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Abbreviations

CAD	Coronary artery disease
CI	Confidence interval
CVD	Cardiovascular disease
CTRU	Clinical Trials Research Unit (re-named NIHI)
DRL	Dr Reddy's Laboratories Ltd
EQ-5D	EuroQol 5 dimension survey
GCP	Good Clinical Practice
GP	General practitioner
HDL	High density lipoprotein
ICH	International Conference on Harmonization
IMPACT	IMProving Adherence using Combination Therapy
IQR	Interquartile range
LDL	Low density lipoprotein
Kanyini GAP	Kanyini Guidelines Adherence with the Polypill
NIHI	National Institute for Health Innovation (previously named CTRU)
NZ	New Zealand
OR	Odds ratio
PHARMAC	New Zealand's Pharmaceutical Management Agency
PHO	Primary Health Organisation
PMS	Practice management system
PVD	Peripheral vascular disease
RCT	Randomised controlled trial

RHP	Red Heart Pill
RR	Risk ratio
RRR	Relative risk reduction
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SCOTT	Standing Committee on Therapeutic Trials
SD	Standard deviation
SPACE	Single Pill to Avert Cardiovascular Events
SUSAR	Suspected unexpected serious adverse reaction
UK	United Kingdom
UMPIRE	Use of a Multidrug Pill in Reducing Cardiovascular Events
US	United States

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Extent of contribution by PhD candidate (%)	70

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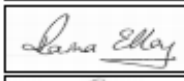
C Raina Elley		18/08/2014
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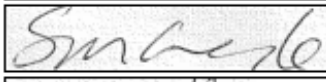
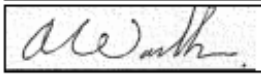
Sue Crengle		5/10/2014
Angela Wadham		19/08/2014

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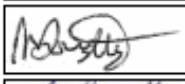
Robert N Doughty		26/08/2014
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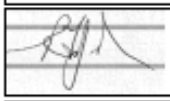
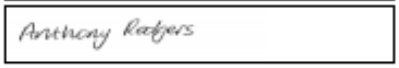
Rod Jackson		19/08/2014
Anthony Rodgers		15/08/2014

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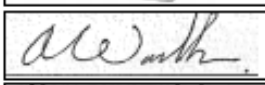
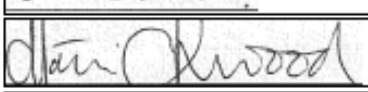
Angela Wadham		19/08/2014
Matire Harwood		19/11/2014
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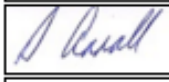
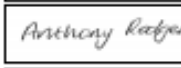
Bruce Arroll		18/08/2014
Anthony Rodgers		18/08/2014
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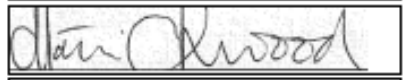
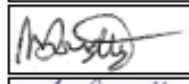
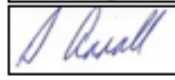
Matire Harwood		19/08/2014
Rob Doughty		26/08/2014
Bruce Arroll		18/08/2014

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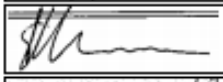
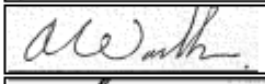
Stephen Vander Hoorn		25/08/2014
Angela Wadham		19/08/2014
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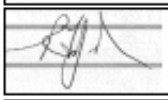
Rod Jackson		19/08/2014
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Chapter 1. Introduction

1.1. Rationale

Cardiovascular disease is the leading cause of death,[1] and a major and increasingly important contributor to the overall burden of disease globally.[2] The burden of cardiovascular disease is distributed unequally, with over 80% of such deaths occurring in low and middle income countries,[3] and greater mortality rates experienced by Māori, the indigenous population of New Zealand, compared with non-Māori.[4]

Cardiovascular disease is often preventable, as demonstrated by the substantial reduction in cardiovascular mortality rates since the 1980s in New Zealand[4] and other high-income countries.[3] There are two broad levels of prevention: (1) primary prevention, in which strategies target risk factors prior to the establishment of disease and (2) secondary prevention, in which strategies seek to stop or slow down the progression of disease after it has been established.[5] The observed reduction in the burden of cardiovascular disease has been attributed to action both at the level of primary prevention (e.g. reducing smoking and the consumption of saturated fat) and secondary prevention (e.g. providing aspirin, statins and blood pressure lowering agents to people following a myocardial infarction).[3] While the focus of this thesis is on the primary and secondary prevention of cardiovascular disease using medication, comprehensive strategies to reduce the burden of cardiovascular disease span the disease continuum by incorporating policy and environmental change through to end of life care.[6]

For people with established cardiovascular disease, the combination of antiplatelet, statin and blood pressure lowering therapy is estimated to reduce the risk of cardiovascular disease by over 50% and is hence recommended for all such people without contraindications by New Zealand, Australian, European and the United States guidelines.[7-11]

Three primary prevention strategies are of particular relevance to reducing the burden of cardiovascular disease. Geoffrey Rose described the ‘population’ strategy (lowering the mean level of a risk factor, e.g. cholesterol, across the whole population) and the ‘high risk’ strategy (targeting activities to those with high levels of an individual risk factor).[12] A third cardiovascular prevention strategy, the ‘high cardiovascular risk’ strategy, has emerged,

which involves targeting activities to those estimated to be at high absolute risk of their first cardiovascular event.[13] Cardiovascular risk is estimated by mathematical equations, such as the Framingham Risk Function,[14] which take into account multiple risk factors at the same time.[15] High cardiovascular risk strategies have been predicted to prevent more deaths than either the population or high risk strategies.[13]

Cardiovascular risk assessment has been an integral component in New Zealand's efforts to reduce the national cardiovascular disease burden for over a decade[16] and is an accepted strategy for guiding treatment decisions for the primary prevention of cardiovascular disease in Australia,[17] Europe[10] and the United States.[18] International guidelines are broadly consistent in recommending greater intensity of cardiovascular preventive medication (statins and blood pressure lowering agents) with higher cardiovascular risk.[10 17-20] However, there is inconsistency across guidelines regarding the use of antiplatelet therapy for the primary prevention of cardiovascular disease.

New Zealand guidelines recommend antiplatelet therapy for people with 5-year absolute risk of cardiovascular disease greater than 20%.[7] The United States Preventive Services Task Force also recommends aspirin for primary prevention, but for men aged 45 to 79 years and women aged 55 to 79 years when the potential benefit of a reduction in myocardial infarction (ischemic strokes in women) outweighs the potential harm of an increase in gastrointestinal haemorrhage.[21] In contrast, Australian[8] and European[10] guidelines recommend avoiding aspirin entirely for primary prevention. The situation is further complicated because there is a growing body of evidence regarding the potential benefit of aspirin in the prevention of cancer.[22-24]

Internationally, many people do not receive guideline-recommended cardiovascular preventive medications even when guidelines clearly and consistently indicate that benefits outweigh harms. For example, the Prospective Urban Rural Epidemiology (PURE) study found that use of at least three of four recommended medications (aspirin, statin, angiotensin-converting enzyme inhibitor [or angiotensin-receptor blocker] and another blood pressure lowering drug) among people with established cardiovascular disease was 44% among respondents in high-income countries, 13% among those from upper-middle and 3% among those from lower-middle and low-income countries.[25] Even if cardiovascular preventive medications are prescribed and dispensed, their preventive potential is dependent on adherence to them.[26] Less than 50% of those prescribed medications for chronic conditions

are estimated to be adherent long-term.[26] One strategy that has the potential to improve the use of guideline-recommended medications and adherence to those medications is a fixed dose combination of medications, or 'polypill'.[27] A key recommendation of a 2001 World Health Organization meeting was that such a pill be developed for, and evaluated in, people with established cardiovascular disease.[28]

This thesis reports the results of two pieces of work. The first is a systematic review and modelling of the benefits and harms of aspirin in the primary prevention of cardiovascular disease. The second is the IMProving Adherence using Combination Therapy (IMPACT) randomised controlled trial, which compared polypill-based care with usual care among New Zealand patients at high risk of cardiovascular disease in a primary care setting.

1.2. Aim and objectives

The overall aim of this thesis was to investigate the effectiveness and safety of a cardiovascular polypill containing aspirin.

There were two objectives:
1. To investigate the benefits (reduction in cardiovascular events) and harms (increase in major bleeds) of treatment with aspirin when added to statin and blood pressure lowering medication in different age, sex and cardiovascular risk subgroups among people without established cardiovascular disease (systematic review and modelling).
2. To investigate the effectiveness of a polypill-based treatment strategy in improving medication adherence and cardiovascular risk factors, and to assess its safety, in a trial of New Zealand patients at high risk of cardiovascular disease (the IMProving Adherence using Combination Therapy, IMPACT, trial).

1.3. Contributions and funding

The literature and systematic reviews were conducted by the candidate. Eligible meta-analyses identified by the systematic review were critically appraised by the candidate and Associate Professor Raina Elley. Dr Sue Wells checked or adjudicated disagreement between the reviewers. Eligible randomised controlled trials identified by the systematic review and not included in eligible meta-analyses were critically appraised by the candidate. The candidate extracted the data from the eligible meta-analyses and trials. The modelling was

designed by the candidate and Associate Professor Raina Elley, with assistance from Dr Sue Wells and Professor Norman Sharpe. The modelling was conducted by the candidate.

Although the design of the IMPACT trial was initiated in 2003, the trial was conducted (recruitment, follow-up and analysis) from 2010 to 2013, due to regulatory delays. The candidate joined the team in 2006. The candidate undertook the following tasks on the IMPACT trial:

- Contributed to amendments to trial design
- Completed trial protocol and led development of case record forms
- Prepared the first application for approval to use the polypill in the trial under Section 30 of the Medicines Act
- Determined trial website requirements
- Recruited Primary Health Organisations, general practices and general practitioners onto the trial
- Trained general practitioners on trial and trial procedures
- Identified potentially eligible patients by querying electronic practice management systems
- Trained and provided ongoing advice and support to project managers and research nurses on the medical aspects of the trial
- Reviewed all serious adverse events and ensured that these were properly documented
- Developed the process for the adjudication of pre-specified events by an independent, blinded Clinical Adjudication Committee
- Contributed (substantially) to trial funding applications
- Led the analysis of trial results, specified how analyses were to be conducted, defined all outcomes, checked all code and independently checked primary outcomes and conducted some analyses
- Led the interpretation of results and writing of trial protocol, recruitment and final results manuscripts

The trial had three principal investigators: Professor Anthony Rodgers (from 2003 until 2009), Associate Professor Raina Elley (from 2009 until 2011) and Associate Professor Chris Bullen (from 2011 until trial completion). Principal investigators were responsible for completion of the trial, directing the research, and reporting directly to funding, ethics and regulatory agencies.

Drs Sue Crengle and Matire Harwood provided leadership for the recruitment of Māori onto the trial and the analysis of results for Māori as co-principal investigators. Ms Puti Wilson (research fellow January 2006 to July 2007) advised on how to maximise suitability of trial conduct and materials to Māori, and facilitated relationships with Māori-led Primary Health Organisations and other groups. Dr Sonia van Gesell provided maternity leave cover for the candidate for five months in late 2011.

Mr Stephen Vander Hoorn wrote the statistical analysis plan. Dr Arier Lee (2006), Ms Xenia Chen (2007), Ms Joy Jiang (2010 to 2012), Mr Avinesh Pillai (2012 to 2013) and Ms Varsha Parag (2013) provided statistical input. The analysis of the main trial results was conducted by Ms Varsha Parag and was led by the candidate.

Project managers on the trial were Ms Angela Wadham (December 2005 to March 2007, and, as Senior Project Manager, January 2010 to December 2013), Dr Jo Lorimer (March 2006 to July 2007) and Ms Liz Glen (January 2010 to May 2011). The project managers organised management and steering committees, managed trial timeframes, outputs and the budget, ensured that International Conference on Harmonisation Good Clinical Practice was adhered to, prepared the trial ethics application and liaised with the ethics committee, liaised with Dr Reddy's Laboratories Ltd for supply of the trial medication and reporting of any adverse events from IMPACT and other trials using the same medication around the world, arranged for importation of the polypill from India to New Zealand, and trained and managed research nurses and pharmacies.

