

**The cost-effectiveness of fixed-dose combinations for preventive
cardiovascular pharmacotherapy**

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by
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Abstract of a thesis submitted in partial fulfilment of the
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Abstract

Background: Pharmaceutical non-adherence as a consequence of large pill burdens is a noted issue in the management of cardiovascular disease risk (CVD), particularly for populations with high CVD risk or with coexisting comorbidities. Non-adherence to pharmaceuticals means the intended health benefit of the pharmaceutical is not realised and the targeted risk factor remains inadequately controlled. Fixed-dose combinations (FDCs) pharmaceuticals that combine one or more active compounds into a single pill are one method of reducing pill burdens. A body of literature illustrates that CVD FDC pharmacotherapy improves adherence and risk factor control, resulting in a reduction of CVD events and health system savings. Given this background, this thesis aimed to determine if switching individuals from monotherapies (an anti-hypertensive: amlodipine; and a statin: atorvastatin, [A+A]) to an equivalent FDC (amlodipine with atorvastatin, [FDC AA]) would be a health generating and cost-effective intervention for the primary prevention of CVD in the New Zealand context.

Methods: Key parameters were identified in literature searches and meta-analyses were performed to determine the clinical efficacy for the FDC AA. An existing CVD multi-state life-table Markov model created by the BODE³ Research Group using rich New Zealand longitudinal data was adapted to model the effect of switching from A+A to the FDC AA in a population of New Zealand men aged 60 to 64 in 2011. The two disease life-tables (stroke and coronary heart disease) were age, sex, and ethnicity-specific (Māori and non-Māori). The model population was separated into five-year strata of absolute CVD risk ($0 \leq 5\%$, $5 < 10\%$, $10 < 15\%$, $15 < 20\%$, $> 20\%$). The intervention period was five years. Initial uptake was the same for both regimens, but adherence and clinical efficacy were greater for FDC AA than the A+A regimen (based on the literature). The medication adherent population received the risk reduction benefits and therefore had lower CVD incidence within each risk stratum. Health system costs and quality-adjusted life-years (QALYs) were accrued over a lifetime horizon and discounted at 3% annually (with variation in sensitivity and scenario analyses).

Results: This was the first study to consider the cost-effectiveness of a CVD FDC in New Zealand and the first internationally to assess a CVD FDC by strata of CVD risk. Overall and within each of the CVD risk stratum, the use of the FDC AA resulted in additional QALY gains and additional cost-offsets (net cost-savings) compared to the use of A+A (albeit not significantly for costs). The incremental cost-effectiveness ratio (ICER) in favour of switching to the FDC AA from A+A across all CVD risk strata ranged from cost-saving to \$3,570 per QALY gained (or 280 QALYs per million dollars spent for the latter) at the upper bound of the 95% uncertainty interval (95%UI). The absolute QALYs gained and the cost-offsets (savings) were greatest in the lowest CVD risk strata ($0 \leq 5\%$) with regimen switching resulting in an additional 167 QALYs gained and NZ\$ 3.41 million in cost-offsets (savings). The total

QALYs gained and cost-offsets (savings) from regimen switching, decreased as CVD risk increased. But the per capita results suggested that individuals with the highest CVD risk, benefited the most from switching to the FCD AA regimen.

Conclusions: This work provides modelling-level evidence that replacing the use of two monotherapies with a fixed-dose combination (a statin and anti-hypertensive) appears to be a cost-saving to very cost-effective intervention for the primary prevention of CVD in New Zealand. Further research in other age/sex groups and with other types of CVD FDCs is required to increase the generalisability of these results. The results of this thesis provide strong support for health authorities in high-income countries, such as New Zealand, to consider the inclusion of such FDCs in CVD prevention guidelines, placing a higher value on reducing pill burdens and improving adherence. If such FDCs are not available, then regulatory authorities could solicit the pharmaceutical industry to apply for such products to be registered in their jurisdictions.

Keywords: cost-effectiveness, cost-utility, fixed-dose combinations, adherence, cardiovascular disease, pill burdens, New Zealand.

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Glossary

AU\$: Australian dollars

A+A: Amlodipine and atorvastatin monotherapy combination

ACER: Average cost-effectiveness ratio

BODE³: Burden of Disease Epidemiology, Equity, Cost-effectiveness Programme, University of Otago

BP: Blood pressure

Can\$: Canadian dollars

CAD: Coronary artery disease

CCB: Calcium channel blocker – a class of anti-hypertensive pharmaceutical

Cerebrovascular disease: Stroke

CHD: Coronary heart disease

Cost-offset: The reduction in total health system costs adjusting for the costs of treatment and also from improved health attributed to the treatment eg, increased costs from longer life.

CPI: Consumer price index

CVD: Cardiovascular disease

DALY: Disability-adjusted life-years

DBP: Diastolic blood pressure

FDC: Fixed-dose combination – 2 or more active agents combined in a single pill form. Shorthand denoted: pharmaceutical x/pharmaceutical y

FDC AA: Single pill amlodipine and atorvastatin (FDC)

GBD: Global Burden of Disease Study

GST: Goods and services tax

HDL: High-density lipoprotein

HIV: Human immunodeficiency virus

ICER: Incremental cost-effectiveness ratio (equals the change in costs between the intervention and comparator divided by the change in QALYs between the intervention and comparator)

IHD: Ischaemic heart disease

I²: Measure of heterogeneity in meta-analyses

LDL: Low-density lipoprotein

LDL-C: Low-density lipoprotein cholesterol

MoH: Ministry of Health

Monotherapy combination: Multiple individual pharmaceuticals containing one active agent each taken as separate pills but also taken simultaneously. Shorthand denoted pharmaceutical x + pharmaceutical y

NZ: New Zealand

OECD: Organisation for Economic Co-operation and Development

OR: Odds ratio

PBS: Pharmaceutical Benefits Scheme – Australia

PHARMAC: Pharmaceutical funding body in New Zealand

Pill Burden: the total number of individual pharmaceutical agents prescribed

QALY: Quality-adjusted life-years

RCT: Randomised control trial

RR: Relative risk

TB: Tuberculosis

TIPS: The Indian Polycap study

UK: United Kingdom

US\$: United States dollars

YLD: Year of life lived in disability

YLL: Year of life lost

WHO: World Health Organization

95%CI: 95% confidence interval

95%UI: 95% uncertainty interval - Range represents the 95% interval of multiple Monte Carlo simulations

Chapter 1: Introduction

1.1 Context

Cardiovascular disease (CVD) is associated with a considerable disease burden that impacts the health of individuals at a substantial cost to both the health system and society generally.^{1,2} Internationally, primary prevention interventions that aim to reduce CVD risk by targeting CVD risk factors either at a population level (ie, mass-media campaign for tobacco control) or individual-level (ie, green prescription and pharmaceuticals) are numerous. Pharmaceutical interventions to reduce the risk of a future CVD event are common. Often multiple pharmaceuticals taken concurrently are required to adequately reduce a patient's absolute CVD risk.^{3,4} Large pill burdens are not uncommon in CVD prevention, especially for those at high CVD risk or with comorbidities and are documented to negatively influence pharmaceutical adherence (not taking a pharmaceutical as prescribed). Non-adherence to pharmaceuticals is a noted issue in CVD management, with adherence after a year reported being as low as 50%.⁵ Non-adherence to prescribed pharmaceuticals means the intended clinical result of the pharmaceutical is not realised and the patient's risk of having a cardiovascular event is not reduced.^{5,6} Fixed-dose combinations (FDCs) that combine multiple pharmaceuticals into a single pill form are one identified method to reduce pill burdens and increase adherence.⁷ A variety of two to five-agent combinations are available for CVD.

Economic evaluations aim to quantify the costs and consequences of an intervention, both monetary and otherwise and compare their ability to achieve a common goal. Information from economic evaluations should be considered by decision-makers in addition to clinical need, acceptability and suitability, to ensure that limited healthcare resource are expended as effectively and efficiently as possible.⁸ The pressure on healthcare resources could intensify in the coming years as a result of ageing populations. It is predicted that the future demand for healthcare is going to outweigh the availability of healthcare and that the retired population may be larger than the working-age population who make up the healthcare workforce and who are contributing to taxes that fund services including the healthcare system.⁹

In the face of a significant burden of CVD, an increasing demand for healthcare resources, high usage of CVD pharmaceuticals for which adherence is known to be poor, in addition to potential improvements in clinical efficacy with the use of a FDC and the potential cost-savings as a result of reduced CVD related health service utilisation, it is worthwhile investigating whether the use of FDCs are a more cost-effective approach to reduce absolute CVD risk compared to the same pharmaceuticals taken separately (business as usual).^{2,5,7,10}

1.2 Study aims

This thesis aimed to determine the health gains, cost impacts and cost-effectiveness of prescribing FDC for the prevention of cardiovascular disease (relative to the same agents taken as individual pills) by absolute CVD risk– initially in a selected group of New Zealand men aged 60 to 64 years.

1.3 Study objectives

The objectives of this study are:

1. To summarise the current knowledge base of FDCs in the treatment and management of CVD in the literature using examples.
2. To conduct a literature review of the cost-effectiveness of FDCs in CVD management globally and any meta-analyses of key parameters if required.
3. To establish the health gains, health system costs and cost-effectiveness of a two-agent CVD prevention pharmaceuticals compared to individual pills – starting with a select group from the New Zealand population and by strata of absolute CVD risk.
4. To determine whether health gains, costs and cost-effectiveness differ by a variety of factors considered in scenario and sensitivity analyses.

1.4 Thesis outline

Chapter 2 details the burden of CVD, pill burdens and non-adherence and describes how FDCs could potentially help address the outlined issue. The first part of Chapter 3 aims to summarise the existing literature of CVD FDCs, the second section describes the results of a structured review regarding the cost-effectiveness of CVD pharmaceuticals. Chapter 4 outlines the modelling methodology and principles used in this thesis as well as the selection of intervention inputs. Chapter 5 describes the results of this study. Chapter 6 discusses the results of this study, how they align with existing literature and what additional information this study adds. This Chapter also discusses the strengths and limitations of this study. Chapter 6 concludes this thesis by briefly summarising the findings of this study and considers potential implications for further research and for policy-makers.

Chapter 2: Background

2.1 The CVD burden

CVD poses a significant burden on the health of populations worldwide and New Zealand.² In the early 2010s, ischaemic heart disease and stroke were among the top three causes of death both globally and within New Zealand.^{1, 11} CVD is also associated with a significant morbidity burden with the health loss attributed to coronary heart disease (CHD) and stroke in the 2010s being the leading causes of health loss globally and the second and sixth causes of health loss respectively in New Zealand.^{12, 13} The burden of CVD disease in New Zealand disproportionately affects Māori (indigenous population) with CVD mortality almost two times greater for Māori than non-Māori.¹ Although the majority of the CVD health burden is experienced by those aged over the age of 40, the CVD health burden for Māori typically begins to occur at earlier ages.¹

The health burden of CVD results in a significant financial burden on the government-funded health system to provide the primary and secondary care services required by populations with CVD or at high risk of having a CVD event. In a report by the National Health Committee in New Zealand,¹⁴ CHD was estimated to cost NZ\$228 million while stroke, including rehabilitation cost, cost approximately NZ\$114-120 million in 2011/12.¹⁴ These costs do not represent the additional costs that arise from various community support services. Further costs to the government-funded health system are incurred by hospitalisations attributed to CVD risk factors (eg, to stabilise very high blood pressure (BP), subsidising CVD pharmaceuticals and subsidising general practitioner (GP) visits).¹⁴

At a societal level, the burden of CVD is also evident. The societal costs of CVD incorporate income, taxation and productivity losses associated with an individual taking time off work, prematurely retiring or dying before ending paid employment as a result of CVD.⁸ The cost associated with individuals receiving government support due to CVD illness is also considered as a societal cost of CVD. An Australian-based study found the annual cost associated with labour force absenteeism due to CVD in the 45 to 64-year age group in 2009 was AU\$1.1 billion in loss of income, AU\$85 million in taxation losses and AU\$225 million in Government support, when compared to the cost and income if the same group participated in the labour force to the same degree as those without CVD.¹⁵ New Zealand data shows similar patterns with employment rates and individual earnings significantly lower in the six months following a stroke or CHD event, whereas income support increased.¹⁶

2.2 Addressing the CVD burden

Globally and for New Zealand, the burden of CVD is significant.² If age-specific trends in CVD incidence (where CVD rates increase as age increases) do not decline substantially, the burden of CVD has the potential to increase because the number of people living in older age groups is increasing due to ageing populations.^{17, 18} Previous research has demonstrated that reducing the burden of CVD is likely to reduce costs and improve the health and well-being of the New Zealand population.^{19, 20} The large burden of CVD is primarily due to the high prevalence and cost of modifiable risk factors.^{1, 13} Internationally and within New Zealand, there are many interventions that aim to reduce the overall burden of CVD by addressing one or more CVD risk factors.² The focus of this thesis is the use of CVD pharmaceuticals that target CVD risk factors for the primary prevention of CVD.

2.3 Pharmaceuticals in CVD and absolute CVD risk

Pharmaceuticals common in the management of CVD are anti-hypertensives which act to reduce elevated BP, statins which aim to reduce high blood cholesterol levels and aspirin, an anti-coagulating pharmaceutical which prevents blood clots that have the potential to result in a CVD event.²¹ In 2017, four of the ten most prescribed medicines in New Zealand were for CVD. Atorvastatin (statin) and aspirin (anti-coagulant) had 1.26 million prescriptions each, while metoprolol succinate and cilazapril (both anti-hypertensives) had 0.97 and 0.79 million prescriptions respectively.¹⁰

Historically, the treatment and management of CVD considered each CVD risk factor in isolation, with clinicians intervening only if an identified risk factor was above a defined arbitrary threshold.²² More recently, CVD treatment and management has moved to focus on an individual's absolute CVD risk.²² In contrast to the historical risk approach, the absolute CVD risk approach considers an individual's risk of having a CVD event by evaluating all major CVD risk factors together. This approach acknowledges that CVD is a complex disease with several interrelated risk factors that together influence an individual's risk of a CVD event. Furthermore, the approach acknowledges that CVD risk factors and hence absolute CVD risk occur on a spectrum where even slight increases in risk are noteworthy. Importantly, the approach allows the subsequent action to mitigate an individual's CVD risk to be proportional to the overall level of risk identified.^{23, 24}

Based on the above holistic understanding of CVD, the renowned Framingham Heart Study^{23, 24} developed CVD risk equations that synthesise an individual's absolute CVD risk or the probability that an individual will have CVD event in a given period. These risk equations, commonly presented as charts or as software programs, provide an easy to use, summative measure which can be used to identify those at increased risk of a CVD event and guide a treatment decision, ultimately preventing CVD events.^{23, 24} New Zealand specific risk equations have been available since the early 1990s.^{21, 25}

Updated New Zealand CVD equations for the primary prevention of CVD were released in February 2018.³ The new guidelines were generated from a large body of New Zealand specific data and incorporated additional variables. The updated guidelines aimed to improve the specificity of the risk equations, particularly for Māori, Pacific and South Asian populations.³

The new risk equations collate the following variables and generate a probability of a CVD event occurring in the next five years: age, gender, ethnicity, *New Zealand deprivation quintiles (NZDEP)*, family history of CVD and diabetes, patient medical history of CVD including *atrial fibrillation*, diabetes (and *diabetes duration*), *renal function*, smoking, blood pressure, blood cholesterol, blood glucose, body mass index and *CVD pharmaceutical use* (anti-hypertensive, statin and anticoagulants). The new variables are in italics.³ Screening for CVD is recommended for the general population from the age of 45 for men and 55 for women.³ This age range has not changed from the previous guidelines.²¹ CVD risk screening for Māori, Pacific and South Indian populations is recommended from the aged of 35 for men and 40 for females, acknowledging different CVD risk profiles.³ This age range is five years younger than the screening ages recommended in the 2012 guidelines.²¹ Individuals with a five-year absolute CVD risk score of 5-10% are advised to consider the use of anti-hypertensives and lipid-lowering pharmaceuticals (2012 guidelines five-year absolute CVD risk score of 10-20%) while individuals with a 15% or greater chance of a CVD event in the next 5 years are strongly advised to commence use of anti-hypertensive, statins and anticoagulants (2012 guidelines five-year absolute CVD risk score of 20%+).^{3, 21} Overall, the 2018 primary care guidelines for CVD more accurately reflect the current CVD burden and suggest screening at younger ages for high-risk populations and early pharmaceutical intervention for everyone. The 2018 CVD guidelines became available just prior to the completion of this thesis, as a consequence, the absolute CVD risk scores discussed throughout this thesis relate to the 2012 CVD guidelines.²¹

2.4 Pill burdens and pharmaceutical adherence

Based on the results of the CVD risk assessment, individuals, especially those at high CVD risk, can end up taking four or more pharmaceuticals (multiple anti-hypertensives, a statin and an anticoagulant).²¹ An individual's pill burden or the total number of pills prescribed, may be increased further by the presence of co-morbidities that may also require pharmaceutical treatment (eg, diabetes). An Australian based study⁶ found that among a high-risk CVD population the median self-reported pill burden was seven different pharmaceuticals. On average four of the seven pharmaceuticals were for CVD.⁶

A primary concern that arises when individuals are required to take numerous pharmaceuticals is a decline in adherence. Non-adherence to CVD pharmaceuticals (not taking prescription medicine as prescribed), is a noted issue in CVD management.²⁶⁻²⁸ A meta-analysis conducted by Naderi et al⁵

examined prescription refill data as a proxy for adherence to CVD pharmaceuticals from 20 international studies and approximately 380,000 people. The study found that overall adherence to CVD pharmaceuticals – defined as 75% or more days covered by a prescription over a two year period – was only 57% (97%CI: 50–64%).⁵ This measure is likely to underestimate the true values as it does not consider those who collected their prescriptions but failed to take the pharmaceutical as prescribed. Another study that looked at the long-term adherence of anti-hypertensive pharmaceuticals used in phase four clinical trials found that after a year, approximately half of all patients had ceased taking their prescribed pharmaceutical altogether.²⁹

Non-adherence of pharmaceuticals is an important issue because if a pharmaceutical is not taken as prescribed the intended positive impact (clinical efficacy) of the prescribed pharmaceutical may not be observed. Reduced clinical efficacy means that the risk factor and the individual's absolute CVD risk may not be reduced by the magnitude that could be achieved if the pharmaceutical was taken as prescribed, with consequence to the health of the individual and the healthcare system.³⁰ For example, a study by Sokol et al in 2005³¹ found that patients with hypercholesterolaemia and hypertension who had greater than 80% adherence (measured by access to prescribed pharmaceuticals) had significantly (statistically) lower all-cause hospitalisations than those who achieved less than 80% adherence. In addition, non-adherent patients had significantly higher medical costs than those with good adherence (albeit not statistically significant at all levels of adherence).³¹

Non-adherence is complex and multifactorial. A large pill burden is just one factor among others (including patient's age and education level as well as the patient-doctor relationship) which influences adherence.²⁶⁻²⁸ With non-adherence, a notable issue in CVD, several different methods to improve adherence have been explored. One method aimed explicitly at reducing pill burdens and simplifying complex pharmaceutical regimes with the aim of improving adherence, is combining several pharmaceuticals that are prescribed as individual pills into a single pill form. This is called a fixed-dose combination (FDC) (or single-pill combination).³²

2.5 Fixed-dose combinations

Fixed-dose combination (FDC) pharmaceuticals, defined as a single pill containing two or more active agents that utilise independent biological pathways, is one method used to reduce a patient's pill burden and increase adherence.³² FDCs are used in current clinical practice for the management and treatment of a variety of health conditions.

The primary benefit of using FDCs is improved adherence when compared to the same pharmaceutical agents taken as separate pills. FDCs act to reduce an individual's pill burden and simplify complex pharmaceutical regimens, consequently improving adherence of the remaining pharmaceuticals.

Improved adherence to pharmaceuticals is essential so that the intended clinical efficacy of the prescribed pharmaceutical can occur. The pharmaceutical components of FDCs typically have slightly lower dosages than the same components taken as separate pills. As a result, FDCs may be more tolerable and have fewer adverse effects than the same components as individual pills without compromising clinical efficacy.⁷ FDCs also have the potential to be lower in cost than the same components taken individually. The cost to individuals in terms of prescription costs and the cost the healthcare system in terms of the cost of dispensing pharmaceuticals may be less as only one pill needs to be dispensed or prescribed instead of multiple.^{7, 33} It is important to note that the cost reduction potential of FDCs are country-specific and depend on a number of factors including pharmaceutical price and availability, the proportion of pharmaceutical cost the user pays and the relative cost of the FDC pharmaceutical to its components, which is influenced by the availability of generic pharmaceuticals over brand-name pharmaceuticals that are generally more expensive.³⁰

FDC pharmaceuticals also have several limitations. Specifically, components of FDC pharmaceuticals are somewhat unmodifiable in their dosage (though of course some FDC tablets can potentially be halved). This is an issue if the clinician would like to modify the dosage of components within the FDC to tailor the pharmaceutical to better meet an individual's risk profile or if the individual experiences adverse effects that can be attributed to one of the FDCs components.⁷ For this reason, FDCs for CVD are often suggested to be prescribed in the first instance and a change to appropriate monotherapies is recommended if issues arise. Contrary to strong existing evidence, concerns have been raised regarding the possibility that FDCs may result in individuals taking more pharmaceuticals than necessary and that reducing pill burdens by one or two pharmaceuticals (two pills into one pill) may have little overall significance.^{34, 35} There is also a possibility that individual components of the FDC may be cheaper than their FDC equivalent.^{7, 33} As mentioned above, the costs associated with FDC are country-specific and depend on a variety of factors. A summary of the benefits and limitations of FDCs is detailed in Table 1.

Table 1: Summary of criteria, potential advantages and disadvantages of FDC pharmaceuticals

Criteria	<ul style="list-style-type: none"> • Contain two or more active pharmaceutical agents in a single pill form. • Active components of the FDC must work independently of one another
Potential advantages	<ul style="list-style-type: none"> • Typically improves adherence, consequent increase in clinical efficacy • Should simplify complex pharmaceutical plans and reduce pill burdens • May reduce dispensing costs (country-specific) • May be cheaper than the two individual components (pharmaceutical/country-specific) • May be cheaper for the user – one prescription cost vs multiple (country-specific) • Should typically increase tolerability (reduced adverse effects)
Potential disadvantages	<ul style="list-style-type: none"> • The clinician is typically unable to adjust the dosage of individual pharmaceutical components (eg, when wanting to evaluate/remove an adverse effect that is likely to be attributable to an individual component) • Potentially more expensive than multiple individual pharmaceuticals (pharmaceutical/country-specific)

2.5.1 FDC use in treatment and management of health conditions

FDC pharmaceuticals are widely used in modern medicine to treat and manage health conditions including infection with human immunodeficiency virus (HIV),³⁶ malaria,³⁶ tuberculosis (TB),³⁶ asthma,³⁷ diabetes,³⁸ pain relief,³⁹ fertility control,⁴⁰ and CVD prevention.⁴¹ Common to all these health conditions is the need for several different pharmaceutical agents to be taken concurrently to achieve a common outcome be it pain relief, contraception, eradication of a malaria parasite or reduction of CVD risk. The consistent profile of pharmaceuticals used to treat these conditions makes their combination into a FDC rational. The common primary benefit cited for the use of FDC in these health conditions is improved adherence and simplified pharmaceutical regimes that consequently improves the clinical efficacy, tolerability and acceptability of the pharmaceuticals.³⁶ Furthermore, in the case of asthma and hospital-based pain relief, FDCs allow better long-term management by strategically combining pharmaceuticals which act over different time horizons.^{37, 39} In the case of infectious diseases such as TB, HIV and malaria, improved adherence to treatment with FDCs is critical to reducing the evolution of pharmaceutical-resistant disease strains (via evolutionary processes).³⁶ Additionally, some combinations have the unique feature of opposing the adverse effects created by the other. Many of these conditions pose a large burden on both the health of individuals and the healthcare

system, so the potential clinical effectiveness gains as a result of good adherence and the potential cost-savings associated with dispensing and prescribing fewer pharmaceuticals and reducing overall healthcare expenditure is significant.^{39, 7, 37} FDCs are seen to be particularly favourable in the treatment of infectious diseases in low-income countries that have a large burden of infectious disease and where cost of treatment is a barrier.³⁶

2.5.2 FDCs in CVD

Analogous to the health conditions discussed above, the rationale for using FDCs in CVD prevention is reducing large pill burdens to increase adherence and consequently the clinical efficacy of the pharmaceutical.^{5, 7, 30} Guidelines internationally concur that two to three different anti-hypertensive pharmaceuticals are typically required to manage high blood pressure and that the same two to three anti-hypertensive in addition to a statin and aspirin are required to actively reduce high CVD risk.^{21, 42-44} Despite the availability of several CVD-specific pharmaceutical agents spanning several pharmaceutical classes, the pharmaceutical profile for the treatment and management of CVD is largely similar. The consistent similarities of pharmaceutical profiles within CVD management, in addition to acknowledged issues with adherence, makes the use of FDCs in CVD management a rational development. Indeed, a variety of two- to five-agent CVD FDC pharmaceuticals have been developed and are used internationally. The usage and availability of CVD FDC varies dramatically between countries due to differences in health system organisation, pharmaceutical cost and pharmaceutical approval as well as the personal preference of clinicians.^{7, 45, 46} The current usage of FDC in the treatment of CVD FDC will be explored in greater detail in Chapter 3.

Chapter 3: Literature review

This Chapter comprises of two literature reviews. The first review aims to summaries the existing published literature concerning CVD FDCs generally. The reviews begins with a discussion of the literature concerning FDC that address a single CVD risk factor and proceeds to discuss the available literature concerning the FDCs that address multiple CVD risk factors. The first review concludes by detailing the CVD FDCs that are currently available in New Zealand. The second review is more specific and aims to summaries the exisiting literature where the cost-effectiveness of CVD FDCs were examined. Two-agent FDC are explored independently to polypills.

3.1 Literature review of CVD FDCs

The use of FDCs in the treatment and management of CVD is not new. FDCs and their perceived treatment benefits were referenced in the literature for the treatment of hypertension as far back as the 1950s, with the first two and three-agent anti-hypertensive FDCs available in the 1960s.⁷ Coinciding with the move to consider absolute CVD risk approach in the early 2000s, FDCs that target two or more different CVD risks were developed. Specifically, a two-agent FDC that combines a cholesterol-lowering statin with an anti-hypertensive⁴⁷ and a polypill, a four- to five-agent pill which combines several anti-hypertensives with a statin and aspirin.⁴⁸⁻⁵⁰

As has already been discussed in the Introduction of this thesis, the use of FDCs in CVD is a logical solution to reducing pill burdens. Several international guidelines, including European Guidelines on Hypertension, British Hypertension Society and Joint National Committee Seven for High Blood Pressure (JNC7), mention the use of two-agent anti-hypertensive agents where appropriate, acknowledging an adherence improvement as a result of simplifying pill regimens.^{43, 44, 51} Although international guidelines to date do suggest the use of several different classes of CVD drugs to best manage high CVD risk, multi-risk factor FDCs are not specifically mentioned.

