduced risk of mortality among type 2 diabetic patients after incident MI.

10.4.1 Strengths and limitations

In addition to the strengths presented in "Chapter 9, 9.4.1", this study has some more strengths. Firstly, this study comprehensively assessed the effect of different combinations among MI patients with a comorbid type 2 DM. Secondly, this study

controlled for some diabetic-related time-invariant and time-varying confounders, including HbA1c value, duration of diabetes, previous use of diabetes medications.

This study has some limitations besides that presented in “Chapter 9, 9.4.1”. First, this study did not estimate the individual effect of ACEIs and ARBs in combination therapy on long-term survival. Secondly, this study did not investigate the effect of different generations of BBs on long-term outcomes due to the research complexity and time constraints. Further studies are required to explore this area. Thirdly, this study only focuses on cardiovascular medications; thus, the study cannot determine the effect of different antidiabetic medications or their potential interaction with cardiovascular medications on long-term survival in patients with MI and DM. Further studies are required in this area.

10.5 Conclusion

My study suggests that combination therapy of four cardiovascular medications may improve long-term survival in patients with MI and type 2 diabetes. APAs, LRMs, ACEIs/ARBs, BBs and CCBs were probably the optimal constituents of combination therapy in the present study

Chapter 11: Impact of multiple cardiovascular medications on mortality in patients with myocardial infarction and chronic obstructive pulmonary disease

11.1 Introduction

CVD is a leading cause of death in people with chronic obstructive pulmonary disease (COPD), with up to one-third dying of CVD(Sin et al., 2006). Ischaemic heart disease and COPD are the first and third leading cause of death in the world(World Health Organization, 2020). Some clinical and epidemiologic evidence has demonstrated an association between the two diseases(DRAKE, 1951; Thomas, 1958). Several studies have found a higher risk of MI and a higher risk of death following MI in people with COPD than without(Curkendall et al., 2006; Feary et al., 2010; Rothnie et al., 2015; Stefan et al., 2012). MI and COPD share the major important risk factor, smoking. In addition, some traditional risk factors of MI are also common in patients with COPD, including hypertension, hypercholesterolemia, diabetes and older age(Divo et al., 2012; Mannino et al., 2008). Moreover, some evidence has shown that COPD-specific systemic inflammation might independently worsen prognosis after MI(Bäck, 2008; Ross, 1999). Patients with COPD should be treated according to usual guidelines for secondary prevention after MI(National Institute for Health and Care Excellence, 2020c). Despite the clear evidence of the effects and safety of beta-blockers and other cardiovascular medications, some prior studies have shown a general

reluctance to use them in patients with COPD for secondary prevention after MI(Kvan et al., 2006; S.R Salpeter et al., 2003; Stefan et al., 2012). In my drug utilization study (Chapter 5), patients with CVD and COPD were less likely to receive five or more cardiovascular medications than those without COPD. There is little evidence that patients with MI should be treated differently in the presence of COPD. It is unclear whether different single cardiovascular medications in combination therapy confer an additive benefit on long-term survival in COPD patients after MI. Further, the optimal constituents of combination therapy have not been well recognised. Therefore, this study aimed to investigate the effect of multiple cardiovascular medications on long-term survival in patients with COPD after their incident MI event.

11.2 Method

The study cohort design, exposure definition, data extraction and statistical analysis refer to **Chapter 6**, 6.2 Methods.

11.2.1 Study population

This study included patients with a first diagnosis of MI between January 2007 and December 2016, and with a history of COPD before their first MI event. Inclusion criteria included patients who were aged 45 or above and who had been registered for at least three years in the THIN database before the first MI event. I excluded patients who died or who had an occurrence of a further cardiovascular event within the first 90 days following their incident MI event. Patients were followed from the initial event until the end of December 2016 and were censored if they left

their general practice during the study period. The outcome was all-cause mortality. For each patient, the follow-up was divided into contiguous periods of six months, each defined with specific entry and exit points.

11.2.2 Data extraction and confounders

The data of demographic and clinical characteristics six months prior to each entry point and prescriptions three months prior to each entry point were extracted from the THIN database. In addition to variables mentioned in "**Chapter 6**, 6.2.6 Data extraction and confounders", Haemoglobin A1c (HbA1c) value, duration of diabetes, previous use of diabetes medications were also included as confounders. Diabetes medications were identified based on medications classified in the BNF Chapter 6.1: Drugs used in diabetes.

11.2.3 Sensitivity analysis

The E-value method was used to assess the robustness of findings due to unmeasured confounding. A sensitivity analysis was conducted to evaluate the effect of combination therapy (⩾2 classes) omitting one class compared with one class. In addition, to assess the role of thiazide-type diuretics in the combination therapy, I repeated the fifth sensitivity analysis by only keeping thiazide-type DRs from the overall DRs.

11.3 Results

The study consisted of 2893 men (62.8%) and 1711 women (37.2%) who had experienced the initial MI event from 1 January 2007 to 31 December 2016 and

who had a history of COPD before the initial MI event. Overall, 3.2% of patients did not receive cardiovascular medications, 1.9% received one, 3.5% received two, 5.9% received three, 12.2% received four, 24.8% received five, 22.6% of patients received six, and 26.0% received seven or more cardiovascular medications during the 90 days following their initial MI event.

The mean age at the start of follow-up was 69.8 (SD, 11.5) years, and the mean follow-up time was 3.4 (SD, 2.5) years. In total, the study recorded 926 deaths during the follow-up, and the crude death rate was 59.6/1000 person-years. Table 11-1 shows the baseline characteristics of the patients at their initial MI events based on the number of cardiovascular medications received during the first 90 days.

Table 11-1 Baseline characteristics of study patients at their initial MI events, 2007-2016.

	Cardiovascular treatment groups									
No. of CV medications	**Total**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**≥7**	**P value**
	n = 2847	n = 117 (4.1)	n = 67 (2.4)	n = 137 (4.8)	n = 217 (7.6)	n = 435 (15.3)	n = 767 (26.9)	n = 574 (20.2)	n = 533 (18.7)	
Sex, %										
Men	1576 (55.4)	64 (54.7)	30 (44.8)	70 (51.1)	115 (53.0)	233 (53.6)	436 (56.8)	333 (58.0)	295 (55.4)	0.38
Women	1271 (44.6)	53 (45.3)	37 (55.2)	70 (48.9)	102 (47.0)	202 (46.4)	331 (43.2)	241 (42.0)	238 (44.7)	
Age, (years) mean ± SD	72.0 ± 10.1	74.6 ± 10.1	74.0 ± 10.2	72.5± 11.0	74.1 ± 9.5	72.5 ± 10.4	71.2 ± 10.2	70.9 ± 10.2	72.3± 9.8	<0.01
Smoking (%)										
Current	1051 (36.9)	51 (43.6)	23 (34.3)	54 (39.4)	71 (32.7)	164 (37.7)	286 (37.3)	221 (38.5)	181 (34.0)	0.09
Former	1416 (49.7)	51 (43.6)	40 (59.7)	67 (48.9)	114 (52.5)	215 (49.4)	388 (50.6)	273 (47.6)	268 (50.3)	
Never	360 (12.6)	14 (12.0)	3 (4.5)	14 (10.2)	31 (14.3)	48 (11.0)	91 (11.9)	77 (13.4)	82 (15.4)	
Missing	20 (0.7)	<5	<5	<5	<5	8 (1.8)	<5	<5	<5	
Alcohol (%)										
Current	1361 (47.8)	53 (45.3)	36 (53.7)	59 (43.1)	102 (47.0)	204 (46.9)	380 (49.5)	278 (48.4)	249 (46.7)	0.39
Former	172 (6.0)	5 (4.3)	6 (9.0)	14 (10.2)	9 (4.2)	29 (6.9)	42 (5.5)	31 (5.4)	36 (6.8)	
Never	508 (17.8)	21 (18.0)	10 (14.9)	16 (11.7)	43 (19.8)	76 (17.5)	126 (16.4)	107 (18.6)	109 (20.5)	
Missing	806 (28.3)	38 (32.5)	15 (22.4)	48 (35.0)	63 (29.0)	126 (29.0)	219 (28.6)	158 (27.5)	139 (26.1)	
BMI status (%)										
Normal (18.5-24.9 kg/m2)	865 (30.4)	38 (32.5)	19 (28.4)	42 (30.7)	84 (38.7)	146 (33.6)	242 (31.6)	176 (30.7)	118 (22.1)	<0.01
Overweight (25.0-29.9 kg/m2)	840 (29.5)	27 (23.1)	21 (31.3)	37 (27.0)	58 (26.7)	124 (28.5)	252 (32.9)	166 (28.9)	155 (29.1)	
Obesity (≥ 30.0 kg/m2)	675 (23.7)	23 (19.7)	13 (19.4)	24 (17.5)	31 (14.3)	91 (20.9)	151 (19.7)	153 (26.7)	189 (35.5)	
Missing	324 (11.4)	15 (12.8)	7 (10.5)	27 (19.7)	27 (12.4)	45 (10.3)	89 (11.6)	62 (10.8)	52 (9.8)	

BP status (%)										
Normal (BP < 140/90 mmHg)	1592 (55.9)	74 (63.3)	37 (55.2)	89 (65.0)	121 (55.8)	265 (60.9)	401 (52.3)	297 (51.7)	645 (57.8)	0.13
Stage 1 hypertension (BP ≥ 140/90 mmHg)	920 (32.3)	28 (23.9)	23 (34.3)	40 (29.2)	82 (37.8)	123 (28.3)	256 (33.4)	200 (34.8)	168 (31.5)	
Stage 2 hypertension (BP ≥ 160/100 mmHg)	235 (8.3)	11 (9.4)	5 (7.5)	6 (4.4)	11 (5.1)	33 (7.6)	74 (9.7)	53 (9.2)	42 (7.9)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	58 (2.0)	4 (3.4)	<5	0	<5	7 (1.6)	19 (2.5)	15 (2.6)	8 (1.5)	
Missing	37 (1.3)	0	0	2	0	7 (1.6)	14 (1.8)	8 (1.4)	6 (1.1)	
TC status (%)										
Optimal (<5.2 mmol/L)	1227 (43.1)	50 (42.7)	23 (34.3)	57 (41.6)	95 (43.8)	171 (39.3)	320 (41.7)	235 (40.9)	276 (51.8)	<0.01
Intermediate (5.3-6.2 mmol/L)	645 (22.7)	33 (28.2)	15 (22.4)	21 (15.3)	43 (19.8)	101 (23.2)	170 (22.2)	149 (26.0)	113 (21.2)	
High (>6.2 mmol/L)	351 (12.3)	12 (10.3)	9 (13.4)	19 (13.9)	26 (12.0)	50 (11.5)	100 (13.0)	73 (12.7)	62 (11.6)	
Missing	624 (21.9)	22 (18.8)	20 (29.9)	40 (29.2)	53 (24.4)	113 (26.0)	177 (23.1)	117 (20.4)	82 (15.4)	
Townsend score (%)										
1 (least deprived)	370 (13.0)	18 (15.4)	11 (16.4)	12 (8.8)	31 (14.3)	52 (12.0)	97 (12.7)	82 (14.3)	67 (12.6)	0.30
2	441 (15.5)	20 (17.1)	9 (13.4)	18 (13.1)	33 (15.2)	89 (20.5)	121 (15.8)	84 (14.6)	67 (12.6)	
3	546 (19.2)	19 (16.2)	15 (22.4)	25 (18.3)	37 (17.1)	76 (17.5)	150 (19.6)	126 (22.0)	98 (18.4)	
4	601 (21.1)	25 (21.4)	12 (17.9)	38 (27.7)	52 (24.0)	86 (19.8)	151 (19.7)	112 (19.5)	125 (23.5)	
5 (most deprived)	532 (18.7)	17 (14.5)	15 (22.4)	28 (20.4)	41 (18.9)	88 (20.2)	136 (17.7)	104 (18.1)	103 (19.3)	
Missing	357 (12.5)	18 (15.4)	5 (7.5)	16 (11.7)	23 (10.6)	44 (10.1)	112 (14.6)	66 (11.5)	73 (13.7)	
History of PCI (%)	320 (11.2)	7 (6.0)	<5	6 (4.4)	6 (2.8)	56 (12.9)	114 (14.9)	77 (13.4)	50 (9.4)	
Comorbidity										
Hypertension	1464 (51.4)	63 (53.9)	33 (49.3)	55 (40.2)	101 (46.5)	192 (44.1)	353 (46.0)	322 (56.1)	345 (64.7)	<0.01
Hyperlipidaemia	410 (14.4)	17 (14.5)	14 (20.9)	22 (16.1)	27 (12.4)	54 (12.4)	102 (13.3)	80 (13.9)	94 (17.6)	0.19