Research nurses were Ms Anne Blundell, Ms Denise Miller, Ms Puti Nicholls, Ms Anna Ruri and Ms Julia Thompson. Their role was to assist general practitioners in the recruitment of participants, to undertake all trial assessments and to serve as the primary point of contact for participants during the trial. Ms Anne Blundell, Ms Puti Nicholls and Ms Anna Ruri focused on recruitment of Māori participants given their expertise in this area.

Data managers that contributed to the trial were Ms Amanda Milne, Ms Rina Prasad, Ms Tamsin Scott, Ms Michelle Jenkins and Mr John Faatui. The website was developed and information technology support provided by Mr Barry Gray, Mr Johan Strydom and Ms Colleen Ng.

The candidate was supported throughout the work undertaken in this thesis by a National Heart Foundation of New Zealand Research Fellowship (1384). The candidate received

reimbursements for travel and accommodation to attend international collaborative meetings on the polypill from the National Heart Foundation of New Zealand (2014), The George Institute for Global Health (2012) and Dr Reddy's Laboratories Ltd (2007 and 2008).

The IMPACT trial received project grants from the following organisations:

- Health Research Council (06/582, 2005, main grant)
- National Heart Foundation (1376, 2010, for recruitment of Māori)
- New Zealand Lotteries Grants Board (230904-310308, 2012, for recruitment of Māori)
- Health Research Council partnership grant, with co-funding from the Auckland region District Health Boards (12/889, 2013, for end of trial visit, cost analysis and medication behaviour analysis)
- University of Auckland (Elsie Shrimpton Fund [2012], Te Kupenga Hauora Māori [2013] and Faculty Research Development Fund [2012])
- PHARMAC, New Zealand's Pharmaceutical Management Agency (A499735-QA24208, 2012)
- Auckland Medical Research Foundation (2012).

IMPACT trial staff members were supported by National Heart Foundation Research Fellowships (candidate, Professor Rodgers and Dr Natasha Rafter).

Dr Reddy's Laboratories provided, free of charge, the Red Heart Pill for use in the trial. Dr Reddy's Laboratories Ltd also provided some compensation for the costs of the delay in the IMPACT trial between 2007 and 2009 due to pill formulation issues.

1.4. Structure of the thesis

This thesis has two main sections: (1) systematic review and modelling of the benefits and harms of aspirin in primary prevention, and (2) the IMProving Adherence using Combination Therapy (IMPACT) trial. The burden of cardiovascular disease and preventive strategies are outlined, followed by a review of the effectiveness and safety of aspirin for the primary prevention of cardiovascular disease and the polypill trials conducted to date. The evidence regarding the potential benefit of aspirin in the primary prevention of cancer is briefly reviewed. Previous meta-analyses and randomised controlled trials of aspirin in primary prevention are systematically reviewed and updated risk estimates obtained to model the likely benefits (reduction in cardiovascular events) and harms (increase in major bleeds) of

treatment with aspirin in different age, sex and cardiovascular risk subgroups. The methods of the IMPACT trial are described and its results presented and discussed. An overall summary of the two sections and concluding statements are presented at the end of the thesis.

The objectives of each chapter were to:

- Chapter 2: Provide an overview of the literature and to place the thesis in the context of the current evidence base
- Chapter 3: Describe the methods and findings of a systematic review of, and to then model, the benefits and harms of aspirin in the primary prevention of cardiovascular disease
- Chapter 4: Describe the methods of the IMPACT trial
- Chapter 5: Present the findings of the IMPACT trial
- Chapter 6: Discuss the findings of the IMPACT trial, including comparison with other trials
- Chapter 7: Summarise the research in this thesis, discuss the implications of the research and indicate possible directions for future research

Chapter 2. Literature review

2.1. Introduction

The term ‘cardiovascular disease’ describes a group of diseases, including myocardial infarction and stroke, which are characterised by atherosclerosis.[3] Atherosclerosis is a complex process in which fatty material and cholesterol (plaques) are deposited inside the lumen of arteries, accumulating over many years.[3] Plaques can rupture and form clots, blocking the blood supply to vital organs such as the heart (resulting in coronary or ischaemic heart diseases such as myocardial infarction) or brain (leading to stroke and other cerebrovascular diseases).[3] Despite some improvements in mortality rates, cardiovascular disease remains a major cause of New Zealand and global mortality, morbidity and socioeconomic and ethnic inequalities in health outcomes.[1 2 4 29-31] Of particular concern in New Zealand is that indigenous Māori, who comprise 15% of the total population of New Zealand,[32] are disproportionately affected by the burden of cardiovascular disease compared with non-Māori.[4]

In this chapter, literature on the burden of cardiovascular disease and preventive strategies is briefly summarised. The effectiveness and safety of aspirin for primary prevention is reviewed, including consideration of New Zealand and other major national guidelines and the meta-analyses and trials used to justify disparate recommendations. The concept of the cardiovascular polypill is introduced and trials conducted to date summarised.

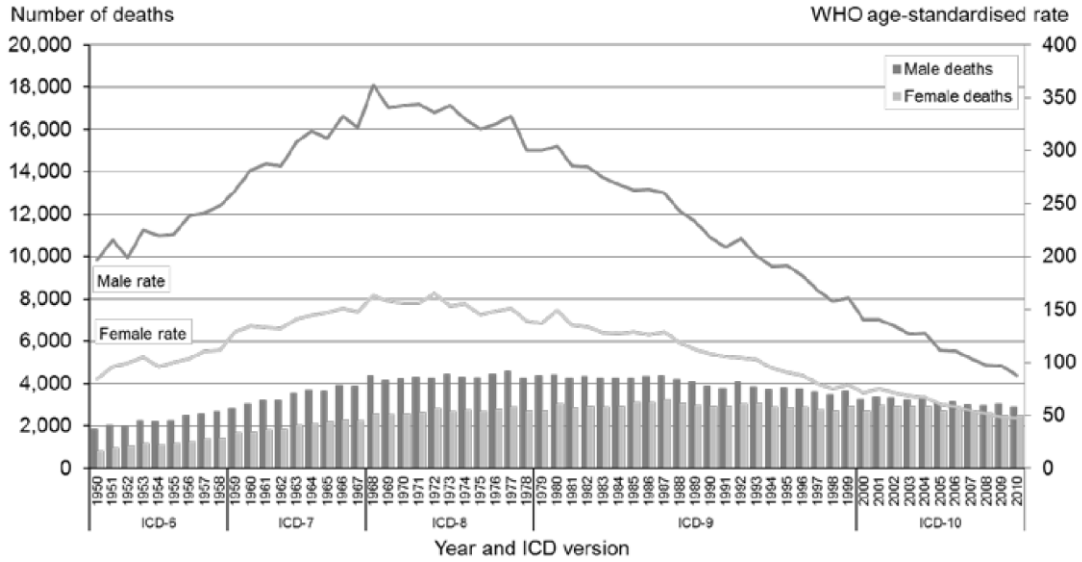
2.2. Cardiovascular disease: importance, prevention, guidelines and implementation

2.2.1. The importance of cardiovascular disease

Coronary heart disease is the second leading cause of death in New Zealand, despite a reduction in coronary heart disease mortality rates of approximately 70% over the last 30 years (Figure 1).[4] Most deaths due to coronary heart disease in New Zealand are among people aged 65 years and older (90% of non-Māori deaths, 57% of Māori deaths), although many occur among Māori aged 45 to 64 years (10% of non-Māori deaths, 39% of Māori deaths).[4] Men are more likely to die from coronary heart disease than women (Figure 1).[4]

For example, in 2010 the age-standardised mortality rate for non-Māori men was 88 per 100,000 and 48 per 100,000 among non-Māori women.[4]

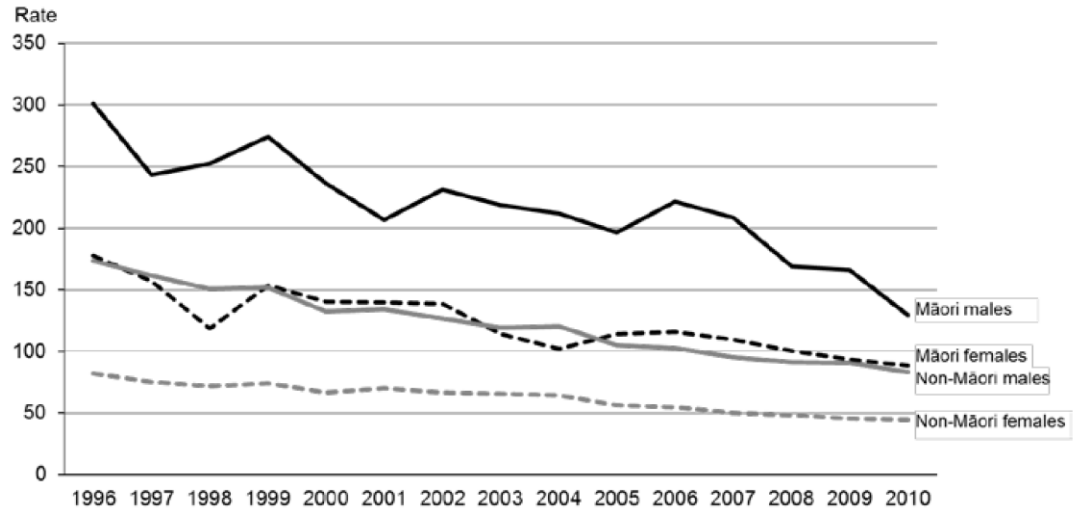
Figure 1. Coronary heart disease deaths and mortality rates in NZ, by sex, 1950-2010



Mortality rates age-standardised per 100,000
Source: Ministry of Health[4]

Coronary heart disease mortality rates have reduced for Māori, but remain substantially higher than for non-Māori (Figure 2).[4] For example, in 2010 the age-standardised mortality rate from coronary heart disease was 56% higher for Māori than non-Māori men, and the rate for women was 99% higher for Māori than non-Māori.[4] Disparities are most pronounced for Māori aged 45 to 64 years, who are three times more likely to die from coronary heart disease than non-Māori of the same age (151 vs 49 per 100,000 in 2010).[4]

Figure 2. Coronary heart disease mortality rates in NZ, by sex and ethnicity, 1996-2010



Mortality rates age-standardised per 100,000
Source: Ministry of Health[4]

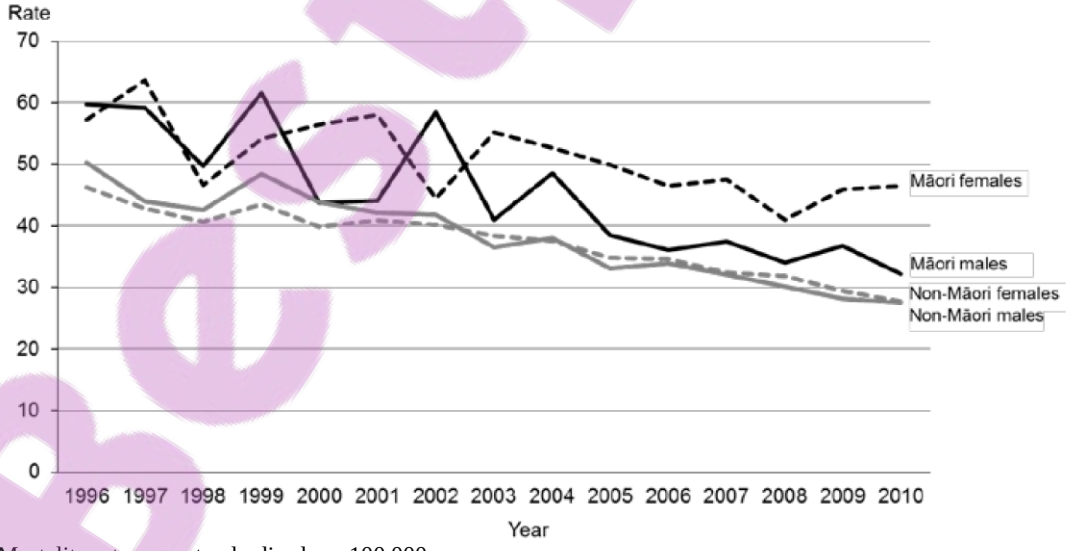
Cerebrovascular disease is the third leading cause of death in New Zealand, despite a reduction in mortality rates of approximately 70% over the last 30 years (Figure 3).[4] As with coronary heart disease, most cerebrovascular deaths occur among people aged 65 years and older (93% non-Māori, 62% Māori); although many also occur among Māori aged 45 to 64 years (6% non-Māori, 30% Māori).[4] Unlike coronary heart disease, cerebrovascular mortality rates are similar in men and women (Figure 3).[4]