3.1.1 Single risk factor CVD FDCs

Two-agent anti-hypertensive FDC

Two-agent anti-hypertensive FDCs are currently the most common CVD FDCs in terms of their use and the number of combinations available internationally. Consequently, the body of literature concerning two-agent FDCs is vast. The positive impact that two-agent FDCs have on pharmaceutical adherence is reported in a meta-analysis by Gupta et al 2010.⁵² This analysis considered 15 randomised control trials (RCTs) and cohort studies (32,000 participants) and found that compliance (synonymous with adherence) among those taking a two-agent hypertensive was significantly greater than those taking the same two agents as individual pills (odds ratio (OR) = 1.21, 95%CI: 1.03 to 1.43). The study also

reported that individuals taking the FDC had greater benefit (in terms of lowering blood pressure) and fewer adverse events than those taking two-agents separately. These latter findings, however, were not statistically significant.⁵² An earlier review conducted by Bangalore et al in 2007⁵³ mirrored the findings of Gupta et al 2010⁵² in finding two-agent anti-hypertensive FDCs reduced the risk of non-compliance by 24% (relative risk (RR) = 0.76, 95%CI: 0.71 to 0.81).⁵³ To date, the studies by Bangalore et al and Gupta et al appear to be the only meta-analyses published that investigate two-agent anti-hypertensive FDCs compared to the same agents taken as separate pills.⁵⁴

Further to improvements in adherence and clinical efficacy, two-agent anti-hypertensive FDCs also demonstrate a cost-saving potential if the price to the consumer and the government to obtain and dispense the FDC is cheaper than the cost of two individual pills. This cost-saving potential is demonstrated in Akazawa and Fukuoka 2013⁵⁵ who monitored patient pharmaceutical expenditure over a policy change that made FDCs prescriptions more accessible in Japan. This is also the case with Stankus et al 2009⁵⁶ who investigated the potential cost savings accrued in a hypothetical scenario analysis should a proportion of Canadians currently taking one of two combinations of anti-hypertensives switch to the corresponding FDC. Both studies found annual pharmaceutical expenditure would decrease significantly should more people take FDCs compared to combination monotherapy (Akazawa and Fukuoka: a 17% decrease in pharmaceutical expenditure; Stankus et al for a 100% population switch: Can\$45 million saving annually). Akazawa and Fukuoka also noted an increase in expenditure for some individuals who moved from monotherapy to the FDC as the FDC was more expensive than a single pill.⁵⁵

The other significant benefit cited for the use of FDC is the longer-term gains in terms of reduced healthcare utilisation and associated health system costs that are a result of improved blood pressure control due to FDC use. A study conducted by Yang et al 2010⁵⁷ used a retrospective cohort design to investigate differences between those taking a variety of two-agent anti-hypertensive FDC compared to two separate pills in the United States. Further to observing a statistically significant improvement in adherence among those taking FDCs, the study found that those whose treatment was initiated with a FDC had significantly fewer all-cause hospitalisations and emergency department visits than those treated with the same components as separate pills. Those taking the FDCs had 29% fewer CVD hospitalisations than those on the same pharmaceutical as separate pills (incident rate ratio= 0.71, 95%CI: 0.69 to 0.72). Furthermore, FDC initiation was associated with a significant reduction in all-cause medical costs and CVD-related medical costs, with the latter reducing by US\$180 per patient for those initiated on FDC compared to separate individual pills in the six months following initiation of treatment. This reduction was despite the significant difference in pharmaceutical costs that were higher for those in the FDC group compared to those taking the same components taken as separate pills.⁵⁷ Results of several other studies echo the results of Yang et al 2010, however, it must be noted

that the results are not always statistically significant and that multiple different FDCs were studied.³⁰

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Three-agent anti-hypertensive FDCs

Acknowledging that many people may require up to three different anti-hypertensive pharmaceuticals to adequately control of their elevated blood pressure, three triple anti-hypertensive FDCs have been developed. The combinations combine valsartan, olmesartan or aliskiren with amlodipine and hydrochlorothiazide. To date all three combinations are approved in the United States,⁵⁹ the combination with valsartan is approved by the European Medicine Agency,⁶⁰ and the olmesartan combination is approved in Australia.⁶¹ Currently, no triple anti-hypertensive FDC is available in New Zealand. The body of evidence surrounding the clinical efficacy and adherence advantage of triple anti-hypertensive FDC therapy is limited. Several studies demonstrate that the FDC has superior clinical efficacy in terms of blood pressure reduction compared to two of the agents as monotherapies.⁶²⁻⁶⁴ Studies comparing the FDCs directly to its monotherapy combinations as well as studies investigating the possible difference in adherence and long-term CVD endpoints are lacking. Further research in this area is required.

Two-agent lipid-lowering FDCs

FDCs that combines a statin with ezetimibe, a drug that limits cholesterol absorption from the small intestine, has recently become available following the successful use of the two agents as a monotherapy combination to reduce cholesterol among individuals who fail to adequately reduce their cholesterol with lifestyle changes and statins alone. A body of literature supports the clinical efficacy of this FDC compared to a statin alone,^{46, 65} but as with the triple anti-hypertensive FDCs, further research into the FDCs impact on adherence, longer-term clinical endpoints and costs is required. Presently the combination of ezetimibe and a statin (either simvastatin, atorvastatin or rosuvastatin) are available in the United States,⁵⁹ Europe,⁶⁰ and Australia.⁶¹ The FDC combination of simvastatin with ezetimibe (Zimybe) is currently available in New Zealand with a Special Authority.⁶⁶

3.1.2 Multi-risk factor FDCs

The recent introduction of multi-risk factor CVD FDCs has revitalised interest in CVD FDCs. In 2017, the Cochrane Collaboration⁴¹ conducted a review of the effect of FDCs that contained at least one anti-hypertensive and one lipid-lowering component for the prevention of atherosclerotic CVD. The study aggregated 13 RCT (total participants=9059) which compared two to five agent CVD FDCs to usual care, placebo or equivalent monotherapy. Overall, the review found that the CVD FDCs significantly reduced systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C) levels (moderate evidence quality) and that adherence improved by 44% (26% to 65%). No statistically significant difference in mortality and CVD event rates were observed in this review, but this could be due to the

short duration of the trials, which would not capture the long-term effects of treatment. Treatment with a FDC was associated with a slight increase in the risk of an adverse event (RR = 1.6, 95% confidence interval (95%CI): 1.09 to 1.25). Overall the reviewers evaluated the quality of the evidence to be low and the heterogeneity of the included studies was high. Further longer-term research is required to see if the observed changes in risk factors result in changes to the risk of CVD events and CVD-mortality.⁴¹ Meta-analyses that consider more homogenous FDCs (in terms of type and number of active components) would also be desirable.

Anti-hypertensive with a statin two-agent FDCs

FDCs that combine an anti-hypertensive with a statin are currently the most available and utilised multi-risk factor FDC for CVD prevention. The combination of amlodipine, a calcium channel blocker (CCB) with atorvastatin is currently available in Australia⁶¹ and the United States.⁵⁹ To date, no such FDCs are available in New Zealand.

Several RCTs to date have been conducted demonstrating the significant effect that the amlodipine/atorvastatin FDC has on lowering blood pressure and cholesterol levels simultaneously. Erdine et al 2009,⁶⁷ for example, conducted a 14-week non-comparison RCT that included participants from 27 countries (Latin America, Middle East, Africa and Asia-Pacific) who ranged from low to high CVD risk. The study observed significant reductions in mean SBP and diastolic blood pressure (DBP) after 14 weeks (-20.2 and -11.5 mmHg respectively) as well as total cholesterol levels which reduced by 21.6%. Adverse events experienced by all study participants that resulted in the discontinuation of therapy were relatively low (3.6%). Excluding those with known CHD and/or diabetes mellitus, the 10-year Framingham CVD risk decreased from 13.4% to 6.2% over the 14-week study period.⁶⁷ Further to the observed improvement in clinical efficacy with the use of the FDC amlodipine with atorvastatin, adherence was also greatly improved.

Another study by Patel et al 2009⁶⁸ found that those who took this type of FDC were 1.95 times as likely to be adherent (defined as >80% pill days covered (PDC)) than those taking the component separately over six months. Adherence was still markedly greater among those taking the FDC compared to two separate pills at one year (adjusted OR = 2.71, 95%CI: 2.46 to 2.99). A similar increase in adherence with this FDC was observed in an Australian study by Simons et al⁶⁹ and an American study by Chapman et al.⁷⁰ The study by Chapman et al in 2010⁷⁰ was a retrospective cohort study using administrative claims data in the United States. The study identified individuals taking either a CCB like amlodipine or a statin like atorvastatin, who during an index period were switched to the single pill FDC or had either a CCB or a statin added to their regimen (resulting in them taking the same two components as separate pills). In addition to finding that those taking the single pill FDC were 4.7 times as likely to be adherent (proportion of days covered by a prescription greater than 80%), the study also

found that those taking the FDC who were adherent experienced fewer CVD events than those taking a CCB and a statin separately (Hazard ratios: 0.79, $p < 0.05$; 0.61, $p < 0.05$ respectively when compared to non-adherent CCB and statin separately).⁷⁰

‘Polypill’ for CVD prevention

This type of polypill is a CVD FDC that combines aspirin and a statin with several different anti-hypertensives that was suggested as a method to prevent CVD in the early 2000s. Yusuf et al 2002⁷¹ suggested the combination and the following year Wald and Law published a study that boldly predicted that if everyone aged 55 years and older with existing CVD was treated with their six-agent ‘polypill’ (aspirin, a lipid-lowering agent, folic acid and 2–3 anti-hypertensives), then CHD and stroke deaths would reduce by 88% (95%CI: 84 to 91%) and 80% (95%CI: 71 to 85%) respectively. They argued that population-wide treatment based on CVD alone would benefit a third of the population, while 8–15% would experience adverse effects.⁷²

Since Wald and Law’s publication,⁷² several RCTs have been conducted internationally to investigate the benefit of a ‘polypill’ for CVD prevention. The results from three major polypill RCTs, namely, IMPACT,⁵⁰ UMPIRE⁴⁸ and Kanyini-GAP⁴⁹ that consider a four-agent polypill (aspirin, statin and two anti-hypertensives) are summarised in Table 2. Although all three studies show major improvements in self-reported adherence when compared to usual care, the effect of the ‘polypill’ on primary clinical endpoints such as SBP or DBP and LDL cholesterol is minimal. Furthermore, no effect on CVD events has been observed, possibly due to most studies not containing enough power or duration to detect a significant difference. Adverse effects experienced by those on the polypill appear to be greater than those on usual care which could have contributed to the trial discontinuation rates.⁴⁸⁻⁵⁰

Internationally, the benefit of the CVD polypill to effectively reduce CVD risk is debated. Primarily, countries and organisations are concerned with the idea of mass population-level pharmaceutical treatment and the associated risk of removing the focus from individual health changes and over medicating a population. Furthermore, despite improved adherence, short-term gains (blood pressure and LDL reduction) and long-term gains (reduced CVD events, hospitalisations and costs) are yet to be observed. Currently, only a three-agent polypill containing aspirin, a statin and an anti-hypertensive has been approved for secondary CVD prevention in 15 European countries (including Spain, Sweden, Finland, Germany and Austria) and Chile as a direct substitution for those already taking the polypill components as monotherapy. Although approved, the polypill is only marketed in Germany, Greece, Romania and Spain.⁷³ The polypill has been submitted for approval to appear on the World Health Organization (WHO) essential medicine list in 2013 and 2015 and to the PHARMAC Pharmaceutical Schedule in New Zealand in 2016. On all occasions, the submission was declined for the reasons described above. In addition, concern was raised regarding the effect the polypill will have on an

individual's pill burden with PHARMAC quoting "...the convenience of taking one FDC polypill (instead of multiple single pills) would be minimal in those patients who are already taking a number of pharmaceuticals for multiple comorbidities".⁷⁴ Further research is currently being conducted and is required in this area to add data about the advantages/disadvantages of polypill use.

Table 2: Summary of three major 'polypill' RCTs (Kanyini-GAP, IMPACT, UMPIRE)

Study and Population	Polypill (vs Usual Care (UC))	Adherence	Change in SBP	Change in LDL	CVD event outcomes
Kanyini-GAP ⁴⁹ 623 participants from Australia aged 18 or over with established CVD or five-year CVD risk of 15% or greater.	Aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and either atenolol 50 mg or hydrochlorothiazide 12.5 mg	70.1% Polypill vs 46.9% usual care RR 1.49 (95%CI: 1.30 to 1.72)	-1.5 mmHg (95%CI: -4.0 to 1.0)	-0.08 mmol/L (95%CI: -0.06 to -2.22)	No significant difference
IMPACT ⁵⁰ 513 participants from New Zealand 18 or over with established CVD or five-year CVD risk of 15% or greater.	Aspirin 75 mg, simvastatin 40 mg and lisinopril 10 mg with either atenolol 50 mg or hydrochlorothiazide 12.5 mg	81% polypill vs 46 % usual care RR 1.75 (95%CI: 1.52 to 2.03)	-2.2 mmHg (95%CI: -2.6 to 1.2)	-0.05 mmol/L (95%CI: -0.17 to 0.08)	No significant difference
UMPIRE ⁴⁸ 2004 participants from India, United Kingdom, Ireland and the Netherlands, aged 18 or over with established CVD or five-year CVD risk of 15% or greater.	5 mg aspirin, 40 mg simvastatin, 10 mg lisinopril and 50 mg atenolol OR 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril and 12.5 mg hydrochlorothiazide	86.3% Polypill vs 64.7% usual care RR 1.33 (95%CI: 1.26 to 1.41)	-2.6 mmHg (95%CI: -4 to -1.1)	-0.1 mmol/L (95%CI: -0.17 to -0.05)	No significant difference

3.1.3 New Zealand CVD FDCs

In New Zealand, in 2017 there were six, two-agent FDCs available on the PHARMAC Pharmaceutical Schedule 2017 (Table 3) These six FDCs cover four pharmaceutical classes, five contain two anti-hypertensive components and one contains two lipid-lowering agents.⁶⁶ Australia, by comparison, had 23 two-agent CVD FDCs covering seven pharmaceutical classes that go beyond two-agent anti-hypertensives.⁶¹

Table 3: FDC available in New Zealand 2017

Class	Brand name	Generic Name/Chemical Compounds
ACE Inhibitors with Diuretics	Apo-Cilazapril/Hydrochlorothiazide	Cilazapril (5 mg) with hydrochlorothiazide (12.5 mg)
	Accuretic 10	Quinapril (10 mg) with hydrochlorothiazide (12.5 mg)
	Accuretic 20	Quinapril 20 mg with hydrochlorothiazide (12.5 mg)
Angiotensin II Antagonist with Diuretics	Arrow-Losartan & Hydrochlorothiazide	Losartan potassium (50 mg) with hydrochlorothiazide (12.5 mg)
Potassium Sparing Combination Diuretics	Frumil	Amiloride hydrochloride (5 mg) with furosemide (40 mg)
	Moduretic	Amiloride hydrochloride (5 mg) with hydrochlorothiazide (50 mg)
Cholesterol Lowering	Zimbye	Ezetimide (10 mg) with simvastatin (10, 20, 40, 80 mg)
Source: PHARMAC 2017 ⁶⁶		

3.1.4 Conclusions

The current body of evidence suggests that, in general, CVD FDCs are likely to result in superior adherence and clinical efficacy compared to two agents taken separately, usual care or placebo. Furthermore, there is some evidence to suggest that improved adherence and clinical efficacy should result in longer-term reductions in: CVD incidence and mortality, CVD-related hospitalisations and CVD-related hospital and pharmaceutical expenditure. Literature supporting the clinical efficacy of CVD FDCs is vast due to the requirement of clinical trials to bring new pharmaceuticals to market. However, further research is required to add evidence to the use of FDCs as a method to improve adherence, reduce CVD disease burden and reduce costs. Future research that compares CVD FDCs to the same components as monotherapies, rather than a single pharmaceutical or another pharmaceutical regime, would be desirable as switching people currently on the monotherapy components to the corresponding FDC is one of the primary aims of a FDC (second to initiating people on combination therapy). RCTs may fail to observe the real-world effectiveness of the FDC on adherence due to differences between a trial setting and the real world. Short study durations that limited the ability to observe longer-term benefits, the funding of studies by pharmaceutical companies that have a vested interest the studies results and poor study design are limitations in the existing literature which should be noted and considered in all future research. It is also important to note that although the availability of FDCs in many countries is increasing, this does not necessarily translate to FDC uptake. Country-specific research that compares the cost of the FDCs with the costs

of the equivalent monotherapies, cost to the government, individual or another third party (ie, insurer), as well as physician and patient acceptability in prescribing an FDC, is also required.

3.2 Literature review of the cost-effectiveness of CVD FDCs

The terms listed in Table 4 were searched in OVID Medline (1946 to present [02/2017] with daily update), PubMed and Scopus in February 2017. In an additional search, the terms ‘cost-effectiveness’ AND ‘polypill’ AND ‘cardiovascular disease’ were searched in OVID Medline (1946 to present [02/2017] with daily update) and PubMed. Search results were restricted to those published from 2007 onwards and those published in the English Language. Search results were downloaded to Endnote. Duplicate publications were identified and excluded. Further exclusions were made if the study FDC had greater than two pharmaceutical components, if the outcome was not deemed to be associated with cardiovascular disease (ie, HIV), if one or more of the FDC pharmaceutical components did not target a specific CVD risk factor (ie, not an anti-hypertensive, lipid-lowering or anti-platelet pharmaceutical) and if the study did not look at cost-effectiveness broadly (ie, studies that just compared costs and lacked an effectiveness component). Studies that summarised other studies such as reviews or opinion publications were also excluded. The reference lists of included publications were also examined to identify additional relevant research. An additional search was conducted in February 2018 to identify any new publications.

Table 4: Summary of literature review search terms

Relating to cost-effectiveness	Cost-utility, effectiveness, cost-effectiveness, cost-benefit analysis, economic evaluation
Relating to FDC	Fixed-dose combinations, fixed combinations, FDC
Relating to CVD	Ischaemic heart disease, myocardial ischemia, coronary disease, coronary artery disease, coronary heart disease, cardiovascular disease, stroke, hypertensive, hypertension, anti-hypertensive agent, blood pressure, hypercholesterolemia, cholesterol

After exclusions, five studies concerning the cost-effectiveness of two-agent FDCs were identified (two looked at an anti-hypertensive, lipid-lowering FDC, two looked at a two-agent anti-hypertensive FDC and one looked at a two-agent FDC of which both components were lipid-lowering) and nine publications concerning the cost-effectiveness of various polypills (aspirin, a statin and at least one anti-hypertensive). The literature concerning two-agent FDCs is explored separately to the literature regarding polypills. The identified publications are summarised in Appendix One.

3.2.1 Two-agent CVD FDCs

Summary of identified studies

Two of the identified studies investigated the cost-effectiveness of the FDC amlodipine (an anti-hypertensive) with atorvastatin (a statin) (FDC AA) in a Korean primary prevention context. The earlier study by Liew et al 2009⁷⁵ considered the cost-effectiveness of a FDC AA compared to business-as-usual using a lifetime Markov model. The model considered a Korean health system perspective and included Korean-specific health system costs, pharmaceutical costs and utility values. A decline in adherence in the first year from 100% to 69% was also incorporated in the model. The characteristics of the modelled population were informed by a national data collection which was used in conjunction with Asian specific CVD risk equations to determine the population's risk of having a CVD event. Blood pressure and cholesterol changes as a result of the FDC AA were modelled annually and modified the risk of having a CVD event. The study concluded that the FDC was likely to be a cost-effective means of preventing CVD with an incremental cost-effectiveness ratio of 7,773,063 South Korean Won (KRW) per QALY gained (US\$ 5979 per QALY gained). The subsequent study by Park et al in 2015,⁷⁶ considered the use of FDC AA compared to the same two agents as monotherapy for the primary prevention of CVD in a diabetic population (requiring both statin and anti-hypertensive therapy). A simple decision tree model was used in which the percentage of LDL goal attainment was determined based on differing rates of adherence. Both pharmaceuticals were assumed to be equal in efficacy. Pharmaceutical costs were Korean specific and related to adherence. The study concluded that the FDC AA was likely to be a cost-effective method of primary CVD prevention with the average cost-effectiveness ratio for the FDC AA smaller (more favourable) than for that for A+A.

Briseno et al 2010⁷⁷ considered the cost-effectiveness of the FDC ezetimibe and simvastatin compared with rosuvastatin (all lipid-lowering agents). The effectiveness component, percentage change in LDL cholesterol levels from baseline to week eight, was derived from a retrospective review of 296 patients records in a Mexican cardiology ward. The effectiveness of treatment was compared to the pharmaceutical cost of treatment. Briseno et al 2010⁷⁷ concluded that rosuvastatin was more cost-effective at reducing LDL-cholesterol than the ezetimibe and simvastatin FDC with the cost per 1% reduction in LDL levels for rosuvastatin being approximately half that of the FDC.

The study by Glasziou et al 2010⁷⁸ was different to the other identified studies as it considered the cost-effectiveness of FDC being accessed in a clinical trial. This "ADVANCE trial" was a multicentre RCT in type two diabetes patients who were randomised to receive either the FDC perindopril with indapamide or placebo (both anti-hypertensive agents) in addition to any other existing CVD pharmaceutical. Health-related quality of life was measured in the trial, but the difference between the trial arms was not statistically significant. The cost per death averted was alternatively considered

as the measure of effectiveness. Healthcare and pharmaceutical costs for the Australian subset of the trial were determined through record linkage. The study concluded that the FDC was likely to be cost-effective with a cost per life-year saved of AU\$49,000. One other identified study considered the cost-effectiveness of a two-agent anti-hypertensive FDC. Kawalec et al 2015⁷⁹ investigated the cost-effectiveness for indapamide with amlodipine FDC compared to the two agents as dual monotherapy for the prevention of CVD in Poland. The Markov model considered two situations, one in which the FDC was assumed to have better adherence and clinical outcomes, and one where both treatments had equal adherence. In both cases, the use of the FDC was cost-saving compared to equivalent monotherapies.

Evaluation of identified studies

The volume of literature concerning the cost-effectiveness of two-agent FDC combinations is small with just five studies identified. Comparison of each of the studies as an intervention for CVD prevention is difficult due to the notable difference in study rigour, modelling methodology and modelling principles.

Liew et al 2009⁷⁵ was the only identified study that specifically investigated the cost-effectiveness of a FDC for the primary prevention of CVD and consistently used Korean specific information to inform model inputs. Glasziou et al 2010⁷⁸ also achieved consistency in model inputs with the majority of the model inputs informed by the ADVANCE trial. Both Glasziou et al⁷⁸ and Park et al⁷⁶ considered the use of FDC in a diabetic population. The population in Briseno et al⁷⁷ was the least specific. The distinction between primary and secondary prevention was not clear in the studies by Glasziou et al,⁷⁸ Park et al,⁷⁶ Kawalec et al,⁷⁹ and Briseno et al.⁷⁷

FDCs are designed to be bioequivalent to their monotherapy components and improve adherence. As such, the appropriate study comparator should be the equivalent monotherapies. Differences in adherence should also be considered. Park et al 2015⁷⁶ and Kawalec et al 2015⁷⁹ were the only identified studies to consider monotherapies as a comparator and incorporate an adherence component. Liew et al's⁷⁵ comparison of business-as-usual could be considered representative of equivalent monotherapies if the majority of included patient's business-as-usual included therapy with an anti-hypertensive and a statin. But it was not clear whether or not this was the case. Future economic evaluations of CVD FDCs should endeavour to have the equivalent monotherapies as the comparator and incorporate adherence.

Effectiveness is a key component in cost-effectiveness studies. All five identified studies used different effectiveness measures (quality-adjusted life years (QALYs)^{75, 79}, the percentage decrease in LDL levels⁷⁷, percentage of LDL goal attainment⁷⁶ and deaths averted⁷⁸). QALYs are considered the gold-standard of effectiveness measurement in health economic evaluation as they combine both the

morbidity and mortality burden of a condition and can be compared between other health conditions. Liew et al 2009⁷⁵ and Kawalec et al 2015⁷⁹ were the only studies to consider QALYs as an effectiveness measure. QALYs were measured in the study by Glasziou et al,⁷⁸ but the difference between the trial arms was not statistically significant. The number of CVD and non-CVD deaths averted were alternatively used as the effectiveness component. Although all the effectiveness measures used in the identified studies provide useful information, they limit the comparability between the studies and limit the ability of decision-makers to evaluate different interventions to achieve a common goal.

Although the pharmaceutical components in the FDCs evaluated are aimed at reducing CVD risk factors, the ultimate goal is reducing absolute CVD risk and the occurrence of CVD events (both fatal and non-fatal). The study by Liew et al 2009⁷⁵ used data on changes in surrogate CVD endpoints (reductions in blood pressure and cholesterol) to inform changes in absolute CVD and hence CVD events over a lifetime model horizon thus considering the long-term implications of FDC use. Glasziou et al⁷⁸ considered the deaths averted over the five-year duration of the RCT with the difference in deaths averted evidence of the primary endpoints. Park et al⁷⁶ and Briseno et al⁷⁷ only considered the change in surrogate markers over a one-year period. Assessing differences over a long enough time to observe changes in CVD events greatly strengthens the quality of evidence the study provides.

Finally, the comparability of identified results to each other and the generalisability to the population beyond those considered in the studies is limited by the use of country-specific costs. The cost of pharmaceuticals and health services that were incorporated in each model are impacted by structure and funding of the healthcare system in each country. The Glasziou et al⁷⁸ study used Australian specific costing information, which may be moderately generalisable to New Zealand as the healthcare system structure is relatively similar. Nevertheless, pharmaceutical costs are typically considerably lower in New Zealand compared to Australia.^{80, 81} The studies by Liew et al,⁷⁵ Park et al⁷⁶ and Glasziou et al⁷⁸ were affiliated in sponsorship or personnel with pharmaceutical companies that manufactured the FDC being studied. It is reasonable to assume that both of these pharmaceutical companies have a vested interest in the outcome of both papers as it has the potential to influence the pharmaceutical's utilisation. As such interpretation and generalisation of the results of these studies should be done with caution.

3.2.2 CVD prevention with polypills

Summary of identified studies

Nine studies investigating the cost-effectiveness of polypills for CVD prevention were identified in the literature. Two studies considered the cost-effectiveness of a five-agent polypill (aspirin, a statin and three anti-hypertensives) for the primary prevention of CVD. Bautista et al 2013⁸² considered a hypothetical Latin America population with baseline characteristics informed by a multi-national Latin

America survey while the study by Zomer et al 2013⁸³ was conducted in Australia using microsimulation of patient-level data identified from an Australian database. Both studies used a Markov model in which the risk of experiencing a CVD event was determined by geographic specific CVD risk equations. Bautista et al 2013⁸² compared the polypill to no-treatment while Zomer et al 2013⁸³ compared the polypill to multiple combinations of monotherapies. Changes in blood pressure and cholesterol levels within each of the pharmaceutical interventions were informed by the Indian Polycap study (TIPs) and consequently changed the risk of a CVD event. Both studies measured effectiveness in terms of QALYs and costs in terms of health system costs. In Bautista et al 2013,⁸² the polypill was estimated to cost US\$50 per year, while Zomer et al 2013⁸³ assumed the cost was 25% less than the equivalent monotherapies. Bautista et al 2013⁸² concluded that the use of the polypill for the primary prevention of CVD in those at high CVD risk (10-year absolute CVD of 15% or more) or those with abdominal obesity, was likely to be cost-effective. Zomer et al 2013⁸³ concluded the polypill may be an effective method of primary CVD prevention but not a cost-effective method with a cost of approximately AU\$200,000 per QALY gained.