Arrhythmia	383 (13.5)	16 (13.7)	8 (11.9)	19 (13.9)	31 (14.3)	53 (12.2)	84 (11.0)	78 (13.6)	94 (17.6)	0.07
Heart Failure	430 (15.1)	11 (9.4)	7 (10.5)	23 (16.8)	24 (11.1)	59 (13.6)	90 (11.7)	89 (15.5)	127 (23.8)	<0.01
PVD	339 (11.9)	22 (18.8)	7 (10.5)	15 (11.0)	34 (15.7)	46 (10.6)	70 (9.1)	64 (11.2)	81 (15.2)	<0.01
Diabetes	494 (17.4)	12 (10.3)	11 (16.4)	21 (15.3)	39 (18.0)	62 (14.3)	109 (14.2)	103 (17.9)	137 (25.7)	<0.01
Dementia	53 (1.9)	5 (4.3)	0	<5	8 (3.7)	12 (2.8)	17 (2.2)	3 (0.5)	4 (0.8)	<0.01
Asthma	1278 (44.9)	52 (44.4)	30 (44.8)	65 (47.5)	104 (47.9)	190 (43.7)	344 (44.9)	261 (45.5)	232 (43.5)	0.96
Peptic ulcer disease	252 (8.9)	14 (12.0)	7 (10.5)	16 (11.7)	16 (7.4)	43 (9.9)	74 (9.7)	39 (6.8)	43 (8.1)	0.32
RA	119 (4.2)	<5	6 (9.0)	6 (4.4)	11 (5.1)	16 (3.7)	31 (4.0)	25 (4.4)	20 (3.8)	0.66
CKD	554 (19.5)	19 (16.2)	17 (25.4)	30 (21.9)	52 (24.0)	81 (18.6)	115 (15.0)	112 (19.5)	128 (24.0)	<0.01

BMI = body mass index; BP = blood pressure; TC = total cholesterol; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PCI = percutaneous transluminal coronary intervention; PVD = peripheral vascular disease; RA = rheumatoid arthritis;

Figure 11-1 shows the risk of all-cause mortality in patients prescribed with different numbers of cardiovascular medications. Compared with monotherapy, the risk of all-cause mortality was lower in patients with combination therapy: 53% (95% CI: 25%-71%) lower with two medications, 53% (95% CI: 29%-69%) lower with three medications, 71% (95% CI: 56%-81%) lower with four medications, 72% (95% CI: 58%-81%) lower with five medications, 62% (95% CI: 42%-75%) lower with six medications and 73% (95% CI: 59%-82%) lower with seven or more medications. Conversely, patients with no use of cardiovascular medications were associated with an increased risk of all-cause mortality (adjusted HR: 1.87, 95% CI: 1.24-2.82) compared with monotherapy. Figure 11-2 shows decreased risks of mortality in patients with two (adjusted HR: 0.52, 95% CI: 0.33-0.82), three (adjusted HR: 0.50, 95% CI: 0.32-0.76), four (adjusted HR: 0.25, 95% CI: 0.17-0.38), five (adjusted HR: 0.35, 95% CI: 0.23-0.54) and six (adjusted HR: 0.17, 95% CI: 0.08-0.37) specific classes of cardiovascular medications compared with patients prescribed one class. Patients with a six-class combination had the lowest risk of mortality but with wider CI.

Number of CV medications	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥7	62	934	66.4	0.42 (0.28-0.62)	0.41 (0.26-0.64)
6	72	1142	63.0	0.40 (0.27-0.59)	0.38 (0.24-0.59)
5	120	2002	59.9	0.38 (0.27-0.55)	0.40 (0.27-0.61)
4	118	2234	52.8	0.35 (0.25-0.51)	0.38 (0.25-0.57)
3	117	1373	85.2	0.59 (0.41-0.85)	0.53 (0.35-0.79)
2	79	673	117.3	0.80 (0.54-1.17)	0.70 (0.45-1.09)
1	46	326	141.2	1	1
0	165	488	338.3	2.46 (1.72-3.53)	2.30(1.50-3.52)

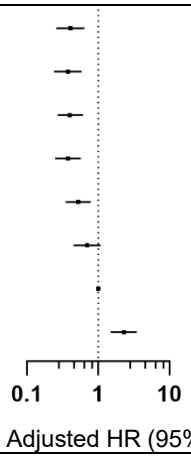


Figure 11-1 Risk of all-cause mortality in patients prescribed cardiovascular medications

Number of CV classes	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
6	2	77	25.8	0.15 (0.04-0.61)	0.16 (0.03-0.75)
5	45	832	54.1	0.32 (0.21-0.49)	0.34 (0.21-0.55)
4	80	2145	37.3	0.22 (0.15-0.32)	0.26 (0.17-0.40)
3	97	1423	68.2	0.42 (0.29-0.61)	0.45 (0.30-0.68)
2	72	645	111.6	0.70 (0.47-1.03)	0.65 (0.42-1.01)
1	47	307	152.9	1	1
0	165	488	338.3	2.26 (1.59-3.23)	2.13 (1.41-3.23)

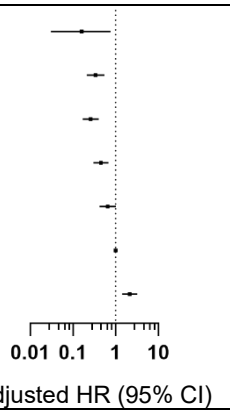


Figure 11-2 Risk of all-cause mortality in patients prescribed six specific classes of cardiovascular medications

Combination	Number of deaths	Person-years	Mortality (per 1000 person-years)	Crude HR	Adjusted HR
APAs+LRMs+ACEIs/ARBs+CCBs+DRs+BBs	2	77	9.4	0.13 (0.03-0.59)	0.09 (0.02-0.50)
APAs+LRMs+ACEIs/ARBs+BBs	23	1134	7.4	0.11 (0.06-0.20)	0.15 (0.05-0.40)
APAs+LRMs+ACEIs/ARBs+CCBs	12	411	10.7	0.16 (0.07-0.35)	0.15 (0.04-0.56)
APAs+LRMs+ACEIs/ARBs+CCBs+BBs	4	159	9.2	0.13 (0.04-0.40)	0.15 (0.04-0.61)
APAs+LRMs+ACEIs/ARBs+DRs	14	265	19.3	0.28 (0.13-0.58)	0.18 (0.06-0.53)
APAs+LRMs+ACEIs/ARBs+DRs+BBs	26	485	19.6	0.29 (0.15-0.55)	0.23 (0.08-0.61)
APAs+LRMs+ACEIs/ARBs	23	555	15.1	0.23 (0.12-0.45)	0.24 (0.09-0.63)
APAs+LRMs+BBs	15	249	22.0	0.34 (0.16-0.70)	0.26 (0.09-0.74)
APAs+ACEIs/ARBs+DRs+BBs	5	51	35.6	0.51 (0.18-1.46)	0.26 (0.06-1.08)
APAs+LRMs+DRs	10	78	46.7	0.73 (0.32-1.66)	0.27 (0.08-0.88)
APAs+LRMs	14	238	21.4	0.34 (0.16-0.72)	0.28 (0.10-0.76)
APAs+ACEIs/ARBs+BBs	6	90	24.4	0.37 (0.15-0.93)	0.31 (0.08-1.24)
APAs+LRMs+ACEIs/ARBs+CCBs+DRs	13	161	29.5	0.47 (0.22-1.00)	0.37 (0.12-1.16)
APAs+LRMs+ACEIs/ARBs+DRs	8	105	27.8	0.44 (0.18-1.07)	0.37 (0.07-1.92)
APAs+ACEIs/ARBs+DRs	9	60	54.8	0.81 (0.36-1.81)	0.46 (0.12-1.68)
LRMs+ACEIs/ARBs+BBs	5	91	20.1	0.31 (0.11-0.84)	0.50 (0.11-2.23)
LRMs	4	69	21.1	0.33 (0.11-1.04)	0.50 (0.09-2.87)
APAs+ACEIs/ARBs	11	85	47.0	0.76 (0.35-1.63)	0.60 (0.19-1.94)
APAs+LRMs+DRs+BBs	19	98	70.8	1.10 (0.54-2.25)	0.71 (0.22-2.32)
LRMs+ACEIs/ARBs	9	71	46.6	0.73 (0.30-1.73)	0.87 (0.23-3.323)
APAs alone	17	103	60.2	1	1

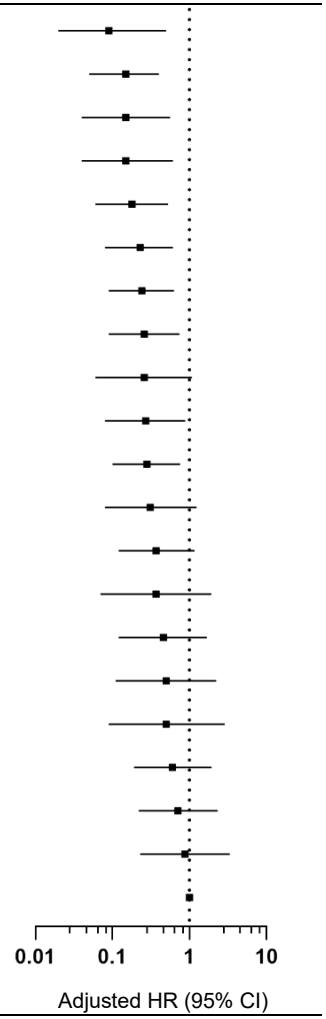


Figure 11-3 Risk of all-cause mortality in the 20 most commonly used regimens containing the six specific classes of cardiovascular medications compared with antiplatelet agents alone

In the analysis of the effect of the 20 most commonly used regimens containing APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs versus APAs alone, I found a significantly lower risk of mortality in combinations containing APAs, LRMs, ACEIs/ARBs, BBs and CCBs (Figure 11-3). In patients with the combination treatment of APAs, LRMs, ACEIs/ARBs and BBs, the risk of mortality was lowered by 88% (95% CI: 60%-96%) compared with APAs alone. When adding CCB to the four-combination therapy, the combination appeared to be associated with the lowest risk of mortality (adjusted HR: 0.08, 95% CI: 0.02-0.37). The combination of the six classes medications also showed a lower HR of mortality but with wider confidence intervals (adjusted HR: 0.11, 95% CI: 0.02-0.52). Similarly, the combination containing APAs, LRMs, ACEIs/ARBs and DRs showed a lower HR of mortality but with wider confidence intervals (adjusted HR: 0.13, 95% CI: 0.03-0.63).

11.3.1 Sensitivity analyses

Figure 11-4 shows the results of the effect of combination therapy omitting one of the specific six classes (APAs, LRMs, ACEIs/ARBs, CCBs, DRs, and BBs) on all-cause mortality compared to one class therapy. All combination therapy with two or more of the specific six classes appeared to reduce the risk of all-cause mortality by 69% (95% CI: 57%-78%). When removing LRMs, APAs, ACEIs/ARBs or CCBs, combination therapy reduced the risk of all-cause mortality by 26% (95%CI: 6%-42%), 44% (28%-56%), 35% (19%-47%) or 46% (34%-56%), respectively. Combination therapy without DRs (adjusted HR: 0.47, 95% CI: 0.38-0.59) or BBs

(adjusted HR: 0.46, 95% CI: 0.37-0.57) showed lower HRs for mortality. Figure 11-5 shows the results of the effect of combination therapy omitting one of the specific six classes (APAs, LRMs, ACEIs/ARBs, CCBs, thiazide-type DRs, and BBs) on all-cause mortality compared to one class therapy. The HR for all-cause mortality of the combination without thiazide-type DRs (adjusted HR: 0.51, 95% CI: 0.40-0.64) was higher than the HR of all combination therapy (adjusted HR: 0.46, 95% CI: 0.38-0.58). The result was similar to the combination without CCBs (adjusted HR: 0.50, 95% CI: 0.40-0.63). The E-values for the three main analyses of all-cause mortality ranged from 3.15 to 24.49.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.40 (0.27-0.59)	0.37 (0.22-0.43)
Without LRMS	0.58 (0.40-0.83)	0.64 (0.42-0.97)
Without ACEIs/ARBs	0.65 (0.46-0.91)	0.55 (0.38-0.81)
Without CCB	0.28 (0.21-0.39)	0.36 (0.25-0.51)
Without **DRs**	0.27 (0.20-0.38)	0.24 (0.16-0.35)
Without BBs	0.42 (0.29-0.59)	0.41 (0.28-0.60)
All combinations (≥ 2 classes)	0.27 (0.20-0.36)	0.31 (0.22-0.43)

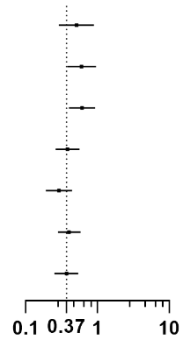


Figure 11-4 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

Combination therapy with the specific six classes	Crude HR (95% CI)	Adjusted HR (95% CI)
Without APAs	0.26 (0.09-0.75)	0.47 (0.22-1.00)
Without LRMS	0.52 (0.23-1.19)	0.48 (0.26-0.92)
Without ACEIs/ARBs	0.38 (0.18-0.82)	0.50 (0.29-0.86)
Without CCB	0.30 (0.15-0.60)	0.39 (0.24-0.63)
Without **thiazide-type DRs**	0.28 (0.14-0.55)	0.35 (0.22-0.56)
Without BBs	0.36 (0.18-0.73)	0.51 (0.31-0.83)
All combinations (≥ 2 classes)	0.28 (0.14-0.56)	0.37 (0.23-0.58)

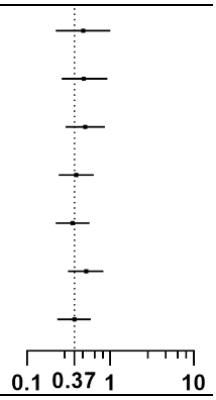


Figure 11-5 Effect of combination therapy omitting one of the specific six classes of cardiovascular medications compared to one class on all-cause mortality.