Figure 3. Cerebrovascular disease deaths and mortality rates in NZ, by sex, 1950-2010

Mortality rates age-standardised per 100,000
Source: Ministry of Health[4]

Māori women had the highest age-standardised mortality rate from cerebrovascular disease in 2010, followed by Māori men and then by non-Māori men and women (Figure 4).[4]

Figure 4. Cerebrovascular disease mortality rates in NZ, by sex and ethnicity, 1996-2010

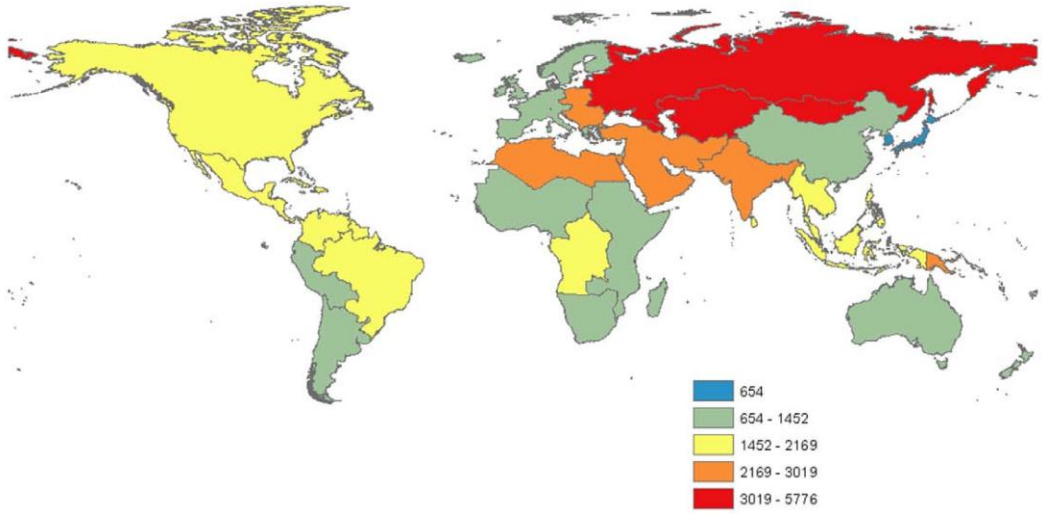


Mortality rates age-standardised per 100,000
Source: Ministry of Health[4]

Coronary heart disease accounted for the loss of 9.3% of disability-adjusted life years in New Zealand in 2006, almost twice the burden of the second-ranked condition.[29] Stroke accounted for the loss of 3.9% of disability-adjusted life years.[29] Collectively, 'vascular and blood disorders' (primarily coronary heart disease and stroke) were one of the two greatest contributors to health loss in New Zealand in 2006 (ranked first for men and second for women).[29] Vascular and blood disorders were the second leading contributor to the loss of disability-adjusted life years among people aged 45-74 years, becoming the leading contributor among people aged 75 years and over in 2006. Māori experienced 2.5 times the health loss of non-Māori from vascular and blood disorders in 2006, and vascular and blood disorders were the leading cause of absolute inequality in health loss between Māori and non-Māori, accounting for 26% of the total Māori excess burden of disease that year.[29]

Globally, coronary heart disease was the most common and stroke the second most common cause of death in 2010.[1] This ranking was the same as in 1990[1] and is projected to remain the same in 2030.[30] Coronary heart disease was the largest and stroke the third largest cause of disability-adjusted life years lost globally in 2012.[2] This was an increase in ranking for both ischaemic heart disease and stroke, which were the third and fourth largest contributors to the global burden of disease, respectively, in 2000.[2] The burden of cardiovascular disease is distributed unequally globally, with over 80% of deaths due to ischaemic heart disease or stroke occurring in low and middle income countries in 2008.[3] Eastern Europe, Central Asia, North Africa/Middle East and South Asia had the highest age-standardised rates of disability-adjusted years lost in 2010 due to ischaemic heart disease (Figure 5).[31]

Figure 5. Disability-adjusted life years lost from ischaemic heart disease by region globally, 2010

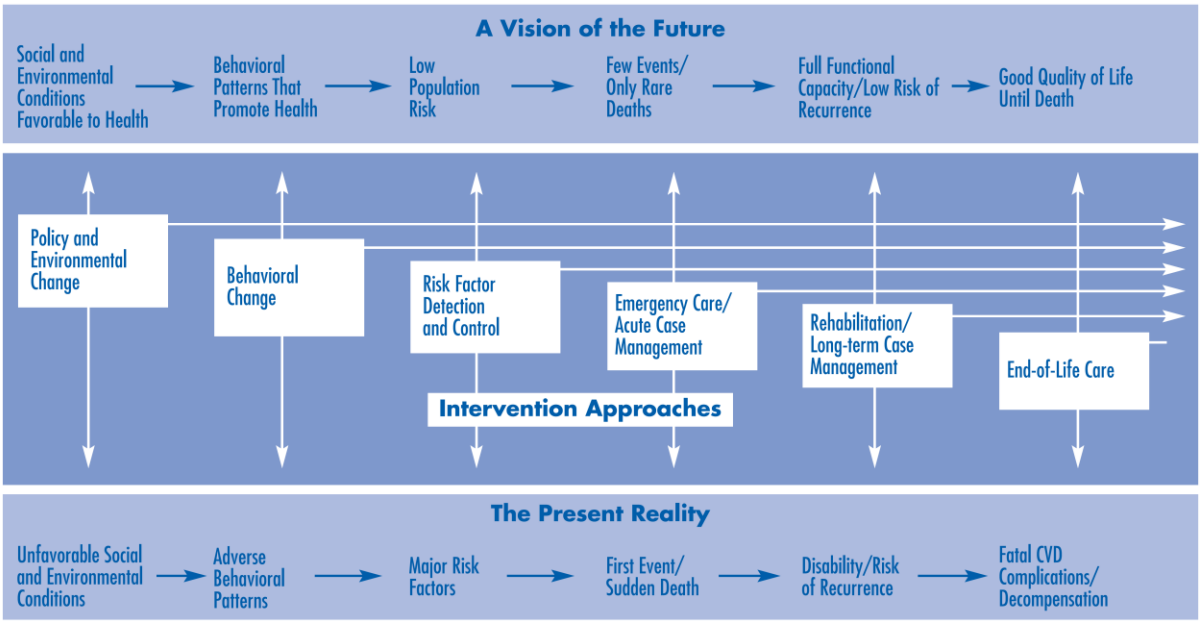


Source: Global Burden of Disease Study, Moran et al[31]

2.2.2. The role of prevention and the high risk strategy

Cardiovascular disease is preventable, as demonstrated by the substantial reduction in cardiovascular mortality rates since the 1980s in New Zealand[4] and other high-income countries.[3] There are two broad levels of prevention: (1) primary prevention, in which strategies target risk factors prior to the establishment of disease and (2) secondary prevention, in which strategies seek to stop or slow down the progression of disease after it has been established.[5] The observed reduction in the burden of cardiovascular disease has been attributed to action both at the level of primary prevention (e.g. reducing smoking and the consumption of saturated fat) and secondary prevention (e.g. providing aspirin, statins and blood pressure lowering agents to people following a myocardial infarction).[3] For example, a New Zealand analysis estimated that half of the reduction in coronary heart disease mortality in Auckland between 1982 and 1993 was due to reductions in major risk factors, and the other half from medical treatment.[33] While the focus of this thesis is on the primary and secondary prevention of cardiovascular disease using medication, comprehensive strategies to reduce the burden of cardiovascular disease, such as the Centers for Disease Control and Prevention 2003 Public Health Action Plan to Prevent Heart Disease and Stroke (Figure 6), span the disease continuum by incorporating policy and environmental change through to end of life care.[6]

Figure 6. Centers for Disease Control and Prevention Public Health Action Plan to Prevent Heart Disease and Stroke



Source: Centers for Disease Control and Prevention 2003[6]

The major risk factors for cardiovascular disease are increasing age, male sex, tobacco smoking, diabetes, increasing systolic blood pressure and increasing cholesterol.[7] Although age and sex are not amenable to change, the other major risk factors for this disease can be targeted.[3 7] Geoffrey Rose described two prevention strategies: the 'population' strategy (lowering the mean level of a risk factor, e.g. cholesterol, across the whole population) and the 'high risk' strategy (targeting activities to those with high levels of an individual risk factor).[12] A third cardiovascular prevention strategy has emerged: the 'high cardiovascular risk' strategy, in which treatment decisions are based on an individual's absolute risk of having a cardiovascular event, usually within a five or ten year time period.[13] Absolute cardiovascular risk is estimated by mathematical models that take into account multiple risk factors, such as age, sex, smoking status, blood pressure and cholesterol levels, at the same time.[15] These models are usually derived from cohort studies with data on risk factors and outcomes.[34 35] The most well-known tool for cardiovascular risk assessment is the Framingham Risk Function, which was based on the United States' Framingham Heart Study, a longitudinal cohort of white people.[14] A study that modelled these three prevention strategies for the Canadian population found that the number of deaths likely to be avoided with the high cardiovascular risk strategy (using New Zealand cardiovascular risk assessment and management guidelines[36]) was over twice that of the high risk strategy (treating people with a total cholesterol concentration greater than 6.2 mmol/L with statins) and almost seven times that of the population strategy (lowering cholesterol uniformly across the population).[13]

Cardiovascular risk assessment has been an integral component in New Zealand's efforts to prevent cardiovascular disease for over a decade[16] and is also an accepted strategy for guiding treatment decisions for the primary prevention of cardiovascular disease in Australia[17], Europe[10] and the United States.[18] The Framingham Risk Function is currently used as the basis of cardiovascular risk assessment in New Zealand (5-year risk, adjusted for family history and ethnicity)[7] and Australia (5-year risk).[37] United States guidelines are based on a different set of equations, derived from the Framingham and other cohorts, and provide sex- and race-specific estimates for the 10-year risk of cardiovascular disease.[18] European guidelines are based on the Systematic Coronary Risk Evaluation Project (SCORE) risk equation,[38] derived from European cohorts.[10]

2.2.3. Guidelines for the management of cardiovascular disease

New Zealand cardiovascular risk guidelines are based on the high cardiovascular risk strategy.[7 36 39 40] The overarching principle of the guidelines is that all decisions regarding cardiovascular preventive medications should primarily be based on absolute risk of cardiovascular disease rather than individual risk factor levels.[7 36 39 40] The latest version recommends antiplatelet, blood pressure lowering and statin therapy for people with established cardiovascular disease or those with 5-year risk of cardiovascular disease of more than 20%.[7] Lifestyle advice (diet, physical activity and smoking cessation) is recommended, irrespective of absolute risk, with higher intensity advice and follow-up recommended for those at higher risk of cardiovascular disease (Figure 7).[7]

Figure 7. NZ cardiovascular risk management recommendations

Cardiovascular risk	Lifestyle	Drug therapy	Follow-up
Established CVD	Intensive lifestyle advice (diet, physical activity, smoking cessation) simultaneously with drug treatment	Strong evidence of benefit from BP-lowering, statins and antiplatelet therapy in this group	Risk factor monitoring initially at 3 months, then as clinically indicated
CVD risk calculated >20%	Intensive lifestyle advice (diet, physical activity, smoking cessation) simultaneously with drug treatment	Strong evidence of benefit from BP-lowering, statins and antiplatelet therapy in this group	Annual review or as clinically indicated
10% to 20%	Specific individualised lifestyle advice (diet, physical activity, smoking cessation)	Good evidence demonstrating benefit from BP-lowering and/ or statin therapy in this group. The absolute benefits will be smaller at lower levels of combined risk, with increasing benefit of treating both BP and lipids for those with higher five-year combined risk Shared decision-making approach to consider benefits and harms of drug treatment of modifiable risk factors	As clinically indicated, with a more intensive focus for higher combined risk patients If patient not on drug treatment, offer CVD risk assessment at reassessment – at one year for 15% to 20% risk and every two years for 10% to 15% risk
<10%	Lifestyle advice (diet, physical activity, smoking cessation)	Evidence of benefit from BP-lowering and statin therapy in this group is unclear; use a shared decision-making approach to consider benefits and harms of treatment of modifiable risk factors	Offer further CVD risk assessment in 5 to 10 years

Source: Ministry of Health[7]

Guidelines from Australia, Europe and the United States recommend antiplatelet and statin therapy for people with established cardiovascular disease, as well as blood pressure lowering therapy if needed to lower blood pressure below target levels.[8-11] This combination of medications is estimated to reduce the risk of coronary heart disease and stroke by over 50%, based on estimates from meta-analyses of randomised controlled trials (Table 1).