A four-agent polypill (aspirin, a statin and two anti-hypertensives) was evaluated in four of the identified studies. Each of the identified studies were heterogeneous. Firstly, the study by Laba et al 2014⁸⁴ considered the cost-effectiveness of the polypill compared to usual care for the secondary prevention of CVD by piggy-backing onto the Kaynini-GAP polypill RCT conducted in Australia. The study utilised the trial data and determined healthcare resource and pharmaceutical use through record linkage. The results of this study were primarily a cost-evaluation with no effectiveness component noted. The study concluded that the polypill had significantly lower pharmaceutical costs compared to usual care, but there was no difference in healthcare resource costs. The second study by Ito et al 2012⁸⁵ also considered the polypill as a secondary prevention measure and compared it to other adherence-improving interventions, namely, mailed education and disease management. A comprehensive lifetime Markov model of a hypothetical population of Americans aged over the age of 65 was used, with changes in pharmaceutical adherence as a result of each intervention modulating the risk of a secondary CVD event. The model measured effectiveness in QALYs and the costs reflected intervention costs as well as the pharmaceutical costs and health system costs. The study estimated that the polypill alone had an average cost-effectiveness ratio of US\$133,000 per QALY gained compared to usual care (no adherence-improving interventions). The polypill was the most expensive intervention per QALY gained except for the polypill in combination with disease management, which was more expensive. The study by Ndinjock et al 2011⁸⁶ looked at the cost-effectiveness of treating the population over the age of 40 with high CVD risk established by African-specific risk equations with the polypill compared to treating the population with high blood pressure or cholesterol with monotherapies. Anticipated reductions in CVD events for the polypill were taken from Wald et al's

(2003) proposed polypill predictions. Costs were limited to pharmaceutical costs. Treating people based on CVD risk rather than addressing individual risk factors was considered to be the more cost-effective method of CVD prevention when the number needed to treat and deaths averted were balanced against each other. Lastly, Megiddo et al 2013⁸⁷ considered the polypill for secondary prevention of CVD in India compared to equivalent monotherapies. The model method used was not clear in the publication. Nevertheless, the polypill was considered to be less costly than the equivalent monotherapies and no difference in adherence was noted. The study concluded that the polypill was a positive intervention for the secondary prevention of CVD resulting in a smaller cost per disability-adjusted life-year (DALY) averted than the equivalent monotherapies.

Becerra et al 2015⁸⁸ was the only study of those identified that looked at the use of a three-agent polypill (combined aspirin, an anti-hypertensive and a lipid-lowering component). The study compared the polypill to the same components taken as monotherapies for the secondary prevention of CVD in a primary care setting in the United Kingdom. The model considered a health system perspective Markov model with a 10-year time horizon. The authors stated that no clinical trial data about the polypill were available, so the clinical efficacy was assumed to be equal to the combination of elements taken individually. Inputs on adherence were derived from the UMPIRE study, a study which looked at four-agent polypill. In the base-case the polypill was assumed to improve adherence by 20% compared to monotherapies, preventing 15% more CVD events, resulting in an incremental cost-effectiveness ratio (ICER) of GBP8,200 per QALY. This was considered by the authors to be cost-effective.

Ong et al 2014⁸⁹ and Ferket et al 2017⁹⁰ were the only studies identified in the literature review of this thesis to evaluate a polypill that did not contain aspirin. Both studies considered the cost-effectiveness of a polypill combining a statin and three anti-hypertensives. Ong et al 2014⁸⁹ study examined the effect of the four agent-polypill as a CVD prevention measure for indigenous Australians and compared to statins alone, two different anti-hypertensive classes taken as monotherapy and a healthy lifestyle intervention. Ferket et al 2017⁹⁰ alternatively compared the polypill as a population-wide intervention to treating CVD risk factors in patients with high CVD risk for the primary prevention of CVD in the United Kingdom. Ong et al 2014⁸⁹ considered a health system perspective, lifetime Markov model. The efficacy of the polypill was considered to be the multiplicative effect of the four individual components taken simultaneously and the cost was modelled to be between AU\$50 and AU\$500 per person per year. The polypill was found to be the most cost-effective option to reduce CVD in Australian indigenous population. At the highest proposed cost of \$500 annually for the polypill, the intervention resulted in AU\$13,000 per DALY averted when provided at mainstream GP clinics and AU\$21,000 per DALY averted from indigenous health centres.⁸⁹ Ferket et al 2017⁹⁰ used a comprehensive microsimulation model of 260,000 patients in the UK and included the disutility of taking a daily pill for the population of patients who would not otherwise need to take a CVD pharmaceutical. Ferket et al

2017⁹⁰ concluded that treating patients at high CVD risk was a more cost-effective method of primary CVD prevention than widespread use of the polypill. Although the polypill could be considered an effective strategy, it came at a higher cost.⁹⁰

Evaluation of identified studies

The evidence concerning the cost-effectiveness of the polypill is small with just nine studies identified. Several of the identified studies support the hypothesis that the polypill is a cost-effective or cost-saving method for reducing CVD risk, while others conclude it may be an effective but not cost-effective strategy or not cost-effective at all. As with the literature identified for two-agent FDCs, there is a large degree of heterogeneity between the studies methods, models and principles which makes comparison difficult. Several studies considered the polypill for primary CVD prevention,^{82, 83, 89, 90} while others considered the use of the polypill for secondary care services.^{85, 87, 88} Several studies compared the polypill to various pharmaceutical components while other studies compared the polypill to other intervention strategies (ie, other adherence-improving interventions, risk factor approach). Furthermore, there was a breadth of countries studied, from developing countries in Latin America and Africa, to high-income countries including the United Kingdom, the United States and Australia. Not only does the risk of a CVD event differ between countries due to population differences in CVD risk factors, each country has a unique health system structure which influences the cost of health system services and pharmaceutical costs in the model.

When considering the evidence of the cost-effectiveness of the polypill it is important to bear in mind the strength of evidence concerning the clinical efficacy of the polypill and the uncertainty surrounding the pharmaceutical cost of the polypill. As has been discussed in the previous section of this thesis, the clinical efficacy of the various polypills have only been considered in a small number of RCTs, which did not show any statistically significant difference in surrogate CVD endpoints despite improved adherence. Most of the identified studies used information from these RCT to determine the clinical efficacy of the polypill. Furthermore, at the time of this thesis, only a couple of polypill formulations were approved for use in a small selection of countries. Consequently, the price of the polypill if it was to be funded in the countries studied, was uncertain. Where the cost of the polypill was unknown in the identified literature, it was estimated based on assumptions that it would be equivalent or a proportion of the cost of monotherapy^{83, 85, 87} or based on expert opinion.^{82, 89} Although informing the efficacy of the polypill from the available trials and estimating the cost is reasonable given the limited information available, it is important to consider the effect these assumptions could have on the overall cost-effectiveness. The incremental efficacy and cost of the polypill to the comparator, be it a pharmaceutical or non-pharmaceutical intervention, is an important driver of the resulting cost-effectiveness ratio and should be considered when interpreting and applying the results of cost-effectiveness studies.

3.2.3 Conclusions

Overall the literature concerning the cost-effectiveness of two-agent FDC and CVD polypill was sparse. The identified literature suggests that two-agent CVD FDC and CVD polypill could be a cost-effective method of addressing evident CVD burdens globally. However, overall the results are inconclusive. The identified literature is heterogeneous with large variation in modelling methodology, assumptions and principles, the comparison used and the source of model inputs. The heterogeneity between the identified studies makes comparison between the studies difficult. None of the identified studies were conducted in a New Zealand context.

Chapter 4: Methods

This Chapter begins by describing why the FDC amlodipine with atorvastatin was chosen to be modelled in this thesis. Following a brief overview of the multi-state life-table model used in this thesis, the process of selecting the input parameters for both the intervention (FDC amlodipine with atorvastatin) and comparison (amlodipine and atorvastatin) are described. The Chapter concludes by describing the model scenario and sensitivity analyses that were carried out.

4.1 Justification of study pharmaceuticals

As previously discussed in this thesis, there are many different FDCs used in the prevention and treatment of CVD. After considering a range of possible two-agent FDCs to model, a decision was made to model the cost-effectiveness of a two-agent FDC that contained an anti-hypertensive component, amlodipine (a CCB) and a lipid-lowering component, atorvastatin (a statin). The FDC of amlodipine with atorvastatin will be referred to subsequently as FDC AA. The FDC AA is part of a relatively new and emerging area of CVD FDC pharmaceuticals that target multiple CVD risk factors simultaneously in a single pill form. This approach aligns with CVD guidelines internationally⁹¹ and in New Zealand²¹ which emphasise the importance of considering absolute CVD risk. The FDC AA is currently approved in several countries including the United States,⁵⁹ Australia⁶¹ and several European countries including France, Spain, Poland, Austria, Finland and Hungary.⁹² However, the FDC AA is not currently available in New Zealand.⁶⁶ The results of this research could therefore be useful for New Zealand decision-makers considering the funding of the FDC AA in the future. In addition, atorvastatin was the sixth most prescribed medicine in New Zealand in 2016 with 1.2 million prescriptions, while CCBs like amlodipine had just over one million prescriptions in the same year.¹⁰ In New Zealand, it is estimated that 21% and 25% of Māori women and men aged 60 to 64 respectively are taking both a statin and an anti-hypertensive. The percentage is slightly lower for non-Māori with 12% of women and 15% of men estimated to take both a statin and an anti-hypertensive in 2013.⁹³ These figures illustrate a significant population whom, if a FDC AA was shown to be cost-effective in the New Zealand context, could benefit from switching from two monotherapies to the FDC AA.^{93, 94} Accordingly, this thesis models the cost-effectiveness of a scenario where individuals currently taking amlodipine and atorvastatin as two separate pills (A+A) switched to take the FDC AA (ie, to study the marginal health gain, costs and cost-effectiveness of the FDC AA compared to A+A).

4.2 Ethics and funding

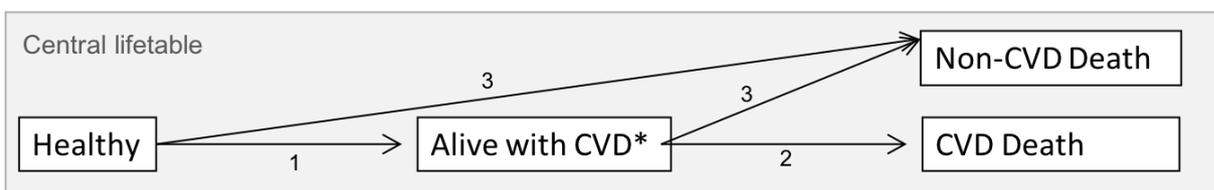
The work in this thesis was conducted, funded and approved as part of a larger Health Research Council awarded to the Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE³) (project number 10/248, Ethics Committee reference number H13/049.).

4.3 CVD multi-state life-table

4.3.1 Model overview

The cost-effectiveness of switching from the A+A to the FDC AA regimen was evaluated in this thesis using an existing CVD multi-state life-table (MSLT) model. This CVD MSLT model had been adapted from the validated Tobacco Control MSLT model that was developed previously by the BODE³ research group, with a number of related research publications.^{19, 95-97} The model functions to collate the morbidity and mortality experience in terms of QALYs as well as the health system costs that would accrue over the lifetime of a group of adult New Zealanders (specifically men aged 60 to 64 years) with or without a specified intervention. In this case, the intervention was the FDC AA compared to the A+A regimen.

Conceptually, the CVD MSLT model has three interrelated life-tables. The central life-table of the model represented the life experience of the entire modelled population over time between three health states; 'healthy', 'alive with CVD' and 'dead' (see Figure 1). No transitioning between 'alive with CVD' and 'healthy' was permitted in the model to reflect the chronic, non-remitting nature of CVD. Running in parallel to the central life-table were two additional disease life-tables. These two disease lifetables stratify the movement to, within and from the 'alive with CVD' state to consider the experience of CHD (ie, alive with CHD) and stroke (alive with stroke) separately. (The three life-tables are conceptually outlined in Figure 2).



1: CVD incidence, 2: CVD case-fatality rate, 3: background mortality rate (adjusted for CVD deaths)

* CVD includes CHD and stroke only

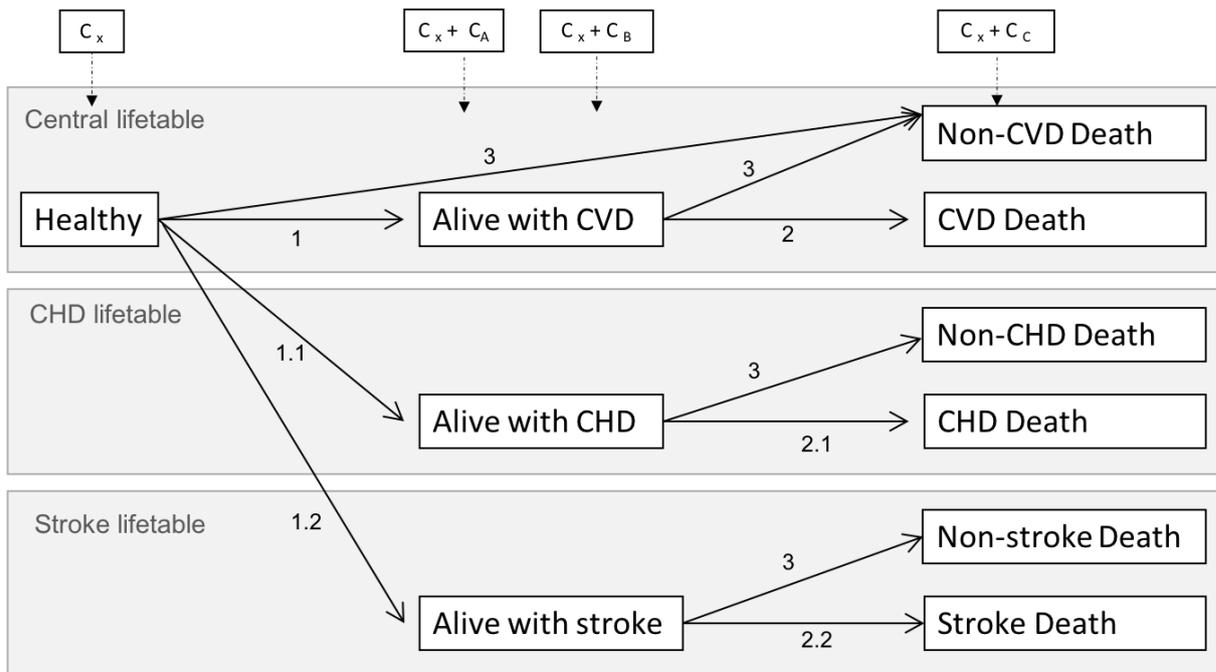
Figure 1: CVD MSLT model showing state transitions

Within the central life-table, a proportion of the model population each cycle transitioned from a 'healthy' state to an 'alive with CVD' state. This transition represents the sum of the transition from 'healthy' to 'alive with CHD' or 'alive with stroke', which occurred simultaneously in the disease life-tables. The transition from 'healthy' to 'alive with CHD' was informed by the incidence rate for CHD while the transition from 'healthy' to 'alive with stroke' was informed by the incidence rate for stroke. The incidence rates for stroke and CHD and therefore the transitional probability between the 'healthy' state and 'alive with CHD' or 'alive with stroke' state were age, sex and ethnicity-specific (albeit in this version of the model, just for 60 to 64-year-old men).

The transition from an 'alive with CVD' state to 'death' in the central life-table represented the sum of the transition from 'alive with CHD' and 'alive with stroke' to 'death by CHD', 'death by stroke' and 'death by non-CVD causes'. The transition from 'alive with CHD' and 'alive with stroke' state to 'CHD death' or 'stroke death' was informed by the case-fatality rates for CHD and stroke respectively. Death from other causes was informed by the New Zealand population mortality rate, which was adjusted for CVD deaths to avoid double counting. The adjusted background mortality rate also informed the transition probability from the 'healthy' state to 'death by non-CVD causes'. The case-fatality rates for stroke and CHD, in addition to the background mortality rate, were also all age, sex and ethnicity specific.

The annual incidence and case-fatality rate (CFR) for CHD and stroke decreased by 2% annually in the model to reflect the ongoing decline in CHD and stroke. The proportion of the population residing in each health state at any one time was representative of the disease prevalence and was a function of the incidence rate (inflow) and CFR (outflow) for each disease. Further details on how the CVD disease incidence rates, prevalence and CFRs were calculated from New Zealand epidemiological data using DISMOD II is outlined in the supplementary material of the tobacco MSLT.¹⁹

Essentially, the entire model cohort is represented in the central life-table, but the experience of those who experienced CVD (either stroke or CHD) will be captured in the CHD and stroke life-tables that are run in the model simultaneously. It is important to note that it was possible for individuals to exist in more than one disease life-table in the model at any one time (hence the name MSLT). For example, it is possible for someone to have prevalent CHD disease and stroke simultaneously. The transitional probabilities are adjusted to take this into account. The incidence and case-fatality rates are also adjusted to reflect recurrent stroke or CHD events. The model only considered the life-tables for stroke and CHD. As a result, the benefit of an intervention on conditions other than CHD and stroke are not be captured in this model.



Transition probabilities (ages, sex and ethnicity specific)

1: CVD incidence, 1.1: CHD incidence, 1.2: Stroke incidence, 2: CVD case-fatality rate (CFR), 2.1: CHD CFR, 2.2: stroke CFR, 3: Background mortality rate adjusted for CVD deaths.

Health system costs

C_x : baseline healthy system cost, C_A : health system cost of first year of CVD, C_B : health system cost of prevalent CVD, C_C health system cost in final year of life

Figure 2: Systematic representation of the CVD MSLT health states, transition probabilities and health system costs.

4.3.2 Health impact (QALYs gained)

The health impact or time spent in poor health was quantified in the model by QALYs. QALYs aggregate changes in mortality (number of years of life lived) and morbidity (health associated quality of each year lived) experienced by a population. Mortality is informed by changes in life-expectancy while morbidity is informed by disability weights. Disability weights aim to quantify the severity of disability experienced by a condition on a scale of zero (full health and no disability), to one (severe disability equivalent to death). Primary prevention interventions, like the one in this thesis, involve modelling with the aim of reducing the incidence of disease and consequently both disease morbidity and mortality. Nevertheless, the QALYs gained by a primary prevention intervention for CVD are generally influenced more by a gain in life expectancy rather than a quality of life improvement.

The disability weight for those in the central life-table were determined by dividing the total years of life lived in disability from the 2006 New Zealand Burden of Disease Study (NZBDS) (2011 projected estimates) by the total population size. The resulting disability weight were then adjusted to avoided double counting of CVD morbidity. Disability weights in the two CVD life-tables were determined by dividing the years of life spent in disability with CHD or stroke by the prevalence of the respective

disease. The calculated annual disability weights were assigned to each health state and were accrued by the proportion of the population residing in each health state with each annual model cycle. All disability weights in the model were age and sex-specific and were accrued with each annually model cycle. The model used a disability weight for non-fatal stroke of 0.226 and 0.081 for non-fatal CHD.

4.3.3 Costs

The CVD MSLT model takes a health-system perspective. Consequently, the model considered costs associated with the health system in the treatment and management of CVD disease. The model benefited from rich costing and health event data from the New Zealand HealthTracker database which records all health events and costs that occur as part of the publicly funded health system in New Zealand.⁹⁸ The unit resource costs linked to each health event included inpatient hospitalisation, outpatient attendance, laboratories usage, as well as pharmaceuticals. Primary care costs were limited to average capitation funding allocated to an individual to attend a GP. Individual's in the database were assigned a unique identifier, which allowed their health journey and their associated healthcare costs to be collated. The information provided by HealthTracker, although comprehensive, still has limitations. Notably, data on palliative care data is currently absent as is information on any health events that occurred in the private healthcare sector (approximately 17% of New Zealand health expenditure). Both limitations were accounted for in the model by price scaling (for further information see supplementary text two from Blakely et al 2015).¹⁹

Data from HealthTracker captured between 2006 and 2010 was used to determine the average annual health system cost by age and sex associated with four distinct periods in the life course of the model population.⁹⁹ Firstly, the proportion of the model who were 'alive' in the model ('healthy' state or 'alive with CVD' state) at each annual model cycle were assigned an annual health system cost ($Cost_x$) (Figure 2). In addition to the base cost ($Cost_x$) further costs were applied to:

- The proportion of the population in the first year of incident CVD (CHD or stroke) to represent the additional cost associated with diagnosis and treatment initiation ($Cost_{x+A}$);
- The proportion of the population with prevalent CVD (CHD or stroke) who were not in the first year of having the disease, nor in the last six months of life, to represent the ongoing cost associated with CHD or stroke events ($Cost_{x+B}$);
- The proportion of the population in last six months of life (CHD, stroke or generally) ($Cost_{x+C}$) to represent the increased use and cost of healthcare associated with end of life.

All costs were in 2011 New Zealand dollars. Due to the nature of the MSLTs, it is important to note that the above costs were not always mutually exclusive. For example, it was possible to have a prevalent

stroke and be in the first year of a CHD diagnosis. To avoid double counting and the overestimation of healthcare costs, this was adjusted for by considering the number of people who would experience this (see Kvizhinadeze et al 2016⁹⁹ for further information).

4.3.4 Model population

The existing BODE³ Tobacco Control MSLT which was adapted to create a CVD MSLT model, modelled the entire New Zealand population alive in 2011 (the baseline year of the model) based on 2006 New Zealand Census data projected estimates. The CVD MSLT model adaption currently considers a subset of this original population, namely, men aged 60 to 64 years who in 2011 were alive, did not have prevalent CVD (including stroke and CHD) and who were not taking any CVD preventive pharmaceuticals. Adapting the model to include only men aged 60 to 64 years is only the first stage of the model's development. The group of men aged 60 to 64 years was chosen as a starting point because it is an age-group who experience a significant burden of CVD at a large cost to both the health of individuals and the healthcare system.^{1, 13} Interventions to reduce absolute CVD risk in this age-group, therefore, have the potential to improve population health and reduce health expenditure. Furthermore, improving the health of this age-group could increase their longevity and the productivity of the New Zealand workforce to the benefit of workers themselves (if they wish to keep working after age 65 years) and to society as a whole. Table 5 shows the model population numbers by CVD risk strata.

4.3.5 CVD risk strata

Within the central life-table and subsequent CVD life-tables, the study population was stratified into groups of five-year absolute CVD risk (ie, the risk of having a CVD event in the next five years). The purpose of this division was to consider the health gains, costs and cost-effectiveness of treatment within each risk group, acknowledging that baseline absolute CVD risk could influence the capacity to benefit from treatment and the resulting cost-effectiveness ratio. The division of the population into five-year absolute CVD risk strata was informed by the proportions of individuals at each level of risk in a publication by Knight et al in 2017.^{93, 94} Knight et al used New Zealand specific data and CVD risk equations to simulate absolute CVD risk strata in a synthetic New Zealand population. The CVD risk proportions were applied to the original adult population considered in the MSLT model as part of the model's adaption to the CVD MSLT model (with this process being performed for other, still unpublished, BODE³ work on the cost-effectiveness of triple therapy for preventing CVD). The incidence rate of having a CVD event was adjusted to be specific to each CVD risk strata. For further information on the division of the population by absolute CVD risk see Appendix Two.

Table 5: Model Population numbers by CVD risk strata

(men in New Zealand aged 60 to 64 years with no prior CVD and not on CVD preventive medications)

CVD Risk Strata	Non-Māori	Māori
Risk Stratum 5: >20% (highest risk)	58	42
Risk Stratum 4: >15%, ≤20%	273	162
Risk Stratum 3: >10%, ≤15%	1941	739
Risk Stratum 2: >5%, ≤10	20,194	2500
Risk Stratum 1: >0%, ≤5% (lowest risk)	37,464	837
Risk Strata Combined	59,930	4280

4.3.6 Model baseline

As in the tobacco MSLT, the baseline scenario of the CVD MSLT represented ‘business as usual’ (BAU) (do nothing). Reconfiguring the model baseline to represent the intended BAU of this thesis, the A+A, regimen was not possible due to the time constraints of this thesis. Consequently, the model was set up to run twice, once with the model intervention inputs for A+A compared to BAU and a second time with the intervention inputs for FDC AA compared to BAU. The resulting QALY gains and health system costs from FDC AA compared to BAU were then subtracted from the QALYs gained and the health system costs from A+A compared to BAU. The implications of this are discussed further in the Discussion, Section 6.5.2.

Table 6 outlines the parameters, sources and parameter uncertainty of the model inputs that collectively comprise of the model baseline or BAU scenario.

Table 6: Baseline CVD MSLT model parameters

Input parameter	Source	Heterogeneity	Uncertainty	Time trend	Distribution
Population	Statistics New Zealand (SNZ) population estimates in 2011	By age-group, sex and ethnicity	Nil	Closed population.	n/a
All-cause mortality rate (excluding CHD and stroke mortality)	As per BODE ³ Tobacco Control MSLT (see ¹⁹) (Based 2011 New Zealand mortality rate and historical trends, SNZ)	By age-group, sex and ethnicity	Nil	Annual mortality decline of 2.25% for Māori and 1.75% for non-Māori until 2026, 0% decline thereafter	n/a
CVD (CHD and stroke) incidence, prevalence and CFR	As per BODE ³ Tobacco Control MSLT (see ¹⁹) (Estimated using DISMOID II software)	By age-group, sex and ethnicity	± 5% SD	Continual decline in CHD and stroke assumed as per NZBDS Decline of 2.0% annually for CHD and stroke incidence and CFR.	Log-normal
Total Morbidity	As per BODE ³ Tobacco Control MSLT (see ¹⁹) (per capita YLD from NZBDS)	By age-group, sex and ethnicity	± 10% SD	Assumed constant (ie, no trend)	Log-normal
CVD morbidity	As per BODE ³ Tobacco Control MSLT (see ¹⁹) (YLD from NZBDS/disease prevalence in 2006, projected to 2011 adjust for comorbidities)	By age-group and sex	± 10% SD	Assumed constant (ie, no trend)	Normal
Health System Costs	As per BODE ³ Tobacco Control MSLT (see ¹⁹) (HealthTracker data)	NZ\$ 2011 by age-group and sex	± 10% SD	Assumed constant (ie, no trend)	Log-normal

4.3.7 The intervention (FDC AA compared to A+A)

The key intervention inputs in the model were the intervention (pharmaceutical regimen) uptake and regimen adherence and clinical efficacy. The selection of model inputs for the intervention A+A and the FDC AA is discussed in detail in Section 4.4. In the model, intervention uptake determined the proportion of the baseline model population who would receive either pharmaceutical intervention. Pharmaceutical adherence then influenced the proportion of the uptake population who receive the additional clinical benefit of being prescribed either pharmaceutical intervention. Uptake was determined at the start of the model while adherence changed annually over the five-year intervention period. The clinical efficacy of either intervention was associated with the proportion of the population who were adherent and modulated the incidence of stroke and CHD. Changing the incidence rate of stroke and CHD influences the proportion of the population with prevalent CVD disease and consequently CVD deaths. Measuring the difference in the health gains (QALY) and costs that accrued over the modelled populations lifetime as a result of differences in uptake, adherence and clinical efficacy between the FDC AA and A+A was the focus of this thesis.

The model considers annual transitions between health states, a five-year intervention period and a lifetime horizon. During the five-year intervention period, the adherence rates and clinical efficacy for the proportion of the population who receive either intervention (uptake) were applied. The annual pharmaceutical cost for each intervention accrued over the intervention period as did the QALYs gained and the health system costs associated with the proportion of the population residing in each health state. After five years, the intervention effect was assumed to be turned off (ie, no one in the population receives the benefit or cost of taking either intervention – as at this point it is likely that patients will be reassessed and potentially shift into different risk categories and experience changes in their management). Over the remainder of the model's lifetime horizon, the model continued to accrue health benefits in terms of QALYs and health system costs until the entire original cohort has either died of CVD, died from other causes, or has reached the age of 110 years. All QALYs and costs accrued in the model were discounted annually at 3%. The timeline of model events is summarised in Figure 3.