11.4 Discussion

This cohort study estimated the effectiveness of increasing numbers, classes and combinations of cardiovascular medications on all-cause mortality in patients with COPD after their incident MI event. The results showed that increasing the numbers and classes of cardiovascular medications appeared to produce additional benefits on long-term survival. APAs, LRMs, ACEIs/ARBs, CCBs and BBs appeared to be the optimal constituents of combination therapy associated with reduced risk of mortality after MI.

This study found that compared with monotherapy, combination therapy with more than three medications can provide potentially greater benefits on long-term survival for COPD patients after their incident MI events. Contrary to combination therapy, patients with no use of cardiovascular medications had up to three times higher risk of mortality than monotherapy.

APAs, LRMs, ACEIs and BBs are recommended by international guidelines, and the combination of the four medication is normally considered as EBCP for secondary prevention after MI(Skinner et al., 2007; World Health Organisation, 2002). Some evidence has shown that COPD-related systemic inflammatory status may affect platelet reactivity and responsiveness to antiplatelet agents(Campo et al., 2014; R. Wang et al., 2013). Gianluca *et al.* found that on-treatment platelet reactivity is significantly higher in COPD patients undergoing PCI. Lower drug responsiveness was also observed in COPD patients on dual antiplatelet therapy (aspirin + clopidogrel) compared with patients without COPD(Campo et al., 2014). In the present study, APAs are shown to be an

important constituent in combination therapy to reduce all-cause mortality. This indicates that antiplatelet therapy still plays a pivotal role in secondary prevention after MI in COPD patients. My results found that LRMs played a key role in combination therapy, reducing the risk of all-cause mortality. Several previous studies have also suggested that statin treatment can improve survival among COPD patients(Cao et al., 2015). In addition, some studies have reported that statins may be associated with an anti-inflammatory effect in the lungs and the airways(J.-H. Lee et al., 2005), lower incidence of exacerbations(Blamoun et al., 2008; M.-T. Wang et al., 2013) and lower risk of MI(Mancini et al., 2006; Sheng et al., 2012) in COPD patients. In the present study, ACEIs/ARBs was proven to be one of the most important constituents in the combination therapy. Several observational studies reported that ACEIs/ARBs were associated with decreased pneumonia and mortality in patients with COPD(Lai et al., 2018; Mancini et al., 2006; Mortensen et al., 2009; Su et al., 2019). However, there is still a lack of evidence from RCTs to examine the effect of ACEIs/ARBs on outcomes in COPD patients after MI. In addition, two studies found that ARBs appeared to be associated with better survival outcomes than ACEIs(Mancini et al., 2006; Su et al., 2019). Patients receiving ARBs were also less likely to have cough compared with those receiving ACEIs(Caldeira et al., 2012). There is little evidence of whether ARBs were superior to ACEIs on long-term survival in COPD patients after MI. Further research is required in this area. Beta-blocker therapy is one of the evidence-based medications and is recommended by guidelines for the secondary prevention after MI. It has traditionally been considered contraindicated in patients

with COPD, because cases of acute bronchospasm were reported during non-cardiovascular BBs use(Chobanian, 2003; Tattersfield, 1991; Woolcock et al., 1991). A meta-analysis of RCTs has suggested that cardioselective BBs do not produce a significant reduction in airway function or increase the incidence of COPD exacerbations in COPD patients(S.R Salpeter et al., 2003). Clear evidence from observational studies has also demonstrated the use of BBs is associated with improved survival after MI in patients with COPD(Coiro et al., 2017; Gottlieb et al., 1998; Quint et al., 2013). Consistently, results in the present study also found BBs produced additive benefits in combination therapy on long-term survival after MI in patients with COPD. However, the use of BBs remains low, with only 55.7% of COPD patients received BBs following their first MI in this study. Base on existing evidence, clinicians should try to initiate selective BBs in secondary prevention of MI in COPD patients instead of withholding BBs for fear of side-effects. Hypertension is an important risk factor for MI. Besides ACEIs/ARBs, DRs and CCBs have been proven to be acceptable initial antihypertensive agents. There is still a lack of outcome data from RCTs designed to evaluate the effects of diuretics and CCBs in the treatment of hypertension in patients with COPD(Dart et al., 2003). In this study, CCBs showed a moderately additive benefit in combination therapy on long-term survival after MI in COPD patients. In summary, evidence-based medications (APAs, LRMs, ACEIs/ARBs and BBs) were proven to be central components in combination therapy associated with reduced risk of mortality after MI in COPD patients. CCBs can provide additive benefits, combined with the previous four components.

11.4.1 Strengths and limitations

In addition to the strengths presented in “Chapter 9, 9.4.1”, this study has some more strengths. Firstly, this study firstly comprehensively assessed the effect of different combinations among MI patients with a comorbid COPD. Secondly, this study controlled for some COPD-related time-invariant and time-varying confounders, including FEV1, duration of COPD, records of exacerbations, previous use of medications for COPD.

This study has some limitations besides that presented in “Chapter 9, 9.4.1”. Firstly, this study did not estimate the individual effect of ACEIs and ARBs in combination therapy on long-term survival. It is still unknown if ARBs were superior to ACEIs on long-term survival in MI patients with COPD. Secondly, this study did not investigate the effect of cardioselective BBs on long-term outcomes. Further studies are required to explore this area. Thirdly, this study only focuses on cardiovascular medications; thus, the study cannot determine the effect of different medications for COPD or their potential interaction with cardiovascular medications on long-term survival in patients with MI and COPD. Further studies are required in this area. Finally, the power of this study was still limited. Some results had a wide CI due to relatively small sample size. However, the main results still had a clear direction to show the effect of the exposure of interest on the outcome. Further studies in a large population are encouraged to confirm the study findings.

11.5 Conclusion

My study suggests that combination therapy of four cardiovascular medications may be optimal for long-term survival in patients with MI and COPD. APAs, LRMs, ACEIs/ARBs and BBs were the optimal constituents of combination therapy in the present study.

Chapter 12: Overall discussion

This PhD research focused on cardiovascular polypharmacy in patients with CHD or stroke. Firstly, a systematic review and meta-analysis was conducted to assess the impact of the EBCP on mortality and cardiovascular events in secondary prevention of CVD (Chapter 2). This was followed by a drug utilisation study to investigate the initial prescription patterns of CV medications in the first 90 days following the incident CHD or stroke and estimate the association between potential risk factors and cardiovascular polypharmacy (Chapter 5). The impact of multiple CV medications on long-term survival was then assessed in all patients following their incident ischemic stroke/TIA (Chapter 6) and those with co-morbidities of type 2 diabetes (Chapter 7) or COPD (Chapter 8). This was followed by a study to investigate the impact of multiple CV medications on long-term survival among patients following their incident MI (Chapter 9) and those with co-morbidities of type 2 diabetes (Chapters 10) or COPD (Chapter 11). This chapter presents the key findings of this PhD research, implications for clinical practice, strengths and limitations, recommendations for future research, and also highlights contribution to current knowledge.

12.1 Overview of the key findings

12.1.1 Effect of evidence-based therapy for secondary prevention of cardiovascular disease: systematic review and meta-analysis

This systematic review and meta-analysis of observational studies assessed the

effects of EBCP (containing antiplatelet agents, lipid-lowering medications, ACEIs/AEBs and beta-blockers) on mortality and major cardiovascular events in patients with CVD (Chapter two). The results showed that a combination of the four-class medications was associated with a decreased risk of all-cause mortality and cardiovascular events compared to either monotherapy or no therapy. In addition, increasing the number of components of EBCP therapy can produce additive survival benefit.

This systematic review inspired the design of this PhD project, because it found some gaps in the research about cardiovascular polypharmacy in secondary prevention of CVD. Firstly, most studies included in the systematic review were based on patients with CHD. There was limited evidence on the effects of cardiovascular combination therapy among patients with stroke. According to the recommendations of the NICE guidelines, the use of CV medications in secondary prevention is not identical for CHD and stroke(Intercollegiate Stroke Working party, 2016; National Institute for Health and Care Excellence, 2020c). Secondly, most of the included studies only focused on the four classes of CV medications, i.e., antiplatelet agents, beta-blockers, ACEIs/ARBs and statins. There was a lack of evidence of the benefits for some other commonly used medications, e.g., CCB and diuretics. In addition, these previous studies did not state if patients exclusively exposed to CV medications of interest. For example, a MI patient may concurrently have other CV medications (e.g., CCB or diuretics for anti-hypertensive treatment). These concurrent medications may induce bias. Thirdly, there was an absence of studies to assess the long-term (longer than one year) impact of cardiovascular

combination therapy. Finally, there was limited evidence on the effects of combination therapy for secondary prevention of CVD in patients with different comorbidities.

Based on these key findings from the systematic review, the following drug utilisation study and cohort studies were conducted to address these research gaps.

12.1.2 Initial usage of cardiovascular medications and factors associated with cardiovascular polypharmacy in patients with cardiovascular diseases

A cross-sectional study was conducted to investigate a comprehensive overview of initial prescription patterns of CV medications after incident CHD or stroke in the UK. This study also examined the potential factors associated with the probability of cardiovascular polypharmacy (Chapter 5). This study found that 40.6% of patients received cardiovascular polypharmacy (≥5 CV medications) in the first 90 days following their initial events of CHD or stroke. The results also identified sub-optimal adherence to guideline recommendations for the usage of CV medications in 'real-world' UK patients. Male, younger age, current smoker, high BMI, higher deprivation score and multiple comorbidities were associated with an increased likelihood of receiving cardiovascular polypharmacy. In addition, patients with a history of PCI, hypertension, hyperlipidaemia, heart failure, diabetes, chronic kidney disease and arrhythmia were more likely to receive five or more CV medications. Conversely, having a history of dementia, COPD or asthma was associated with a decreased probability of receiving cardiovascular polypharmacy.

NICE guidelines recommend multiple CV medications to patients who have established CVD(Intercollegiate Stroke Working party, 2016; National Institute for Health and Care Excellence, 2020a, 2020c). However, the results found that among these patients, those with a relatively lower risk of CVD were associated with a lower probability of cardiovascular polypharmacy.

12.1.3 Impact of multiple cardiovascular medications on mortality after an incidence of ischemic stroke or transient ischemic attack

This cohort study reported the long-term impact of multiple medications on all-cause mortality in patients following their incident ischemic stroke or TIA (Chapter 6). The results suggested that increasing the numbers and classes of CV medications conferred additional benefits on long-term survival compared to monotherapy. The combined use of four or five CV medications appeared optimal to improve long-term survival after stroke or TIA. A combination therapy containing APAs, LRMs, ACEIs/ARBs and CCBs was associated with improved survival after stroke or TIA. This four-medication combination was associated with a 61% reduction in mortality compared with APAs alone. This study did not find a significant additional benefit from BBs in combination therapy on long-term survival of stroke patients. Similar to the results in drug utilisation study (Chapter 5), patients with underuse or no use of CV medications were mostly at a relatively lower risk of CVD (e.g. younger age and with fewer comorbidities) at baseline (note: patients with established stroke are already in a very high risk of CVD and death(World Health Organization, 2007)). However, the results of this cohort study found that patients with no use of CV medications had a higher risk of mortality

compared to monotherapy. This finding indicates that guideline compliance deserves better attention in secondary prevention for patients with established stroke.

12.1.4 Impact of multiple cardiovascular medications on mortality in patients with ischemic stroke and type 2 diabetes

In this cohort study, I found that increasing the numbers and classes of CV medications appeared to produce additional benefits on long-term survival among patients with type 2 diabetes after incident ischemic stroke or TIA (Chapter 7). Patients with five medications were associated with the lowest risk of mortality compared to monotherapy. There was a high prevalence of hypertension (74.5%) among this group of patients. In addition to APAs, LRMs and ACEIs/ARBs, CCB and thiazide-type DRs (two of first-line antihypertensive agents) also conferred additive benefits on long-term survival in type 2 diabetic patients after stroke. The combination containing these five medications was associated with a 69% reduction of all-cause mortality compared to APAs alone.

12.1.5 Impact of multiple cardiovascular medications on mortality in patients with ischemic stroke and chronic obstructive pulmonary disease

This cohort study suggested that increasing the numbers and classes of CV medications appeared to produce additional benefits on long-term survival in COPD patients after incident ischemic stroke or TIA (Chapter 10). APAs, LRMs and ACEIs/ARBs appeared to be the central constituents of combination therapy associated with the reduced risk of mortality. The combination of these three classes of medications was associated with a 62% reduction in the risk of mortality.

LRMs played the most important role in combination therapy. This may attribute to LRMs' potential anti-inflammatory effect in the lungs benefits and reduced exacerbations in COPD patients. CCBs and DRs did not show a clear additive effect in combination therapy.

12.1.6 Impact of multiple cardiovascular medications on mortality after an incidence of myocardial infarction

This cohort study reported the long-term impact of multiple medications on all-cause mortality in patients following their incident MI (Chapter 9). The results found that patients prescribed with four CV medications appeared optimal to decrease the risk of all-cause mortality after MI. Contrary to combination therapy, patients with no use of CV medications had a higher risk of mortality. In line with the results from my systematic review study (Chapter 2) and guideline recommendation(National Institute for Health and Care Excellence, 2020c), the optimal constituents of combination therapy were APAs, LRMs, ACEIs/ARBs and BBs. The combination of these four-class medications reduced all-cause mortality by 79% compared with the use of APAs alone. This result was similar to the finding of my systematic review study (Chapter 2) that compared with patients with none or one component of EBCP, where the all-cause mortality was reduced by 78% in patients with optimal EBCP.