Table 1. Estimated relative reduction in the risk of coronary heart disease and stroke with individual and combined cardiovascular preventive medications

Medication	**Estimated relative risk reduction**	
	CHD	**Stroke**
BP lowering*	22%	41%
Statin†	24%	15%
Aspirin‡	20%	19%
All 3 medications §	53%	59%

BP=blood pressure; CHD=coronary heart disease
*Source: Law meta-analysis 2009.[41] Based on a reduction in BP of 10/5 mm Hg.
†Source: Cholesterol Treatment Trialists' Collaboration meta-analysis 2012.[42] Based on a reduction in low density lipoprotein cholesterol of 1 mmol/L.
‡Source: Antithrombotic Trialists Collaboration meta-analysis 2009.[43]
§It was assumed that the joint effect of multiple medications is likely to be multiplicative (i.e. when a joint effect is the product of the risk ratios[44]), based on evidence from major trials[43 45-49] and as indicated by several authors.[27 43 50 51]

Despite varying methods of measuring absolute risk and advice regarding the use of specific medications, international guidelines are broadly consistent in recommending higher intensity treatment with cardiovascular preventive medications (statins and blood pressure lowering agents if blood pressure is above a certain level) with increased cardiovascular risk levels.[10 17-20]

There is very strong evidence from individual participant data meta-analyses of randomised controlled trials demonstrating that statins and blood pressure lowering therapy reduce cardiovascular events in both primary and secondary prevention, across strata of baseline cardiovascular risk and that their benefits greatly outweigh their harms.[42 52] The Cholesterol Treatment Trialists' Collaborators undertook a meta-analysis of individual participant data from 174,149 participants of randomised controlled trials comparing statin therapy with control, or more with less intensive statin regimens.[42] They found that statin therapy was associated with a 21% (95% confidence interval, CI, 19% to 23%) reduction in the risk of major vascular events (coronary events, strokes or coronary revascularisations) for every 1.00 mmol/L reduction in the level of low density lipoprotein cholesterol.[42] This proportional effect was largely irrespective of age, sex, baseline low density lipoprotein cholesterol level or previous vascular disease.[42] They found that the proportional reduction in major vascular events was at least as big in the two lowest risk categories (baseline 5-year risk of a major vascular event <5% and ≥5 to <10%) as in the higher risk categories (baseline

5-year risk of a major vascular event ≥10%).[42] The Cholesterol Treatment Trialists' Collaborators concluded that the benefits greatly exceeded any known harms of statin therapy (myopathy, rhabdomyolysis, haemorrhagic stroke, diabetes) among both primary and secondary prevention populations, and irrespective of baseline risk of a cardiovascular event.[42]

The Blood Pressure Lowering Treatment Trialists' Collaboration completed a meta-analysis of individual participant data from 67,475 people randomised to blood pressure lowering therapy or placebo, or more with less intensive blood pressure lowering regimens.[52] They found no statistical heterogeneity in the proportional reduction in the risk of cardiovascular disease with blood pressure lowering therapy across groups defined by different baseline levels of 5-year cardiovascular risk (<11%: risk ratio, RR, 0.82, 95% CI 0.73 to 0.93; 11-15%: RR 0.85, 95% CI 0.75 to 0.96; 15-21%: RR 0.87, 95% CI 0.78 to 0.98; >21%: RR 0.85, 95% CI 0.76 to 0.95).[52]

However, there is inconsistency across guidelines regarding the use of antiplatelet therapy for the primary prevention of cardiovascular disease. As noted, the latest New Zealand guidelines recommend aspirin for people with 5-year absolute risk of cardiovascular disease greater than 20%.[7] Aspirin was recommended at a lower threshold of cardiovascular risk in earlier versions of the New Zealand guidelines (5-year absolute risk of cardiovascular disease greater than 15%).[36 39 40 53] The United States Preventive Services Task Force also recommends aspirin for primary prevention, but for men aged 45 to 79 years and women aged 55 to 79 years when the potential benefit of a reduction in myocardial infarction (ischemic strokes in women) outweighs the potential harm of an increase in gastrointestinal haemorrhage.[21] In contrast, Australian[8] and European[10] guidelines recommend avoiding aspirin for primary prevention.

2.2.4. Implementation of guidelines

New Zealand and international guidelines recommend antiplatelet, blood pressure lowering and statin therapy for people with established cardiovascular disease.[7-9 11 19] While not all of these medications are appropriate for all patients because of the presence of contraindications and issues with tolerability, this is unlikely to fully explain why only 59% of New Zealand people hospitalised for a cardiovascular event or procedure in the preceding 10 years were dispensed one of each of these three classes of medication in at least three of the four quarters of 2011.[54] In the first year following their admission for an acute coronary

event in 2007, 59% of New Zealand people were dispensed a statin for 80% or more of the time.[55] With extended follow-up over three years, 66% of New Zealand people were found to have been dispensed a statin for at least 80% of the time.[56] A nationally representative survey of Australian primary care in 2008 found that 50% of people with established cardiovascular disease were prescribed all three categories of preventive treatment (antiplatelet, statin and blood pressure lowering medication), and 38% of those at high risk but without established cardiovascular disease were prescribed blood pressure lowering and statin therapy.[57] The Prospective Urban Rural Epidemiology (PURE) study surveyed people with a history of coronary heart disease or stroke during the period 2003 to 2009 regarding their use of four recommended cardiovascular preventive medications: aspirin, statin, angiotensin-converting enzyme inhibitor (or angiotensin-receptor blocker) and another blood pressure lowering drug.[25] Only 44% of respondents in high-income countries (13% in upper-middle and 3% in lower-middle and low-income countries) reported taking at least three of the four recommended preventive medications.[25]

Suboptimal use of recommended medications is more pronounced among people at high risk of their first cardiovascular event.[58] Dispensing data for such people are available from New Zealand's PREDICT primary care cohort.[58] This is a growing cohort in which anonymised (via encrypted National Health Index number) data are recorded on a central database when their primary care practitioner uses PREDICT, a web-based clinical decision support programme for assessing and managing cardiovascular risk.[58] This data can be linked by the encrypted identifier to national databases, such as for hospitalisations and pharmaceutical dispensing. Seventy percent of people with a history of cardiovascular disease and 36% of people with 5-year risk of cardiovascular disease of at least 15%, who had their first cardiovascular risk assessment with PREDICT between 2006 and 2009 were, as recommended by contemporaneous guidelines,[36 39] dispensed both a blood pressure and lipid lowering agent in the six months following the assessment.[58]

Even if cardiovascular preventive medications are prescribed and dispensed, their preventive potential is dependent on adherence to them.[26] Adherence has been defined as "*the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*".[26] A 2003 World Health Organization report estimated that less than 50% of those prescribed long-term medications for chronic conditions take their medications regularly.[26] Similarly low rates of adherence (less than 40%) have been reported among

people taking cardiovascular preventive medications.[59] Non-adherence to cardiovascular preventive medications has been associated with increased vascular events,[60] mortality, hospitalisations and costs.[59] A systematic review identified four key potentially modifiable barriers to patient adherence: cost, regimen complexity, medication beliefs and, among patients with diabetes, depression.[61] One strategy that has the potential to improve the use of guideline-recommended medications and adherence to those medications is a fixed dose combination of medications, or 'polypill'.[27] A key recommendation of a 2001 World Health Organization meeting was that such a pill be developed for, and evaluated in, people with established cardiovascular disease.[28]

2.3. Effectiveness and safety of aspirin for the primary prevention of cardiovascular disease

While guidelines consistently recommend statins and blood pressure lowering medications for those at high risk of their first cardiovascular event, there is variation in recommendations on the use of aspirin in the primary prevention setting. This section investigates the effectiveness and safety of aspirin for primary prevention using guidelines from New Zealand, Australia, the United States and Europe on the primary prevention of cardiovascular disease as a starting point.

2.3.1. International guideline recommendations

New Zealand[7] and United States[21] guidelines recommend aspirin for primary prevention for certain people, whereas guidelines from Australia[8] and Europe[10] recommend avoiding aspirin for the primary prevention of cardiovascular disease. Each of the guidelines has used different meta-analyses to justify their recommendation regarding aspirin although many of the same randomised controlled trials have been included (Table 2). In order to understand the differences between recommendations, the trials included in the meta-analyses supporting the recommendations were reviewed, followed by the meta-analyses themselves.

Table 2. NZ, Australian, US and European guidelines on the use of aspirin for the primary prevention of cardiovascular disease

Country	Recommendation	Meta-analyses supporting recommendation	Trials included in the meta-analyses
NZ 2013[7]	"*Aspirin can be considered for these high-risk primary prevention people, taking into account harms and benefits"* ('high-risk' = ≥20% 5-year risk of cardiovascular disease)	Overall: • Sanmuganathan 2001[62] • Hayden 2002[63] [From the 2003[36] guideline; no references found in the 2013[7], 2012[40], 2009[39] or 2005[53] guidelines]	• British Doctors' Trial[64] • Physicians' Health Study[65] • Hypertension Optimal Treatment trial[66] • Thrombosis Prevention Trial[67] • Primary Prevention Project[68]
Australia 2012[8]	*"Aspirin or other antiplatelet therapy is not routinely recommended for primary prevention of cardiovascular disease"*	Overall: • Antiplatelet Trialists' Collaboration 1994[69], 2002[70] and Antithrombotic Trialists' Collaboration 2009[43] • Berger 2006[71] Diabetes: • Calvin 2009[72] • de Berardis 2009[73] • Pignone 2010[74] • Zhang 2010[75]	• British Doctors' Trial[64] • Physicians' Health Study[65] • Hypertension Optimal Treatment trial[66] • Thrombosis Prevention Trial[67] • Primary Prevention Project[68] • Women's Health Study[76] • Early Treatment of Diabetic Retinopathy Study[77] • Antiphospholipid Antibody-Acetylsalicylic Acid trial[78] • Prevention of Progression of Arterial Disease and Diabetes trial[79] • Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial[80]
Europe 2012[10]	*"Aspirin or clopidogrel cannot be recommended in individuals without cardiovascular or cerebrovascular disease due to the increased risk of major bleeding"* *"Antiplatelet therapy with aspirin is not recommended for people with diabetes who do not have clinical evidence of atherosclerotic disease"*	Overall: • Antithrombotic Trialists' Collaboration 2009[43] Diabetes: • De Berardis 2009[73]	• British Doctors' Trial[64] • Physicians' Health Study[65] • Hypertension Optimal Treatment trial[66] • Thrombosis Prevention Trial[67] • Primary Prevention Project[68] • Women's Health Study[76] • Early Treatment of Diabetic Retinopathy Study[77] • Prevention of Progression of Arterial Disease and Diabetes trial[79] • Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial[80]
US 2009[21]	*"Encourage men age 45 to 79 years* [women age 55 to 79 years] *to use aspirin when the potential benefit of a reduction in myocardial infarction* [ischemic strokes in women] *outweighs the potential harm of an increase in gastrointestinal hemorrhage"*	Overall: • Berger 2006[71] Bleeding: • Hernandez-Diaz 2006[81] (note this is not a meta-analysis)	• British Doctors' Trial[64] • Physicians' Health Study[65] • Hypertension Optimal Treatment trial[66] • Thrombosis Prevention Trial[67] • Primary Prevention Project[68] • Women's Health Study[76]