Starting point (2011)	Closed cohort of New Zealand men aged 60-64 who in 2011 did not have prevalent CVD and were not taking any CVD medications.	
	A+A* Individuals prescribed amlodipine 5mg and atorvastatin 20mg as two separate pills.	FDC AA* Individuals prescribed FDC AA (5mg/20mg).
5-year intervention period (2011-2015)	<ul style="list-style-type: none"> • Treatment specific adherence and clinical efficacy applied. Consequent reduction in CHD/stroke incidence with each annual model cycle. • Pharmaceutical costs associated with treatment accrue. • Fatal and non-fatal (incident) CHD or stroke events in addition to health system costs and QALYs accrue with each annual model cycle. 	
Year 6+ (2016-2061)	<ul style="list-style-type: none"> • Intervention effect turned off (ie. no further medication exposure). • Model continues until all individuals in the model reach 110 year of age, have died from CVD or have died from other causes. • Fatal and non-fatal (incident) CHD or stroke events continue to accrue with each annual cycle of the model as does the associated cost and QALYs. 	

* Intervention uptake population only

Figure 3: Timeline of events over the lifetime model horizon

4.3.8 Uncertainty and variation

Modelling future outcomes inevitably involves uncertainty. Uncertainty in the model can arise due to population heterogeneity, stochastic uncertainty (or chance), as well as uncertainty concerned with the model and parameter inputs. Heterogeneity was considered in the model through the division of the model population into CVD risk strata which allowed for more specific differences in health and cost outcomes by CVD risk to be observed. Parameter and model input uncertainty was considered through applying uncertainty margins. Inputs that had uncertainty published in the literature (ie, the 95%CI:of the clinical efficacy relative risks) were utilised if available. Remaining model inputs were assigned an uncertainty estimate of +/- 5% or 10% standard deviation of the mean, depending on the evaluated uncertainty of these variables (see Table 6 for baseline parameter uncertainty and

Table 12 input parameter uncertainty). Each CVD risk stratum was simulated 2000 times in Microsoft Excel using an Ersatz add in to permit Monte Carlo simulations for all model variables with specified uncertainty. Monte Carlo simulation allows for the random selection of a value from the uncertainty range of all model inputs with assigned uncertainty. It aims to address both stochastic uncertainty (proportion of the population with the same characteristics has a different experience in the model

each time it is run due to chance) and model uncertainty (uncertainty around the central estimate). Despite these efforts to consider uncertainty in the model, it is possible that the true level of uncertainty is greater still (eg, no separate models were built to assess the role of model structure uncertainty).

4.4 Intervention parameter selection

4.4.1 Clinical efficacy of the FDC AA regimen

Search method

A search of the literature was conducted in April 2017 using the MeSH search terms amlodipine besylate/atorvastatin calcium AND Efficacy in PubMed. Search results were limited to those published in the English language and those conducted in human subjects. Nineteen studies were identified in the search and were downloaded to Endnote where abstracts were reviewed for relevance. Studies were excluded if they did not involve a FDC, were a review or expert opinion publication or had an irrelevant comparison group (ie, the comparison group is the same FDC taken at a different time of day). After exclusions, six studies were included in the review. Reference lists of included publications were examined to identify any further publications not identified in the original search. A further five studies were added to the search from examining reference lists, bring the total number of studies in the review to 11.

Summary of included studies

The 11 identified studies in the structured review included multiple different clinical trials. The CAPABLE study conducted in the United States was the subject of two publications (Ferdinand et al 2009¹⁰⁰ and Flack et al 2008¹⁰¹). The GEMINI study was conducted in 27 countries and was the subject of the publications by Erdine et al 2009⁶⁷ and Blank et al 2005.¹⁰² Five of the studies, Flack et al 2008,¹⁰¹ Erdine et al 2009,⁶⁷ Blank et al 2005,¹⁰² Hobbs et al 2009¹⁰³ and Ferdinand et al 2009¹⁰⁰ were no comparison titration-to-goal studies where participants at the discretion of their doctor could have their dosage titrated up or down to receive any of the available eight doses of the pharmaceutical in order to best target their high blood pressure and high cholesterol (amlodipine/atorvastatin: 5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, 10/80 mg). The remaining six studies¹⁰⁴⁻¹⁰⁹ focused on the lower doses of the pharmaceutical, primarily, 5/10 mg and 10/10 mg. Most of the studies investigated the use of the FDC AA as a primary prevention measure. Studies ranged in participant numbers from 117 to 2245, spanned 14-52 weeks in duration and were set in a range of populations globally. All included studies except, Zeng et al,¹⁰⁷ were in some way affiliated or sponsored by Pfizer Pharmaceuticals, the company who held the original patent for this FDC under the brand name Caduet.¹¹⁰ A summary of key characteristics of the included publications are available in Appendix Three.

The rationale for chosen model parameter input for the clinical efficacy of the FDC AA

Of the identified studies, no single study appeared to stand out as superior to the others in terms of size and methodological quality. However, the studies by Flack et al 2008,¹⁰¹ Erdine et al 2009,⁶⁷ Hobbs et al 2009¹⁰³ and Blank et al 2005¹⁰² appeared to be relatively well-conducted non-comparison, titration-to-goal, clinical trials with comparable study designs (see Table 7). In order to produce the best value of clinical efficacy for the FDC AA for the model in this thesis, a meta-analysis of the four similar studies was conducted by the author. None of the studies were over a long enough period to observe a difference in CVD endpoints (rates of CHD and stroke). However, all papers published data on the change in SBP, DBP and LDL-C from baseline. The aim of the meta-analysis was therefore to determine the mean difference in SBP, DBP and LDL-C over the study period that could be attributed to the FDC AA. The determined mean difference in blood pressure and cholesterol was then applied to published standardised relative risk for stroke and CHD events published by Karmali et al 2016.¹¹¹

The meta-analysis was conducted using Cochrane Review Manager software (RevMan 5.3). Three separate random effect analyses were conducted to determine the mean differences in SBP, DBP and LDL-C respectively from baseline over the study period as a result of taking the FDC AA. Random effects analyses were used as each study was conducted in a different population. Each of the published studies published baseline blood pressure and cholesterol values and the mean change in the same variables over the study period. Final values for blood pressure and cholesterol levels at the end of the studies and the associated error were not published but were calculated from the baseline and change from baseline values. Hobbs et al¹⁰³ did not publish any error measurements for baseline or change from baseline values for SBP, DBP, LDL-C. The author of this study was emailed to obtain this information and while contact was established, no relevant data was received prior to the completion of this thesis. Excluding this study based on the absence of error measurements seemed unreasonable, so a decision was made to average the error associated with the other three trials and apply this to the Hobbs et al 2009 study. Removing Hobbs et al (2009) from the meta-analysis did not affect the overall measure of effect significantly but including it increased participant numbers greatly. Figure 4, Figure 5 and Figure 6 show the results of the three meta-analyses.

Table 7: Summary of studies used in the meta-analysis to determine the best parameter for FDC AA efficacy for use in the model

Study author/reference:	Blank 2005 ¹⁰²	Erdine 2009 ⁶⁷	Flack 2008 ¹⁰¹	Hobbs 2009a ¹⁰³	Hobbs 2009b ¹⁰³
Study name	GEMINI Study	Gemini- AALA	CAPABLE	JEWEL 1	JEWEL 2
Setting/s	United States	123 centres across 27 countries Australia, Asia, Latin America, Africa/Middle East	United States (African American population)	122 centres in United Kingdom and Canada	113 centres across 11 European Countries
Population Group	Men and women aged 18-80 years with hypertension and dyslipidaemia who qualified for treatment according to their respective local guidelines.				
Key inclusion/exclusion criteria	Exclude if blood pressure at goal (LDL-C could be at goal), already treated with amlodipine + atorvastatin monotherapy, taking any CCB or atorvastatin as monotherapy at maximum dose. History of CVD in 3 months pre-screening. (Flack et al also excluded MI event in past six months).				
Study Design	Open label, non-comparison, titration-to-goal. Eight doses amlodipine/atorvastatin - 5/10, 10/10, 5/20 10/20, 5/40, 10/40, 5/80, 10/8 mg. Lifestyle change recommended to all participants Anti-hypertensive pharmaceutical other than CCB permitted, no other lipid-lowering pharmaceutical. No washout period.				
Baseline population (n)	1220	1649	499	1138	1107
Proportion of participants who completed the study	89.8%	92.1%	74.9%	87.6%	87.8%
Duration (weeks)	14	14	20	16	16

The results of the meta-analyses demonstrated statistically significant reductions in SBP, DBP and LDL-C as a result of treatment with the FDC AA over the study period. SBP changed by a mean of -18.92 mmHg (95%CI: -21.31 to -16.57), DBP changed by a mean of -10.90 mmHg (95%CI: -11.89 to -9.92) and LDL-C changed by a mean of 1.04 mmol/L (95%CI: -1.17 to -0.91) from baseline over the average 16-week study duration. Little variation was evident within the individual studies measure for SBP, DBP or LDL-C but there was considerable heterogeneity found in the meta-analyses (the high I^2 results). The same studies in these meta-analyses were the subject of a pooled analysis by Feldman et al 2012.¹¹² Although this publication only states the results by age strata (no aggregate analysis presented), the values for change in blood pressure and cholesterol are relatively similar in magnitude to those calculated in the meta-analysis in this thesis. Relative risks for stroke, CHD and vascular events were then generated by applying the mean difference from baseline determined in the meta-analyses to standardised relative risks published by Karmali et al 2016.¹¹¹ The resulting RR were then integrated to produce a RR reduction for CHD and stroke respectively. The 95% confidence intervals and standard deviations were generated using Ersatz sampling (see Table 8 for more detail).

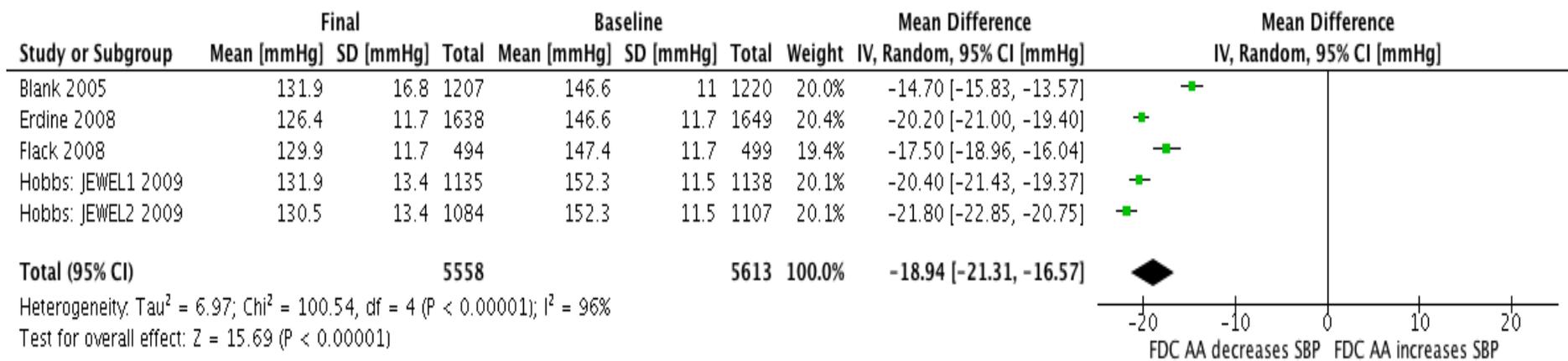


Figure 4: Random effects meta-analysis of change in SBP from baseline with FDC AA treatment.

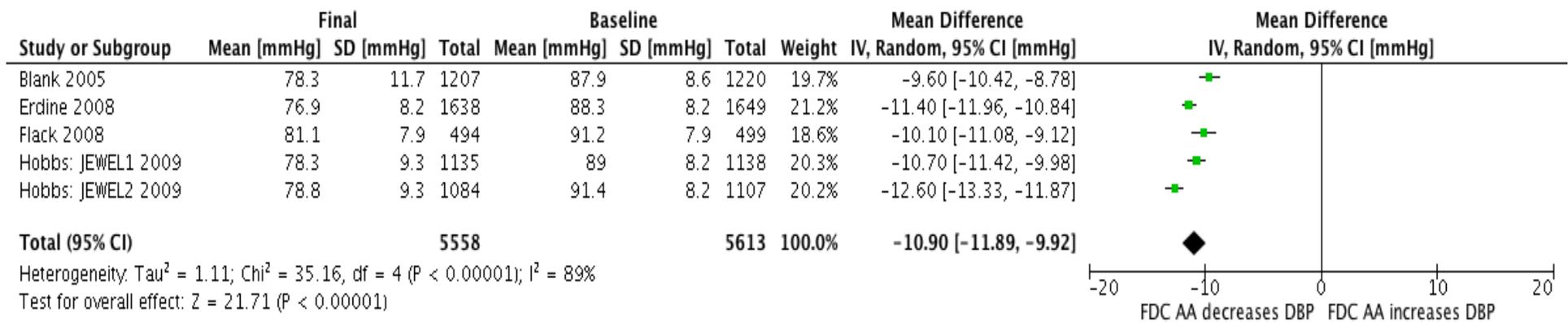


Figure 5: Random effects meta-analysis of change in DBP from baseline with FDC AA treatment

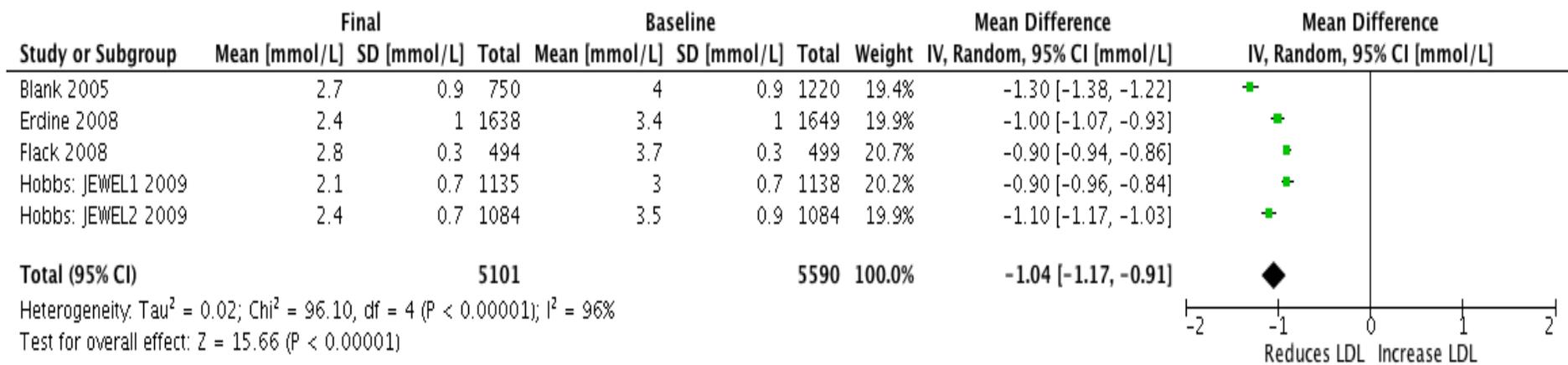


Figure 6: Random effects meta-analysis of change in LDL-C from baseline with FDC AA treatment.

Table 8: Combined clinical efficacy of the FDC AA regimen in reducing the risk of CVD events (used as a parameter input into the model)

CVD (Fatal and non-fatal events combined)	Meta-analysis results (see above)	Standardised RR ¹¹¹	Resulting RR
Stroke (A)	-18.94/-10.9 mmHg (SBP/DBP)	RR for stroke per 10/5 mmHg BP reduction 0.54 (95%CI: 0.45 to 0.65)	0.31 (SD 0.106)
CHD (B)	-18.94/-10.9 mmHg (SBP/DBP)	RR for CHD per 10/5 mmHg BP reduction 0.79 (95%CI: 0.72 to 0.86)	0.64 (SD 0.065)
Vascular events (C)	-1.04 mmol/L (change in LDL)	RR per 1mmol/L reduction in LDL major vascular events 0.75 (95%CI: 0.70 to 0.80)	0.74 (SD 0.106)
Combined RR for stroke events from taking the FDC AA regimen (A*C)			0.237 (SD 0.082)
Combined RR for CHD events from taking the FDC AA regimen (A*B)			0.476 (SD 0.058)

Abbreviations: RR (relative risk), 95%CI (95% confidence interval), SD (Standard deviation)

Ersatz Excel plugin used to generate combined mean and 95%CI by running 2000 iterations of a log-normal distribution

Excluded studies

The remaining studies were not considered to inform the efficacy of FDC AA because they either studied a lower dose of FDC (5 mg/10 to 10/10 mg)^{105, 106, 108, 109} than the dose chosen to be modelled (see Section 4.4.2) or they examined a scenario that did not align with the intended modelling base-case (ie, goal attainment by diabetes and metabolic syndrome status,¹⁰⁰ best time of day to take pharmaceutical¹⁰⁷). Neutel et al 2009¹⁰⁴ was the only study that considered the same dose that was modelled in this thesis. However, the strength of evidence determined in the meta-analysis of the four titration-to-goal studies was considered a better source of evidence to inform the clinical efficacy of FDC AA than the Neutel et al 2009 study.

FDC AA Adverse events

Adverse events that lead to discontinuation of FDC AA appear to be relatively low. In the four studies considered in the above meta-analysis (Flack et al 2008,¹⁰¹ Erdine et al 2009,⁶⁷ Hobbs et al 2009¹⁰³ and Blank et al 2005¹⁰²) adverse events ranged from 3.2% to 7.4% (over the 14 to 20 weeks duration of the studies). Adverse events were not directly included in the model directly. Rather it was assumed that discontinuation of the FDC due to adverse events would be partly captured in the adherence rate.

4.4.2 Pharmaceutical dose

It is important to note that clinical efficacy calculated in the meta-analysis above did not represent the clinical efficacy associated with a specific dose of the FDC AA, but rather the average clinical efficacy

across all available doses. However, because each available dose of FDC AA differs in cost, it was necessary to select a single dose that the pharmaceutical price could be based on. The FDC AA is currently available in eight doses with the amlodipine component being five mg or 10 mg and the atorvastatin component ranging from 10, 20, 40 or 80 mg.^{59, 61} It was decided that best way to determine the dose that would be modelled in this thesis would be to average the mean final dose of the same four titration-to-goal studies considered in the FDC AA clinical efficacy meta-analysis^{67, 101-103} (ie, the doctor and/or pharmacist could modulate the dose of each component to best address the patient's risk profile). The average mean dose reached at the end of each of these four studies was calculated to be 7.3 mg of amlodipine and 24.6 mg of atorvastatin. This most closely matches with the possible dose, 5 mg of amlodipine and 20mg of atorvastatin, which was chosen as the dose to model in this study for both the FDC and the two agents taken separately (see Table 9).

Table 9: Calculation of FDC AA mean pharmaceutical dose

Study	Amlodipine (mg)	Atorvastatin (mg)
Blank (2005) ¹⁰²	7.1	26.2
Flack (2008) ¹⁰¹	8.2	26.4
Erdine (2009) ⁶⁷	7.1	19.7
Hobbs (2009) ¹⁰³ J1*	7.3	26.8
	J2*	6.7
Average	7.3	24.6
*JEWEL 1 (J1) and JEWEL 2 (J2) refer to two different populations within the same study		

4.4.3 Clinical efficacy of A+A

Clinical efficacy of amlodipine monotherapy

In the first instance, the Cochrane Library was searched for any reviews concerning the efficacy of amlodipine compared to placebo or usual care. No appropriate reviews were found. Subsequently, a structured review was carried out using the following MeSH search terms in PubMed: Meta-analysis AND amlodipine AND hypertension AND cardiovascular disease. The same search strategy and protocol used in the FDC AA clinical efficacy search was employed here. The search identified 16 studies. None of the identified studies were considered appropriate to inform the model input of amlodipine clinical efficacy. Most of these studies were concerned with combination therapy, compared amlodipine directly to other anti-hypertensives, focused on stroke or CHD not both and were conducted in specific populations (ie, people with diabetes).

Two subsequent searches were conducted with the aim of determining the clinical efficacy of CCBs or anti-hypertensives more broadly. The following searches were conducted in PubMed in July 2017. Search 1: "Blood Pressure"[MeSH] AND "Meta-Analysis" [Publication Type] AND "Calcium Channel

Blockers"[MeSH]. Search 2: "Blood Pressure"[MeSH]) AND "Anti-hypertensive Agents"[MeSH] AND "Meta-Analysis" [Publication Type]. The same search strategy described above to refine the research results was used here. Search One returned 31 publications and after exclusions, three studies remained. Search Two returned 192 publications, 19 of which were deemed relevant upon scoping. Six publications were read in full. The three relevant studies identified in Search One also appeared in Search Two. A summary of the included studies can be found in Appendix Four.

Overall the meta-analysis conducted by Thomopoulos et al 2015¹¹³ was considered the best study to inform the parameter of amlodipine efficacy. The study was the most recent review of the six studies considered and looked at the primary prevention impact of each anti-hypertensive class on CVD risk compared to placebo or usual care. In total, the meta-analysis considered 55 studies and approximately 200,000 people and appeared to be well-conducted. The CCB analysis within the meta-analysis (10 RCTs, approximately 30,000 people) included a sensitivity analysis of four studies which were conducted in entirely hypertensive cohorts who were taking no or minimal baseline pharmaceuticals. This sensitivity analysis is of value as it aligns with the aim of this thesis, which is focused on a primary prevention intervention. See Table 10 for the relative risks used.

Another review by Law et al in 2009,¹¹⁴ received strong consideration to inform this input parameter as it was also a large-scale, well-conducted meta-analysis that considers the efficacy of anti-hypertensive on the risk of CVD by pharmaceutical class. However, this review included fewer studies overall, partly due to an earlier publication date (CCB analysis similar) and did not distinguish between studies that considered hypertensive or normotensive cohorts, or those considering the pharmaceuticals for primary or secondary care. Briasoulis et al 2014¹¹⁵ was not considered as it looked at the effect of anti-hypertensives on a population of people aged 65 or older and none of the other data inputs were age-specific. The other remaining publications¹¹⁶⁻¹¹⁸ were not utilised as they considered comparisons not relevant to this input parameter or where inferior in quality of evidence to Thomopoulos et al 2015.¹¹³

Amlodipine adverse events

Amlodipine, in general, appears to be a well tolerate pharmaceutical with a low risk of adverse events. Notably, the adverse event rate with amlodipine does not vary significantly from the adverse event rate of other first-line hypertension pharmaceuticals.¹¹⁹

Clinical efficacy of atorvastatin monotherapy

Before a structured search of the literature was conducted, the Cochrane Library was first searched to see if any reviews were conducted concerning the clinical efficacy of atorvastatin. One review conducted by Adams et al in 2015¹²⁰ was identified which aimed to determine the mean percentage change from baseline of LDL-C with atorvastatin among those with or without CVD. The review collated

296 studies involving 38,817 participants and compared atorvastatin to baseline or placebo. The Cochrane Library reviews are considered the gold standard of meta-analyses and systematic reviews. Given this reputation, the large number of included studies and participants, in addition to the high quality of included studies (determined by Cochrane), this study was chosen to inform the clinical efficacy of atorvastatin in this model. The study duration did not allow for changes in CVD event rates to be observed. As per the clinical efficacy parameter of the FDC AA, the mean difference in LDL-C from baseline for 20 mg of atorvastatin (1.09 mmol/L) was applied to the standardised RR for major vascular events 1 mmol/L reduction in LDL-C as reported by Karmali et al 2016.¹¹¹ Major vascular events include fatal and non-fatal CHD and stroke. See Table 10 for final relative risk.

Atrovastatin adverse events

The same Cochrane Review by Adams et al 2015¹²⁰ reported that there was no statistically significant difference in the rate at which people withdrew from the study due to the adverse effects of all doses of atorvastatin (odds ratio 0.98 (95%CI: 0.68 to 1.40)). A total of 34 studies were included in this analysis and the Cochrane Review determined that the quality of evidence of this measure was very low. The measure does not appear to separate withdrawals due to study pharmaceutical related adverse events or general adverse events. Adverse events were not directly considered in this model as it was assumed they would be reflected in the pharmaceuticals adherence rates. Including adherence rates may have resulted in some double counting.

Combined clinical efficacy for A+A

The relative risk for the clinical effect of amlodipine and atorvastatin on stroke, CHD and vascular events respectively where combined to give an overall relative risk that represents the clinical efficacy of those taking amlodipine and atorvastatin as two separate pills for stroke and CHD respectively (see Table 10 for more detail).

Table 10: Combined clinical efficacy of amlodipine and atorvastatin as two separate pills for CVD event reduction (for parameter input into the model)

Input	CVD event	Source	Adaption	Value
Clinical Efficacy Amlodipine	Stroke (for BP reduction) [A]	Thomopoulos et al 2015 ¹¹³	RR for CCB vs usual care/placebo includes fatal and non-fatal stroke events.	Relative risk = 0.63 (95%CI: 0.53 to 0.76)
	CHD (for BP reduction) [B]	Thomopoulos et al 2015 ¹¹³	RR for CCB vs usual care/placebo includes fatal and non-fatal CHD events	Relative risk = 0.74 (95%CI: 0.58 to 0.94)
Clinical Efficacy Atorvastatin	Vascular event reduction [C]	Adams et al 2015 ¹²⁰ + Karmali et al 2016 ¹¹¹	Mean change LDL-C from baseline 20 mg atorvastatin from Adams et al 2015 (1.09 mmol/L) applied to standardised relative risk per 1 mmol/L reductions in LDL-C from Karmali et al 2016 (RR 0.74 95%CI: 0.66 to 0.81). Measure aggregates fatal and non-fatal stroke and CHD	Relative Risk = 0.73 (95%CI: 0.68 to 0.78)
Combined RR for stroke events from taking the A+A regimen [A*C]				0.460 (SD 0.023)
Combined RR for CHD events from taking the A+A regimen [B*C]				0.540 (SD 0.028)

Abbreviations: RR (relative risk), 95%CI (95% confidence interval), SD (Standard deviation)

Ersatz Excel plugin used to generate combined mean and 95%CI by running 2000 iterations of a log-normal distribution

4.4.4 Adherence

Method

A structured search of the literature was conducted in April 2017 using the search terms amlodipine besylate/atorvastatin calcium AND adherence in PubMed. The process of restriction, review and evaluation was repeated as previously detailed. Of the 19 studies originally identified in the search, five studies were included in the final review. After examining the reference lists of the included publications, one further publication was added bringing the total number of studies included in the review to six.

Summary of identified studies

Of the six included studies, five were conducted using a retrospective cohort study design, four of these studies looked at administrative claim data of insurance enrollees in the United States and one looked at prescription claims data in Australia. The only study not retrospective in nature was by Zeng et al 2016¹⁰⁷ who utilised a case-control study design. Four of the six identified studies were in some way affiliated or sponsored by Pfizer Pharmaceuticals. A summary of the publications is available in Appendix Five.

Rationale for selecting the best study for informing the adherence parameter

Of the identified studies, probably the best study to inform the adherence input parameter for modelling purposes is that by Patel et al 2008.⁶⁸ Although this study is the oldest publication identified in this literature review, it appears to provide the strongest evidence available regarding the adherence of the FDC AA. The study compares the adherence of the FDC AA with amlodipine and atorvastatin taken as two separate pills in a population of 4,703 United States nationals (one-year analysis n=3561), which is the precise comparison that was aimed for in this New Zealand modelling work. The study looked at adherence using pill days covered over a six month and 12 month time horizon. The study population of United States nationals is probably of reasonable generalisability to New Zealand as the United States is another high-income English-speaking country. The adherence results of this study were of a similar magnitude to those in the other studies identified in the search. Furthermore, most of the cost-effectiveness studies identified in the literature review Section of this thesis (Section 3.2) base adherence on the data from the Patel et al study.^{68, 75, 76}

Patel et al⁶⁸ found that after one year 63.9% of people taking the FDC AA regimen were adherent (greater than 80% pill days covered (PDC)) compared to 33.1% to 43.6% for those taking two separate pills (amlodipine and atorvastatin, amlodipine and a statin, CCB and atorvastatin or CCB +statin). As a value, specifically for amlodipine and atorvastatin adherence as separate pills at one-year was not published in this paper, the average of the adherence range at one-year for the two separate pills was calculated to inform the adherence parameter of the A+A regimen (38.4%). Ideally, adherence in the model would begin at 100%, decrease in the first year to the values outlined in Patel et al⁶⁸ and then remain constant over the remainder of the five-year intervention period. Due to characteristics of the existing model and the time constraints of this thesis, changing the model to represent adherence in this way was not considered possible. Consequently, adherence values were assumed to begin at 100% and decrease to 63.9% and 38.4% respectively over the five-year intervention period (an annual decrease of 7.2% for FDC AA and 12.3% for A+A). The implications of representing adherence in this way are discussed in the Discussion, Section 6.5.3.