12.1.7 Impact of multiple cardiovascular medications on mortality in patients with MI and type 2 diabetes

In this cohort study, multiple CV medications were shown to be associated with a reduced risk of all-cause mortality in patients with type 2 diabetes after MI (Chapter

10). The four classes of CV medications (APAs, LRMs, ACEIs/ARBs and BBs) of EBCP were proven to confer additive benefits on long-term survival. The EBCP was associated with 88% (95%CI: 60%-96%) reduction of all-cause mortality compared to APAs alone. However, APAs appeared to make a moderate contribution in combination therapy to the beneficial effects observed. This may be attributed to hyperactive platelets and antiplatelet resistance in patients with diabetes(Creager et al., 2003; Ferroni et al., 2004). BBs have traditionally been prescribed with cautions for patients with diabetes because of potential side effects on serum glucose and lipid levels(Bell, 2003). In this study, BBs still played a significant positive role in combination therapy improved survival among type 2 diabetic patients after MI. Hypertension was very common (71.7%) in patients with both MI and type 2 diabetes. CCBs were shown to confer an additive benefit on long-term survival of patients with MI and type 2 diabetes, but DRs were not.

12.1.8 Impact of multiple cardiovascular medications on mortality in patients with MI and chronic obstructive pulmonary disease

This cohort study has shown that multiple CV medications were associated with a reduced risk of all-cause mortality in COPD patients after incident MI compared to monotherapy (Chapter 11). The four classes of CV medications (APAs, LRMs, ACEIs/ARBs and BBs) of EBCP were proven to confer additive benefits on long-term survival. The EBCP was associated with 85% (95%CI: 60%-95%) reduction of all-cause mortality compared to APAs alone. BBs have been traditionally considered contraindicated in patients with COPD, because cases of acute bronchospasm were reported during non-cardiovascular BBs use(Chobanian,

2003; Tattersfield, 1991; Woolcock et al., 1991). In this study, BBs appeared to confer additive benefits on long-term survival in COPD patients after MI. Strong evidence from previous studies has also suggested that the use of BBs is associated with improved survival in COPD patients(Coiro et al., 2017; Gottlieb et al., 1998; Quint et al., 2013). However, there was only 55.7% of COPD patients who received BBs following their incident MI in this study. Therefore, guideline compliance deserves better attention in this group of patients.

12.2 Implications for clinical practice

12.2.1 Secondary prevention after ischemic stroke or TIA

Based on findings from Chapter 5, 6, 8 and 10, the following implications for clinical practice in secondary prevention after ischemic stroke or TIA have been identified:

1. The combined use of APAs, LRMs and ACEIs/ARBs can be initiated for secondary prevention after the incident ischemic stroke or TIA to improve long-term survival. CCBs are superior to DRs in reducing the risk of mortality. They can be considered as the preferred treatment in combination with ACEIs if blood pressure cannot be adequately controlled by ACEIs alone in patients with ischemic stroke. There is no clear evidence that supported a beneficial effect of BBs on long-term survival after stroke or TIA.
2. Combination therapy is possibly necessary and beneficial to improve long-term survival among individuals who have had an ischemic stroke or TIA regardless of the risk level for CVD. Patients who have had a stroke or TIA

event are already considered as at high risk of mortality and recurrent cardiovascular events. Pharmacotherapy prescribed by healthcare professionals should adhere to the guideline recommendations even in those patients at a relatively lower risk of CVD (e.g., with younger age, with normal BMI or with fewer comorbidities).

3. The first and second implications are also appropriate for patients with a history of type 2 diabetes after an incident stroke or TIA. This group of patients is at extremely high risk of mortality and CVD. Hypertension is also highly prevalent. Considering the potential benefits of ACEIs/ARBs on blood pressure control, glycaemic control and protection of renal function in patients with diabetes, ACEIs/ARBs can be considered to be initiated for secondary prevention therapy. It is recommended that the combination of APAs, LRMs and ACEIs/ARBs should be initiated in this group of patients following their incident stroke or TIA.
4. The first and second implications are appropriate for patients with a history of COPD after an incident stroke or TIA.

12.2.2 Secondary prevention after MI

Based on findings from Chapter 5, 7, 9 and 11, the following implications for clinical practice in secondary prevention after MI have been identified:

1. The combined use of APAs, LRMs, ACEIs/ARBs and BBs should be initiated for secondary prevention after the incident MI to improve long-term survival. This combination is associated with around 80% reduction of all-cause mortality compared to the use of APAs alone.

2. This combination therapy is necessary and beneficial to improve long-term survival among all individuals who have had a MI regardless of the CVD risk level. Pharmacotherapy prescribed by healthcare professionals should adhere to the guideline recommendations even in those patients at a relatively lower risk of CVD.
3. The first and second implications are also appropriate for patients with type 2 diabetes after MI. BBs have traditionally been prescribed with cautions for diabetic patients because of potential side effects on serum glucose and lipid levels. However, clinicians are still advised to initiate these medications, because their benefits on long-term survival and cardioprotective function may overweigh those potential side effects in this group of patients. In addition, hypertension is highly prevalent in type 2 diabetic patients with MI. CCB can be considered as the preferred treatment in combination with ACEIs if blood pressure cannot be adequately controlled by ACEIs alone in this group of patients.
4. The first and second implications are also appropriate for patients with COPD after MI. Similar to patients with type 2 diabetes, BBs are always considered contraindicated in patients with COPD because of historical concerns that BBs could be harmful in patients with COPD. There is convincing evidence which has demonstrated the safety of cardioselective BBs in COPD. My study also has suggested the additive benefits of BBs in combination therapy on the long-term survival in COPD patients after MI. However, there remains distinct underuse of BBs in 'real-world' patients with

COPD in my study. Healthcare professionals can consider to initiate BBs in this group of patients instead of withholding them because of side-effects.

12.3 Strengths and limitations

This section emphasizes the overall strengths and limitations of this PhD research.

12.3.1 Overall strengths

1. In the absence of RCTs, I did a systematic review of observational studies based on the research of over ten thousand literature (Chapter 2). I did extensive analyses to explore the effects of cardiovascular combination therapy in secondary prevention for CVD, and comprehensively explored the limitations of previous studies and research gaps in this area. The systematic review provided a strong research background for the following studies.
2. The drug utilisation study (Chapter 5) and cohort studies (Chapter 6-11) were based on a large UK population-based primary care practice database. As such, it is likely to reflect the usual healthcare in the UK.
3. The drug utilisation study provided a comprehensive overview of initial prescription patterns of CV medications and cardiovascular polypharmacy in patients with new diagnoses of CHD or stroke.
4. There is a lack of studies to assess the cardiovascular combination therapy in secondary prevention in patients with stroke, and in patients with CVD and comorbidities. My PhD project firstly conducted large, long follow-up database-base cohort studies to explore the impact of multiple CV

medications on all-cause mortality in general patients with stroke or MI, and particularly in patients with concurrent type 2 diabetes or COPD.

5. All of the cohort studies compared different numbers, classes and combinations of CV medications which comprehensively demonstrated the effects of combination therapy on long-term survival.
6. In the cohort studies, to remove potential effects of other CV medications which were not of interest on the outcome, I defined exposure groups as patients who were exclusively using the selected CV medications of interest.
7. In the cohort studies, to control for confounding due to both time-invariant and time-varying confounders that may lead to treatment switching or informative censoring, I used the MSMs method to estimate the risk of mortality. MSMs assume no unmeasured confounding. I used the E-Value estimate to demonstrate the robustness of the results to unmeasured confounding.
8. In cohort studies, the results were robust in a wide range of sensitivity analyses.

12.3.2 Overall limitations

1. The PhD project used observational data. Therefore, residual confounding cannot be excluded. Selection bias, measurement bias could also occur. Further evidence from RCTs are required.

2. The THIN database only provides records of prescriptions; therefore, I was not able to determine if medications were actually dispensed, taken or used by patients in line with the directions for administration.
3. The THIN database does not capture data for hospital treatment, treatment in some care homes or nursing homes, and over the counter (OTC) medications (e.g., aspirin available OTC), I was not able to address any medication usage not included in records from general practice.
4. In the cohort studies, I had no information on the severity of CVD. The severity of the disease can influence both the drug prescription and outcomes. I adopted measures to balance heterogeneity between different exposure groups to some extent: (1) I included patients who had the first diagnosis of stroke or MI event, (2) excluded patients who died or had a nonfatal cardiovascular event during the first 90 days after the incident CVD event, and (3) I adjusted for risk factors of CVD when estimating mortality hazard ratios. In the cohort studies among patients with concurrent type 2 diabetes or COPD, I also adjusted for treatment for diabetes or COPD, the length of the duration having diabetes or COPD, and laboratory test related to the two comorbidities.
5. In the cohort studies, I only estimated the effect of CV medications by their major classification so my studies cannot determine the effects of sub-classes of these CV medications on long-term outcomes.

6. In the cohort studies, I only focused the effects of the number and classes of CV medications and did not address the dosage issue due to the complexity of the research question and analysis.
7. Hospital Episode Statistics (HES) data is not available in my PhD project. Therefore, I was not able to assess hospital CVD events.
8. In the cohort studies in patients with type 2 diabetes or COPD, some results had a wide CI due to relatively small sample size. However, the main results still had a clear direction to show the effect of the exposure of interest on the outcome. Further studies in a large population are encouraged to confirm the study findings.

12.4 Contribution to the knowledge

12.4.1 What is already know in this research area?

1. Concurrent use of different CV medications is common in patients with CVD.
2. Historically, polypharmacy has been considered negatively, but it is now increasingly recognised that an appropriate number of CV medications (i.e. cardiovascular polypharmacy) is necessary and beneficial in patients with CVD.
3. A few CVD drug utilisation studies from literature only focused on limited classifications of CV medications rather than providing a comprehensive overview of utilisation patterns.
4. Few studies have been undertaken on the potential factors associated with the probability of cardiovascular polypharmacy.

5. In 2003, Wald and Law proposed that a fixed-dose combination pill, called polypill, consisting of a statin, BP-lowering agents, aspirin and folic acid, could potentially reduce the risk of CVD by 80% in individuals from age 55. There were no definitive conclusions supporting the mortality benefit of polypill compared with usual care from RCT level evidence.
6. There was a lack of RCT-level evidence on the effectiveness of the combination therapy in secondary prevention of CVD.
7. Some previous observational studies examined the impact of EBCP in secondary prevention of CVD and suggested the beneficial impact of EBCP on mortality and cardiovascular events. However, most of theses studies only focused on CHD patients.
8. There was a paucity of evidence for the benefit of combination therapy in secondary prevention for stroke patients.
9. There was a lack of studies specifically evaluate the impact of combination therapy in secondary prevention for CVD patients with different comorbidities.
10. There was limited evidence on additional benefits conferred by increasing the number of combined use of CV medications.
11. There were few studies assessing the impact of combination therapy in secondary prevention of CVD on long-term outcomes.
12. Except for the four classes of medications of EBCP, there was a lack of evidence of additional benefits for some other commonly used CV medications (e.g., diuretics and CCBs) in combination therapy.

12.4.2 What does this PhD project add to the current knowledge?

1. The drug utilisation study provides a comprehensive overview of CVD drug patterns (including drug numbers and classifications) in UK patients with new diagnoses of coronary heart disease or stroke.
2. Male, younger age, currently smoking, higher deprivation score, history of hypertension, hyperlipidaemia, and multiple comorbidities were associated with the increased use of cardiovascular polypharmacy.
3. Combination therapy is beneficial and necessary to improve long-term survival among all individuals who have had a stroke or MI regardless of the risk level of CVD.
4. APAs, LRMs, ACEIs/ARBs and CCBs, each individual class of medication can confer an additional benefit on long-term survival in combination therapy among patients after incident ischemic stroke or TIA, which also apply to those patients concurrently with type 2 diabetes or COPD.
5. EBCP, the combination therapy containing APAs, LRMs, ACEIs/ARBs and BBs, can improve long-term survival among patients after incident MI, which also apply to those patients concurrently with type 2 diabetes or COPD.

12.5 Recommendations for future research

The findings from this PhD project serve as a foundation for further research of optimal pharmacotherapy for secondary prevention of CVD. I recommend that further research should address the following concerns:

1. Further studies are needed to assess the effects of sub-classes of CV medications on long-term outcomes. For example, the sensitivity analysis in my cohort studies found different effects of overall DRs and thiazide-type DRs in combination therapy on long-term survival. As another example, some previous studies reported that ARBs might be superior to ACEIs in patients with COPD. This indicates that there is a wide space for the research on pharmacotherapy in secondary prevention of CVD.
2. Further studies are needed to compare the impact of dual-antiplatelet therapy and mono antiplatelet therapy in combination therapy for the secondary prevention of CVD. Some previous studies have suggested that dual antiplatelet therapy is more effective than monotherapy for secondary prevention of CVD. Dual antiplatelet therapy is also recommended as regular therapy in secondary prevention after MI. However, my drug utilisation study found there was still an under-use of dual antiplatelet therapy among patients with MI. It is unclear if dual antiplatelet therapy is superior to monotherapy in combination therapy among patients after MI or stroke.
3. Further studies should evaluate the impact of combination therapy on major cardiovascular events. The outcome of my cohort studies was all-cause death. The occurrence of cardiovascular events is also an important outcome for secondary prevention of CVD. It is unclear if combination therapy can decrease the risk of subsequent cardiovascular events after the incident CVD event.