NZ=New Zealand; US=United States

2.3.2. Trials included in the meta-analyses supporting recommendations

Ten randomised controlled trials were included in the meta-analyses supporting recommendations on the use of aspirin in primary prevention (Table 3). The British Doctors' Trial 1988[64] and Physicians' Health Study 1989[65] involved healthy male physicians from the United Kingdom and United States, respectively. The Physician's Health Study was a two-by-two factorial trial and as well as being randomised to aspirin or aspirin placebo, participants were randomised to beta carotene or beta carotene placebo.[65] The Thrombosis Prevention Trial 1998 was conducted among United Kingdom men at high risk of a first ischaemic heart disease event, either because of high individual estimated risk or because they resided in a region with very high mortality rates of ischemic heart disease.[67] Participants were randomised to aspirin or aspirin placebo as well as to warfarin or warfarin placebo.[67] The Hypertension Optimal Treatment trial 1998 included men and women from Europe, North and South America and Asia, with hypertension characterised by a diastolic blood pressure of 100 to 115 mm Hg.[66] Participants were randomised to one of three diastolic blood pressure target groups: $\leq$90 mm Hg, $\leq$85 mm Hg or $\leq$80 mm Hg.[66] All participants received felodipine 5mg daily and additional blood pressure lowering therapy, and dosages were adjusted to reach the randomised target diastolic blood pressure.[66] In addition to being randomised to one of three diastolic blood pressure target groups, Hypertension Optimal Treatment trial participants were randomised to aspirin or placebo aspirin.[66] The Primary Prevention Project 2001 was undertaken among men and women from Italy aged 50 years or greater and with at least one risk factor for cardiovascular disease.[68] Participants were randomised to aspirin or no aspirin, and also to vitamin E or no vitamin E in a two by two factorial trial.[68] The Women's Health Study 2005 randomised United States healthy female health professionals aged 45 years and older to aspirin or placebo, as well as to vitamin E or placebo vitamin E.[76] In the Antiphospholipid Antibody Acetylsalicylic Acid trial 2007 people with antiphospholipid syndrome and no prior history of arterial or venous thrombosis were randomised to aspirin or placebo.[78]

The three other trials were conducted solely in patients with diabetes: the Early Treatment Diabetic Retinopathy study 1992,[77] the Prevention of Progression of Arterial Disease and Diabetes trial 2008[79] and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial 2008.[80] The United States Early Treatment Diabetic Retinopathy Study involved men and women with diabetes and diabetic retinopathy who were randomised to aspirin or placebo.[77] At baseline 49% of Early Treatment Diabetic Retinopathy Study

participants had a history of cardiovascular disease (defined as coronary artery disease, congestive heart failure, myocardial infarction or intermittent claudication).[77] The frequency of baseline history of specific cardiovascular conditions was: myocardial infarction (6%), stroke (2%), transient ischaemic attack (2%), coronary artery disease (8%, defined as angina[82]), congestive heart failure (3%) and intermittent claudication (9%).[77] The Scottish Prevention of Progression of Arterial Disease and Diabetes trial included men and women with diabetes and asymptomatic peripheral arterial disease (lower than normal ankle brachial pressure index) and without symptomatic cardiovascular disease.[79] Participants were randomised to aspirin or placebo aspirin, and also to antioxidant or placebo antioxidant.[79] The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial randomised men and women with diabetes to aspirin or no aspirin.[80]

The key features of the trials are provided in Table 3.

Table 3. Trials included in meta-analyses supporting NZ, Australian, US and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease

Trial	N	%CVD	% Women	% Diabetes	Aspirin daily dose	Control	Additional randomly allocated treatment (trial design)	Follow-up, months
BDT 1988[64]	5,139	8%†	0%	2%	500mg	No aspirin	Nil	66.1 (mean)
PHS 1989[65]	22,071	1%†	0%	2%	325 (alt days)	Placebo	Beta carotene (2x2)	60.2 (mean)
ETDRS 1992[77]	3,711	49%	44%	100%	650	Placebo	Nil	60.0 (mean)
HOT 1998[66]	18,790	3%†	47%	8%	75	Placebo	BP-lowering agents for randomly assigned target BP (2x3)‡	45.6 (mean)
TPT 1998[67]	5,085	<1%†	0%	Not stated	75	Placebo	Warfarin (2x2)	76.3 (mean)
PPP* 2001[68]	4,495	4%†	57%	17%	100	No aspirin	Vitamin E (2x2)	43.8 (mean)
WHS 2005[76]	39,876	<1%†	100%	2.6%	100 (alt days)	Placebo	Vitamin E and beta carotene§ (2x2x2)	121.2 (mean)
APLASA 2007[78]	98	0%	90%	6%	81mg	Placebo	Nil	27.6 (mean)
POPADAD 2008[79]	1,276	0%	56%	100%	100	Placebo	Antioxidant (2x2)	80.4 (median)
JPAD 2008[80]	2,539	0%	45%	100%	81 or 100	No aspirin	Nil	52.4 (median)

APLASA=Antiphospholipid Antibody Acetylsalicylic Acid study; BDT=British Doctors' Trial; BP=blood pressure; CVD=cardiovascular disease; ETDRS=Early Treatment Diabetic Retinopathy study; HOT=Hypertension Optimal Treatment trial; JPAD=Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial; N=number of participants; NZ=New Zealand; PHS=Physicians' Health Study; POPADAD=Prevention of Progression of Arterial Disease and Diabetes trial; PPP=Primary Prevention Project; TPT=Thrombosis Prevention Trial; US=United States; WHS=Women's Health Study

*Data in this table is from original trial publication in 2001. A subsequent publication from the trial in 2003 reported data on 289 additional participants (all of whom had diabetes).[83]

†CVD defined as myocardial infarction, cerebrovascular disease, angina, peripheral arterial disease or heart failure and obtained from the Antithrombotic Trialists' Collaboration 2009 individual participant data meta-analysis.[43]

‡All participants received felodipine with the addition of other BP-lowering agents according to a five-step regimen to achieve the randomly allocated target diastolic BP ($\leq$90, $\leq$85 or $\leq$80 mm Hg).[66]

§Beta carotene stopped after mean 22.8 months after PHS results published showing no effect on vascular outcomes.[84]

All of these trials are considered relevant to the question of the effectiveness and safety of aspirin for primary prevention with the exception of the Antiphospholipid Antibody Acetylsalicylic Acid trial[78] (because it was conducted in people with antiphospholipid syndrome thereby limiting the generalisability of its findings) and the Early Treatment Diabetic Retinopathy study[77] (because 49% of participants had established cardiovascular disease at baseline). The key findings of the eight relevant trials are summarised in Table 4.

Table 4. Results of randomised controlled trials included in meta-analyses supporting NZ, Australian, US and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease

Trial	**N**	**Effect of aspirin on cardiovascular events (95% CI)**	**Effect of aspirin on major bleeding**	**Possible interaction between effect of aspirin and other randomly allocated treatment**
BDT 1988[64]	5,139	Aspirin vs control, per 10,000 person years: Nonfatal MI 42.5 vs 43.3 (NS); Nonfatal stroke 32.4 vs 28.5 (NS); Death (MI or stroke) 63.2 vs 62.3 (NS)	Aspirin vs control, per 10,000 person years: Nonfatal non-cerebral bleed 10.6 vs 7.4 (NS); Fatal gastric bleed or peptic ulcer 1.6 vs 3.2	Not applicable
PHS 1989[65]	22,071	Fatal or nonfatal: MI **RR 0.56 (0.45 to 0.70)**; Stroke RR 1.22 (0.93 to 1.60)	Bleeding GI ulcer: **RR 1.77 (1.07 to 2.94)** Bleed requiring transfusion: **RR 1.71 (1.09 to 2.69)**	Beta carotene was not found to have an effect on vascular outcomes[85]
HOT 1998[66]	18,790	Fatal or nonfatal MI or stroke or other CVD death: **RR 0.85 (0.73 to 0.99)**	Nonfatal major bleeds: **129 (asp) vs 70 (placebo), p< 0.001**	Interaction not assessed statistically; all received BP-lowering agents
TPT 1998[67]	5,085	Fatal or nonfatal: IHD **proportional reduction 20% (1 to 35%)**; Stroke proportional reduction 3% (-45% to 35%)	Major bleed (fatal, cerebral or required transfusion and/or surgery): 20 (asp) vs 13 (no asp)	No statistically significant interaction between aspirin and warfarin on CVD or bleeding outcomes
PPP* 2001[68]	4,495	CVD death, non-fatal MI, non-fatal stroke, angina, TIA, PAD, revascularisation procedure: **RR 0.77 (0.62 to 0.95)**	Non-fatal major bleeds: **1.1% (asp) vs 0.3% (control), p=0.0008** Fatal bleeds: 3 (asp) vs 1 (control)	Vitamin E was found to have no effect on either vascular or bleeding outcomes.[68]
WHS 2005[76]	39,876	CVD death, non-fatal MI, non-fatal stroke: RR 0.91 (0.80 to 1.03)	GI bleed requiring transfusion: **RR 1.40 (1.07 to 1.83)** Fatal GI bleeds: 2 (asp) vs 3 (placebo)	Neither Vitamin E nor beta carotene significantly modified the effect of aspirin on the primary or secondary end points
POPA-DAD 2008[79]	1,276	CVD death, MI, stroke, above ankle amputation for critical limb ischaemia: HR 0.98 (0.76 to 1.26)	GI bleed: HR 0.90 (0.53 to 1.52)	No evidence was found of any interaction between aspirin and antioxidant.
JPAD 2008[80]	2,539	All atherosclerotic events: HR 0.80 (0.58 to 1.10)	Bleed requiring transfusion: 4 (asp) vs 0 (control)	Not applicable

Asp=aspirin; BDT=British Doctors' Trial; BP=blood pressure; CI=confidence interval; CVD=cardiovascular disease; GI=gastrointestinal; HOT=Hypertension Optimal Treatment trial; HR=hazard ratio; IHD=ischaemic heart disease; JPAD=Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI=myocardial infarction; N=number of participants; NS=not significant; NZ=New Zealand; PAD=peripheral arterial disease; PHS=Physicians' Health Study; POPADAD=Prevention of Progression of Arterial Disease and Diabetes trial; PPP=Primary Prevention Project; RR=risk ratio; TIA=transient ischaemic attack; TPT=Thrombosis Prevention Trial; US=United States; WHS=Women's Health Study

*Data in this table is from original trial publication in 2001. A subsequent publication from the trial in 2003 reported data on 289 additional participants (all of whom had diabetes).[83]

Statistically significant results in bold

Aspirin significantly reduced myocardial infarction or a composite cardiovascular outcome in half of the trials. Aspirin was more consistently associated with an increase in major bleeding across the trials. There was no evidence of an interaction between the effects of aspirin and additional randomly allocated treatment in five factorial trials. The other factorial trial (the Hypertension Optimal Treatment trial) treated all participants with felodipine (in addition to aspirin or placebo aspirin), with additional blood pressure lowering agents added to achieve different, randomly assigned, diastolic blood pressure levels.[66]

2.3.3. Meta-analyses supporting recommendations

Sanmuganathan 2001

The New Zealand guideline recommendation supporting the use of aspirin in primary prevention is based on meta-analyses by Sanmuganathan 2001[62] and Hayden 2002.[63] Sanmuganathan and colleagues sought to determine the cardiovascular and coronary risk thresholds at which the benefits of aspirin outweighed its harms.[62] Their meta-analysis used aggregate data from published trial reports and included 48,540 people from four randomised controlled trials of aspirin for primary prevention: the British Doctors' Trial,[64] the Physicians' Health Study,[65] the Hypertension Optimal Treatment trial[66] and the Thrombosis Prevention Trial.[67] [62] Participants were predominantly male (82%) with relatively low risk of cardiovascular disease (weighted mean of absolute risk of cardiovascular disease 0.92% per year in the control groups). Sanmuganathan and colleagues only included data for participants not receiving warfarin from the Thrombosis Prevention Trial *"to avoid possible interactions between treatments*".[62] This exclusion may not be justified given that there were no statistically significant interactions between the effects of aspirin and warfarin on either cardiovascular or bleeding events.[67]