The study conducted in Australia by Simons et al in 2011⁶⁹ received strong consideration for use in the New Zealand modelling work. Studies conducted in Australia are generally considered to have reasonable generalisability to the New Zealand population (at least for the New Zealand European population). The study included a large study population and unlike Patel et al⁶⁸ it was conducted independently to Pfizer. However, one major limitation of this study is that the cost of amlodipine at all doses is less than the general co-payment threshold, which is not recorded by Medicare. Therefore, the data on amlodipine monotherapy is only representative of concessional patients (patients who have a health card to receive discounted medical care and prescriptions due to low-income or being a

high-users) which the study estimates represent 65% of amlodipine users. This potentially introduces a selection bias if those that were included in the monotherapy arm of this study were different in some way from those in the single-pill arm of this study. With such a high proportion not being represented in this study, it was considered unwise to use this study to inform an input parameter.⁶⁹ Notably, however, the confidence limits of the study by Simons et al⁶⁹ is contained within the 95%CI for adherence from Patel et al.⁶⁸

The following paragraph outlines the reason why the remaining articles were not chosen to inform adherence in the model. The study conducted by Zeng et al 2016¹⁰⁷ had the primary focus of investigating whether the time of day the pharmaceutical was taken affects the clinical efficacy. Compliance with the FDC AA was a secondary aim and no measure of association was measured in this study resulting in an inferior study result than the other studies. The two studies conducted by Chapman et al in 2009¹²¹ and 2010⁷⁰ used unspecified CCBs or statins in their comparison group. This is an issue for two reasons: 1) it does not match the primary comparison this thesis intended on modelling (ie, a FDC AA compared to amlodipine and atorvastatin taken as individual pills; 2) it would be more difficult to determine the effectiveness parameters. Finally, the study conducted by Hussein et al in 2010¹²² focuses on the effect of previous statin and CCB use on the odds of adherence. While this is a useful and interesting study, it goes beyond the aims of this thesis and the capacity of the CVD model.

4.4.5 Intervention cost

As the model used in this thesis used a health system perspective, the intervention costs considered were the cost to the government to provide the FDC AA or A+A (pharmaceutical cost) and the out-of-pocket co-payment costs for the patient (prescription cost).

Pharmaceutical cost

The FDC AA is not currently available in New Zealand.⁶⁶ As a result, the likely price of such a pharmaceutical on the New Zealand market is unknown. Initially, price scaling between pharmaceuticals in Australia was considered as the best method to estimate the cost of the FDC AA in New Zealand as a mean percentage difference in price between Australia and New Zealand pharmaceuticals could be applied to the known price of FDC AA in Australia. However, it became apparent that Australia has unique regulations around FDCs.¹²³ For most of the FDCs approved in Australia, it is conditional that they remain cheaper than their monotherapy components. Furthermore, the price of the FDC is linked to the cost of their components meaning any price decreases applied to the components are translated to the price of the FDC. However, if a second brand of the FDC is introduced, the link between the FDC and its components no longer applies and the FDC is ultimately subject to market forces. Competition for FDCs is not as significant as it is for most

monotherapies, so the price of FDCs generally ends up being more expensive than their monotherapy components.¹²³ Because of these unique regulations and the large potential variation in the cost of FDCs in Australia, using price scaling to determine the cost of FDC AA in New Zealand would have generated a price estimate with little applicability to New Zealand. The FDC is also currently approved in some European countries and the United States but the funding of pharmaceuticals in these countries differs significantly to New Zealand and consequently were considered not to provide a reasonable comparison for price scaling.

Given the above, an alternative method, which estimated the price of the FDC AA based on the price of amlodipine and atorvastatin monotherapy was used. Basing the price on current monotherapies is often used in polypill research where the price is also often unknown.^{83, 85} As published on the 2017 PHARMAC pharmaceutical schedule, five mg of amlodipine monotherapy costs the New Zealand Government \$0.01 per pill and 20 mg of atorvastatin \$0.03 per pill (both in 2011 NZ\$). Thus, an individual in the comparison group of this analysis who was prescribed both amlodipine and atorvastatin would have a total cost to the New Zealand Government of \$0.04. The base case of the FDC intervention, therefore, assumed the FDC costs to be the same as the same two agents as monotherapy. This, therefore, meant that the health cost differences between the two regimens became the marginal difference in prescription costs (two for monotherapy, one for the FDC) and the differences in health costs (via the differences in clinical efficacy and relative adherence of the two regimens).

Prescription costs

Amlodipine and atorvastatin are both listed in the 2017 Pharmaceutical Schedule as potentially three-month prescriptions, meaning that three months or 90 days of the pharmaceutical can be dispensed at the same time.⁶⁶ As a result, an individual who is taking the pharmaceutical as prescribed would be expected to require four repeat prescriptions a year. In 2017, the total cost per prescription for a fully subsidised pharmaceutical (like amlodipine or atorvastatin) was \$5.44 exclusive of GST (with this amount changing slightly in most years). This cost includes the cost to the pharmacy to procure, store and dispense the pharmaceutical.¹²⁴⁻¹²⁶ After adjustment using the international consumer price index (CPI) published by Organisation for Economic Co-operation and Development (OECD),¹²⁷ the prescription cost in 2011 New Zealand dollars (model baseline) was calculated to be \$5.21. At this cost, an individual taking both amlodipine and atorvastatin as two separate pills as prescribed over a 12-month period would have a prescription cost of \$41.68 exclusive of GST (($\$5.21 \times 4$ prescriptions annually) $\times 2$ pharmaceuticals). If the same conditions were to apply to the FDC AA if it was available in New Zealand (as per the assumptions used, ie, fully subsidised and available as 90-day prescriptions) the annual prescription cost of a single fully subsidised pharmaceutical would be \$20.84 excluding GST ($\5.21×4 prescriptions annually) (Table 11).

The calculated prescription cost of the FDC AA assumes that a patient was prescribed the FDC AA during a routine GP appointment that would have occurred regardless since the patients in the comparison group in this model are already taking the amlodipine and atorvastatin as separate pills (ie, the patient would have to go to the doctor to collect a repeat prescription four times a year regardless of the regimen). Therefore, there is no difference in annual GP visits and associated costs between the two groups. Additionally, it is assumed that once the switch to FDC AA has occurred, no additional GP appointments are required due to issues specifically related to the FDC AA.

Table 11: Pharmaceutical costs per 90-day prescription period, per year and intervention period (all prices excluding GST)

Pharmaceutical agent/combination	Pharmaceutical Cost	Prescription Cost	Total cost (Pharmaceutical + Prescription cost)		
	Pharmaceutical cost per pill (price/pill)	Prescription cost (per 90 days)	Per prescription period (90 day)	Annually (365 days)*	Five-year intervention period (1825 days) *
Amlodipine single pill (5 mg)⁶⁶	\$0.01	\$5.21	\$6.11	\$24.78	\$123.90
Atorvastatin single pill (20 mg)⁶⁶	\$0.03	\$5.21	\$7.91	\$32.08	\$160.40
Amlodipine (5 mg) + Atorvastatin (20 mg)	\$0.04	\$10.42	\$14.02	\$56.85	\$284.29
FDC AA (5 mg/20 mg)	\$0.04	\$5.21	\$8.81	\$35.73	\$178.65

All prices are in 2011 NZ. * = (cost per 90 day prescription period/90) x number of days)

4.4.6 Intervention uptake

Intervention uptake or the proportion of the model population who received either intervention (be prescribed either FDC AA or A+A) was also estimated. This was informed by recent modelling work by Knight et al 2017,^{93, 94} which was also used to inform the stratification of the population into CVD risk strata. Based on the figures by Knight et al^{93, 94} on the proportion of people in the model population who were on either an anti-hypertensive, a statin, or both, 46% of Māori men and 38% of non-Māori men within each risk stratum were assumed to receive either intervention.

4.4.7 Summary of intervention parameters

Table 12 summarises all the intervention input parameters for both FDC AA and A+A, their source and their uncertainty.

4.4.8 Scenario and sensitivity analyses

Several sensitivity and scenario analyses that varied intervention input parameters were carried out. The rationale and detail of each analysis is outlined in Table 13

Table 12: Summary of intervention inputs FDC AA and A+A

Input Parameter	Source	Value	Uncertainty
FDC AA – 5 mg Amlodipine/20 mg Atorvastatin			
Clinical Efficacy	Random effects meta-analysis of change in SBP and LDL-C from baseline from Blank et al 2005, ¹⁰² Flack et al 2008, ¹⁰¹ Erdine et al 2009 ⁶⁷ and Hobbs et al 2009. ¹⁰³ (Figure 4, Figure 5 and Figure 6). The resulting change in SBP and LDL-C applied to standardised RR for CVD events published in Karmali et al 2016 ¹¹¹ . Ersatz Excel plugin used to generate combined mean and 95%CI by running 2000 iterations of a log-normal distribution (Table 8).	Relative Risk	Stroke 0.237 (SD 0.082), CHD 0.476 (SD 0.058)
Adherence	Adherence declined uniformly over the five-year intervention period from 100% at baseline to 63.9% for the FDC AA (annual decrease of 7.2%) ⁶⁸	Annual decrease of 7.2%	n/a
Intervention Cost (pharmaceutical and prescription cost)	FDC AA 2011NZ\$0.04 per pill (estimated), prescription cost 2011NZ\$5.21 – Price scaling from 90-day prescription period to estimate five-year cost (Table 11).	2011 NZ\$178.65	SD ± 10% of the point estimate gamma distribution
A+A – 5 mg Amlodipine + 20 mg Atorvastatin			
Clinical Efficacy	Change in LDL-C from Adams et al 2015 ¹²⁰ (Atorvastatin) applied to standardised RR from Karmali et al 2016. ¹¹¹ RR for Amlodipine from Thomopoulos et al 2015 ¹¹³ (Amlodipine). Multiplication of RR for stroke, CHD and vascular events. Ersatz Excel plugin used to generate combined mean and 95%CI by running 2000 iterations of a log-normal distribution (Table 10).	Relative Risk	Stroke 0.460 (SD 0.023). CHD 0.540 (SD 0.028)
Adherence	Adherence declined uniformly over the five-year intervention period from 100% at baseline to 38.4% for A+A (an annual decrease of 12.3%). ⁶⁸	Annual decrease of 12.3%	n/a
Intervention Cost (pharmaceutical and prescription cost)	A+A 2011NZ\$0.04 per pill (PHARMAC) two x prescription cost 2011NZ\$10.42 – Price scaling from 90-day prescription period to estimate five-year cost ⁶⁶	2011 NZ\$284.29	SD ± 10% of the point estimate gamma distribution
Parameters common to FDC AA and A+A			
Intervention Uptake	Modelling work by Knight et al 2017 ^{93,94} in a synthetic New Zealand population estimated that 46% of Māori and 38% of non-Māori of NZ men aged 60 to 64 were currently either on an anti-hypertensive, a statin or both.	46% of Māori and 38% of non-Māori within each risk stratum	SD ± 10% of the point estimate gamma distribution
Intervention duration	To approximate five-year absolute risk reduction after which it is assumed that the absolute risk level would be reassessed by the GP.	Five years	n/a
Abbreviations: RR (relative risk), SBP (systolic blood pressure), LDL-C (low-density lipoprotein cholesterol), SD (standard deviation), 95%CI (95% confidence interval)			

Table 13: Description of scenario and sensitivity analyses

Model input sensitivity analysis	
Cost of FDC AA	In the base-case, the cost of FDC AA was \$0.04 per pill. Two sensitivity analysis were done which considered a price of \$0.02 and \$0.08 per pill.
Discount rate	The discount rate for both QALYs and costs was varied to 0% and 6% annually (relative to 3% in the base-case).
Intervention parameter scenario analysis.	
Equity analysis	Māori experience an inequitable burden of CVD. This scenario analysis explored the impact on results if Māori had the same capacity to benefit from treatment (same background-mortality and morbidity rate) as non-Māori.
Worse-case uptake and adherence	The lower values of the 95% confidence interval for both adherence and uptake for both the FDC AA and A+A regimen were used in the model rather than the mean.
Ethnic group variation in adherence	Adherence to pharmaceuticals among Māori has sometimes been reported to be lower than non-Māori. A sensitivity analysis was considered were adherence rates of Māori were 11% lower than that of non-Māori. ¹²⁸
Equal Efficacy	FDC are generally required to be at least equal in efficacy to their monotherapy components. In this sensitivity analysis, the clinical efficacy (relative risk, RR) for the FDC AA was reduced to be equal to the clinical efficacy of A+A. The primary difference between the use of the FDC AA and A+A becomes a function of the difference in adherence and the prescription cost.
Uptake at the start of modelling for both regimens to 80%	The proportion of the study population prescribed either pharmaceutical at baseline was increased to 80% for both Māori and non-Māori to explore the magnitude of potential health gain that could be expected if more people than currently, take preventive CVD pharmaceutical, in particular, FDC.
Time Horizon	The QALYs gained and the cost-offsets over five-year, 10-year and 20-year time horizon were considered (relative to a lifetime horizon in the base-case).

Chapter 5: Results

This Chapter describes the results generated by the BODE³ CVD MSLT model if New Zealand men aged 60 to 64 years, who were free of CVD and assumed to be taking A+A, switched to the FDC AA. The Chapter begins by describing the results from the base-case analysis overall and by five-year absolute CVD risk (Section 5.1). Section 5.2 compares the results of two sensitivity analyses with the base-case results and Section 5.3 describes the results of the various scenario analyses. The Chapter concludes by considering the impact of all sensitivity analyses on the base-case results and overall cost-effectiveness (Section 5.4).

5.1 Base-case results

5.1.1 Overview

The base-case analysis examined the difference in the QALYs gained and health system costs if a population of New Zealand men aged 60 to 64 with no history of CVD and assumed to be taking A+A as two separate pills, were offered to switch to the FDC AA. Intervention uptake for both pharmaceutical regimens was 46% for Māori and 38% for non-Māori within each risk stratum (the best estimate for the proportion of men in this age group taking both an anti-hypertensive and a lipid-lowering pharmaceutical and therefore eligible to switch to the FDC AA). Adherence was assumed to decline uniformly over the five-year intervention period from 100% at baseline to 63.9% for the FDC AA (an absolute decrease of 7.2 percentage points per year) and to 38.4% for A+A (an absolute decrease of 12.3 percentage points per year). Health gains (QALYs) and costs were accrued over a lifetime horizon and were discounted at 3% annually. Table 14 shows the incremental QALYs gained, the cost-offsets (net cost-savings) and the incremental cost-effectiveness ratio (ICER) by CVD risk strata if this cohort of men switched from A+A to use the FDC AA under the conditions of the base-case. Figure 7 and Figure 8 illustrate the QALYs gained and the cost-offsets (savings) on a cost-effectiveness plane.

5.1.2 Risk strata combined

Overall, under the conditions of the base-case, switching from A+A to the FDC AA was cost-saving (95% uncertainty interval (95%UI): cost-saving to \$3,570 per QALY gained) (Table 14). That is, switching to use the FDC AA for five-years resulted in additional health benefit and greater cost-offsets (savings) over a lifetime time horizon than the use of A+A under the same conditions. Overall, switching to use the FDC AA resulted in an additional 86.2 QALYS (95%UI: 0.00 to 386) gained in this age-cohort of men and an additional -\$1.24 million dollars (95%UI: -\$6.10 million to \$0.028 million) in cost-savings compared to the use of A+A (discounted at 3% annually).

5.1.3 Results by risk stratum

Within each of the five CVD risk strata, the use of the FDC AA resulted in additional QALY gains and additional cost-offsets (savings) than the use of A+A (albeit not significant – ie, there was a small chance of a positive cost). The ICER in favour of the FDC AA in risk stratum one (lowest CVD risk) ranged from cost saving to \$2.12 per QALY gained (or 472,000 QALYs per million dollars spent) at the upper bound of the 95%UI. The use of FDC AA in risk stratum four and five (highest CVD risk) ranged from cost-saving to \$3,940 per QALY (or 253 QALY per million dollars spent) and \$3,570 per QALY gained (or 280 QALYs per million dollars spent) respectively, compared to the use of A+A. (see Table 14, Figure 7 and Figure 8)

The total QALYs gained were greatest in risk stratum one and two (since these strata had the largest numbers of simulated individuals) and decreased as CVD risk increased. The QALYs gained per 1,000 people who took either pharmaceutical regimen at baseline in each CVD risk stratum (per capita) shows the opposite pattern in QALYs gained. That is, the per capita QALY gains were greatest in the highest CVD risk strata and decreased as CVD risk decreased. The largest per capita health gain was observed in risk stratum five with 78.1 QALYs per 1,000 people who received medication. The smallest per capita health gain was observed in risk stratum one with 11.4 QALYs per 1,000 people. The absolute QALYs gained were larger for non-Māori than Māori. However, the per capita QALY gains, which remove the influence of differing population numbers between Māori and non-Māori, showed the QALYs gained by Māori in risk stratum one and two were similar between Māori and non-Māori. Across risk stratum four to five the additional QALYs gained per capita were slightly larger for non-Māori than Māori. The cost-offsets (savings) illustrate a similar pattern to the QALYs gained with the greatest absolute cost-offsets being observed in risk stratum one and two, decreasing in magnitude as CVD risk increases. None of the absolute cost-offsets (savings) were significant (ie, there was a chance the cost could be positive) . The cost-offset per capita did not differ considerably by risk strata.

Table 14: The additional health gain (QALYs), the additional cost-offsets (savings) and the incremental cost-effectiveness ratio if the estimated 38% non-Māori and 46% of Māori men aged 60 to 64 years in 2011 who were assumed to be on A+A switched to the FDC AA – The base-case (five-year intervention period, lifetime time-horizon, 3% annual discount rate)

Risk Strata: five-year absolute CVD risk (uptake population n=Māori; Non- Māori)	Non-Māori QALYs gained	Māori QALYs gained	QALYs gained (ethnic groupings combined)	Cost-offsets Ethnic groupings combined (NZ\$2011 million)	ICER (NZ\$ per QALY) All ethnic groups
A. Overall					
Risk Stratum 5: >20% (n= 19; 22)	1.93 (1.17 to 5.05)	1.30 (0.97 to 3.77)	3.23 (1.42 to 7.80)	-\$0.009 (\$-0.034 to \$0.012)	Cost-saving (Cost-saving to \$3,940)
Risk Stratum 4: >15%, ≤20% (n= 73; 104)	6.79 (3.80 to 17.8)	3.83 (2.96 to 10.9)	10.6 (4.40 to 26.1)	-\$0.049 (\$-0.139 to \$0.027)	Cost-saving (Cost-saving to \$3,570)
Risk Stratum 3: >10%, ≤15% (n= 333; 738)	32.2 (14.2 to 80.0)	12.6 (8.04 to 34.4)	44.7 (15.6 to 105)	-\$0.324 (\$-0.825 to \$0.147)	Cost-saving (Cost-saving to \$4,000)
Risk Stratum 2: >5%, ≤10 (n= 1125; 7674)	168 (84.1 to 429)	24.8 (13.6 to 67.6)	193 (81.5 to 474)	-\$2.53 (\$-6.25 to \$0.822)	Cost-saving (Cost-saving to \$3,160)
Risk Stratum 1: >0%, ≤5% (n= 377; 14,236)	163 (74.1 to 404)	4.72 (2.61 to 12.3)	167 (73.0 to 412)	-\$3.41 (\$-7.63 to \$0.535)	Cost-saving (Cost-saving to \$2.12)
Risk Strata Combined (n=1,962; 22,773)	76.8 (0 to 636)	9.89 (0 to 49.2)	86.2 (0 to 386)	-\$1.24 (\$-6.10 to \$0.028)	Costs-saving (cost-saving to \$3,570)
B. QALYs / 1,000 people & \$ per person who received either pharmaceutical regimen at the start of the model (uptake)					
Risk Stratum 5	87.6	68.8	78.1	-\$221	–
Risk Stratum 4	67.2	52.5	59.5	-\$275	–
Risk Stratum 3	43.7	37.9	41.5	-\$301	–
Risk Stratum 2	21.9	22.0	21.9	-\$287	–
Risk Stratum 1	11.4	12.5	11.4	-\$233	–
Range represents the 95% uncertainty interval (95%UI) of 2000 Monte Carlo simulations per risk stratum Note: approximately 8% of the 2000 Monte Carlo simulations were excluded from calculations due to the occurrence of negative QALYs. Negative QALYs occurred due to the two pharmaceutical regimens being modelled sequentially and subtracting the respective outputs. Had the regimens been modelled in parallel, negative QALYs would not have been possible (see Section 6.5.2 of this thesis for further detail). QALYs (quality-adjusted life-years); ICER (incremental cost-effectiveness ratio) All numbers rounded to three meaningful digits					

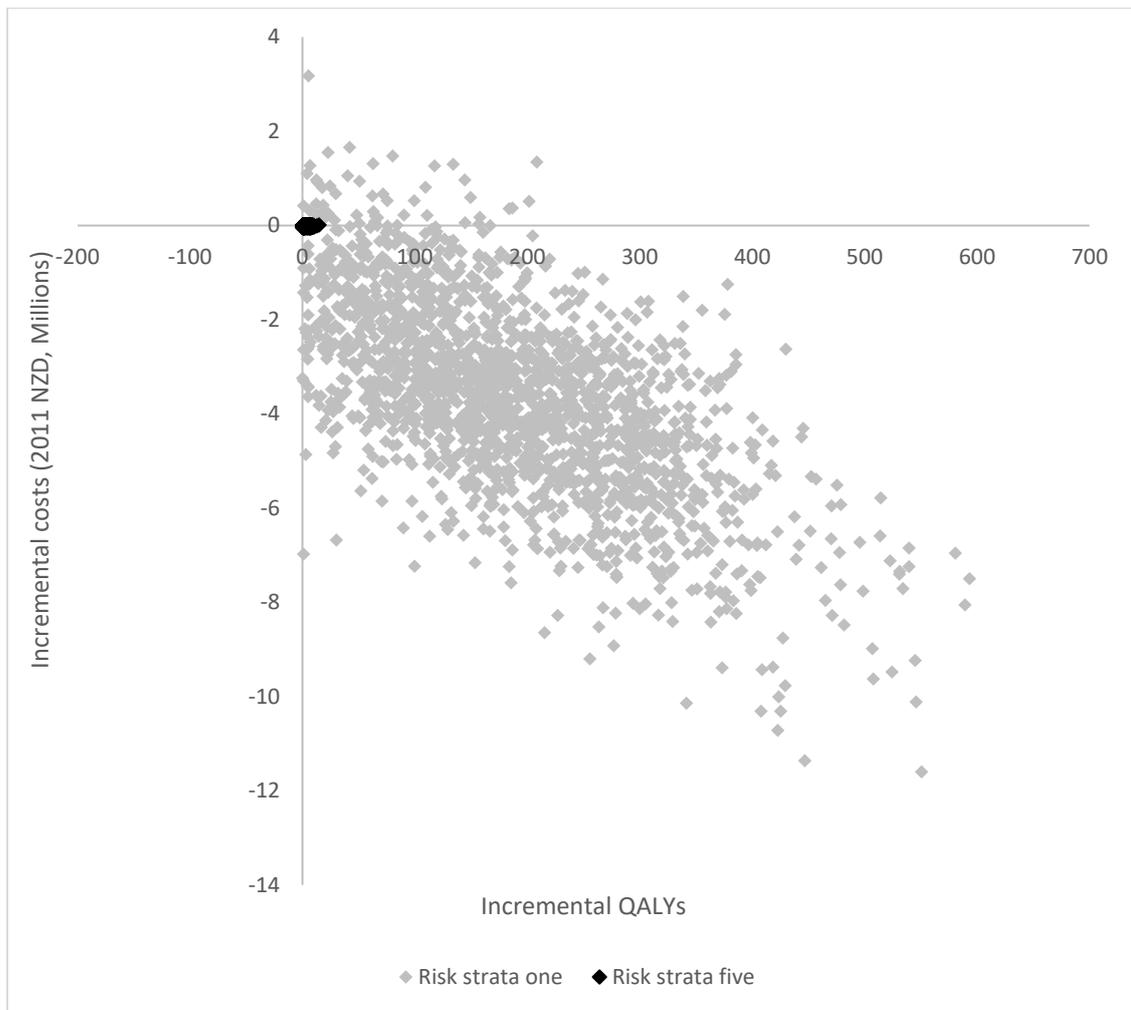


Figure 7: Cost-effectiveness plane showing the incremental cost-offset and QALYs gained if the proportion of New Zealand men aged 60 to 64 who were assumed to be taking A+A switched to the FDC AA by five-year absolute cardiovascular disease risk strata (risk stratum one and five only)– Results of 2000 Monte Carlo simulations per CVD risk stratum. (Base-case conditions, five-year intervention period, lifetime horizon, 3% annual discount rate, outliers excluded*)

* Approximately 8% of the 2000 Monte Carlo simulations were excluded from calculations due to the occurrence of negative QALYs. Negative QALYs occurred due to the two pharmaceutical regimens being modelled sequentially and subtracting the respective outputs. Had the regimens been modelled in parallel, negative QALYs would not have been possible (see Section 6.5.2 of this thesis for further detail).

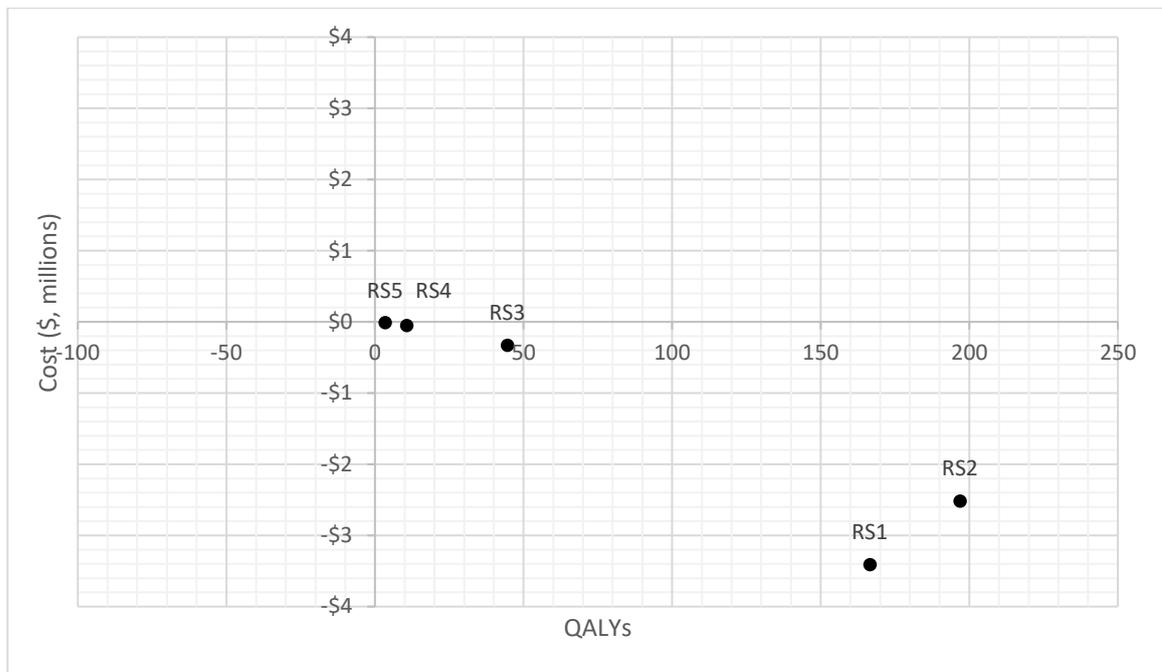


Figure 8: Cost-effectiveness plane showing the base-case mean values (with no uncertainty) for the incremental cost-offsets and QALYs gained by each risk stratum (RS) if the proportion of New Zealand men aged 60 to 64 who were assumed to be taking A+A switched to the FDC AA

5.2 Sensitivity analyses

Two sensitivity analyses were run in which the model discount rate (base-case 3%, sensitivity analysis 0% and 6%) and cost of the FDC AA (base-case \$0.04 per pill, sensitivity analysis \$0.02 and \$0.08 per pill) were varied. The details of each sensitivity analysis have been summarised previously in Table 13.