4. Further studies are recommended to explore the impact of cardiovascular combination therapy for secondary prevention of CVD in patients with other common comorbidities, for example, dementia, chronic kidney disease and painful conditions. These patients with comorbidities are more likely to under a burden of extreme polypharmacy. However, CVD is still the main cause of death among these patients. Optimal pharmacotherapy in secondary prevention of CVD is essential and maybe most efficient to improve survival in this group of patients.
5. Furthermore, in CVD patients with comorbidities, medications prescribed for comorbidities may influence cardiovascular therapy in secondary prevention of CVD. Therefore extending the research from cardiovascular polypharmacy to multi-condition polypharmacy would be useful. For example, further research could compare the impact of long-acting β-agonists and long-acting anticholinergics in combination with EBCP on long-term survival among COPD patients after MI.
6. Moreover, further research could investigate the adherence to evidence-based pharmacotherapy in the secondary prevention of CVD. The reason for the sub-optimal prescription of evidence-based medications is still unclear. Measures to improve adherence of evidence-based combination therapy in secondary prevention are worthy of exploring.
7. In addition, the results of my research provide more clinical foundation for further studies on “polypill“ in the secondary prevention of CVD. I provide evidence of optimal compositions of polypill in patients with MI or ischemic

stroke, and those patients with comorbidity of type 2 diabetes or COPD. Further trials, observational studies, pharmaceutical studies and economic studies can be conducted on polypill contained compositions that my research recommended.

12.6 Conclusions

This PhD project has filled multiple gaps in the area of cardiovascular polypharmacy in patients with CHD or stroke. Multiple CV medications treatment was common in patients with CVD in the UK. High-risk factors of CVD were associated with a higher possibility of prescribing cardiovascular polypharmacy. Combination therapy is beneficial and necessary to improve long-term survival among individuals who have had an ischemic stroke or MI regardless of the risk level of CVD. APAs, LRMs, ACEIs/ARBs and CCBs were the optimal constituents of combination therapy in secondary prevention to improve long-term survival after ischemic stroke or TIA, which also apply to those patients who concurrently had with type 2 diabetes or COPD. APAs, LRMs, ACEIs/ARBs and BBs were the optimal constituents of combination therapy in improving long-term survival after MI, which also apply to those patients with a coexisting condition of type 2 diabetes or COPD. There still exists sub-optimal pharmacotherapy for secondary prevention of CVD in general practice. Guideline compliance deserves better attention in term of improving long-term survival in patients with CVD.

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Appendices

Appendix A. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	56
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	56-57
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	58
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	The protocol was registered on PROSPERO. ID: CRD42018078069
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	58
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	58

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	59-60
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	60
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	60
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	61
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	65-69, Appendix C
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	62-84

Appendix B. Search strategy

Database		Search terms
MEDLINE		**Cardiovascular diseases**
	1	exp cardiovascular disease/
	2	exp Coronary Disease/
	3	exp Myocardial Ischemia/
	4	exp heart disease/
	5	exp acute coronary syndrome/
	6	exp angina pectoris/
	7	exp myocardial infarction/
	8	(isch?emi* adj3 heart).tw.
	9	(myocard* adj3 (infarct* or re?vascular* or ischemi* or ischaem*)).tw.
	10	(coronary adj3 disease*).tw.
	11	((coronary or cardiovascular or ischemic) adj event*).tw.
	12	(heart adj (disease* or attack* or infarct*)).tw.
	13	(cardiac adj3 disease).tw.
	14	(morbid adj5 (heart* or cardiovascula* or coronary* or isch?em* or myocard*)).tw.
	15	angina or MI.tw.
	16	chd or cad.tw.
	17	exp Stroke/
	18	(stroke or stokes or cerebrovasc* or cerebral vascular or apoplexy or (brain adj2 accident*)).tw.
	19	(brain* or cerebral or lacunar) adj2 infarct*).tw.
	20	or/1-19
		Cardiovascular drugs
	21	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
	22	hydroxymethylglutaryl-CoA reductase inhibitor*.tw.
	23	HMG CoA reductase inhibitor*.tw.

Database		Search terms
	24	HMG Co A reductase inhibitor*.tw.
	25	statin*.tw.
	26	exp colesevelam/
	27	colestyramine/
	28	colestipol/
	29	ezetimibe/
	30	fibric acid derivative/
	31	nicotinic acid/
	32	(atorvastatin or cerivastatin or dalvastatin or fluindostatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin or meglutol or mevinolin* or monacolin* or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol or bezafibrate or bezalip or ciprofibrate or modalim or clofibrate or fenofibrate or lipantil or supralip or gemfibrozil or lopid or procetofen or tocofibrte or transferal or theofibrate or etofylline clofibrate or duolip or acipimox or olbetam or nicotinic acid or niaspan).tw.
	33	or/21-32 **[Lipid modifiers]**
	34	exp Platelet Aggregation Inhibitors/
	35	[Adenosine Diphosphate/ai [Antagonists & Inhibitors]]
	36	(antiplatelet agents* or anti-platelet agent*).tw.
	37	(antiplatelet therap* or anti-platelet therap*).tw.
	38	thrombocyte aggregation inhibit*.tw.
	39	platelet aggregation inhibit*.tw.
	40	(antithrombocytic agent* or anti-thrombocytic agent*).tw.
	41	(antithrombocytic therap* or anti-thrombocytic therap*).tw.
	42	adenosine diphosphate receptor inhibit*.tw.
	43	(adenosine reuptake inhibit* or adenosine re-uptake inhibit*).tw.
	44	(aspirin or acetylsalicylic acid or dipyridamole or eptifibatide or ticlopidine or clopidogrel or cilostazol or (P2Y12 adj2 antagonis*) or prasugrel or cangrelor or ticagrelor or elinogrel tirofiban or picotamide or ticlid or beraprost or aggrenox or ditazole).tw.
	45	or/34-44 **[Antiplatelet agents]**

Database		Search terms
	46	exp thiazides/
	47	exp sodium chloride symporter inhibitors/
	48	exp sodium potassium chloride symporter inhibitors/
	49	exp Mineralocorticoid Receptor Antagonists/
	50	((loop or ceiling) adj diuretic?).tw.
	51	aldosterone antagonist*
	52	(amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide? or torasemide or torsemide or chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide or spironolactone or eplerenone).tw.
	53	or/46-52 **[Diur]**
	54	exp angiotensin-converting enzyme inhibitors/
	55	angiotensin converting enzyme inhibit*.tw.
	56	(ace adj2 inhibit*).tw.
	57	acei.tw.
	58	(alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or saralasin or snitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw.
	59	or/54-58 **[ACEI]**
	60	renin/ai
	61	(aliskiren or ciprokiren or ditekiren or enalkiren or remikiren or rasilez or tekturna or terlakiren or zankiren).tw.
	62	renin inhibit*.tw.
	63	or/60-62 **[RI]**

Database		Search terms
	64	exp angiotensin receptor antagonist/
	65	(angiotensin adj3 (receptor antagon* or receptor block*)).tw.
	66	arb?.tw.
	67	(abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan ormilfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan).tw.
	68	or/64-67 **[ARB]**
	69	calcium channel blocking agent/
	70	(amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw.
	71	(calcium adj2 (antagonist? or block* or inhibit*)).tw.
	72	or/69-71 **[CCB]**
	73	exp adrenergic beta-antagonists/
	74	(acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol ormepindolol ormethylthiopropranolol ormetipranolol ormetoprolol ormoprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or

Database		Search terms
		tribendilol or xibenolol).tw.
	75	(beta adj2 (adrenergic? or antagonist? or block* or receptor?)).tw.
	76	or/73-75 **[BB]**
	77	exp adrenergic alpha antagonists/
	78	(alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw.
	79	(andrenergic adj2 (alpha or antagonist?)).tw.
	80	((andrenergic or alpha or receptor?) adj2 block*).tw.
	81	or/77-80 **[AB]**
	82	53 or 59 or 63 or 68 or 72 or 76 or 81
	83	(33 and 45) or (33 and 82) or (45 and 82)
	84	Evidence based.tw.
	85	83 or 84
		Combination
	86	Drug Combinations/
	87	Drug treatment, combination/
	88	(polypill* or (drug* adj2 combin*) or ((multi* or several) adj2 (ingredient* or component* or therap* or treatment* or intervention*)) or policap or quintapill or (single adj2 pill* adj2 comb*) or single-pill or Red Heart pill*).tw.
	89	(((mono* or single* or dual* or double* or triple*) adj3 (therap* or treatment* or intervention*)) or (intensive adj2 (lowing or reduction or management or therap* or treatment* or intervention*))).tw.
	90	or/86-89
	91	20 and 85 and 90
EMBASE		**Cardiovascular diseases**
	1	exp cardiovascular disease/
	2	exp heart disease/
	3	exp Coronary Disease/

Database		Search terms
	4	exp heart infarction/
	5	exp Myocardial Ischemia/
	6	exp angina pectoris/
	7	(isch?emi* adj3 heart).tw.
	8	(myocard* adj3 (infarct* or re?vascular* or ischemi* or ischaem*)).tw.
	9	(coronary adj3 disease*).tw.
	10	((coronary or cardiovascular or ischemic) adj event*).tw.
	11	(heart adj (disease* or attack* or infarct*)).tw.
	12	(cardiac adj3 disease).tw.
	13	(morbid adj5 (heart* or cardiovascula* or coronary* or isch?em* or myocard*)).tw.
	14	angina.tw.
	15	MI.tw.
	16	CHD or CAD.tw.
	17	exp Stroke/
	18	(stroke or stokes or cerebrovasc* or cerebral vascular or apoplexy or (brain adj2 accident*)).tw.
	19	(brain* or cerebral or lacunar) adj2 infarct*).tw.
	20	or/1-19
		Cardiovascular drugs
	21	exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
	22	(HMG CoA reductase inhibitor*) or (HMG Co A reductase inhibitor*)
	23	statin*.sh.
	24	exp bile acid sequestrant/
	25	exp colesevelam/
	26	colestyramine/
	27	colestipol/
	28	ezetimibe/
	29	fibric acid derivative/
	30	nicotinic acid/

Database		Search terms
	31	(atorvastatin or cerivastatin or dalvastatin or fluindostatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin or meglutol or mevinolin* or monacolin* or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol or bezafibrate or bezalip or ciprofibrate or modalim or clofibrate or fenofibrate or lipantil or supralip or gemfibrozil or lopid or procetofen or tocofibrte or transferal or theofibrate or etofylline clofibrate or duolip or acipimox or olbetam or nicotinic acid or niaspan).tw.
	32	or/21-31 **[lipid modifiers]**
	33	exp Antithrombocytic Agent/
	34	exp Phosphodiesterase Inhibitor/
	35	Defibrotide/
	36	platelet aggregation inhibit*.sh.
	37	(antiplatelet agents* or anti-platelet agent*).sh.
	38	(antiplatelet therap* or anti-platelet therap*).sh.
	39	thrombocyte aggregation inhibit*.sh.
	40	(antithrombocytic agent* or anti-thrombocytic agent*).sh.
	41	(antithrombocytic therap* or anti-thrombocytic therap*).sh.
	42	adenosine diphosphate receptor inhibit*.sh.
	43	phosphodiesterase inhibit*.sh.
	44	(adenosine reuptake inhibit* or adenosine re-uptake inhibit*).sh.
	45	(aspirin or acetylsalicylic acid or dipyridamole or eptifibatide or ticlopidine or clopidogrel or cilostazol or (P2Y12 adj2 antagonis*) or prasugrel or cangrelor or ticagrelor or elinogrel tirofiban or picotamide or ticlid or beraprost or aggrenox or ditazole).sh.
	46	or/33-45 **[Antiplatelet agents]**
	47	exp thiazide diuretic agent/
	48	exp loop diuretic agent/
	49	exp Aldosterone Antagonist/
	50	(amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide? or chlorthalidone or chlortalidone or

Database		Search terms
		phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide or spironolactone* or eplerenone*).sh.
	51	or/47-50 **[Diur]**
	52	exp dipeptidyl carboxypeptidase inhibitor/
	53	angiotensin converting enzyme inhibit*.sh.
	54	(alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or saralasin or snitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).sh.
	55	or/52-54 **[ACEI]**
	56	exp renin inhibitor/
	57	(aliskiren or ciprokiren or ditekiren or enalkiren or remikiren or rasilez or tekturna or terlakiren or zankiren).sh.
	58	renin inhibit*.sh.
	59	or/56-58 **[RI]**
	60	exp angiotensin receptor antagonist/
	61	(angiotensin adj3 (receptor antagon* or receptor block*)).sh.
	62	(abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan ormilfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan).sh.
	63	or/60-62 **[ARB]**
	64	calcium channel blocking agent/
	65	(amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS

Database		Search terms
		or Verelan PM).sh.
	66	(calcium adj2 (antagonist? or block* or inhibit*)).sh.
	67	or/64-66 **[CCB]**
	68	exp beta adrenergic receptor blocking agent/
	69	(acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol ormepindolol ormethylthiopropranolol ormetipranolol ormetoprolol ormoprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).sh.
	70	or/68-79 **[BB]**
	71	exp alpha adrenergic receptor blocking agent/
	72	(alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).sh.
	73	((andrenergic or alpha or receptor?) adj2 block*).sh.
	74	or/72-74 **[AB]**
	75	(51 or 55 or 59 or 63 or 67 or 70 or 74)
	76	(32 and 46) or (32 and 75) or (46 and 75)
	77	Evidence based.tw.
	78	76 or 77
		Combination
	79	Drug Combinations/
	80	(polypill* or (drug* adj2 combin*) or ((multi* or several) adj2 (ingredient* or

Database		Search terms
		component* or therap* or treatment* or intervention*)) or policap or quintapill or (single adj2 pill* adj2 comb*) or single-pill or Red Heart pill*).tw.
	81	(((mono* or single* or dual* or double* or triple*) adj3 (therap* or treatment* or intervention*)) or (intensive adj2 (lowing or reduction or management or therap* or treatment* or intervention*))).tw.
	82	or/79-81
	83	20 and 78 and 82

Appendix C: Summary of results of included studies

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
Al-Zakwani 2012	ACS	1-month mortality 12-month mortality	EBCP: antiplatelet agent + ACEIs/ARBs + BBs + ST	0 EBC	OR 0.97 (0.71, 1.32) OR 1.20 (0.86, 1.67)	Age, gender, family history of CAD, diabetes mellitus, chronic renal failure, khat chewing, smoking status, heart rate, systolic blood pressure, Killip class score, ST-elevation myocardial infarction, GRACE risk score, in-hospital recurrent ischemia, inhospital re-infarction, in-hospital congestive heart failure, in-hospital cardiogenic shock, in-hospital stroke, in-hospital percutaneous coronary intervention and in-hospital coronary artery bypass graft.	Multivariable logistic regression
Al-Zakwani 2018	ACS	1-month mortality 6-month mortality 12-month mortality	EBCP: antiplatelet therapy+ACEI/ARB+BBs+ST	Sub-EBCP	OR 0.43 (0.24, 0.79) OR 0.52 (0.38, 0.72) OR 0.58 (0.44, 0.75)	Age, gender, prior MI, prior stroke,smoking, hypercholesterolemia, hypertension, comorbidity, PCI and hospital bleeding.	Multivariable logistic regression model
Amann 2014	AMI	All-cause mortality	EBCP: antiplatelet agent + ACEIs/ARBs + BBs + ST	Sub-EBCP	HR 0.63 (0.53, 0.74)	Age, gender, employment, smoking, type of AMI, reperfusion therapy, any in-hospital complication, history of stroke, diabetes, hyperlipidemia, and hypertension.	Multivariable Cox regression
Bauer 2010	ACS	1-year mortality	≤3 EBCs of ASA, clopidogrel, ACEI/ARB, BBs and ST	4-5 EBCs	OR 1.6 (1.4, 1.9)	Age, gender, prior MI, prior stroke, smoking, hypercholesterolemia, hypertension, comorbidity, PCI and hospital bleeding.	Multivariable logistic regression models
Bramlage 2010	ACS	1-year mortality	≤3 drugs of ASA, clopidogrel, ACEI/ARB, BBs and ST	4-5 drugs	OR 1.6 (1.4, 1.9)	Age, gender, prior MI, prior stroke,smoking, hypercholesterolemia, hypertension, comorbidity, PCI and hospital bleeding.	Multiple logistic regression models

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
Bezin 2017	ACS	All-cause death or MACE	1 EBC of Antiplatelet agents, ACEI/ARB, BBs and ST	4 EBCs	HR 1.76 (1.25, 2.48)	Age, gender, prior MI, prior drug use, prior medical consultations, patient status, characteristics of the initial ACS, comorbidies and use of CV drugs.	Cox regression
			2 EBCs	4 EBCs	HR 1.54 (1.22, 1.94)		
			3 EBCs	4 EBCs	HR 1.25 (1.07, 1.47)		
Bezin 2018	ACS	All-cause death or MACE	3 EBCs	Full EBCP		Age, gender, prior drug use, prior medical consultations, income status, characteristics of the initial ACS, PCI, CABG, comorbidies and use of CV drugs.	Multivariable time-dependent Cox proportional hazards model
			ACEIs/ARBs + APAs + BBs		HR 1.46 (1.33, 1.60)		
			ACEIs/ARBs + APAs + STs		HR 0.99 (0.89, 1.10)		
			ACEIs/ARBs + BBs + STs		HR 1.11 (0.98, 1.25)		
			APAs + BBs + STs		HR 1.30 (1.17, 1.43)		
			2 EBCs	Full EBCP			
			ACEIs/ARBs + APAs		HR 1.42 (1.22, 1.66)		
			ACEIs/ARBs + BBs		HR 1.39 (1.16, 1.67)		
			ACEIs/ARBs + STs		HR 1.13 (0.94, 1.36)		
			APAs + BBs		HR 1.64 (1.43, 1.88)		
			APAs + STs		HR 1.33 (1.14-1.55)		
			BBs + STs		HR 1.52 (1.28-1.81)		
			Single EBC	Full EBCP			
			ACEIs/ARBs only		HR 1.80 (1.39-2.32)		
			APAs only		HR 1.96 (1.62-2.38)		
			BBs only		HR 1.86 (1.52-2.26)		
			STs only		HR 1.69 (1.48-1.93)		
			No EBC	Full EBCP	HR 2.27 (2.00-2.58)		
		All-cause death	3 EBCs	Full EBCP			
			ACEIs/ARBs + APAs + BBs		HR 1.30 (1.12, 1.50)		
			ACEIs/ARBs + APAs + STs		HR 0.97 (0.83-1.13)		
			ACEIs/ARBs + BBs + STs		HR 1.18 (1.01-1.38)		
			APAs + BBs + STs		HR 1.51 (1.33-1.72)		
			2 EBCs	Full EBCP			
			ACEIs/ARBs + APAs		HR 1.24 (0.97-1.58)		

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
			ACEIs/ARBs + BBs		HR 1.53 (1.20-1.96)		
			ACEIs/ARBs + STs		HR 1.48 (1.19-1.83)		
			APAs + BBs		HR 2.00 (1.66-2.41)		
			APAs + STs		HR 1.55 (1.27-1.89)		
			BBs + STs		HR 1.80 (1.47-2.20)		
			Single EBC	Full EBCP			
			ACEIs/ARBs only		HR 1.68 (1.16-2.43)		
			APAs only		HR 2.52 (1.95-3.25)		
			BBs only		HR 2.23 (1.76-2.82)		
			STs only		HR 1.85 (1.56-2.20)		
			No EBC	Full EBCP	HR 2.55 (2.15-3.01)		
Bramlage 2010	AMI	1-year mortality	EBCP: ACEIs/ARBs + BBs + ST + ASA + clopidogrel unless contraindicted	0-1 EBC	OR 0.260 (0.179, 0.379)	Age, cardiac arrest on presentation, heart rate, systolic BP, Killip class, ST-segment deviation, abnormal cardiac biomarker, serum creatinine, previous MI and HF and in-hospital revascularisation	Multivariate analysis (without clear discription)
			2-4 EBCs		OR 0.486 (0.346, 0.684)		
			ST+ACEI/ARB+ASA+clopidogrel		OR 0.627 (0.339, 1.156)		
			ST+BBs+ASA+clopidogrel		OR 0.248 (0.149, 0.411)		
			ST+ACEI/ARB+BBs+ASA		OR 0.158 (0.034, 0.746)		
			ST+ACEI/ARB+BBs+clopidogrel		OR 0.398 (0.254, 0.612)		
			ST+BBs+ACEI/ARB		OR 0.482 (0.199, 1.170)		
			BB+ACEI/ARB+ASA+clopidogrel		OR 0.364 (0.228, 0.583)		
Chen 2017	CHD	All-cause mortality	EBCP: antiplatelet agents + ACEIs/ARBs + BBs +ST	$\leq$ 2 EBCs	HR 0.60 (0.42, 0.87)	Age, sex, pre-hypertension, pre-diabetes, current smoker, BMI, ACS, nation, revascularization, marital status, previous MI, previous PCI, OMT before admission, serum creatinine,	Multivariate Cox regression
			3 EBCs		HR 0.76 (0.54, 1.08)		
	ACS	All-cause mortality	EBCP		HR 0.62 (0.40, 0.96)		
			3 EBCs		HR 0.85 (0.56, 1.3)		

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
	Stable angina	All-cause mortality	EBCP 3 EBCs		HR 0.45 (0.22, 0.91) HR 0.42 (0.21, 0.84)	glucose, triglyceride, low density lipoprotein, white blood cell, platelet and systolic BP.	
Cirillo 2019	ACS	MACCE NACE	OMT OMT	Non-OMT Non-OMT	HR 0.52 (0.30-0.89) HR 0.56 (0.33-0.95)	Age >75, left ventricle ejection fraction, creatinine clearance (CrCl) <30 mL/min/1.73 m2, hypertension, dyslipidemia, DAPT with ticagrelor or prasugrel, DAPT with oral anticoagulants	Cox proportional hazards regression method
Danchin 2005	AMI	1-year mortality	EBCP: Antiplatelet agents + BBs + ST	≤ 2 EBCs	HR 0.52 (0.33, 0.81)	Age, sex, history of hypertension, current smoking, history of CVD, admission systolic BP and heart rate, use of reperfusion therapy, LVEF, Killip class, atrial fibrillation, atrioventricular block, PCI, use of diurerics, digitalis, nitrate, triple combiantion therapy and propensity score.	Multivariate Cox regression; propensity score analysis
Ge 2018	ACS	MACE Death MI Stroke	GDMT	Non-GDMT	HR 0.68 (0.58-0.80) HR 0.61 (0.46-0.80) HR 0.75 (0.56-1.01) HR 0.79 (0.47-1.34)	age, gender, race, body mass index (BMI), DM, hypertension, current smoking, prior PCI, CKD, anemia, STEMI, NSTEMI, multivessel disease (MVD), stent length, sent type, bivalirudin, and participating centers	Adjusted multivariable Cox regression models
Gouya 2007	AMI	All-cause mortality	≤ 2 EBCs of antiplatelet agents, ACEI/ARB, BBs and lipid modifiers	3-4 EBCs	HR 1.64 (0.86, 3.1)	Age and sex	Cox regression
Kopel 2014	AMI	1-year mortality	3-4 EBCs of ASA, ACEI/ARB, BBs and ST	0-2 EBCs	HR 0.66 (0.50, 0.87)	Baseline, admission presentation, in-hospital course variables, pre-admission drug and propensity score	Cox regression
Lafeber 2013	CAD	All-cause mortality MI Ischemic cerebrovascular accident	EBCP: ASA + ST + BP-lowering agents	Sub-EBCP	HR 0.69 (0.49, 0.96) HR 0.68 (0.49, 0.96) HR 0.37 (0.16, 0.84)	Age, gender, BMI, smoking, pack-years of smoking, presence of concomitant vascular disease (CVD, PAOD, AAA), total cholesterol, HDL cholesterol, and systolic BP.	Cox regression; propensity score

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
		Composite vascular outcome			HR 0.66 (0.49, 0.88)		
		Vascular mortality			HR 0.53 (0.33, 0.85)		
		All-cause mortality	2 EBCs	3 EBCs	HR 2.07 (1.69, 2.53)		
		MI			HR 1.44 (1.13, 1.83		
		Ischemic cerebrovascular accident			HR 1.59 (109, 2.32)		
		Composite vascular outcome			HR 1.50 (1.24, 1.81)		
		Vascular mortality			HR 1.97 (1.52, 2.55)		
		All-cause mortality	1 EBC	3 EBCs	HR 2.23 (1.79, 2.78)		
		MI			HR 1.53(1.16, 2.01)		
		Ischemic cerebrovascular accident			HR 1.46 (0.96, 2.23)		
		Composite vascular outcome			HR 1.62 (1.32, 2.00)		
		Vascular mortality			HR 2.30 (1.74, 3.04)		
Lahoud 2012	ACS male	Mortality	Level 4 of EBMs	Level 0 or 1	OR 0.22 (0.11-0.45)	Thienopyridine use, year of discharge, and disease severity as defined by Global Registry of Acute Coronary Events (GRACE) risk score (age, history of congestive heart failure, history of MI, heart rate, systolic blood pressure, initial creatinine level, elevated cardiac biomarkers, and in-hospital percutaneous coronary intervention)	Logistic regression models
			Level 2 or 3		OR 0.33 (0.17-0.65)		
	ACS famale	Mortality	Level 4	Level 0 or 1	OR 0.30 (0.15-0.63)		
			Level 2 or 3		OR 0.38 (0.19-0.79)		
	ACS male	Combined CV events	Level 4	Level 0 or 1	OR 0.43 (0.21-0.90)		
			Level 2 or 3		OR 0.51 (0.25-1.07)		
	ACS famale	Combined CV events	Level 4	Level 0 or 1	OR 0.99 (0.51-1.92)		
			Level 2 or 3		OR 1.11 (0.60-2.16)		
Lee 2010	AMI	6-month mortality	EBCP: antiplatelet agents + ACEIs/ARBs + BBs +ST	2-3 EBCs	HR 0.394 (0.161, 0.963)		Cox regression