Sanmuganathan and colleagues found that aspirin was associated with a 15% (95% CI 6% to 22%) relative reduction in the risk of a cardiovascular event (myocardial infarction, stroke [ischaemic, haemorrhagic or of uncertain cause] or cardiovascular death).[62] This equated to an absolute reduction of cardiovascular events of 0.13% per year among trial participants receiving aspirin.[62] The reduction in cardiovascular events with aspirin was attributed to a reduction in the risk of myocardial infarction (fatal or nonfatal, odds ratio, OR, 0.70, 95% CI 0.62 to 0.79).[62] There was no difference between aspirin and control groups in either the risk of stroke (fatal or nonfatal, OR 1.06, 95% CI 0.91 to 1.24) or death (OR 0.94, 95% CI

0.85 to 1.04).[62] Aspirin was associated with a 73% (95% CI 14% to 163%) relative increase in the risk of a major non-cerebral bleed, an estimate based on data from two of the trials (the Physicians' Health Study[65] and the Thrombosis Prevention Trial[67]) because of differences in the reporting of bleeding outcomes across trials.[62] Sanmuganathan and colleagues estimated that the benefit (absolute reduction in cardiovascular events) and harm (absolute increase in major non-cerebral bleeds) of aspirin were equal when the absolute risk of a cardiovascular event was 0.22% per year, and that the upper 95% confidence limit for this threshold was an absolute risk of a cardiovascular event of 0.8% per year.[62] They made two assumptions: (1) that the relative risk reduction of cardiovascular events with aspirin was 0.15 and remained constant irrespective of absolute cardiovascular risk and (2) that the relative risk increase of major non-cerebral bleeds with aspirin was 0.73, was constant and was independent of absolute cardiovascular risk.[62] Although there is some evidence to support the first assumption,[43] the second assumption appears to be flawed as there is strong evidence from an individual participant data meta-analysis conducted by the Antithrombotic Trialists' Collaboration in 2009 that the risk of a major non-cerebral bleed with aspirin increases, independently, with each of the following cardiovascular risk factors: age, male sex, diabetes, smoking, increasing blood pressure and increasing body mass index.[43]

Hayden 2002

Hayden and colleagues conducted a meta-analysis using the aggregate published trial data of 53,035 participants from five randomised controlled trials of aspirin for primary prevention (the four included in Sanmuganathan 2001[62] plus the Primary Prevention Project 2001 trial[68]). As with the Sanmuganathan meta-analysis, participants were predominantly male (78%), their annual risk of coronary heart disease was low (weighted mean of absolute risk of coronary heart disease 0.5% per year in the control groups) and warfarin participants from the Thrombosis Prevention Trial were excluded.[63] The meta-analysis by Hayden and colleagues was used as the basis for the United States Preventive Services Taskforce 2002 recommendations on the use of aspirin for the primary prevention of cardiovascular events.[86] Hayden and colleagues found that aspirin was associated with a 28% relative reduction in the risk of coronary heart disease (fatal or nonfatal, 95% CI 13% to 40%) and had no effect on the risk of stroke (irrespective of cause, fatal or nonfatal, OR 1.02, 95% CI 0.85 to 1.23) or death (OR 0.93 95% CI 0.84 to 1.02).[63] The effect of aspirin on the

composite outcome of cardiovascular events was not assessed.[63] Hayden and colleagues used estimates from a meta-analysis by Sudlow[87] to describe the effect of aspirin on major gastrointestinal bleeds (OR 1.7, 95% CI 1.4 to 2.1) and haemorrhagic strokes (OR 1.4, 95% CI 0.9 to 2.0).[63] They estimated that if 1000 people with 5-year risk of coronary heart disease of 5% (approximately equivalent to a 5-year risk of cardiovascular disease of 7%[88]) took aspirin for 5 years, 14 (95% CI 6 to 20) coronary heart disease events would be avoided and 3 (95% CI 2-4) major gastrointestinal bleeds would be caused.[63] Hayden and colleagues noted that their estimate of the number of additional major gastrointestinal bleeds was applicable to middle-aged men (who formed the majority of participants from contributing trials) and that the risk of bleeding was likely to be greater in older patients.[63]

Antithrombotic Trialists' Collaboration

A different group of meta-analyses was used to justify the Australian 2012 guideline statement "*Aspirin or other antiplatelet therapy is not routinely recommended for primary prevention of cardiovascular disease"*.[8] These were a series of meta-analyses conducted by the Antithrombotic (previously Antiplatelet) Trialists' Collaboration (1994,[69] 2002[70] and 2009[43]), a sex-specific meta-analysis (Berger 2006[71]) and four meta-analyses that focused on the effect of aspirin among people with diabetes (Calvin 2009,[72] De Berardis 2009,[73] Pignone 2010[74] and Zhang 2010[75]).

The first meta-analysis by the Antithrombotic Trialists' Collaboration was conducted in 1988.[89] While not mentioned in the primary prevention guidelines, and focused on secondary rather than primary prevention, it is summarised here along with the subsequent meta-analyses conducted by this group for completeness. The 1998 meta-analysis investigated the effect of antiplatelet treatment on vascular events (myocardial infarction, stroke or vascular death) among 29,073 patients with established cardiovascular disease from 25 randomised controlled trials.[89] Antiplatelet treatment (mainly aspirin, sulphinpyrazone or aspirin combined with dipyridamole) was associated with a 25% proportional reduction in the risk of a vascular event (95% CI not provided but authors note standard deviation of 3% and one tailed p value of 0.0001).[89] The 1988 Collaboration estimated that for 1000 patients with a 6% risk of vascular death and a 6% risk of a non-fatal vascular event over 2 years, treatment with aspirin over this period was likely to avoid 10 vascular deaths and 20 non-fatal vascular events.[89] No significant differences in the effect of antiplatelets by antiplatelet type or dose, or by participant medical history (coronary or cerebrovascular

disease) were detected.[89] The 1998 Collaboration concluded that *"antiplatelet treatment can reduce the incidence of serious vascular events by about a quarter among a wide range of patients at particular risk of occlusive vascular disease"* and that *"the balance of risk and benefit, however, might be different for 'primary' prevention among people with low absolute risk of occlusive disease if antiplatelet treatment produced even a small increase in the incidence of cerebral haemorrhage".*[89] Strokes were not able to be reliably separated out according to cause (ischaemic or haemorrhagic) in this meta-analysis.[89]

The 1994 Collaboration meta-analysis (of 145 trials with 96,316 participants) sought to determine the effects of antiplatelet therapy on vascular events in the following patient groups: prior myocardial infarction (11 trials), acute myocardial infarction (9 trials), prior stroke or transient ischaemic attack (18 trials), 'other high risk' (such as patients with angina, peripheral vascular disease and diabetes, 104 trials) and primary prevention (3 trials).[69] Two of the primary prevention trials assessed aspirin (the British Doctors' Trial[64] and the Physicians' Health Study[65]) and one small trial assessed sulphinpyrazone (Blakely and Gent,[90] n=292). The 1994 Collaboration found a 10% non-significant relative reduction in the risk of a vascular event among antiplatelet recipients compared with the control group in the primary prevention population (95% CI not supplied but standard deviation 6%).[69] There was a 29% relative reduction in the risk of a nonfatal myocardial infarction (standard deviation 8%) with aspirin compared with control, and no statistically significant difference in the risk of nonfatal stroke (21% relative increase with aspirin, standard deviation 13%), vascular death (3% relative decrease with aspirin, standard deviation 10%) or death from any cause (5% relative decrease with aspirin, standard deviation 7%) in the primary prevention group.[69] Haemorrhagic stroke (fatal or nonfatal) was more common among primary care participants in the antiplatelet than control group (0.3% vs 0.2%, $p<0.05$) as was 'other' (fatal or nonfatal) stroke (1.4% vs 1.2%) although the difference in 'other' stroke was not statistically significant.[69] The 1994 Collaboration concluded that *"there is, as yet, no clear evidence that antiplatelet therapy is indicated for routine use in 'primary prevention' subjects at low risk of occlusive vascular events"*.[69] They further noted that "*antiplatelet therapy protects a wider range of patients at high risk of occlusive vascular disease than is currently treated routinely: it should be considered for almost all with suspected acute myocardial infarction, unstable angina, or a history of myocardial infarction, angina, stroke, transient ischaemic attack, arterial bypass surgery, or angioplasty"*.[69] What remained unclear from

this meta-analysis was whether aspirin was indicated for people without established cardiovascular disease but nonetheless at high risk.

The 2002 Collaboration meta-analysis estimated the effect of antiplatelet therapy on serious vascular events (myocardial infarction, stroke or vascular death) among 135,640 people (from 195 trials) at high risk of occlusive vascular events (over 3% per year on the basis of a previous occlusive event or predisposing condition).[70] The trials had been conducted in patients with myocardial infarction (27 trials), stroke or transient ischaemic attack (28 trials) and 'other high risk' conditions (such as angina, atrial fibrillation, peripheral vascular disease, haemodialysis, diabetes [including some patients with established cardiovascular disease] and carotid disease, 140 trials).[70] Overall, antiplatelet therapy was associated with a 22% proportional reduction in the risk of a vascular event (95% CI not provided but authors note standard error of 2% with p value <0.0001).[70] The 2002 Collaboration found that the proportional risk reductions with antiplatelet therapy were broadly comparable in most categories of patients.[70] Although they did not specifically investigate the effect of aspirin in primary prevention, the 2002 Collaboration noted that "*these results reinforce the value of ensuring that antiplatelet therapy with 75-150mg aspirin daily . . . is considered routinely for all such patients at high or intermediate risk of occlusive vascular events (more than 2% a year), irrespective of whether they have already had a major vascular event*".[70]

In 2009 the Collaboration published a meta-analysis of individual participant data assessing aspirin for the primary prevention of cardiovascular disease.[43] Six randomised controlled trials (the five included by Hayden 2002[63] with the addition of the Women's Health Study[76]) with 95,456 participants (54% women) were included.[43] Participants were at low risk of cardiovascular disease (weighted mean of absolute risk of serious vascular events 0.57% per year in control group).[43] Proportionately, aspirin was associated with a 12% (95% CI 6% to 18%) reduction in the risk of a serious vascular event (myocardial infarction, stroke or vascular death [including sudden death, pulmonary embolism and haemorrhage]) and a 54% (95% CI 30% to 82%) increase in the risk of a major extra-cranial bleed (mainly gastrointestinal and usually defined as a bleed requiring transfusion or resulting in death).[43] There was no statistically significant heterogeneity for either of these outcomes across the six trials.[43] The proportional changes translated to an absolute reduction in serious vascular events of 0.07% per year and an absolute increase in major extra-cranial bleeds of 0.03% per year.[43] The 2009 Collaboration concluded that "*although the currently available trial data could well help inform personally appropriate judgments by individuals about their own use*

of long-term aspirin, they do not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals above a moderate level of risk of coronary heart disease".[43]

The results of the Collaboration's 2009 meta-analysis have a number of advantages over meta-analyses relying on aggregate data obtained from published trial reports because they used individual-level data. These advantages include the ability to:

- Have consistent inclusion and exclusion criteria and statistical analyses
- Handle missing data at the individual level
- Verify original trial results
- Update (and possibly increase duration of) follow-up information
- Calculate and incorporate additional results
- Assess model assumptions and model complex relationships like time dependent effects
- Adjust estimates by baseline factors, calculate results for specific subgroups of participants and determine differential treatment effects across individuals
- Generate and validate risk scores
- Correlate multiple end points when data are provided at multiple time points[91]