Table 15 displays the expected values for the additional QALYs gained and cost-offset (savings) if a population of New Zealand men aged 60 to 64 assumed to be on A+A, switched to FDC AA under the conditions of each sensitivity analysis. As in the base-case, across all model sensitivity analyses, the absolute QALY gained and cost-offsets (savings) were greatest in risk stratum one and two and decreased as CVD risk increased. Furthermore, the observed pattern that the QALYs gained per capita were greatest among those with the greatest CVD risk, was also apparent here. Except for risk stratum five in the 0% discount rate scenario, switching from A+A to the FDC AA remained cost-saving. The ICER in risk stratum five with a 0% discount rate was \$1,400 per QALY (716 QALYs per million dollars spent).

Using a discount rate of 6%, (ie, the QALY gains and cost-offsets (savings) in the future are valued less than QALY gains and cost-offsets today) the number of QALYs gained decreased by approximately 32% while the cost-offsets increased. When a 0% discount rate was used (ie, the QALY gains and cost-offsets were of equal value in the future as QALY gains and cost-offsets today) the number of QALYs gained increased by 55% from the base-case while the cost-offsets (savings) decreased. The percentage

change in QALYs from the base-case was least in risk stratum five and increased as CVD risk increased, while the percentage change in costs was greatest in risk stratum five and decreased as CVD risk increased. Changing the price of FDC AA to be half or double the cost used in the base-case did not affect the QALYs gained as expected and had only a small influence on the magnitude of cost-offsets (savings) from the base-case. Changing the price of the FDC to be half the cost used in the base-case increased the cost-offsets (savings) by approximately 11% on average. Doubling the price of the FDC on the other hand, resulted in a decrease of approximately 23% in the cost-offsets (savings) in each risk strata on average.

Table 15: The additional health gain (QALYs) and the cost-offsets if New Zealand men aged 60 to 64 years in 2011 who were assumed to be on A+A switched to the FDC AA – ethnic groupings combined, sensitivity analyses (0% and 6% discount rate, FDC AA cost 50% and 200%)

Five-year absolute CVD risk strata	Base-case*		0% Discount Rate**		6% Discount Rate**		FDC AA cost 50% ^φ		FDC AA cost 200% ^φ	
	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)
A. Overall										
Risk Stratum 5: >20%	3.42	-\$0.009	4.96	\$0.007	2.45	-\$0.017	3.42	-\$0.01	3.42	-\$0.01
Risk Stratum 4: >15%, ≤20%	10.7	-\$0.050	15.9	-\$0.003	7.47	-\$0.072	10.7	-\$0.06	10.7	-\$0.04
Risk Stratum 3: >10%, ≤15%	44.6	-\$0.326	68.5	-\$0.149	30.4	-\$0.396	44.6	-\$0.360	44.6	-\$0.26
Risk Stratum 2: >5%, ≤10	197	-\$2.51	316	-\$1.98	130	-\$2.62	197	-\$2.79	197	-\$1.96
Risk Stratum 1: 0, ≤5	167	-\$3.41	277	-\$3.27	107	-\$3.26	167	-\$3.87	167	-\$2.49
B. QALYs / 1,000 people & \$ per person who received either pharmaceutical regimen at the start of the model (uptake)^ψ										
Risk Stratum 5 (n=41)	83.0	-\$221	120	\$167	59.2	-\$420	82.7	-\$251	82.7	-\$161
Risk Stratum 4 (n=178)	60.0	-\$281	89.0	-\$15.7	41.9	-\$404	59.8	-\$311	59.8	-\$220
Risk Stratum 3 (n=1,078)	41.4	-\$303	63.5	-\$138	28.2	-\$368	41.4	-\$334	41.4	-\$241
Risk Stratum 2 (n=8,824)	22.3	-\$285	35.9	-\$224	14.7	-\$296	22.3	-\$316	22.3	-\$223
Risk Stratum 1 (n=14,631)	11.4	-\$233	19.0	-\$224	7.34	-\$223	11.4	-\$264	11.4	-\$170
<p>*Base-case: 38% of non-Māori and 46% of Māori men aged 60 to 64 assumed to be on A+A switch to FDC AA, five-year intervention period, lifetime time horizon and 3% annual discount rate</p> <p>** The discount rate of all accrued QALYs and costs discounted varied from the base-case 3% to 0% and 6%. All other conditions as per the base-case</p> <p>^φ FDC AA cost 50% and 200%: The cost of the FDC AA was changed to be 50% and 200% of the base-case cost respectively. All other conditions as per the base-case.</p> <p>^ψ n=46% of Māori and 38% of non-Māori in each CVD risk stratum</p> <p>All values are expected values. All figures are rounded to three meaningful digits.</p>										

5.3 Scenario analyses

In addition to the discount rate and cost of the FDC sensitivity analyses, a range of scenario analysis in which various model or intervention parameters were varied, was done in order to observe the effects of several different plausible scenarios. The considered scenarios include: an equity analysis, worse-case uptake adherence and uptake, ethnic group variation in adherence, equal efficacy of medication regimens, 80% uptake and three different time horizons. Each scenario analysis is summarised in Table 13. Table 17 and Table 18 shows the additional QALYs gained and the cost-offsets (savings) for each scenario. Each scenario analysis will be discussed in turn below.

The three notable patterns that were observed in the base-case analysis were preserved in all six scenario analyses. Firstly, in each analysis, the absolute QALYs gained and the cost-offsets (savings) attributed to switching to the FDC AA from A+A were greatest in risk stratum one and two and decreased as five-year CVD risk increased. Secondly, the additional QALYs gained from switching to the FDC AA adjusted by the number of people who received either pharmaceutical intervention at baseline was greatest in risk stratum five, the stratum with the greatest CVD risk and decreased as CVD risk decreased. This indicates that those with the greatest CVD risk also benefited the most from switching from A+A to the FDC AA. The cost-offsets (savings) per medicated person did not appear to differ substantially by CVD risk strata. Thirdly, switching to the FDC AA from A+A was cost-saving in each CVD risk stratum regardless of the scenario analysis.

5.3.1 Equity analysis

In New Zealand, Māori experience a greater burden of background mortality and morbidity than non-Māori. To avoid the penalising effect of this inequity, an “equity analysis” was run in which non-Māori mortality rates and disability weights were applied to Māori. Essentially, this results in Māori having the same capacity to benefit from treatment with the FDC AA or A+A as non-Māori. Table 16 shows the QALYs gained by Māori in the base-case and the equity analysis scenario. Under this ‘equity analysis’ scenario, the QALYs gained by Māori in all five CVD risk strata increased by approximately 11%. The largest gain in additional QALYs for Māori, in absolute terms, was observed in risk stratum two in which the greatest proportion of the male Māori population in this modelled age-group resides. The QALYs gained per capita were greatest in risk stratum five with eight additional QALYs gained in the ‘equity analysis’ compared to the QALYs gained by Māori in the base-case. The per capita QALYs gained by Māori decreased as CVD risk decreased with risk stratum one gaining one additional QALY under the conditions of equal efficacy compared to the QALYs gained by Māori in the base-case. Overall, the equity analysis scenario had minimal effect on the overall cost-effectiveness of treatment with the FDC AA compared to A+A in each CVD risk stratum. The ethnic groupings combined QALYs

gained increased slightly while the total cost-offsets (savings) under the conditions of equity analysis were approximately equal to the base-case in all risk strata.

Table 16: The additional health gain (QALYs) by Māori men aged 60 to 64 years in 2011 who were assumed to be on A+A and who were switched to the FDC AA: Base-case vs 'equity analysis'.

Risk Strata	Total Māori QALYs gained		Māori QALYs gained per 1,000 people who took the pharmaceuticals (46% of Māori in each risk strata) ^ψ	
	Base-case	Equity analysis	Base-case	Equity analysis
Risk Stratum 5: >20%	1.37	1.52	72.3	80.2
Risk Stratum 4: >15%, ≤20%	3.88	4.31	53.2	59.2
Risk Stratum 3: >10%, ≤15%	12.5	14.0	37.7	42.0
Risk Stratum 2: >5%, ≤10	25.0	27.9	22.3	24.8
Risk Stratum 1: 0, ≤5	4.66	5.17	12.4	13.7
^ψ Risk Stratum 1: n=19, Risk Stratum 2: n=73, Risk Stratum 3: n=333, Risk Stratum 2: n=1,125, Risk Stratum: 1 n=377				

5.3.2 Worse-case adherence and uptake/ethnic group variation in adherence

The 'worse-case uptake and adherence' scenario which used the value of the lower bound of the 95%UI rather the mean for these two parameters, resulted in a modest change from the base-case as both the QALYs gained and the cost-offsets (savings) decreased by approximately 22% in each CVD risk stratum. Ethnic group variation in adherence had an even smaller influence on the cost-effectiveness with the QALYs gained and the cost-offsets (savings) changing by less than 1% (see Table 17).

5.3.3 Equal efficacy of medicated regimens

From all the scenario analyses, the base-case was most sensitive to changes in uptake and clinical efficacy. Lowering the clinical efficacy for the FDC AA to be equal with A+A in the base-case ('equal efficacy' scenario) resulted in a 79% average decrease in the QALYs gained and a 53% average decrease in the cost-offsets (savings) in each CVD risk stratum. Although the cost-effectiveness for switching remained cost-saving in each risk stratum despite these decreases, the cost-effectiveness was greatly decreased (see Table 17).

5.3.4 80% uptake

Changing the proportion of the population who were assumed to be on A+A and switched to FDC AA from 46% for Māori and 38% for non-Māori in the base-case to 80% at the start of the modelling, had the large effect on the cost-effectiveness of FDC AA compared to A+A. This increase in uptake approximately doubled the QALYs gained and the cost-offsets, greatly increasing the cost-

effectiveness. This analysis suggests the potential health gain and cost-savings that could be observed if a greater proportion of people were switched from A+A to the FDC AA (see Table 17).

5.3.5 Varying time horizons

Modelling the future involves uncertainty and the magnitude of this uncertainty increases as the time horizon increases. The base-case analysis looked at the QALYs gained and the cost-offsets (savings) over a lifetime time horizon. In this scenario analysis, the QALYs gained and the cost-offsets (savings) were explored over a five-year, 10-year and 20-year time horizon (albeit with the intervention period still set at five years) (Table 18). The number of QALYs gained overall and within each CVD stratum increased as the time horizon increased. The additional QALYs gained by switching to the FDC AA at five-years, 10-years and 20-years were on average 11%, 34% and 77% of the QALYs gained over a lifetime time-horizon (base-case) respectively within each CVD risk stratum. The cost-offset with treatment with the FDC AA increased in all CVD risk strata as the time horizon increased from five-years to 10-years. Cost offsets (savings) increased further from a 10-year to 20-year time horizon for risk stratum one and two but decreased for risk strata three to five. The cost-offsets (savings) from 20-years to the lifetime horizon considered in the base-case decreased. In risk stratum three, four and five, the greatest cost-offsets (savings) were observed over a 10-year time horizon, while for risk stratum one and two the greatest cost-offsets (savings) were observed over a 20-year time horizon. In all risk strata, the cost-offsets (savings) over the lifetime were the lowest of the four time-horizons.

Table 17: The additional health gain (QALYs) and the cost-offsets (savings) if New Zealand men aged 60 to 64 years in 2011 who were assumed to be on A+A switched to the FDC AA – ethnic groupings combined, scenario analyses.

Five-year absolute CVD risk strata	Base-case*		Equity Analysis**		Worse-case adherence and uptake***		Ethnic group variation in adherence [∞]		Equal efficacy of medications regimens [∇]		80% uptake of both regimens at the start of modelling [♠]	
	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)
A. Overall												
Risk Stratum 5: >20%	3.42	-\$0.009	3.57	-\$0.009	2.67	-\$0.007	3.40	-\$0.009	0.72	\$0.005	6.84	-\$0.022
Risk Stratum 4: >15%, ≤20%	10.7	-\$0.050	11.1	-\$0.050	8.35	-\$0.038	10.6	-\$0.050	2.24	-\$0.023	21.3	-\$0.118
Risk Stratum 3: >10%, ≤15%	44.6	-\$0.326	46.0	-\$0.326	35.0	-\$0.251	44.1	-\$0.326	9.23	-\$0.142	89.8	-\$0.754
Risk Stratum 2: >5%, ≤10	197	-\$2.51	200	-\$2.51	155	-\$1.96	195	-\$2.51	40.0	-\$1.11	408	-\$5.71
Risk Stratum 1: 0, ≤5	167	-\$3.41	167	-\$3.41	131	-\$2.68	164	-\$3.40	33.6	-\$1.66	354	-\$7.62
B. QALYs / 1,000 people & \$ per person who received either pharmaceutical regimen at the start of the model (uptake)[∏]												
Risk Stratum 5 (n=41)	83.0	-\$221	86.3	-\$221	64.6	-\$168	82.1	-\$222	17.5	-\$115	85.5	-\$278
Risk Stratum 4 (n=178)	60.0	-\$281	62.3	-\$281	46.8	-\$215	59.4	-\$281	12.6	-\$128	61.2	-\$339
Risk Stratum 3 (n=1,078)	41.4	-\$303	42.7	-\$303	32.5	-\$233	41.0	-\$303	8.57	-\$132	41.9	-\$351
Risk Stratum 2 (n=8824)	22.3	-\$285	22.6	-\$285	17.5	-\$222	22.0	-\$284	4.54	-\$126	22.4	-\$314
Risk Stratum 1 (n=14,631)	11.4	-\$233	11.4	-\$233	8.95	-\$183	11.2	-\$233	2.30	-\$113	11.5	-\$249
<p>*Base-case: 38% of non-Māori and 46% of Māori men aged 60 to 64 assumed to be on A+A switch to FDC AA, five-year intervention period, lifetime time horizon and 3% annual discount rate</p> <p>**Equity analysis: The morbidity and mortality rates used for non-Māori in the base-case were applied to Māori. All other conditions as per the base-case</p> <p>***Worse-case adherence and uptake: Lower value of the 95%UI for adherence and uptake used rather than the median. All other conditions as per the base-case</p> <p>[∞]Ethnic group variation in adherence: Adherence for both FDC AA and A+A assumed to be 11% lower for Māori than non-Māori. All other conditions as per the base-case</p> <p>[∇]Equal efficacy of medication regimens: Clinical efficacy for FDC AA assumed to be equal to clinical efficacy of A+A in the base-case. All other conditions as per the base-case</p> <p>[♠]80% uptake: initial uptake at the start of the modelling was changed to be 80% for both Māori and non-Māori for the FDC AA and A+A.</p> <p>[∏]n=46% of Māori and 38% of non-Māori in each CVD risk stratum</p> <p>All values are expected values. All figures are rounded to three meaningful digits.</p>												

Table 18: The additional health gain (QALYs) and the cost-offsets (savings) if New Zealand men aged 60 to 64 years in 2011 who were assumed to be on A+A switched to the FDC AA – ethnic groupings combined, various time horizons

Five-year absolute CVD risk strata	5-year time horizon [∇]		10-year time horizon [∇]		20-year time horizon [∇]		Base-case* (lifetime horizon)	
	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)	QALYs gained	Cost-offsets (NZ\$2011 million)
A. Overall								
Risk Stratum 5: >20%	0.416	-\$0.033	1.41	-\$0.035	2.98	-\$0.018	3.42	-\$0.009
Risk Stratum 4: >15%, ≤20%	1.20	-\$0.106	4.00	-\$0.121	8.88	-\$0.082	10.7	-\$0.050
Risk Stratum 3: >10%, ≤15%	4.65	-\$0.474	15.1	-\$0.570	34.9	-\$0.477	44.6	-\$0.326
Risk Stratum 2: >5%, ≤10	19.4	-\$2.50	59.8	-\$3.12	140	-\$3.19	197	-\$2.51
Risk Stratum 1: 0, ≤5	16.5	-\$2.80	48.2	-\$3.47	111	-\$3.88	167	-\$3.41
B. QALYs / 1,000 people & \$ per person who received either pharmaceutical regimen at the start of the model (uptake)^ψ								
Risk Stratum 5 (n=41)	10.1	-\$791	34.0	-\$836	72.2	-\$433	83.0	-\$221
Risk Stratum 4 (n=178)	6.74	-\$597	22.4	-\$679	49.8	-\$461	60.0	-\$281
Risk Stratum 3 (n=1,078)	4.32	-\$440	14.0	-\$529	32.4	-\$442	41.4	-\$303
Risk Stratum 2 (n=8824)	2.19	-\$283	6.78	-\$354	15.9	-\$361	22.3	-\$285
Risk Stratum 1 (n=14,631)	1.13	-\$191	3.30	-\$237	7.57	-\$265	11.4	-\$233
<p>*Base-case: 38% of non-Māori and 46% of Māori men aged 60 to 64 assumed to be on A+A switch to FDC AA. five-year intervention period, lifetime time horizon and 3% annual discount rate</p> <p>[∇] Time-horizon over which QALYs and costs accrued was varied from lifetime in the base-case to five-years, 10-years and 20-years. Intervention period remained five-years. All other conditions as per the base-case.</p> <p>^ψ n=46% of Māori and 38% of non-Māori in each CVD risk stratum</p> <p>All values are expected values. All figures are rounded to three meaningful digits.</p>								

5.4 Evaluation of the ICER – all sensitivity and scenario analyses, overall and by risk strata

Figure 9 illustrates the impact the all the sensitivity and scenario analyses had on the additional QALYs gained and the additional cost-offsets (savings) attributed the use of FDC AA compared to A+A for risk stratum three. The patterns illustrated in this figure are indicative of the impact that all the considered sensitivity and scenario analysis had in all risk strata and for the risk, strata combined.

Overall and across all risk strata the scenario analysis ‘worse-case’ and ‘equal efficacy’ reduced the cost-effectiveness of the FDC AA compared to A+A by resulting in less QALYs gained and fewer costs offset than that observed in the base-case analysis. This effect was more pronounced under the conditions of ‘equal efficacy’ than ‘worse-case’ in all five risk strata. Increasing uptake to 80%, on the other hand, was the only analysis to increase the cost-effectiveness of the FDC AA compared to A+A by increasing the magnitude of both the QALYs gained and the cost-offsets (savings). Using a 0% discount rate increased the QALYs gained but reduced the cost-offset (savings) compared to the base-case in each CVD risk stratum. In risk stratum five using a 0% discount rate, treatment with the FDC AA resulted in a cost of \$7,000. Varying the model time horizon over which QALYs and cost-offsets (savings) could be accrued and using a 6% discount rate resulted in less QALY gain and greater cost-offsets (savings) compared to the base-case. The ‘equity analysis’, ‘ethnic group variation in adherence’ and the two analyses that varied the cost of the FDC, all resulted in only minor changes in the cost-effectiveness relative to the base-case.

The ICER of the FDC AA compared to AA was notably influenced by the scenario analysis ‘five-year time horizon’, ‘10-year time horizon’, ‘equal efficacy’, ‘0% discount rate’ and ‘80% uptake’. With the exception of a 0% discount rate in risk stratum five which resulted in a cost-effectiveness ratio of \$1,400 per QALY (716 QALYs per million dollars spent), all sensitivity and scenario analysis fell in the cost-saving zone of the cost-effectiveness plane. That is, within each risk stratum and all the scenarios considered (except for 0% discount rate in risk stratum five) treatment with the FDC AA resulted in greater QALY gains and cost-offsets (savings) than treatment with A+A.

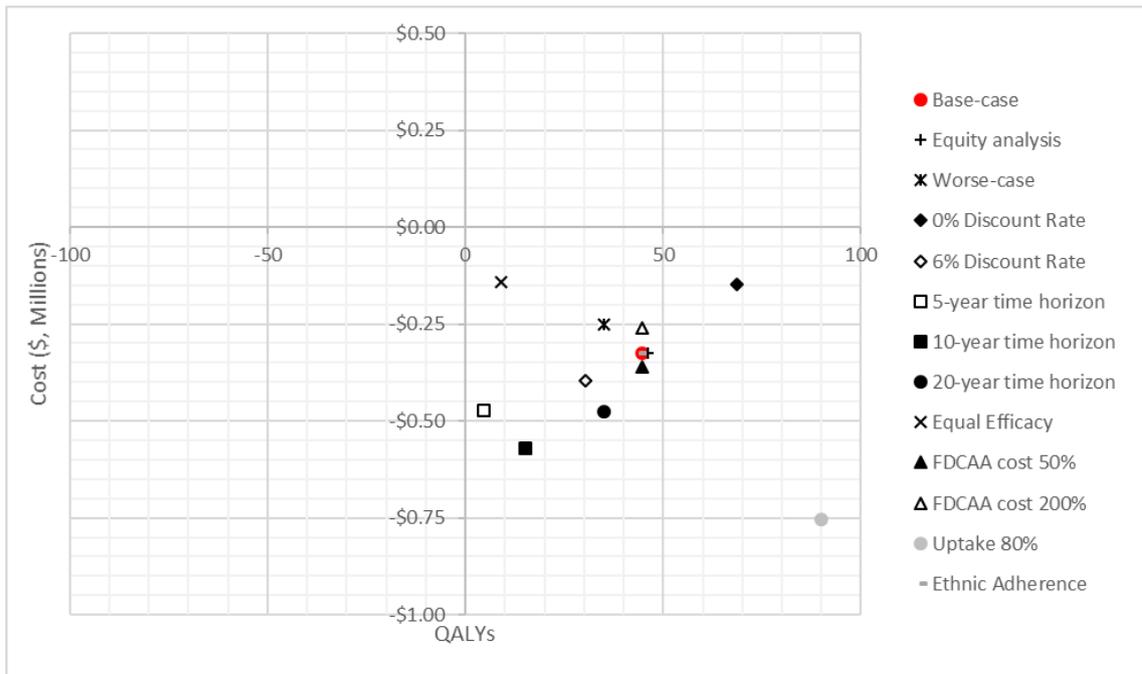


Figure 9: Cost-effectiveness plane showing the additional QALYs gained and the additional cost-offsets attributed to the use of the FDC AA compared to A+A among New Zealand men aged 60 to 64 assumed to be on A+A in 2011 who then switched to the FDC AA (all scenario and sensitivity analyses for risk stratum three).

Chapter 6: Discussion

6.1 Chapter overview

This Chapter begins by discussing and interpreting the main results of this thesis and their relationship to existing literature. Following this, the strength and limitations of the model method, model inputs and intervention parameters are considered. The Chapter then considered the implications and future directions from this research and draws conclusions.

6.2 Main results and interpretation

6.2.1 Introduction

This study aimed to determine the health gain, costs and cost-effectiveness of prescribing a two-agent FDC for the primary prevention of cardiovascular disease (relative to the same agents taken as individual pills) by absolute CVD risk in the New Zealand population. The FDC AA compared to A+A as two separate pills were chosen as the basis of this analysis because it was part of an emerging group of CVD pharmaceuticals that aimed to address multiple CVD risk factors in a single pill. No pharmaceutical formulations that address two or more different CVD risk factors were approved for use in New Zealand at the time of this research commencing. Furthermore, the prevalence of New Zealand adults who use A+A or more generally a CCB and statin as two separate pills is high.^{10, 21, 91} It was therefore hypothesised that there was a large proportion of the adult population who could potentially benefit from switching to the FDC AA and realise the benefits from improved adherence and a reduced pill burden. These benefits potentially included improved pharmaceutical efficacy which may then lead to a reduction in CVD events and associated hospitalisations. Financial savings may also be observed with patients reducing the number of prescriptions they pay for and the health system treating less CVD related events.

An existing MSLT model from the BODE³ Programme was adapted and used to model the incremental difference in the QALYs and the costs accrued over a lifetime, if a cohort of New Zealand men aged 60 to 64 in 2011 who were free from CVD and assumed to be on A+A (46% of Māori and 38% non-Māori) were offered to switch to the FDC AA. The model base-case considered a health system perspective, a five-year intervention period and lifetime horizon over which the accrued QALYs (health benefit) and costs were discounted at 3% annually. Based on the literature, the clinical efficacy of the FDC AA was assumed to be greater than A+A reflecting the potential increase in clinical efficacy that occurs as a result of improved adherence. Adherence was also considered in the model, with an annual decrease in adherence which was greater for A+A than the FDC AA (ie, based on available literature, adherence

was assumed to be greater for FDC AA than A+A). For more detailed information on the intervention inputs see Table 12.

6.2.2 Summary of base-case results

The results of the base-case showed that switching New Zealand men aged 60 to 64 assumed to be on A+A to the FDC AA for the primary prevention of CVD improved health while being cost-saving. That is, switching to use the FDC AA in this population is likely to result in greater health gains (QALYs) and greater cost-offsets (savings) than if the same population remained on A+A, overall and within each stratum of CVD risk. Over the lifetime horizon considered in the model, the use of the FDC AA for five-years resulted in an additional 86.2 QALYs (95%UI 0 to 386) and 1.24 million (95%UI -\$6.10 million to -0.028 million) in cost-offsets (savings) compared to the use of A+A for five-years in the same population (albeit not to a significant level for the costs). The ICER overall ranged from cost-saving to \$3,570 per QALY gained (280 QALYs per million dollars spent). The lowest CVD risk strata had the smallest range of cost-effectiveness ranging from cost-saving to \$2.12 per QALY (470,000 QALYs per million dollars spent). While the remaining four risk strata ranged from cost-saving to \$3,000 to \$4,000 per QALY (333 or 250 QALYs per million dollars spent respectively) at the upper bounds of the 95%UI.

For BODE³ Programme work in New Zealand, a threshold of \$45,000 per additional QALY gained (approximately the GDP per capita in NZ as recommended by the World Health Organization (WHO)¹²⁹) is used when evaluating and comparing the cost-effectiveness of health sector interventions. Given this threshold and an ICER within each CVD risk stratum and overall ranging from cost-saving to \$4,000 per QALY at the upper bounds of the 95%UIs, switching from A+A to the FDC AA appears to be a good value for money method to enhance the primary prevention of CVD in New Zealand. Although the overall cost-effectiveness of the FDC AA compared to A+A was greater the lower the CVD risk strata, considering this threshold suggests that switching to the FDC AA would likely have a positive impact regardless of absolute CVD risk at baseline.