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
				0-1 EBC	HR 0.488 (0.205, 1.165)	Age, anterior MI, Killip class, LVEF, serum creatinine levels and multivessel disease.	
Mukherjee 2004	ACS	6-month mortality	Level IV of EBCP	0 EBC	OR 0.10 (0.03, 0.42)	Age, gender, positive biomarker, new ST elevation, left ventricular ejection fraction, history of diabetes, renal failure, heart failure, and revascularization.	Multivariable logistic regression
			Level III		OR 0.17 (0.04, 0.75)		
			Level II		OR 0.18 (0.04, 0.77)		
			Level I		OR 0.36 (0.08, 1.75)		
Park 2015	ACS	All cause death	EBCP: Antihypertensive agents + lipid modifiers + antithrombotic agents	0 EBC	HR 0.35 (0.13, 0.96)	age, sex, ethnicity, hypertension, diabetes, smoking, history of CHD, history of carotid endarterectomy, systolic BP, BMI, low-density lipoprotein cholesterol, triglyceride, and high-density lipoprotein cholesterol level	Cox regression
			2 EBCs		HR 0.71 (0.26, 1.93)		
			1 EBC		HR 0.89 (0.30, 2.64)		
		Stroke	3 EBCs		HR 0.39 (0.18, 0.84)		
			2 EBCs		HR 0.50 (0.23, 1.09)		
			1 EBC		HR 0.51 (0.21, 1.25)		
		Stroke/CHE/vascular death	3 EBCs		HR 0.39 (0.22, 0.69)		
			2 EBCs		HR 0.45 (0.25, 0.80)		
			1 EBC		HR 0.60 (0.32, 1.14)		
Tay 2008 Younger cohort	AMI	1-year mortality	EBCP: Antiplatelet agents + ACEIs/ARBs +BBss + lipid-modifiers	0 EBC	OR 0.03 (0.02, 0.16)	Age, sex, race, smoking, dyslipidemia, hypertension, diabetes mellitus, history of AMI, prior PCI/coronary artery bypass grafting, revascularization, and Killip class.	Multivariate logistic regression model
			3 EBCs		OR 0.05 (0.03, 0.09)		
			2 EBCs		OR 0.10 (0.06, 0.17)		
			1 EBC		OR 0.28 (0.16, 0.50)		
Elderly cohort	AMI	1-year mortality	4 EBCs	0 EBC	OR 0.10 (0.05, 0.21)		
			3 EBCs		OR 0.16 (0.08, 0.31)		
			2 EBCs		OR 0.18 (0.09, 0.35)		
			1 EBC		OR 0.44 (0.22, 0.87)		
Timoteo 2006	ACS	30-days mortality	3-4 EBCs	1-2 EBCs	OR 0.23 (0.11, 0.48)	Unclear	Kaplan-Meier curves, log-rank test

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
Yan 2007	ACS	1-year mortality	EBCP: antiplatelet/anticoagulant + ACEI + BBs + lipid-modifiers	0-1 EBC	OR 0.54 (0.36, 0.81)	Global Registry of Acute Cardiac Events (GRACE) risk score: adjusted age, cardiac arrest on presentation, heart rate, systolic BP, Killip class, ST-segment deviation, abnormal cardiac biomarker, and serum creatinine.	Multivariable logistic regression
			2-3 EBCs	0-1 EBC	OR 0.65 (0.47, 0.90)		
Zeymer 2011	AMI patients treated with BB	1-year mortality	2 EBCs	ASA+ACEI+ST	OR 1.54 (1.26, 1.87)	Propensity score	Multiple logistic regression models; propensity score
			0-1 EBC		OR 1.67 (1.24, 2.27)		
		MACCE	2 EBCs		OR 1.27 (1.08, 1.49)		
			0-1 EBC		OR 1.49 (1.14, 1.95)		
Hippisley 2005	IHD	All-cause mortality	ST	0 EBC	OR 0.53 (0.33, 0.86)	comorbidity (diabetes, hypertension, congestive cardiac failure, and MI), use of CCBs, smoking status, BMI , and Townsend score	Conditional logistic regression
			ACEI		OR 0.80 (0.65, 0.99)		
			ASA		OR 0.59 (0.50, 0.68)		
			BB		OR 0.81 (0.63, 1.04)		
			ST+ACEI		OR 0.69 (0.43, 1.12)		
			ST+ASA		OR 0.39 (0.29, 0.52)		
			ST+BBs		OR 0.46 (0.26, 0.82)		
			ACEI+ASA		OR 0.54 (0.45, 0.66)		
			ACEI+BBs		OR 0.64 (0.43, 0.94)		
			ASA+BBs		OR 0.38 (0.31, 0.47)		
			ST+ACEI+BBs		OR 0.29 (0.21, 0.41)		
			ST+ACEI+BBs		OR 0.67 (0.30, 1.51)		
			ST+ASA+BBs		OR 0.17 (0.12, 0.23)		
			ACEI+ASA+BBs		OR 0.34 (0.26, 0.46)		
			ST+ACEI+ASA+BBs		OR 0.25 (0.18, 0.35)		
Kirchmayer 2013	AMI	All-cause mortality	EBCP: Eantiplatelet agents + ACEIs/ARBs + BBs + ST	0 EBC	OR 0.67 (0.30, 1.51)	PCI and bypass at index admission, HF, malignant neoplasm, disorders of lipoid metabolism/obesity, diabetes, chronic nephropathies,	Conditional logistic regression
			3 EBCs		OR 0.17 (0.12, 0.23)		
			2 EBCs		OR 0.34 (0.26, 0.46)		

Study	Participants	Outcomes	Intervention	Comparison	Adjusted results	Confounding variables adjusted for	Analysis method
			1 EBC		OR 0.25 (0.18, 0.35)	cerebrovascular disease, diseases of arteries, arterioles and capillaries, hemorrhagic stroke, hematologic diseases, cardiac dysrhythmias, duration of index admission.	
		Reinfarction	EBCP: antiplatelet agents + ACEIs/ARBs + BBs + ST	0 EBC	OR 0.35 (0.21, 0.59)	PCI and bypass at index admission, HF, diabetes, chronic nephropathies, diseases of arteries, arterioles and capillaries, ACE inhibitors/sartans before admission, duration of index admission.	
			3 EBCs		OR 0.59 (0.46, 0.76)		
			2 EBCs		OR 0.59 (0.47, 0.76)		
			1 EBC		OR 0.68 (0.53, 0.87)		
Van 2007	MI	Recurrent MI	OR 0.67 (0.30, 1.51)	0 EBC	OR 0.59 (0.37, 0.94)	diabetes mellitus, angina, use of anticoagulants, antiarrhythmic drugs, digoxin and CCBs, admission for chronic HF and PTCA or coronary artery bypass grafting procedure between first MI and index date	Conditional logistic regression
			OR 0.17 (0.12, 0.23)		OR 0.74 (0.53, 1.03)		
			OR 0.34 (0.26, 0.46)		OR 0.94 (0.70, 1.28)		

Appendix D. Evidence quality assessment, cohort studies

Study*	Selection				Comparability of cohort	Outcome			Overall quality
	Exposed cohort representative	Non-exposed cohort selection	Exposure ascertainment	Outcome not present at start		Assessment	Follow-up length	Follow-up adequacy	
Al-Zakwani 2018	*	*	*	*	**	*	*	*	9
Al-Zakwani 2012	*	*	*	*	**	*	*	*	9
Amann 2014	*	*	*	*	**	*	*	*	9
Bauer 2010	*	*	*	*	**	*	*	*	9
Bezin 2017	*	*	*	*	**	*	*	*	9
Bezin *et al.* 2018	*	*	*	*	**	*	*	*	9
Bramlage 2010	*	*	*	*	**	*	*	*	9
Chen 2017	- (hospital)	*	*	*	**	*	*	*	8
Cirillo 2019	- (8 cardiology institutions)	-	*	*	**	*	*	*	7
Danchin 2005	*	*	*	*	**	*	*	*	9
Ge 2018	*	*	-	*	**	-	*	*	7
Gouya 2007	*	*	*	*	*	*	*	*	8
Gunnell 2013	*	*	*	*	**	-	*	*	8
Kopel 2014	*	*	*	*	**	*	*	*	9

Lafeber 2013	*	*	*	-	**	*	*	*	8
Lahoud 2012	-(hospital)	-	*	*	**	*	*	*	7
Lee 2010	*	*	*	*	**	*	-	*	8
Mukherjee2004	-(Medical Center)	*	*	*	**	*	*	*	8
Park 2015	*	*	*	-	**	*	*	-	7
Tay 2008	- (2 hospitals)	*	*	*	**	*	*	*	8
Timoteo2006	-	*	*	*	-	*	*	-	5
Yan 2007	*	*	*	*	**	*	*	*	9
Zeymer 2011	*	*	*	*	**	*	*	*	9

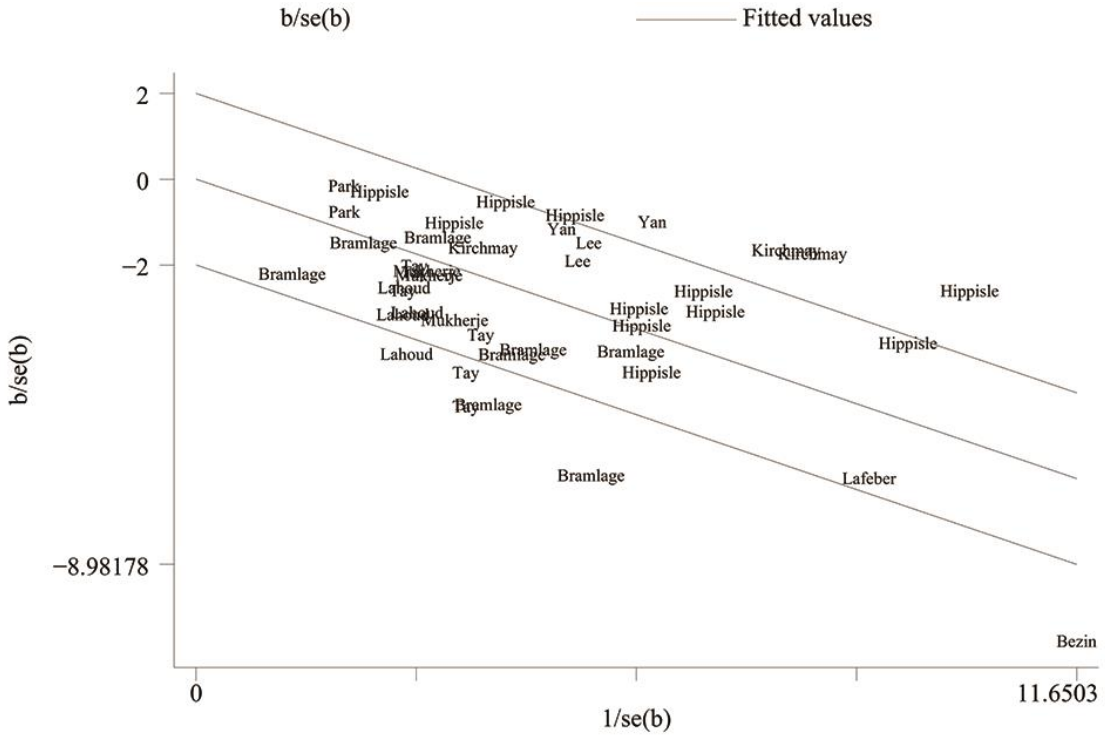
*Newcastle-Ottawa Quality Assessment Scale: 1 star (*) for meeting each criterion, except comparability (design or analysis) can have 2 stars. For comparability in this review: 1 star if controlled for age; 2 stars if also controlled for other important variables, e.g., exercise, body mass index, use of hormone replacement therapy or other relevant drugs

Appendix E. Evidence quality assessment, case-control studies

Study*	Selection				Comparability of cases and controls	Exposure			Overall quality
	Case definition	Cases representative	Control selection	Control definition		Ascertainment method	Same ascertainment both groups	Non-response rate	
Hippisley 2005	-(record linkage)	*	*	*	**	-(medical record only)	*	*	7
Kirchmayer 2013	-	*	*	*	**	-	*	*	7
Van 2007	-	*	*	*	**	-	*	*	7

*Newcastle-Ottawa Quality Assessment Scale: 1 star (*) for meeting each criterion, except comparability (design or analysis) can have 2 stars. For comparability in this review: 1 star if controlled for age; 2 stars if also controlled for other important variables, e.g., exercise, body mass index, use of hormone replacement therapy or other relevant drugs

Appendix F. Galbraith plot for heterogeneity in the primary meta-analysis.



y-axis: the effect size divided by its standard error

x-axis: inverse of the standard error

Calculate the weight of each study on the meta-analysis and the contribution to Q test