The 2009 Collaboration was able to undertake additional analyses because of their access to individual participant data.[43] They assessed the effect of aspirin on serious vascular events and major extra-cranial bleeds (separately) in primary prevention according to the following participant characteristics at baseline: age (<65, $\geq$65 years), sex, history of vascular disease, history of diabetes, history of hypertension, current smoking status, systolic blood pressure (<140, 149 to 159, $\geq$160 mm Hg), diastolic blood pressure (<80, 80 to 89, $\geq$90 mm Hg), total cholesterol (<5.0, 5.0 to 5.9, $\geq$6.0 mmol/L), body mass index (<25.0, 25.0 to 29.9, $\geq$30 kg/m^2) and estimated 5-year risk of coronary heart disease(<2.5%, 2.5 to 5%, 5 to 10%, $\geq$10%).[43]

Global tests for heterogeneity across all of these characteristics were performed to avoid misinterpreting false positive results because of the number of subgroup comparisons.[43] These tests were not statistically significant for the effect of aspirin on serious vascular events (11 degrees of freedom, χ^2_{11}=7.8, p=0.7) or major extra-cranial bleeds (11 degrees of freedom, χ^2_{11}=13.2, p=0.3).[43] The proportional effects of aspirin on serious vascular events and major extra-cranial bleeds therefore did not appear to be significantly affected by age, sex, history of diabetes, history of hypertension, current smoking status, systolic blood

pressure, diastolic blood pressure, cholesterol, body mass index or estimated 5-year risk of coronary heart disease.[43] Further, the 2009 Collaboration meta-analysis demonstrated that the rate ratio for the effect of aspirin on serious vascular events was similar for secondary prevention (0.81, 95% CI 0.75 to 0.87) and primary prevention (0.88, 95% CI 0.82 to 0.94).[43] The 2009 Collaboration concluded that "*if the proportional risk reductions in these different subgroups really are similar, then the absolute risk reductions will depend chiefly on an individual's absolute risk without treatment*".[43]

The 2009 Collaboration estimated the rate ratios for serious vascular events and major extra-cranial bleeds among primary care trial participants without vascular disease at baseline (approximately 93,918 participants) using a Poisson regression model (Table 5).[43] Variables included in the model were aspirin allocation and the following baseline characteristics: age, sex, history of diabetes, smoking status, total cholesterol, blood pressure and body mass index.[43] According to this analysis, the risk of a serious vascular event and the risk of a major extracranial bleed among people without established vascular disease were both greater among older people, men, people with diabetes, current smokers and people with higher blood pressure and body mass index.[43]

Table 5. Independent risk factors for serious vascular and bleeding outcomes from the 2009 Antithrombotic Trialists' Collaboration individual participant data meta-analysis of randomised controlled trials of aspirin in the primary prevention of cardiovascular disease

Risk factor	**Rate ratio (95% CI)**	
	Serious vascular event	**Major extracranial bleed**
Age (per decade)	2.08 (1.99 to 2.17)	2.15 (1.93 to 2.39)
Male sex	1.86 (1.60 to 2.16)	1.99 (1.45 to 2.73)
Diabetes	2.43 (2.16 to 2.74)	1.55 (1.13 to 2.14)
Current smoker	2.03 (1.87 to 2.20)	1.56 (1.25 to 1.94)
Mean BP* (per 20 mm Hg)	1.79 (1.67 to 1.92)	1.32 (1.09 to 1.58)
Total cholesterol (per 1 mmol/L)	1.10 (1.06 to 1.14)	0.99 (0.90 to 1.08)
Body mass index (per 5 kg/m^2)	1.07 (1.02 to 1.11)	1.24 (1.13 to 1.35)

BP=blood pressure; CI=confidence interval
*Mean BP was the mean of systolic and diastolic BP.
Source: 2009 Antithrombotic Trialists' Collaboration[43]

The 2009 Collaboration noted that guidelines that recommend aspirin for people above a threshold of coronary heart disease risk in order to maximise the excess of benefit over harm, "*implicitly assume, however, either that the absolute risk of bleeding remains approximately constant irrespective of risk of coronary heart disease, or that it depends solely on age, whereas the present analyses showed that other risk factors for this disease are also risk factors for bleeding"* and caution that "*even for people at moderately increased risk of*

coronary heart disease, the major absolute benefits and hazards of adding aspirin to a statin-based primary prevention regimen could still be approximately evenly balanced".[43]

Another important consideration when assessing the balance of benefits and harms of aspirin is the effect of adding aspirin to other cardiovascular preventive medications, such as statins.[43] The 2009 Collaboration considers that the joint effects of multiple medications *"might well be approximately multiplicative*".[43] A multiplicative effect is when a joint effect is the product of the risk ratios, in contrast to an additive effect in which the joint effect is the sum of the risk differences associated with individual effects.[44] The 2009 Collaboration estimated that for a person with 5-year coronary heart disease risk greater than 10%, taking aspirin alone would reduce their absolute 5-year risk of a serious vascular event by 2%, whereas if they were already taking medication to halve their risk of coronary heart disease, adding aspirin would only reduce their absolute 5-year risk of a serious vascular event by 1%.[43] Given that aspirin would also increase the person's absolute risk of a major non-cerebral bleed by 1% over 5 years (and assuming that this excess risk is the same irrespective of whether aspirin is taken alone or with other cardiovascular preventive medication), the benefit of aspirin appears to exceed its harms when taken alone but benefits and harms appear to be evenly balanced when taken with other cardiovascular preventive medications in this scenario.[43]

Berger 2006

The Australian guidelines also cite a sex-specific meta-analysis by Berger and colleagues[71] and four meta-analyses assessing the effect of aspirin on people with diabetes (Calvin 2009,[72] De Berardis 2009,[73] Pignone 2010[74] and Zhang 2010[75]). The meta-analysis by Berger and colleagues was published in 2006 and included the same six trials and the same participants as included in the 2009 Antithrombotic Trialists' Collaboration meta-analysis (95,456 participants, 54% women, weighted mean of absolute risk of serious vascular event in control group 0.57%/year), although it was primarily based on aggregate data from published trial reports rather than individual participant data.[71] Berger and colleagues found that the overall effect of aspirin on major cardiovascular events (cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke) was similar for women (OR 0.88, 95% CI 0.79 to 0.99) and men (OR 0.86, 95% CI 0.78 to 0.94).[71] The effect of aspirin on this composite outcome was underpinned by sex-specific differences in the effect of aspirin on myocardial infarction and ischaemic stroke.[71] Aspirin was

associated with a reduction in the risk of ischaemic stroke among women (OR 0.76, 95% CI 0.63 to 0.93) and myocardial infarction among men (OR 0.68, 95% CI 0.54 to 0.86) but aspirin did not have a statistically significant effect on either ischaemic stroke among men (OR 1.00, 95% CI 0.72 to 1.41) or myocardial infarction among women (OR 1.01, 95% CI 0.84 to 1.21).[71] Berger and colleagues found that aspirin increased the risk of a major bleed (not defined in their paper) by a similar proportion among women (68%, 95% CI 13% to 152%) and men (72%, 95% CI 35% to 120%).[71]

Summary of meta-analyses not focusing on diabetes

Conclusions and limitations of the meta-analyses that were used as the basis of national guideline recommendations on the use of aspirin in primary prevention are summarised in Table 6. None included data from the Prevention of Progression of Arterial Disease and Diabetes[79] or Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes[80] trials. Average cardiovascular risk of included participants was relatively low (weighted mean absolute risk of serious vascular events 0.57% per year for the six trials included in the Antithrombotic Trialists' Collaboration and the Berger meta-analyses). The Antithrombotic Trialists' Collaboration meta-analysis[43] was the only one based on individual participant as opposed to aggregate data. The Sanmuganathan[62] and Hayden[63] meta-analyses were based on data predominately from men, and excluded Thrombosis Prevention Trial participants randomised to warfarin despite the absence of statistically significant interaction between the effects of aspirin and warfarin on either cardiovascular or bleeding events.[67] Modelling undertaken by Sanmuganathan and colleagues was based on the assumptions that the risk of a major bleed with aspirin was constant and independent of cardiovascular risk,[62] and those assumption has been questioned by the findings of the Antithrombotic Trialists' Collaboration individual participant data meta-analysis.[43]

Table 6. Conclusions and limitations of meta-analyses used as the basis of NZ, Australian, US and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease

Meta-analysis (included trials)	**N (% women)**	**Conclusions**	**Limitations**
Sanmuganathan 2001[62] (BDT, PHS, HOT, TPT)	48,540 (18%)	*"Aspirin treatment for primary prevention is safe and worthwhile at coronary event risk ≥ 1.5%/year"*	-Based on aggregate data -Only 18% women -Low risk population (weighted mean of absolute risk of CVD in control group 0.92%/year) -Warfarin participants excluded despite no evidence of interaction with aspirin -Assumption that absolute risk of bleeding independent of absolute cardiovascular risk -Following trials not included: PPP, WHS, POPADAD, JPAD
Hayden 2002[63] (BDT, PHS, HOT, TPT, PPP)	53,035 (22%)	*"The net benefit of aspirin increases with increasing cardiovascular risk. In the decision to use aspirin chemoprevention, the patient's cardiovascular risk and relative utility for the different clinical outcomes prevented or caused by aspirin use must be considered"*	-Based on aggregate data -Only 22% women -Low risk population (weighted mean of absolute risk of CHD in control group 0.5%/year) -Warfarin participants excluded despite no evidence of interaction with aspirin -Following trials not included: WHS, POPADAD, JPAD
ATC 2009[43] (BDT, PHS, HOT, TPT, PPP, WHS)	95,456 (54%)	*"The currently available trial data . . . do not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals above a moderate level of risk of coronary heart disease"*	-Low risk population (weighted mean of absolute risk of serious vascular events in control group 0.57% per year) -Following trials not included: POPADAD, JPAD
Berger 2006[71] (BDT, PHS, HOT, TPT, PPP, WHS)	95,456 (54%)	*"For women and men, aspirin therapy reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischemic stroke in women and MI in men. Aspirin significantly increased the risk of bleeding to a similar degree among women and men"*	-Based on aggregate data -Low risk population (weighted mean of absolute risk of serious vascular events in control group 0.57% per year) -Following trials not included: POPADAD, JPAD

ATC=Antithrombotic Trialists' Collaboration; BDT=British Doctors' Trial; CHD=coronary heart disease; CV=cardiovascular; HOT=Hypertension Optimal Treatment trial; JPAD=Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI=myocardial infarction; N=number of participants; NZ=New Zealand; PHS=Physicians' Health Study; POPADAD= Prevention Of Progression of Arterial Disease And Diabetes; PPP=Primary Prevention Project; TPT=Thrombosis Prevention Trial; US=United States; WHS=Women's Health Study

The findings of the meta-analyses are summarised in Table 7 (cardiovascular events) and Table 8 (bleeds). According to these meta-analyses aspirin was consistently associated with a 12% or greater proportional reduction in the risk of a cardiovascular event compared with control, and the magnitude of this benefit was similar for men and women. There did not appear to be a difference in the effect of aspirin according to whether or not participants had diabetes, although the number of included participants with diabetes was small (4% across the six trials). Aspirin was associated with a statistically significant reduction in coronary

heart disease in men and ischaemic stroke in women. None of the meta-analyses demonstrated a statistically significant reduction in all-cause mortality with aspirin.