The health benefit and cost-effectiveness of pharmaceuticals in New Zealand for government subsidisation are routinely assessed by the Pharmaceutical Management Agency (PHARMAC). The economic evaluation results of the pharmaceuticals considered are not made publicly available. However, the 2016/17 and 2015/16 PHARMAC Annual Report indicates that the average cost-effectiveness achieved for funded proposals to the Combined Pharmaceutical Budget (CPB) (includes community pharmaceuticals, hospital pharmaceutical cancer treatments and vaccines) was 38 and 52 QALYs per \$NZ million net costs to the health sector in the respective financial years.^{130, 131} Although, the availability of funding and the number of pharmaceutical proposals competing for funding differs from year to year, comparing the base-case results of this thesis to the published average of the QALYs

achieved by PHARMAC in recent years, demonstrates that the funding of the FDC AA for subsidised use in New Zealand would likely be viewed as a good investment.

Overall, the additional QALYs gained and the additional cost-offsets (savings) attributed to the use of the FDC AA compared to A+A were greater the lower the absolute CVD risk. This pattern is largely influenced by population numbers, which were greater in the lower risk strata (risk stratum one and two) than the higher risk strata (risk stratum four and five). When the results were considered per capita (per 1,000 people who received either pharmaceutical regimen at baseline - uptake), the additional QALYs gained with the use of the FDC AA instead of A+A, were greatest in the highest CVD risk strata (stratum five) and decreased as CVD risk decreased. This suggested, that individuals with higher CVD risk and greater capacity to benefit also achieved the highest benefit from switching to the FDC AA than remaining on A+A (in relative terms). Information like this provides a rationale for prioritising switching the treatment of those who are at greater risk of CVD.

The additional QALYs gained at the group level by switching from A+A to the FDC AA were greater for non-Māori than Māori within in each risk stratum. However, the results per capita exposed to either pharmaceutical regimen at the start of the model show, the additional QALY gained by Māori are slightly greater than non-Māori in risk stratum one and two. The epidemiology of CVD demonstrates that there is an inequity in the proportion of Māori who experience high CVD risk.¹³ Switching from the A+A to the FDC AA, among Māori in CVD risk stratum one and two, appears to be a method which could help to address this inequity by having a greater impact on the health of Māori who also have a greater burden of health need than non-Māori.

6.2.3 Scenario and sensitivity analyses

Clinical efficacy appears to be a large driver of the cost-effectiveness. In the base-case, the clinical efficacy of the FDC AA was greater than A+A. To distinguish between the effect of improved clinical efficacy and adherence with an FDC, the clinical efficacy of the FDC AA was reduced to be equal to that of A+A (as at the very least, FDCs are designed to be equally efficacious as their equivalent monotherapies). Under this assumption, the cost-effectiveness of switching from A+A to the FDC AA remained cost-saving but was substantially reduced in all five CVD risk strata. Other sensitivity analyses that influenced adherence including 'ethnic group difference in adherence' and 'worse-case adherence and uptake' also reduced the cost-effectiveness in all CVD risk strata but by a smaller magnitude than that observed in the 'equal efficacy' scenario analysis. The results of this model appear more sensitive to changes in clinical efficacy than adherence, but further consideration and modelling could be done to examine the relationship between adherence and clinical efficacy.

The other large driver of the cost-effectiveness ratios was intervention uptake. This scenario analysis changed the proportion of the model population who were exposed to either pharmaceutical intervention at the start of the modelling to 80% for both Māori and non-Māori and it approximately doubled the cost-effectiveness in favour of switching to the FDC. The results of this scenario, highlight the substantial health gain and cost-savings that could be seen if a greater proportion of the population in this age-group of men were taking a statin and an anti-hypertensive for the primary prevention of CVD and were preferentially prescribed the FDC AA instead of A+A.

The cost of the FDC AA in the model had little impact on the cost-effectiveness. Halving the price of the FDC AA increased the cost-offsets (savings) by approximately 11% while doubling the cost decreased cost-offsets (savings) by 23%.

Modelling inherently involves uncertainty and this uncertainty increases the further into the future the model runs. At time horizons of five-years, 10-years and 20-years, switching to the FDC AA from A+A remained cost-saving within all CVD risk strata. Although the QALYs gained increased over time, the cost-offsets (savings) were generally greater under a 10-year and 20-year time horizon. These results are likely due to the total health costs of the modelled population increasing the older the cohort gets (especially if they live longer as a result of a reduction in CVD events).

Finally, the discount rate was varied to illustrate the sensitivity of the cost-effectiveness of switching from A+A to the FDC AA if the value society places on short-term costs and benefits compared to long-term costs benefits changes. Except for a 0% discount rate in risk stratum five, the ICER remained cost-saving despite the change in annual discount rate. In risk stratum five with a 0% discount rate, the ICER was \$1400 per QALY (716 QALYs per million dollars spent). This is likely a result of the intervention allowing people to live for longer, which comes at a future cost that is not discounted away. Although no longer cost-saving, this ICER represents a highly cost-effective intervention with a minimal cost per QALY when compared to the arbitrary cost-effectiveness threshold of \$45,000 per QALY as discussed above.

6.3 Relationship of these results to the existing literature

This study was the first study internationally to consider the cost-effectiveness of a FDC by differing levels of CVD risk (to the author's knowledge). It was also the first study of a CVD FDC in a New Zealand context. A study conducted by Selak et al⁵⁰ looked at clinical efficacy and adherence to a CVD polypill in New Zealand context, but the cost-effectiveness of the intervention has not been assessed. The international literature concerning the cost-effectiveness of CVD FDC is limited and is largely dominated by evaluations of the polypill. Five other studies were identified that examined the cost-effectiveness of a two-agent FDC, two of which investigated the cost-effectiveness of the FDC AA. All

five identified studies concluded that the use of a FDC was likely to be cost-effective compared to usual care, placebo, equivalent monotherapies or one pharmaceutical of the same class. However, comparing the results of these studies with the results in this thesis is difficult for multiple reasons. Only one study considered the cost-effectiveness in terms of a cost per QALY gained. The other studies used alternative cost-effectiveness measures such as a cost per death averted and cost per percentage change in LDL cholesterol or SBP which makes the comparison of results difficult. The comparison is made more difficult still by the limited internal and external validity of these studies due to the evaluation method and model structure used as well as the choice of comparator and selection of model inputs. Furthermore, three were sponsored by Pfizer Pharmaceuticals and all involved health system costings that were population and country-specific (ie, Korea, Mexico and Australia). This thesis builds on the limitations identified in the other identified studies by using a more comprehensive model structure that utilised lifetables to inform transition probabilities and reflect the heterogeneous nature of CVD incidence, CFR and background mortality by age, sex and ethnicity.

The available literature on the cost-effectiveness of pharmaceuticals in a New Zealand context is limited. Beyond the average cost-effectiveness range of funded pharmaceuticals published in PHARMAC's annual reports (discussed in Section 6.2.2 above), just one published study concerning the economic evaluation of pharmaceuticals in a New Zealand context was identified. The study by Metcalfe et al in 2003¹³² listed the ICER of 21 pharmaceuticals funded by PHARMAC between 1998 and 2002. The figures presented are difficult to interpret and generalise due to the use of a unique unit (QALYs gained in the first year of a funded proposal) and a high discount rate (10%).

The cost-effectiveness of a variety of other health sector interventions have been assessed in the New Zealand context. The ICER of primary care interventions assessed by the BODE³ research group that used the same modelling methodology and principles as this thesis are more appropriate to compare to the results of this thesis. Of note, is that the ICER of switching from A+A to the FDC AA for the primary prevention of CVD falls into the same realm as a broad range of interventions in tobacco control, dietary salt reduction, falls prevention and cancer treatment and screening which were typically found to be cost-saving or cost-effective below the arbitrary threshold of \$45,000 per QALY.^{133, 134} It should be noted, however, some of the interventions considered by BODE³ consider the entire New Zealand population alive in 2011, while the results of this thesis were restricted to a subset population of New Zealand men aged 60 to 64 in 2011. The relationship of the results from this thesis to the existing BODE³ literature should ideally be reconsidered when the use of the FDC is considered within a broader range of age-groups for the New Zealand adult population.

6.4 Potential generalisability of results

The results of this thesis cover the health gain, health costs and the cost-effectiveness of switching from A+A to the FDC AA for the primary prevention of CVD in New Zealand men aged 60 to 64 years old (free from CVD, no prior CVD pharmaceutical use). Due to the largely similar clinical efficacy of pharmaceuticals within the statin and anti-hypertensive classes,^{113, 114, 135} the results are probably broadly generalisable to the cost-effectiveness of any FDC that contains a statin and an anti-hypertensive as a primary CVD prevention measure. The results can be used to establish hypotheses about the cost-effectiveness of switching to the FDC AA or a statin and anti-hypertensive FDC in broader New Zealand population than considered in this thesis. However, future research that considers the impact of switching from A+A to the FDC AA in other groups where A+A prescription is common would greatly increase the generalisability of the results (ie, a broader age range of New Zealand adults and in women). Restricting the model population to this age group of men could have underestimated the benefit of switching for Māori, as Māori have a younger age structure than non-Māori and experience their largest CVD burden at an earlier age.^{1, 21}

As has been discussed previously in this thesis, adherence and non-adherence is multi-factorial. This thesis focused on switching from A+A to the FDC AA for the primary prevention of CVD. Generalising the results to secondary prevention is likely to be reasonable, however, it is important to note that the multitude of factors that influence non-adherence may be different between a primary prevention and secondary prevention context. Adherence to primary prevention medications for CVD is generally lower than for secondary prevention medications with studies suggesting that increased motivation to manage CVD risk following a CVD event is a contributing factor.^{5, 27, 136} In the context of this thesis, that could mean that the marginal health gain and therefore cost-effectiveness of switching to a FDC could be smaller if the FDC AA was used as a secondary prevention measure. Cultural differences between countries have also been shown to influence adherence with some studies showing that adherence to medications can differ substantially between countries and between different ethnic groups.^{27, 137, 138} The difference in factors that influence adherence between various populations should be considered before generalising the results of this thesis.

Using the results of this thesis to generalise or make an inference beyond New Zealand, particularly to other high-income countries, is possible but should be done with caution. Caution is advised in part because of the highly restricted population group (a narrow age-group, male only) considered in this thesis and in part because of difference between the model inputs that may differ between New Zealand and other countries. The latter may include health system costs, in particular the pharmaceutical cost (ie, it is widely acknowledged that New Zealand typically has considerably lower pharmaceutical costs than other high-income countries^{80, 81}), the proportion of the population

represented in each CVD risk stratum and the burden of medication non-adherence.^{27, 137} The difference in these inputs could influence the resulting cost-effectiveness. However, given switching from A+A to FDC AA regimen appears to be cost-saving, it is reasonable to assume that the same intervention would at least be cost-effective in other high-income countries with similar disease burden and cost-effectiveness thresholds.

6.5 Study strength and limitations

6.5.1 Model methods

MSLT Markov modelling is a methodology that is increasingly being used in the economic evaluation of health interventions. The use of lifetables to better reflect true population heterogeneity in transition probabilities (in this case, disease incidence rates and case-fatality rates all by differing levels of CVD risk) is a key strength of MSLT Markov modelling that is not captured by a simple Markov model or decision tree analysis. Incorporating heterogeneity greatly increases the model's ability to reflect the 'real-world' and produce more generalisable results. Nevertheless, MSLT Markov modelling has limitations. One noteworthy limitation of the MSLT model used in this thesis is that each of the disease lifetables (in this case CHD and stroke) were assumed to occur independently of each other. That is, although a proportion of the population can reside in both life-table simultaneously, the probability (or risk) of having had a stroke is assumed to be independent of an individual's probability (or risk) of having a non-fatal CHD event (a simplifying assumption). Developing a microsimulation model could allow an additional degree of complexity to be included, such as allowing the risk of having a CHD event to be influenced by the time since the previous CVD event. However, the additional level of data required to do this, in addition to the person and computational power to run a microsimulation model was outside of the scope of this thesis.

6.5.2 Model structure

Baseline model input parameters and uncertainty

The MSLT model used in this thesis utilised an existing CVD MSLT which was in the process of being adapted from the established and validated tobacco MSLT¹⁹ (adaption was complete for men aged 60 to 64 in 2011 only). A key strength of using the established MSLT CVD model was the use of rich longitudinal New Zealand specific data on costs and epidemiological parameters that formed the model's foundations. Uncertainty around all baseline model inputs and intervention parameters was incorporated in the model through ranges assigned to each parameter (95% CIs or SD ranges ($\pm 5\%$ or $\pm 10\%$ SD – see Table 6)) which were then sampled from in the 2000 Monte Carlo simulations per CVD risk stratum, as per established BODE³ methods.

Stratification by absolute CVD risk

A fundamental component and a key strength of the adapted MSLT model was the division of the model population into five strata based on five-year absolute CVD risk. To the author's knowledge, this study was the first to consider the cost-effectiveness of a FDC by strata of CVD risk. This adaption allowed this research to address the second aim of this thesis and test the hypothesis, that those who have higher CVD risk are also the group who would potentially benefit the most from switching from A+A to the FDC AA for the primary prevention of CVD. This information is potentially valuable to primary care workers who could prioritise FDC uptake to those where the potential health gain and cost-effectiveness is highest. Two limitations arise as a result of stratifying the population in this way and were a result of the existing model structure. Firstly, the division of the population into CVD risk strata was established at baseline and remained unchanged over the five-year intervention period. After that five-year period, the CVD risk strata were no longer meaningful and the risk of a CVD event for the modelled population after five-years tracked upward as they age. That is, the model did not permit movement between CVD risk strata based on the experience of the cohort during the five-year intervention period or over the remainder of the model time horizon. Secondly, due to lack of available data, intervention parameters such as adherence and uptake could not be different in each risk stratum as may be the case in reality. This second point is discussed further in Section 6.5.3.

The intervention (switching from A+A to the FDC AA)

The model utilised in this thesis was built to compare an intervention to business as usual (the equivalent of doing nothing new). To best compare the cost-effectiveness of switching to the FDC AA from A+A, the latter regimen would have been set as the model baseline and the FDC AA would be the intervention. Due to the time constraints and the scope of this thesis, adapting the model in this way was not feasible. As a result, the model was run in two ways, once with A+A as the intervention (to simulate the baseline) and once with the FDC AA as the intervention. The resulting outputs were then subtracted to generate the differences between the two regimens. Calculating the cost-effectiveness in this way had two caveats which should be noted when interpreting the results. Firstly, the base-case analysis involved 2000 Monte Carlo simulations in which a value for each model parameter was randomly selected from a range of uncertainty. Therefore, when the results of the iterations from A+A and the FDC AA were subtracted, the combination of parameter values that went into generating the result of each intervention could have been different. As a consequence of this and the small magnitude of health gain associated with either pharmaceutical regimen, approximately 8% of the 2000 Monte Carlo simulations resulted in negative QALY gains. If the pharmaceutical regimens could have been run in the same model, negative QALY gains would not be possible, so these iterations were deleted from the overall results. Secondly, the overall ICER does not strictly represent the cost-effectiveness of the population switching from A+A to the FDC AA. That is, in the model, the same

cohort who were modelled to use A+A was not the same cohort who was modelled to use the FDC AA due to uptake probabilities in the model. Therefore, the marginal change (in QALYs and costs) if the same population switched to FDC was therefore not strictly observed – even though the results are likely to provide a reasonable approximation of the uncertainty ranges. Future research could address this if more resources were put into the model building to ensure the most appropriate comparator was set-up as the model baseline.

Population

One limitation of the CVD MSLT is that that the model currently only represents a population of New Zealand men aged 60 to 64 who are not currently taking CVD preventive pharmaceuticals and who are free from CVD. Although this age group of men was chosen as the first stage of the model adaption for several reasons which have been discussed previously, the population modelled is not representative of the cost-effectiveness of switching from the AA to the FDC AA in other adult New Zealand age-groups. Therefore, the cost-effectiveness of switching from A+A to FDC AA should be revisited once the CVD MSLT model adaption for the entire adult New Zealand population is more complete (ie, including all 50+ age-groups and also women).

Perspective

The model adopted a health system perspective. A health system perspective provides valuable information for decision makers, in particular, decision-makers who are concerned with health system funding who are required to make decisions regarding the distribution of a finite health budget to achieve the greatest possible health gain. Benefits and costs from a broader societal perspective would consider additional costs such as productivity costs to an individual and the society (eg, from work absenteeism due to ill health) were outside of the health system perspective taken in this thesis. It is the intention of the BODE³ research group to include productivity costs in future work.

6.5.3 Intervention parameters

Pharmaceutical Uptake

In the base-case, FDC uptake was based on an estimate of the proportion of the model population who were taking either a statin, an anti-hypertensive or both (the rationale being that a patient on a statin, would also likely benefit from being on an anti-hypertensive and vice versa). Although this estimate is based on New Zealand specific data, the proportion of uptake could be higher. For example, recent work by BODE³ on modelling triple therapy as a CVD prevention intervention used an uptake rate of 77% from Wells et al 2017¹³⁸ which represented the use of CVD pharmaceuticals in NZ adults aged 55-64 years of age for the secondary prevention of CVD. A sensitivity analysis in this thesis which considered an 80% intervention uptake (Māori and non-Māori) suggested that a significantly greater gain in QALYs and cost-offsets (savings) could be realised if a greater proportion of the population on

an anti-hypertensive and statin switched for the FDC AA. Modelling the effect of targeting FDC uptake by those deemed eligible in the CVD risk guidelines, or by CVD risk could be beneficial to consider for future research.

Pharmaceutical uptake was unable to be stratified by CVD risk due to the existing model structure and thesis time constraints. Logically, pharmaceutical adherence might be greatest in the higher risk strata and lower in the lowest risk strata (eg, if those at the lowest risk levels perceived less need for risk reduction and possibly preferred to try just lifestyle changes relative to medication). Following this logic, the QALYs gained in the risk stratum four and five are likely to be an underestimation of the real world and risk stratum one and two may possibly be an overestimation. Furthermore, it is likely that the cost-offset would be greater in risk stratum four and five and lower in risk stratum one and two. This is of particular importance to note when considering targeting the use of the FDC to those who could benefit most (those with a higher CVD risk).

Adherence

The difference in adherence between the FDC AA and A+A was a key intervention parameter. In the model, adherence was assumed to decline linearly with each annual model cycle. At the end of the five-year intervention period, 63.9% of the population prescribed the FDC AA were classified as adherent (> 80% of pill days covered) and 38.4% of the population assumed to be taking A+A where classified as adherent. Modelling adherence in this way resulted in some inherent assumptions which may differ from what may occur in the real world. These assumptions and the likely impact of these assumptions on the results of this thesis are outlined below and should be considered when interpreting the results.

Firstly, the body of existing literature concerning adherence to CVD pharmaceuticals suggests that within a population, a decline in adherence is most likely to be observed in the year directly following the initiation of a new pharmaceutical and that adherence levels after that remain relatively constant. Representing adherence in this way in the model was not possible due to the existing model structure and the time constraints of this thesis. The base-case assumption of a linear decline in adherence would likely have resulted in an overestimation in the absolute QALYs gained and cost-offsets (savings) by both pharmaceutical regimens. This is because a greater proportion of the population was classified as 'adherent' for a longer period than if the decline in adherence was just in the first year and then remained constant. However, this thesis was primarily interested in the *difference* in the QALYs gained and the cost-offsets (savings) between the two regimens. Because the decline in adherence was modelled in the same way for both regimens and the difference in adherence was preserved at all time-points, the impact on the marginal differences (in health gain, costs and ICERs) from this assumption are likely to be minimal.

Secondly, adherence and non-adherence are widely acknowledged to be multi-factorial and complex. In this model, adherence is assumed to be dichotomous ('adherent' with >80 days PDC or 'not-adherent' with less than 80 PDC). In reality, adherence (or non-adherence) occurs on a spectrum. The measurement and classification of adherence is greatly contested with a variety of methods used. Simplifying adherence in this way was necessary for modelling and is common within adherence measurements studies. Nevertheless, this simplification has consequences. The model assumes that only the proportion of the cohort who are classified as 'adherent' receive the additional clinical benefit from taking the pharmaceutical regimen (ie, have the risk of a CVD event lowered), while those who were non-adherent do not (ie, do not have their baseline CVD risk lowered). Similarly, those who became non-adherent in a later part of a modelled year, receive no additional benefit from previously being adherent in that year (and so the benefits are underestimated by the model). As a result of these assumptions, it is likely that the total QALY gains and cost-offsets (savings) found in the results are underestimates. However, as above, because the ICER in this thesis represents the difference between the using FDC AA and A+A and the assumption was the same for both pharmaceutical regimens, the influence of this assumption on the ICERs was likely fairly small.

Thirdly, in the model, adherence is assumed to be the same in all five CVD risk strata. Although the association between poor pharmaceutical adherence and increased CVD risk is well established, research on if and how adherence varies by CVD risk is lacking. Without evidence to support the stratification of adherence between CVD risk, the assumption made appears reasonable. Further research in this area would provide valuable information for future modelling involving adherence to CVD pharmaceuticals.

Fourthly, adherence in the model was taken from Patel et al,⁶⁸ a longitudinal study that looked specifically at the adherence of FDC AA relative to its monotherapy components in an American population. Although the Patel et al study was thought to be the best one to inform the adherence model parameter in this thesis, studies of adherence to CVD pharmaceuticals in a New Zealand context¹³⁹ suggests that the adherence could be higher than that of observed in Patel et al. Future research could also explore this issue further. However, it is probably not critical to the *relative* comparison of FDCs to monotherapies.

Clinical efficacy

A key strength of this thesis, was an author conducted meta-analyses for identified trials to inform the overall clinical efficacy of the FDC AA. The meta-analyses analysed four controlled trials that were comparable in study design but were conducted in different populations internationally. The results of the meta-analyses demonstrated that there was statistically significant reduction in SBP, DBP and LDL-C associated with the use of the FDC AA overall and within each study. Although, the 95%CI of the

overall measure was relatively small, the high I^2 value for each of the meta-analyses suggests that heterogeneity between the included studies was high.

The clinical efficacy of the FDC AA and atorvastatin was informed by a surrogate endpoints (LDL-cholesterol and blood pressure reduction) which were then translated to RR reductions in stroke and CHD by applying standardised relative risk reduction equations. In the absence of long-term data regarding the clinical efficacy of the FDC AA and the now well-established link between reductions in these surrogate endpoints and long-term CVD event risks, the assumed stroke and CHD relative risk reductions for both pharmaceuticals were likely a fair representation of the truth. Uncertainty in the clinical efficacy of both pharmaceuticals was in part considered by the 95%CI of each RR and in part by the equal efficacy scenario analysis (where the clinical efficacy of the FDC AA was reduced to be equal to A+A). Although this scenario showed that the overall cost-effectiveness was highly sensitive to the assumed improved clinical efficacy of the FDC over and above the benefit of adherence, it also suggested that in the absence of this improved efficacy, improved adherence and a reduction in prescription costs alone, are likely to still result in health benefits and net cost-savings.

The relative risk reduction associated with using either the FDC AA or A+A was assumed to be same in all CVD risk strata. However, it is generally considered that those with the highest CVD risk receive relatively greater benefit from preventative CVD medications (ie, statins and anti-hypertensives). Overall, this potentially results in an underestimation in terms of the absolute QALYs gained and cost-offset in the higher CVD risk strata and an overestimation in the lower risk strata. As this limitation is the same in both pharmaceutical interventions and this study is concerned with the difference in QALYs gained and costs-offset, it is unlikely to influence the overall study result. Adverse events were not considered in this model, but rather were assumed to be largely represented in the level of adherence (ie, people with adverse effects are more likely to become non-adherent).

Pharmaceutical costs

The likely cost of the FDC AA in the New Zealand context could not be precisely estimated in the model as the FDC AA is not listed on the national pharmaceutical schedule. The price of the A+A regimen was known and was used to estimate the price of the FDC in the model. As the study primarily aimed to determine the additional health gains, cost and cost-effectiveness, of the FDC in terms of improved adherence, efficacy and reduced prescription cost, the cost of FDC was set to be equivalent to the monotherapy components. This method is used in other economic analysis^{83, 85, 87} that model a pharmaceutical with an unknown cost and in the absence of international comparisons (primarily due to the different funding pharmaceutical funding structures in other countries) this was likely to be a reasonable assumption. Two scenario analyses in which the base-case cost of the FDC AA was varied to be double or half the base-case (ie, double or half of the equivalent monotherapy) were carried out

and had very little influence on the magnitude of cost-offsets. Importantly, the cost of the FDC and A+A was based on the 10 mg dose of amlodipine and a 20 mg dose of atorvastatin to best represent the cost of the drug that most closely matched the efficacy determined in the efficacy of the FDC AA. Although the cost is based on a set dose, the price of the monotherapies at all dosages are still below the \$0.08 per pill amount used in the maximum cost scenario analysis. As a result, the price of the FDC AA relative to the monotherapy combinations is unlikely to influence the magnitude of cost-savings and the overall ICER.

The combined pharmaceutical and pharmaceutical prescription cost of both the FDC AA and A+A were applied each annual cycle to those assigned to take the pharmaceutical regimens regardless of adherence. This assumption is likely to be representative of the real world where individuals are likely to pick up their pharmaceutical scripts, regardless of whether they are adherent (>80% PDC) or non-adherent. In reality, there could be one 90-day prescription period of the annual four which may not be filled, but at a 90-day cost of \$8.81 for the FDC AA and \$14.02 for A+A, this is unlikely to influence the overall cost-effectiveness.

Intervention period

Although the model considered the QALYs gained and the cost-offsets (savings) over a lifetime horizon, the intervention period in which the population could benefit from either pharmaceutical was only five-years. Following the five-year intervention period, the morbidity and mortality rates tracked from their values in each strata at the increasing rates seen for the baseline population prior to stratification. That is, in addition to pharmaceutical expenditure no longer being accrued, the additional clinical benefit of taking the pharmaceutical is assumed to stop. The scenario analysis which looked at cost-effectiveness over a five-year time horizon and the scenario that extended the intervention period to 20 years illustrated that despite the intervention period or time horizon, switching regimens is still likely to be cost-saving.

6.6 Conclusions, study implications and possible future directions

Non-adherence to pharmaceuticals and large pill burdens is an important issue in CVD prevention, particularly in populations with a high CVD risk and populations with multiple co-morbidities. Non-adherence will mean that health gain from treatment effects are not realised and there are potentially extra costs to the health system. The use of FDC as a method to reduce pill burdens and consequently improve adherence has been used in a range of health conditions. In CVD, two agent anti-hypertensives have been available since the mid-1950s but the availability of FDCs that target multiple (two or more) CVD risk factors have emerged only in the last two decades.⁷ The impact of FDCs has been documented in many studies in the literature which highlight that improved adherence results in better risk factor control and reduced CVD events. Given the positive impact of FDCs suggested in the

literature, this thesis aimed to investigate if switching from equivalent monotherapies to a FDC was a cost-effective method of the primary prevention of CVD. Therefore, the multi-risk factor reducing FDC AA was modelled as an example and the results were stratified by absolute CVD risk.

This thesis was the first study to consider the health benefit, costs and cost-effectiveness of CVD FDC by stratified levels of CVD risk internationally and was also the first study of a CVD FDC in New Zealand. The results of this work suggest that switching from A+A to the FDC will likely generate additional health gain and be a cost-saving to extremely cost-effective intervention for the primary prevention of CVD for New Zealand men aged 60 to 64. Although the total QALYs gained and the cost-offsets (savings) were greatest in the group at the lowest CVD risk, the per capita results (result per the population who received either pharmaceutical regimen at baseline) suggested that populations with higher CVD risk, benefited the most from switching.

The results of this thesis were generated using a validated model with rich input data and robust methodological principles. However, the generalisability of results is still somewhat limited due to the restricted model population of New Zealand men aged 60 to 64. The results are probably indicative of the general cost-effectiveness of FDC containing a statin and an anti-hypertensive in New Zealand adults, but they can also generate hypotheses for further research for both younger age-groups and also for women. Further New Zealand specific research on the efficacy and adherence of FDCs and comparable monotherapies for CVD is likely to strengthen the understanding and potential of FDCs and enhance the ability to more accurately model the impacts. Further research considering the use of FDCs in secondary prevention would also be of value.