The further from the central line, the greater contribution of heterogeneity

Appendix G. Relative risk and heterogeneity after excluding studies

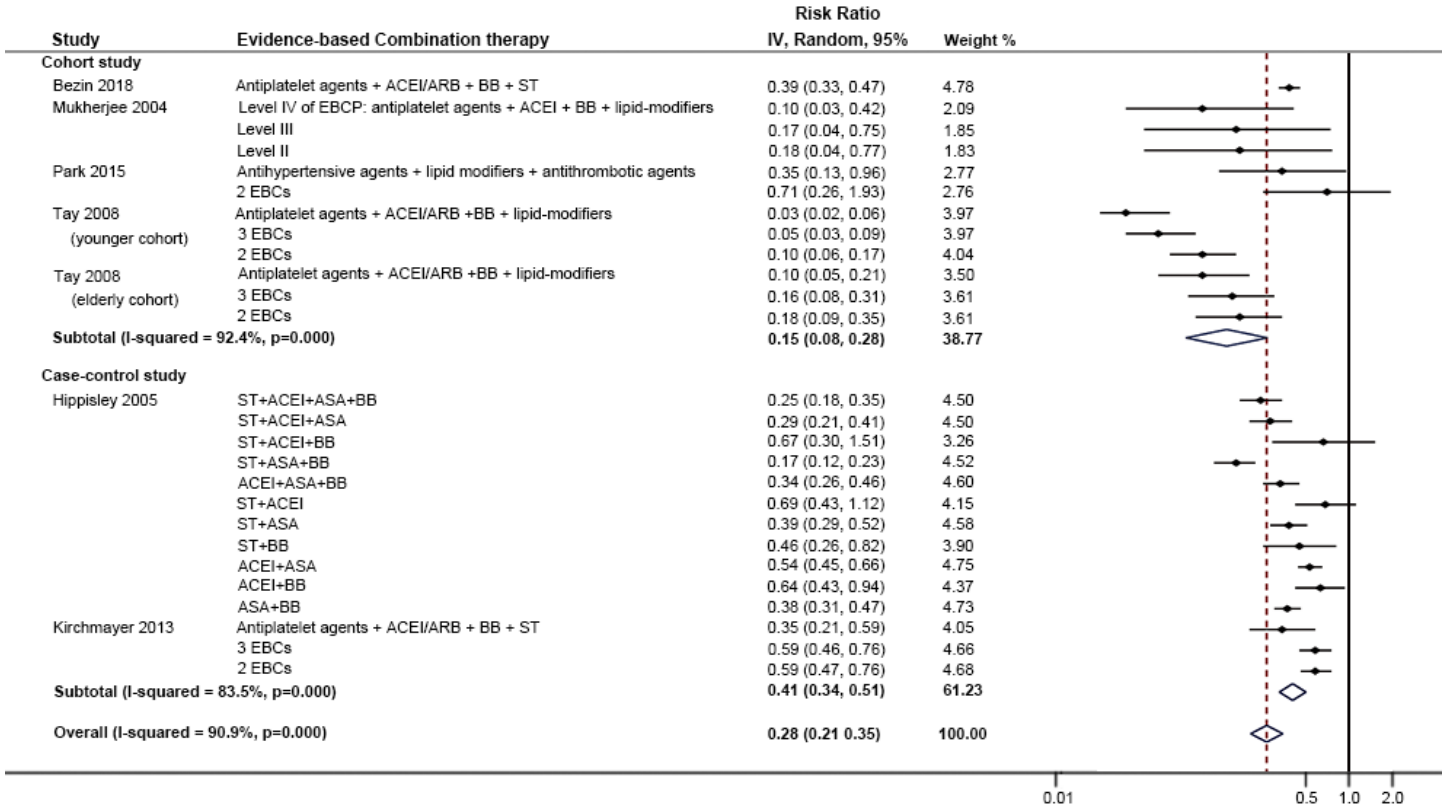
Studies excluded	Random effects model		Test of heterogeneity	
	RR	95% CI	I^2, %	P-value
None	0.33	0.29, 0.39	86.0	<0.01
Bramlage 2010	0.31	0.25, 0.37	88.5	<0.01
Hippisley 2005	0.29	0.23, 0.36	87.5	<0.01
Kirchmayer 2013	0.30	0.25, 0.37	86.1	<0.01
Yan 2007	0.31	0.25, 0.37	86.4	<0.01
Tay 2008	0.40	0.35, 0.45	69.0	<0.01

Appendix H. Subgroup analysis of demographics and study methodology for all-cause mortality (EBCP versus 0-1 component)

Covariate	Classification	No of studies or subsets	Risk ratio of subgroup analysis (95% CI)	Tests for heterogeneity		P value of subgroup difference
				P value	I^2(%)	
Age	<65 years	11	0.17 (0.08, 0.33)	< 0.01	92.6	0.02
	65-75 years	18	0.44 (0.37, 0.51)	< 0.01	56.0	
	>75 years	14	0.33 (0.26, 0.43)	< 0.01	84.6	
Region	Multi-region	2	0.50 (0.25, 1.01)	0.327	0.0	< 0.01
	Asia	8	0.12 (0.07, 0.23)	< 0.01	86.3	
	Europe	24	0.40 (0.35, 0.46)	< 0.01	75.6	
	Canada/USA	9	0.34 (0.24, 0.50)	0.010	60.1	
Disease	Stroke	2	0.50 (0.25, 1.01)	0.327	0.0	0.05
	ACS	10	0.37 (0.28, 0.49)	0.013	56.9	
	CHD	12	0.39 (0.32, 0.49)	< 0.01	82.3	
	AMI	19	0.25 (0.17, 0.36)	< 0.01	91.6	
Follow-up	<1 year	5	0.27 (0.15, 0.49)	0.263	23.7	0.99
	1 year	16	0.26 (0.14, 0.35)	< 0.01	92.0	
	>1 year	22	0.40 (0.34, 0.47)	< 0.01	75.1	
Study type	Retrospective cohort study	7	0.38 (0.33, 0.44)	0.602	0.0	0.08
	Prospective cohort study	22	0.24 (0.17, 0.34)	< 0.01	89.8	
	Case-control study	14	0.41 (0.34, 0.51)	< 0.01	83.5	

Abbreviations: ACS = Acute Coronary Syndrome; AMI = Acute Myocardial Infarction; CHD = Coronary Heart Disease; CI = Confidence Interval; USA = the United States of America

Appendix I. Comparison: EBCP versus 0 EB component, Outcome: all-cause mortality.



Appendix J. Mean number of cardiovascular medications by baseline characteristics

	CHD		Stroke	
Baseline characteristics	**Mean**	**SD**	**Mean**	**SD**
Male	4.8	1.7	3.1	1.7
Famale	4.6	1.9	3.1	1.8
Age groups, years				
45-54	4.7	1.7	2.6	1.7
55-64	4.8	1.7	3.0	1.7
65-74	4.8	1.8	3.3	1.7
75-84	4.8	1.9	3.3	1.8
85 and older	4.5	2.1	3.0	1.8
Smoking status				
Non-smoker	4.7	1.8	3.1	1.7
Current smoker	4.9	1.7	3.0	1.7
Ex-smoker	4.8	1.8	3.2	1.7
Alcohol consumption				
Non-drinker	4.8	1.9	3.2	1.8
Current drinker	4.8	1.7	3.2	1.7
Ex-drinker	4.8	1.9	3.1	1.7
BMI groups				
Normal (18.5-24.9 kg/m^2)	4.6	1.8	2.9	1.7
Overweight (25.0-29.9 kg/m^2)	4.8	1.7	3.2	1.7
Obesity (≥ 30.0 kg/m^2)	5.0	1.8	3.5	1.8
Underweight (< 18.5 kg/m^2)	4.3	1.9	2.5	1.6
BP status				
Normal (BP < 140/90 mmHg)	4.7	1.8	3.1	1.7
Stage 1 hypertension (BP ≥ 140/90 mmHg)	4.8	1.8	3.3	1.7
Stage 2 hypertension (BP ≥ 160/100 mmHg)	4.8	1.8	3.5	1.8
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	5.0	1.9	3.7	1.8

Hypotension (BP < 90/60 mmHg)	4.9	1.8	4.8	1.6
TC status				
Optimal (<5.2 mmol/L)	4.8	1.9	3.4	1.8
Intermediate (5.3-6.2 mmol/L)	4.7	1.8	3.1	1.7
High (>6.2 mmol/L)	4.7	1.8	3.1	1.7
Townsend score				
1 (least deprived)	4.7	1.7	3.1	1.7
2	4.7	1.8	3.1	1.7
3	4.8	1.8	3.1	1.8
4	4.8	1.8	3.1	1.8
5 (most deprived)	4.8	1.8	3.1	1.7
Charlson comorbidity index				
0	4.7	1.7	3.0	1.7
1	4.7	1.8	3.1	1.7
2	4.8	1.9	3.2	1.8
3	5.0	1.9	3.4	1.8
4	5.2	2.0	3.6	1.9
5	5.2	2.1	3.5	1.9
Cormorbidity				
Hypertension	5.1	1.8	3.7	1.8
Without hypertension	4.5	1.7	2.4	1.4
Hyperlipidaemia	5.1	1.7	3.8	1.6
Without hyperlipidaemia	4.7	1.8	3.0	1.7
Arrhythmia	4.9	2.0	3.6	1.9
Without arrhythmia	4.7	1.8	3.0	1.7
Heart failure	5.4	1.9	4.0	2.1
Without heart failure	4.7	1.8	3.1	1.7
Dementia	4.1	2.0	2.4	1.6
Without dementia	4.8	1.8	3.2	1.7

Diabetes	5.2	1.9	3.6	1.9
Without diabetes	4.7	1.8	3.0	1.7
COPD	4.7	1.9	3.1	1.7
Without COPD	4.8	1.8	3.1	1.7
Asthma	4.7	1.9	3.1	1.7
Without asthma	4.8	1.8	3.1	1.7
CKD	5.0	1.9	3.6	1.9
Without CKD	4.7	1.8	3.0	1.7

Appendix K. Summary of characteristics of study patients with competed data at all the entry points

	Cardiovascular treatment groups							
	0 drug	**1 drug**	**2 drugs**	**3 drugs**	**4 drugs**	**5 drugs**	**≥ 6 drugs**	**P value**
Sex, % women	49.2	49.8	47.8	47.3	48.0	48.6	45.8	<0.01
Age, (years) mean ± SD	69.7 ± 12.1	70.7 ± 11.7	70.8± 11.0	71.7 ± 10.5	72.3 ± 10.1	72.2 ± 10.1	71.9 ± 9.9	<0.01
Smoking (%)								
Current	18.5	16.2	17.3	16.0	14.9	12.7	12.5	<0.01
Former	40.1	39.8	40.1	42.4	44.0	44.5	45.8	
Never	41.4	43.9	42.6	41.6	41.1	42.8	41.7	
Alcohol (%)								
Current	70.0	68.9	70.4	71.4	70.9	69.2	70.4	<0.01
Former	11.1	12.1	12.1	11.2	12.0	11.4	10.6	
Never	18.9	19.0	17.5	17.4	17.1	19.4	19.1	
BMI status (%)								
Normal	35.6	35.8	33.3	30.1	26.6	23.1	19.1	<0.01
Overweight	36.9	37.9	39.2	39.7	38.7	37.9	35.7	
Obesity	23.9	23.3	25.2	28.4	33.1	37.6	44.2	

Underweight	3.6	3.0	2.4	1.8	1.6	1.4	1.0	
BP status (%)								
Normal	64.8	66.4	66.5	63.2	60.9	59.5	57.7	<0.01
Stage 1 hypertension	27.5	27.4	27.8	29.8	30.7	30.5	30.5	
Stage 2 hypertension	5.5	4.9	4.3	5.4	6.3	7.4	8.3	
Stage 3 hypertension	2.0	1.3	1.3	1.6	2.1	2.5	3.4	
TC status (%)								
Optimal	62.6	64.8	73.4	77.5	80.6	81.8	82.7	<0.01
Intermediate	25.1	23.9	18.1	15.8	13.7	12.7	12.1	
High	12.2	11.3	8.5	6.7	5.7	5.5	5.2	
Townsend score (%)								
1 (least deprived)	23.0	22.0	22.5	22.0	21.2	19.9	20.3	<0.01
2	22.2	24.3	22.6	22.6	22.9	23.6	22.3	
3	22.4	22.3	21.9	21.8	21.9	21.0	22.1	
4	18.0	18.9	19.0	19.3	19.8	19.9	20.7	
5 (most deprived)	14.3	12.6	14.0	14.4	14.3	15.6	14.6	
History of PCI (%)	0.4	0.3	0.3	0.5	1.0	1.9	3.0	
Comorbidity (%)								
Hypertension	48.4	43.7	46.8	67.9	81.4	88.4	91.8	<0.01

Hyperlipidaemia	15.5	16.2	17.7	18.8	20.6	23.1	25.8	<0.01
Arrhythmia	12.6	11.2	11.6	15.3	20.7	24.4	30.4	<0.01
Heart Failure	3.4	2.5	2.4	3.7	5.8	9.0	15.2	<0.01
PVD	6.0	4.2	5.5	6.3	7.1	8.3	10.2	<0.01
Diabetes	22.2	21.0	23.1	27.3	30.5	37.1	46.9	<0.01
Dementia	5.9	5.7	5.5	4.1	3.4	3.3	2.6	<0.01
COPD	9.6	11.5	11.7	10.9	11.7	9.7	10.5	<0.01
Asthma	12.9	15.6	16.1	15.2	14.5	13.9	12.8	<0.01
Liver disease	1.4	1.1	0.8	0.8	0.6	0.5	0.5	<0.01
Peptic ulcer disease	6.6	5.9	6.5	6.8	6.2	5.9	6.3	0.09
RA	2.4	2.4	2.1	2.4	2.2	1.7	2.1	0.03
CKD	17.4	17.0	17.8	20.8	25.6	30.2	35.2	<0.01

BMI indicates body mass index; BP, blood pressure; TC, total cholesterol; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PCI, percutaneous transluminal coronary intervention; PVD, peripheral vascular disease; RA, rheumatoid arthritis