A large body of international literature exists which demonstrates the positive impact CVD FDC can have on medication adherence and clinical efficacy which follows on to health system cost savings. This thesis adds to a small field of international evidence on the cost-effectiveness of CVD FDC and demonstrates that switching or initiating use of the FDC AA and potentially other CVD FDC compared to the equivalent monotherapies is likely to provide additional health gains to New Zealanders who are prescribed a FDC compared to equivalent monotherapy and be cost-saving to the New Zealand health system. To date, despite the availability of several anti-hypertensive/statin FDCs internationally, no multi-risk factor CVD FDC have been listed on the New Zealand pharmaceutical schedule for subsidised use by New Zealanders. The results of this thesis should encourage pharmaceutical companies who manufacture two-agent multi-risk factor CVD FDC to apply for a pharmaceutical listing in New Zealand and motivate health authorities to consider expanding CVD treatment guidelines to incorporate the use CVD FDC where appropriate. This research also suggests that greater emphasis and recognition of the benefit of FDC in reducing pill burdens and improving adherence is warranted by pharmaceutical funding bodies and medical professionals globally and in New Zealand. If such FDCs

are not available, then regulatory authorities could solicit the pharmaceutical industry to apply for such products to be registered in their jurisdictions.

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Appendix 1: Summary of studies identified in the structured review of CVD FDCs

Table 19: Summary of studies identified in the structured review of CVD FDCs (two-agent FDCs and the polypill)

Study	Population	Exposure	Comparison	Effectiveness	Costs	Model Information	Main results
FDC anti-hypertensive + a statin							
Liew et al 2009 ⁷⁵	Primary prevention in Korea, Korean health system perspective	Amlodipine (5 mg)/ atorvastatin (10.25 mg) (FDC AA)	Current Treatment	QALYs	Pharmaceutical and Health system resource utilisation	<ul style="list-style-type: none"> Markov model 2008 baseline. lifetime horizon Microsimulation, 224 patients, characteristics determined from a national survey Adherence decline in year one for FDC Treatment effect observed through changes in BP and cholesterol which changes absolute CVD risk. 5% annual discount rate 	<p>FDC AA compared to current treatment - 7,773,063 KRW per QALY</p> <p>FDC AA compared to current treatment - 10,378,230 KRW per life year gained</p> <p>(USD \$6000 per QALY, USD \$8000 per life-year gained) (paper reports 1300KRW=\$1)</p>
Park et al 2015 ⁷⁶	Koreans with type two diabetes	Amlodipine / atorvastatin (FDC AA)	Amlodipine + atorvastatin (A+A)	Percentage of patients reaching LDL goal	Medication costs (reflective of adherence)	<ul style="list-style-type: none"> Decision tree model Percentage of patients reaching LDL therapy goals based on adherence to therapy One-year time horizon 	<p>Average cost-effectiveness ratio FDC AA Korean Won 4123 per 1% achievement in LDL goal.</p> <p>Average cost-effectiveness ratio A+A Korean Won 6062 per 1% achievement in LDL goal.</p>

Study	Population	Exposure	Comparison	Effectiveness	Costs	Model Information	Main results
FDC anti-hypertensive + anti-hypertensive							
Glasziou et al 2010 ⁷⁸	Secondary CVD prevention in diabetics (multi-national study)	Perindopril (4 mg)/ indapamide (1.25 mg) plus current BP medication	Placebo + current BP treatment	Deaths averted	Pharmaceutical and health system resource utilisation for Australian subset of study population	<ul style="list-style-type: none"> Economic evaluation piggy-backed on to ADVANCE randomised control trial No difference in adherence Medication taken in addition to existing medications 4.3 years follow-up 5% annual discount rate 	AU\$49,200 per death prevented AU\$10,040 per life-year saved
Kawalec et al 2015 ⁷⁹	CVD prevention in Poland	Indapamide/ amlodipine	Equivalent monotherapy	QALYs	Pharmaceutical and health system	<ul style="list-style-type: none"> Markov model Lifetime horizon Base-case assumed change in adherence changed blood pressure Scenario analysis – no change in adherence 	FDC was cost-saving to the health system compared to equivalent monotherapy
FDC statin + another type of lipid-lowering agent							
Briseno et al 2010 ⁷⁷	Patients treated with for dyslipidaemia in Mexico	Ezetimibe (10 mg)/simvastatin (20 mg) (E/S regimen)	Rosuvastatin (RSV)	Percentage decrease in LDL levels	Pharmaceutical costs	<ul style="list-style-type: none"> Retrospective review of outpatient medical records informed changed in LDL from baseline to 8 weeks. 	Cost per 1% reduction in LDL-C levels US\$2.02 RSV US\$4.09 E/S
Three agent polypill (aspirin + statin + anti-hypertensive)							
Bautista et al 2013 ⁸²	Primary CVD prevention in Latin America	Polypill	No intervention	QALYs	Health system and pharmaceutical cost (polypill estimated at US\$50 per person per year)	<ul style="list-style-type: none"> Markov Model Polypill efficacy from the Indian Polycap Study (TIPs) 3% annual discount rate 	Polypill compared to no intervention: ICER \$268 per QALY for women with 10-year CVD risk greater than 15% ICER \$1041 per QALY for men with a 10-year CVD risk greater than 15%. ICER \$449 per QALY men aged greater than 55

Study	Population	Exposure	Comparison	Effectiveness	Costs	Model Information	Main results
Zomer et al 2013 ⁸³	Primary CVD prevention in Australian population with metabolic syndrome/health system perspective	Polypill	No treatment	QALY	Pharmaceutical costs (polypill cost 75% of sum of monotherapies) + health system resource costs	<ul style="list-style-type: none"> • Markov model • Microsimulation of 1991 patients with metabolic syndrome. Baseline data from an Australian study • Polypill efficacy TIPs • Discount rate 5% 	Polypill compared to no treatment: AUD214,864 per QALY
Three agent polypill (aspirin + statin + two anti-hypertensive)							
Ndinjock et al 2011 ⁸⁶	Random sample of people from Seychelles selected to do a CVD health survey	Polypill	Pharmaceutical treatment of risk factors	Number need to treat annually to prevent one CVD event	Pharmaceutical costs (polypill informed by the literature)	<ul style="list-style-type: none"> • WHO African risk equations used to calculate baseline CVD from survey data • Polypill efficacy TIPs • Clinical efficacy of monotherapies from literature 	Number need to treat annually to prevent one CVD event Targeting BP and Cholesterol - 379 people Polypill CVD risk >10% - 79 people Polypill CVD risk >20% - 92 people
Laba et al 2014 ⁸⁴	Kanyini GAP trial (Australian based polypill RCT), health system perspective	Polypill	Usual care	n/a	Pharmaceutical and medical from Medicare records	<ul style="list-style-type: none"> • Health system and pharmaceutical cost-analysis 	No significant difference in health system expenditure. Mean pharmaceutical cost-savings per patient was \$989 (\$648 to \$1331) per patient per year
Ito et al 2012 ⁸⁵	Secondary CVD prevention, United States/Societal Perspective	Polypill	Mailed education, disease management and combinations of all 3.	QALY	Pharmaceutical, health system and intervention resource costs	<ul style="list-style-type: none"> • Markov Model • Lifetime horizon • 3% annual discount rate • Polypill equal to the cost of monotherapies • Adherence from literature polypill>disease management> mailed education 	Mailed Education and disease management US\$74,000/QALY, Polypill US\$133,000/QALY Only mailed education had an ICER <\$100,000/ALY

Study	Population	Exposure	Comparison	Effectiveness	Costs	Model Information	Main results
Megiddo et al 2015 ⁸⁷	Secondary CVD prevention, India/health system perspective	Polypill	Monotherapy combination	DALY	Pharmaceutical and health system costs	<ul style="list-style-type: none"> Model structure unclear No difference in adherence Polypill cost assumed to be less than equivalent monotherapy 	Polypill \$1690 per DALY averted Monotherapy components - \$6450 per DALY averted
Three agent polypill (aspirin + statin + three anti-hypertensive)							
Becerra et al 2014 ⁸⁸	Secondary CVD prevention, United Kingdom/Health system perspective	Polypill	Various monotherapy combinations	QALY	Pharmaceutical and health system costs	<ul style="list-style-type: none"> Markov Model 10 year time horizon 3.5% annual discount rate Adherence rate UMPIRE trial, greater adherence for polypill Assumed similar efficacy between monotherapies and polypill (ie, adherence is primary difference) 	ICER GBP8200 per QALY (81.5% chance polypill is CE at GBP20,000 per QALY threshold)
Ong et al 2014 ⁸⁹	Primary CVD prevention in Indigenous Australians	Polypill/ Looma Community Health Intervention /Statins /Low dose diuretics / ACE inhibitors	No intervention	DALY	Pharmaceutical, health system and intervention resource costs both government and patient	<ul style="list-style-type: none"> Markov model Clinical efficacy of polypill multiplicative effect of monotherapies Lifetime horizon Polypill cost based on expert opinion 	Polypill was most cost-effective option. \$500 per annually for the Polypill the intervention resulted in A\$13,000 per DALY when provided at mainstream GP clinic and A\$21,000 per DALY from an Indigenous health centre.

Study	Population	Exposure	Comparison	Effectiveness	Costs	Model Information	Main results
Three agent polypill (statin + three anti-hypertensive)							
Ferket et al 2017 ⁹⁰	Primary prevention of CVD in the United Kingdom, health system perspective	Population polypill use	Regular CVD risk assessment	QALY	Pharmaceutical and health system costs	<ul style="list-style-type: none"> • Microsimulation of 260,000 • Lifetime horizon • Modelled risk of CVD, diabetes and non-CVD death • 3.5% annual discount rate • Disutility of daily medication considered 	Prescribing monotherapies to >20% CVD risk group was the most cost-effective strategy. Polypill strategies had greater QALY gains but were more costly.
/ = FDC, + = monotherapy combination, T2DM = type two diabetes mellitus, KRW= Korean Won, QALY = Quality-adjusted life-year, ACER= average cost effectiveness ratio, BP = blood pressure							

Appendix 2: Basic Description of the BODE³ Cardiovascular Disease Multi-State Life-Table Model

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Background to the multi-state life-table model

We adapted the BODE³ Tobacco Control multi-state life-table (MSLT) model from which we have published results from previously.^{1 2 3 4} This model benefits from rich national epidemiological data by sex, age, and ethnicity (Māori and non-Māori), as well as costing data. Results from the CVD component of this model have also been validated via a head-to-head comparison with a separate model with a different structure and using different software (a CVD model built in TreeAge and used for dietary salt interventions^{5 6 7}).

The data in this MSLT Model are used to estimate QALYs gained and net health system costs over the remaining life of the 2011 New Zealand population (n = 4.4 million). The specific adaptations made are outlined in more detail below.

Integrating CVD risk data from a synthetic national population

As the BODE³ Tobacco Control MSLT Model lacked data on grouping individuals by level of absolute CVD risk, we considered work at Auckland University that used New Zealand-specific CVD risk prediction equations.⁸ The variables required for the risk equation predictions were: age, sex, ethnicity, social deprivation, smoking status, diabetes status, personal history of CVD, blood pressure and lipid-lowering medication treatment, systolic blood pressure (SBP), the total cholesterol to high density lipoprotein cholesterol ratio (TC: HDL), and family history of premature CVD (with these obtained from the PREDICT dataset, Auckland University). These risk equations were then applied to a synthetic population of 2,451,229 New Zealand adults to estimate numbers and rates of CVD events. This population was formed by extracting all (anonymised) 30-84-year-old respondents to the 2013 census, with variables on age, sex, ethnicity, social deprivation and smoking. Uncertainty was generated by sampling from 100 synthetic populations. Full details of this synthetic data generation are provided elsewhere.⁸

We first compared the results using the data from the synthetic population with the BODE³ Tobacco Control MSLT Model in its unmodified state. For the particular comparison we aimed to achieve, we focused on the population aged 60-64 years who were not on CVD preventive medication (with

standard deviations of the sampled means) and who had no previous diagnoses of CVD in the BODE³ MSLT Model and no previous diagnoses of the following: CVD, chronic kidney disease, rheumatic heart disease, congestive heart failure and atrial fibrillation.⁸ Table 1 provides an example of the data for non-Māori men aged 60-64 years. We selected this age-group as just an initial starting point, though this age-group is of some particular interest as it is the working age with the highest rate of CVD and improving health in this age-group may enhance productivity (for those citizens who continue in the paid workforce after age 65 years).

Table 1: Example data for the predicted five-year risk of a CVD event for the synthetic national population for non-Māori men (60-64y, with no past CVD events and on no CVD medication, Knight et al⁸)

Five-year cumulative risk (%) category for CVD events (fatal and non-fatal)*	Population (non-Māori men)		Average risk within each risk strata	
	N	SD	%	SD
Risk: >20	56	7	22.9	0.35
Risk: >15, ≤20	265	16	16.8	0.08
Risk: >10, ≤15	1882	42	11.7	0.03
Risk: >5, ≤10	19,577	140	6.5	0.01
Risk: >0, ≤5	36,319	147	3.6	0.005
Total	58,099			
Average risk**			5.0	

* New Zealand guidelines⁹ suggest the following thresholds for commencing consideration of CVD preventive pharmacotherapy: statins at ≥10% risk, anti-hypertensives at ≥10% risk, and antiplatelet therapy at ≥20% risk. But for various reasons these may be out-dated thresholds.¹⁰

** Calculated using the average risk within each stratum of risk.

Building CVD risk stratification to create the BODE³ CVD MSLT Model and re-calibrating it

We then took the BODE³ Tobacco Control MSLT Model and modified it to create the BODE³ CVD MSLT Model. This involved splitting it into three separate components (with replication for each sex/ethnicity grouping in the age 60-64-year-group).

Population A: This was the group who were not on any CVD medications and did not have prevalent CVD in 2011. This group was then divided into five strata of differing levels of five-year absolute risk of a CVD event as per the proportions in the synthetic population work by Knight et al⁸ but with the original MSLT Model population numbers. It is this population that was the intervention population in the model ie, potentially offered CVD preventive pharmacotherapy.

Population B: This was the group with no prevalent CVD in 2011 but who were already on CVD medication. This group were given incidence rates of CVD based on the estimated five-year absolute risk of a CVD event as per the synthetic population work by Knight et al⁸ (but with the original BODE³ MSLT Model population numbers).

Population C: This was the group who had prevalent CVD in 2011, regardless of medication status) Again, the proportion in this group was derived from the synthetic population distribution, but with the original BODE³ MSLT Model population numbers.

Collectively these three groups cover all New Zealand citizens (for each age/sex grouping). In addition, we needed to provide unique case fatality rates (CFRs) for the strata in Group A. There were no New Zealand data for this (the case fatality data exist by age-group only¹¹) so we considered the results from the meta-analysis by Zambon et al 2014¹² and used the regression equation for CVD mortality by CVD incidence (Figure 2(c) in Zambon et al).

There is also evidence that those with elevated CVD incidence also have relatively elevated non-CVD mortality rates (eg, data abstracted from the meta-analysis by Thomopoulos et al 2014¹³ albeit without age-standardisation). Based on this evidence from Thomopoulos et al, we assumed that there was a doubling in non-CVD mortality rates across the five strata of CVD risk in Population A, albeit with wide uncertainty.

To maximise overall model coherence, and comparability with other BODE³ cost-utility analyses, we then performed the additional scaling steps so as to achieve 100% matching of the cumulative count of incident cases of CVD after five years, and then 100% matching of the number of CVD deaths after five years in the revised model with the original BODE³ Tobacco Control MSLT Model. This involved minor scaling of the CVD incidence rates, the case fatality rates and the background mortality rate.

Addendum

Since the analysis by Tal Sharrock for this thesis in 2017, we have performed in 2018 automated optimisation processes and also more sophisticated long-term model calibration of this CVD MSLT Model. As a result there are likely to be minor differences between the work in this thesis and future studies using similar interventions in this same model.

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Appendix 3: Summary of publications identified in the structural review for the clinical efficacy of the FDC AA

Table 20: Summary of publications identified in the structural review for the clinical efficacy of the FDC AA

Trial	Study Design/Study Population	Intention to treat population (competed study)	Exposure	Comparison	Duration (weeks)	Change in Low Density Lipoprotein (LDL) and Systolic Blood Pressure (SBP)
Flack et al 2008 ^{101ψ}	Open Label, non-comparative trial (CAPABLE trial) African Americans	374 (75%)	FDC AA *	No comparison	20	Mean percentage change from baseline LDL: -23.6% (95%CI:-26 to -21.2) Mean change from baseline SBP: -17.5±14.8 mmHg
Erdine et al 2008 ^{67ψ}	Open Label, non-comparative trial (Gemini-AALA study) (Australia, Asia, Latin America, Africa/Middle East)	1638 (99%)	FDC AA *	No comparison	14	Mean percentage change from baseline LDL: -28.6%(95%CI: -30.2 to -27.0) Mean change from baseline SBP: -20.2 (95%CI: -20.9 to -19.6)
Hobbs et al 2009 ^{103ψ}	Open Label, non-comparative trial (JEWEL I) UK and Canada	2245 (99%)	FDC AA *	No comparison	16	Mean change from baseline LDL: -0.90 mmol/L Mean change from baseline SBP: -20.4 mmHg
	Open Label, non-comparative trial (JEWEL I) Europe					Mean change from baseline LDL: -1.09 mmol/L Mean change from baseline SBP: -21.8 mmHg
Blank et al 2005 ^ψ	Open Label, non-comparative trial (Gemini et al)	1095 (90%)	FDC AA *	No comparison	14	Mean percentage change from baseline LDL: -32.7% (SD:17.9) Mean change from baseline SBP: -17.1 (SD:12.7)
Neutel et al 2009 ^{104ψ}	Randomised, double-blind, placebo controlled trial (CUSP study) – Primary Prevention	117 (90%)	FDC AA (5 mg/20mg)	Placebo	8	Difference in least square mean LDL: -45.6 (95%CI: -52.5 to -38.4) Difference in least square mean SBP: -7.9 (95%CI: -12.7 to -3.0)
Fedacko et al 2013 ^{105ψ}	Open label, observational study (The STRONG DUET study) Slovakia	1406 (99%)	FDC AA + existing treatment (5/10, 10/10 mg)	No comparison	12	Mean LDL baseline/12 weeks: -3.89 (SD:0.80)/2.84 (SD:0.66) Mean SBP baseline/12 weeks: -159.99 (SD:14.10) /132.01 (SD:9.36)

Trial	Study Design/Study Population	Intention to treat population (competed study)	Exposure	Comparison	Duration (weeks)	Change in Low Density Lipoprotein (LDL) and Systolic Blood Pressure (SBP)
Hradec et al 2013 ¹⁰⁶ ^ψ	Post-hoc analysis of CRUCIAL Primary Prevention	1231 (90%)	FDC AA (5/10, 10/10 mg)	Usual Care	52	Percentage difference in least square mean LDL: -26.8 (95%CI: -30.7 to -22.9) Difference in least square mean SBP: -5.9mmHg (95%CI: -8.2 to -3.5)
Zeng et al 2016 ¹⁰⁷ ^ψ	Outpatient case control study Primary Prevention	200 (n/a)	FDC AA (5/20 mg) at 10pm daily	A+A (5+20 mg) 7am daily	8	Absolute difference from baseline LDL: exposure -1.24 (±0.69) comparison: -1.16 (±0.76) Absolute difference from baseline SBP: Exposure: -14.1 (±4.5) Comparison: -14.5 (±4.7)
Zamorano et al 2011 ¹⁰⁸ ^ψ	International, multicentre, prospective, open labelled parallel design cluster randomised control trial. (CRUCIAL) - Asia, Middle East, Europe and Latin America	1324 (88.1% FDC AA, 94% usual care)	FDC AA (5/10 to 10/10 mg)**.	Usual care	52	Percentage difference in least square mean LDL: -27.1 (-30.9 to -23.4) Difference in least square mean SBP: -5.8 mmHg (-8.0 to -3.5)
Grimm et al 2010 ¹⁰⁹ ^ψ	Randomised, double-blinded, double dummy, controlled trial (TOGETHER Study)	245 (88%)	amlodipine (5 to 10 mg)	FDC AA 5 to 10 mg/20 mg)	6	Percentage difference in least square mean LDL: -41.1 (95%CI: -45.8 to -36.3) Difference in least square mean SBP: -3.3 mmHg (95%CI: -6.0 to -0.5)
Ferdinand et al 2009 ¹⁰⁰ ^ψ	Post hoc analysis of the CAPABLE trial (open-label non-comparative, multicentre trial) in high-risk patients	494	FDC AA *	No comparison	20	Only looked at percentage goal attainment

*Doses: 5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, 10/80 mg ** Up titration to 10/20 mg and 10/20 mg was approved in specific country ^ψ: Sponsored by a Pharmaceutical company.

Appendix 4: Summary of publications identified in the structural review for the clinical efficacy of amlodipine

Table 21: Summary of publications identified in the structural review for the clinical efficacy of amlodipine

Author	Study Information	Exposure	Comparison	Number of studies	Number of participants	Analysis	All-Cause Mortality	CVD mortality	CHD	Stroke
Briasoulis et al 2014 ¹¹⁵	Effect of anti-hypertensive on CVD outcomes among those aged 65+ years included in the review, 1970 to 2012 - prospective RCT only Meta-analysis observed intention to treat	Anti-hypertensive with a decrease in BP of 27.3/11.1 mmHg	No drug placebo	18	114,854 approx. 27,000 in anti-hypertensive VS placebo analysis	/	OR 0.85 (0.78 to 0.92) 10 studies approx. 17,000 people	OR 0.78 (0.70 to 0.88) 10 studies approx. 17,000 people	/	OR 0.63 (0.56 to .71) 10 studies approx. 17,000 people
Law et al 2009 ¹¹⁴	RCT trials that looked at the effect of anti-hypertensive and recorded CHD events and strokes. 108 studies compared with placebo, 46 drug comparison trials	anti-hypertensive general and by class	placebo	108	464,000 people	CCB vs placebo	/	/	RR 0.85 (0.78 to 0.92) 22 trials	RR 0.66 (0.58 to 0.75) 9 studies
Thomopoulos et al 2015 ¹¹³	RCT trials from 1966 to 2013 Included intentional and non-intentional blood pressure RCT the included studies had to have a minimum 40% of the study population as anti-hypertensive and all were primary care focused	Each anti-hypertensive class compared with placebo	Placebo/no treatment	55	195267	CCB only	RR 0.87 (0.77 to 0.98) 10 Trials approx. 30,000 people	RR 0.82 (0.70 to 0.97) 8 studies approx. 28,000 people	0.82 (0.65 to 1.05) 8 studies approx. 28,000 people	0.66 (0.58 to 0.75) 9 studies approx. 30,000 people

Author	Study Information	Exposure	Comparison	Number of studies	Number of participants	Analysis	All-Cause Mortality	CVD mortality	CHD	Stroke
Thomopoulos et al 2014 ¹¹⁶	RCT trials from 1966 to 2013 Included intentional and non-intentional blood pressure RCT the included studies had to have a minimum 40% of the study population as anti-hypertensive and all were primary care focused	anti-hypertensive	placebo	68	245,885 people	Intentional trials vs placebo	RR 0.90 (0.85 to 0.95) 32 studies approx. 100,000 people	RR 0.84 (0.78 to 0.90) 30 studies approx. 100,000 people	RR 0.86 (0.81 to 0.92) 31 Studies Approx. 100,000 people	RR 0.70 (0.64 to 0.76) 29 studies approx. 100,000 people
The Blood Pressure Lowering Treatment Trialists' Collaboration, Sundstrom et al 2014 ¹¹⁷	Trials had to have a minimum of 1,000 patients years of planned follow up to be included and the main results had not been published before the study protocol was complete	BP lowering drugs	placebo	11 trials + 26 Randomised groups	67,475 people	See study publication Risk ratio and Risk difference for Stroke, CHD, HF, CVD death and all-cause death per 5-year risk of the event.				

Appendix 5: Summary of publications identified in the structural review FDC AA adherence

Table 22: Summary of publications identified in the structural review FDC AA adherence

Study	Study Type	Population	Number of Participants	Exposure	Comparison	Duration	Adherence Outcome
Zeng et al 2016 ¹⁰⁷	Case-control study	Primary CVD prevention, China	200	FDC AA at 10 pm daily (5 mg/ 20 mg)	A+A at 7 am (5 mg+20 mg)	Eight weeks	Number of pills missing from the prescription bottle. Compliance was greater among FDC AA than A+A
Simons et al 2011 ⁶⁹	Retrospective cohort study using Pharmaceutical Benefits Scheme data from Australia	Analysis of a random 10% sample of Pharmaceutical Benefits Scheme data, Australia	10350	FDC AA	A+A		Adherence: median persistence time (MPT) over six months MPT FDC AA: 35 months (95%CI: 33 to ≥38 months) MPT A+A: 7 months (95%CI: 6-8months) Hazard Ratio of cessation of FDC AA vs FDC AA: 2.17 (95%CI: 2.05. to 2.13)
Chapman et al 2010 ⁷⁰	Retrospective cohort study using administrative claims data in the US	Patients previously taking a CCB or statin who began FDC AA or added a CCB or statin resulting in monotherapy combination	19,447	FDC AA	CCB + Statin	Six months adherence	Adherence: Proportion of days covered (≥ 80% = adherent) 6. months Adjusted odd ratio FDC AA vs CCB+statin: 4.7 (95%CI: :4.22 to 5.23)
Hussein et al 2010 ¹²²	Retrospective study using claims data from lifelink: health plan claims US	Patients continuously enrolled in a managed care over study period with a pharmacy -45.6 (-52.5 to -38.4) claim for FDC AA or CCB +statin in a defined period	35,430	FDC AA	A+A CCB+Statin 4 sub-groups based on CVD drug use in previous year:	6 months	Adherence: Proportion of days covered (≥ 80% = adherent) 6 months Adjusted OR (95%CI:) for adherence FDC AA vs A+A No CCB or Statin: 1.06 (0.87 to 1.30) CCB, no statin: 2.31 (1.71 to 3.13) Statin, no CCB: 1.80 (1.40 to 2.31) CCB+statin: 1.12 (0.98 to 1.27)

Study	Study Type	Population	Number of Participants	Exposure	Comparison	Duration	Adherence Outcome
Chapman et al 2009 ¹²¹	Retrospective cohort study among US enrollees	Patients with hypertension who filled a new prescription for FDC AA or a statin. Prior use of statin, FDC AA or amlodipine in last 360 days was excluded.	4556	Amlodipine switch to FDC AA	Amlodipine add a statin	180 days	Adherence: Proportion of days covered ($\geq 80\%$ = adherent), 180 days Adjusted odds ratio of adherence attainment (>80 PDC) at 180 days follow up FDC AA vs statin add-on odds ratio 1.64 (95%CI:1.42 to 1.89) Persistence greater for FDC AA than A+A
Patel et al 2008 ⁶⁸	Retrospective cohort study of insured US nationals using pharmacy claims data	Patients continually enrolled in healthcare insurance over study period, newly started on CCB or statin	4703	FDC AA	FDC AA/ Amlodipine+ statin /CCB + atorvastatin /CCB + Statin	180 days	Adherence: Proportion of days covered (PDC) ($\geq 80\%$ = adherent) Mean PDC % (180 days): FDC AA 81%, A+A 72%, Adjusted odd ratio of achieving PDC $\geq 80\%$ over 180 days FDC AA vs A+A: 1.95 (95%CI:1.80 to 2.13)