Table 7. Results for cardiovascular outcomes from meta-analyses used as the basis of NZ, Australian, US and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease

	Sanmuganathan 2001[62]	**Hayden 2002**[63]	**ATC 2009**[43]	**Berger 2006**[71]
Number of participants				
Overall	48,540	53,035	95,456	95,456
Women	8,831 (18%)	11,414 (22%)	51,290 (54%)	51,290 (54%)
Diabetes	2,137 (4%)	2,879 (5%)	3,906 (4%)	3,906 (4%)
Relative effect on cardiovascular events (95% CI))*				
Overall	**OR 0.85 (0.78 to 0.94)**	NR	**RR 0.88 (0.82 to 0.94)**	Not reported
Men	NR	NR	**RR 0.88 (0.78 to 0.98)**	**OR 0.86 (0.78 to 0.94)**
Women	NR	NR	RR 0.88 (0.76 to 1.01)	**OR 0.88 (0.79 to 0.99)**
Diabetes	NR	NR	RR 0.88 (0.67 to 1.15)	NR
No diabetes	NR	NR	**RR 0.87 (0.79 to 0.96)**	NR
Relative effect on coronary heart disease events† (95% CI)				
Overall	**OR 0.70 (0.62 to 0.79)**	**OR 0.72 (0.60 to 0.87)**	**RR 0.82 (0.75 to 0.90)**	NR
Men	NR	NR	**RR 0.77 (0.67 to 0.89)**	**OR 0.68 (0.54 to 0.86)**
Women	NR	NR	RR 0.95 (0.77 to 1.17)	OR 1.01 (0.84 to 1.21)
Diabetes	NR	NR	RR 0.95 (0.64 to 1.32)	NR
No diabetes	NR	NR	**RR 0.81 (0.71 to 0.92)**	NR
Relative effect on strokes‡ (95% CI)				
Overall	OR 1.06 (0.91 to 1.24)	OR 1.02 (0.85 to 1.23)	RR 0.95 (0.85 to 1.06)	NR
Men	NR	NR	RR 1.12 (0.91 to 1.37)	OR 1.13 (0.96 to 1.33)
Women	NR	NR	**RR 0.81 (0.66 to 0.99)**	**OR 0.83 (0.70 to 0.97)**
Diabetes	NR	NR	RR 0.82 (0.52 to 1.28)	NR
No diabetes	NR	NR	RR 0.96 (0.83 to 1.13)	NR
Relative effect on ischaemic strokes(95% CI)				
Overall	NR	NR	RR 0.86 (0.74 to 1.00)	NR
Men	NR	NR	RR 1.01 (0.74 to 1.39)	OR 1.00 (0.72 to 1.42)
Women	NR	NR	**RR 0.77 (0.59 to 0.99)**	**OR 0.76 (0.63 to 0.93)**
Diabetes	NR	NR	RR 0.81 (0.51 to 1.30)	NR
No diabetes	NR	NR	RR 0.90 (0.76 to 1.07)	NR
Relative effect on all-cause mortality (95% CI)				
Overall	OR 0.94 (0.85 to 1.04)	OR 0.93 (0.84 to 1.02)	RR 0.95 (0.88 to 1.02)	NR
Men	NR	NR	NR	OR 0.93 (0.85 to 1.03)
Women	NR	NR	NR	OR 0.94 (0.74 to 1.19)

ATC=Antithrombotic Trialists' Collaboration; CI=confidence interval; CVD=cardiovascular disease; NR=not reported; NZ=New Zealand; OR=odds ratio; RR=rate ratio; US=United States

* Cardiovascular events defined as myocardial infarction, stroke (including haemorrhagic) and cardiovascular deaths.

†Coronary heart disease events defined as myocardial infarction (fatal or nonfatal).

‡Strokes defined as fatal or nonfatal strokes of ischaemic, haemorrhagic or unknown cause.

Statistically significant findings in bold

Aspirin was consistently associated with an increase in the risk of major non-cerebral bleeds. The magnitude of the effect of aspirin on such bleeds appeared somewhat greater in the meta-analysis by Berger than the 2009 Antithrombotic Trialists' Collaboration, despite the inclusion of the same trials. There is a discrepancy between the number of major non-cerebral bleeds and haemorrhagic strokes recorded by each meta-analysis: 589 and 169, respectively, in Berger[71] and 554 and 205, respectively, in the Antithrombotic Trialists' Collaboration

2009 meta-analyses.[43] These differences could reflect differences between how meta-analyses extracted data or as a result of re-classification of events by the 2009 Collaboration, which had access to individual participant data.[43]

Table 8. Results for bleeding outcomes from meta-analyses used as the basis of NZ, Australian, US and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease

	Sanmuganathan 2001[62]	**ATC 2009**[43]	**Berger 2006**[71]
Number of participants			
Overall	48,540	95,456	95,456
Women	8,831 (18%)	51,290 (54%)	51,290 (54%)
Diabetes	2,137 (4%)	3,906 (4%)	3,906 (4%)
*Relative effect on major non-cerebral bleeds * (95% CI)*			
Overall	**OR 1.73 (1.14 to 2.63)**	**RR 1.54 (1.30 to 1.82)**	
Men	NR	**RR 1.56 (1.13 to 2.15)**	**OR 1.72 (1.35 to 2.20)**
Women	NR	**RR 1.52 (1.11 to 2.06)**	**OR 1.68 (1.13 to 2.52)**
Diabetes	NR	RR 1.10 (0.52 to 2.34)	NR
No diabetes	NR	**RR1.60 (1.27 to 2.03)**	NR
Relative effect on haemorrhagic stroke‡ (95% CI)			
Overall	NR	RR 1.32 (1.00 to 1.75)	NR
Men	NR	NR	**OR 1.69 (1.04 to 2.73)**
Women	NR	NR	OR 1.07 (0.42 to 2.69)

ATC=Antithrombotic Trialists' Collaboration; CI=confidence interval; NR=not reported; NZ=New Zealand; OR=odds ratio; RR=rate ratio; US=United States

*Major non-cerebral bleeds defined as bleed requiring transfusion or resulting in death.

Note: Hayden 2002[63] not included because they did not conduct their own meta-analysis on bleeding outcomes

Statistically significant findings in bold

The Australian[8] and European[10] guidelines for the primary prevention of cardiovascular disease specifically considered the role of aspirin for primary prevention among patients with diabetes (Table 2). Neither of the guidelines recommended aspirin for primary prevention among patients with diabetes, and the meta-analyses on which these recommendations were based are now discussed.

Calvin 2009

Calvin and colleagues sought to determine whether the effect of aspirin on cardiovascular events and mortality differed among patients with and without diabetes.[72] Their meta-analysis included data for 89,392 patients (11,624 with diabetes) from eight randomised controlled trials: the Antiphospholipid Antibody-Acetylsalicylic Acid trial[78], the Hypertension Optimal Treatment trial[66], the Early Treatment of Diabetic Retinopathy Study[77], the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial[80], the Physicians' Health Study[65], the Prevention of Progression of Arterial Disease and Diabetes trial[79], the Primary Prevention Project[83], and the Women's Health Study[76] (Table 9).[72]

Table 9. Randomised controlled trials included in meta-analyses supporting Australian and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease among patients with diabetes

	BDT[64]	**PHS**[65]	**ETDRS**[77]	**HOT**[66]	**TPT**[67]	**PPP***[83]	**WHS**[76]	**APLASA**[78]	**POPADAD**[79]	**JPAD**[80]
Year results published	1988	1989	1992	1998	1998	2003	2005	2007	2008	2008
Number of partici-pants	5,139	22,071	3,711	18,790	5,085	1,031	39,876	98	1,276	2,539
Number (%) with diabetes	101 (2.0%)	533 (2.4%)	3,711 (100%)	1,501 (8.0%)	68 (1.3%)§	1,031 (100%)	1,027 (2.6%)	6 (6.1%)	1,276 (100%)	2,539 (100%)
% with vascular disease†	8%‡	1%‡	49%	3%‡	<1%‡	4%‡	<1%‡	0%	0%	0%
% women	0%	0%	44%	47%	0%	52%	100%	90%	56%	45%
Aspirin	500mg daily	325mg alt days	650mg daily	75mg daily	75mg daily	100mg daily	100mg alt days	81mg daily	100mg daily	81 or 100mg daily
Control	No aspirin	Placebo	Placebo	Placebo	Placebo	No aspirin	Placebo	Placebo	Placebo	No aspirin
Additional randomly allocated treatment	Nil	Beta caro-tene	Nil	BP target¶	Warfa-rin	Vitamin E	Nil	Nil	Antioxidant	Nil
Duration, months	66.1 (mean)	60.2 (mean)	60 (mean)	45.6 (mean)	76.3 (mean)	44.4 (med-ian)	121.2 (mean)	27.6 (mean)	80.4 (median)	52.4 (med-ian)
Inclusion of trial by meta-analyses										
Calvin [72]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
De Berardis [73]	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Pignone[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Zhang [75]	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes

APLASA=Antiphospholipid Antibody-Acetylsalicylic Acid trial; BDT=British Doctors' Trial; BP=blood pressure; CVD=cardiovascular disease; ETDRS=Early Treatment of Diabetic Retinopathy Study; HOT=Hypertension Optimal Treatment trial; JPAD=Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial, PHS=Physicians' Health Study; POPADAD=Prevention of Progression of Arterial Disease and Diabetes trial; PPP=Primary Prevention Project; TPT=Thrombosis Prevention Trial; WHS=Women's Health Study
*Data extracted from the 2003 report of the Primary Prevention Project that focused on the effect of aspirin on patients with diabetes in the Primary Prevention Project.[83] The original trial report was published in 2001 and reported 289 fewer participants with diabetes.[68]
†Vascular disease defined as myocardial infarction, cerebrovascular disease, angina, peripheral arterial disease or heart failure.
‡Obtained from Antithrombotic Trialists' Collaboration 2009 individual participant data meta-analysis.[43]
§Obtained from Pignone 2010.[74]
¶All participants received felodipine with the addition of other BP-lowering agents according to a five-step regimen to achieve the randomly allocated target diastolic BP (≤90, ≤85 or ≤80 mm Hg).[66]

Four of these trials were included in previously discussed meta-analyses: the Hypertension Optimal Treatment trial,[66] the Physicians' Health Study,[65] the Primary Prevention Project[83] and the Women's Health Study[76]). Three of the additional trials were conducted solely in participants with diabetes: the Early Treatment of Diabetic Retinopathy Study,[77] the Prevention of Progression of Arterial Disease and Diabetes trial[79] and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial.[80] As

previously noted, the Antiphospholipid Antibody Acetylsalicylic Acid trial[78] and the Early Treatment Diabetic Retinopathy study[77] are not considered relevant to considering the effectiveness and safety of aspirin for primary prevention. The Antiphospholipid Antibody Acetylsalicylic Acid trial[78] was conducted in people with antiphospholipid syndrome, thereby limiting its generalisability. Almost half (49%) of the participants in the Early Treatment Diabetic Retinopathy study had established cardiovascular disease at baseline, and results were not presented separately according to the presence or absence of cardiovascular disease at baseline.[77]

Calvin and colleagues found no statistically significant reduction with aspirin on the risk of death (RR 0.97, 95% CI 0.87 to 1.08), myocardial infarction (RR 0.86, 95% CI 0.67 to 1.11) or ischaemic stroke (0.62, 95% CI 0.31 to 1.24) among patients with diabetes.[72] The confidence intervals associated with these risk estimates are wide, especially for ischaemic stroke, and Calvin and colleague noted "*the small number of included trials and the small number of events within these trials reduced the statistical power and therefore the precision of the estimates in our main analysis*".[72] They did not assess the effect of aspirin on bleeding among patients with diabetes because of the small number of events and risk of imprecise estimates.[72] Calvin and colleagues found no evidence of an interaction between the effect of aspirin and diabetes status in between-study subgroup, within-study subgroup or Bayesian randomised effects regression analyses.[72] They also found no evidence of such an interaction in sensitivity analyses in which data from the Antiphospholipid Antibody-Acetylsalicylic Acid trial and the Early Treatment of Diabetic Retinopathy Study were excluded.[72] Calvin and colleagues concluded that their "*estimates of benefit among patients with diabetes remain imprecise*" and that it appeared that the "*relative benefit of aspirin is similar in patients with and without diabetes*".[72]

De Berardis 2009

The meta-analysis by De Berardis and colleagues included data from 10,117 patients with diabetes, from six of the eight trials included in the meta-analysis by Calvin and colleagues (Table 9).[72 73] The two trials that were not included by De Berardis were the Hypertension Optimal Treatment trial[66] and the Antiphospholipid Antibody-Acetylsalicylic Acid trial.[78] The exclusion of the Antiphospholipid Antibody-Acetylsalicylic Acid trial is unlikely to have affected the findings given the small numbers of participants and events in that trial.[78] The Hypertension Optimal Treatment trial was not included because separate

results for people with diabetes were not found.[73] De Berardis found no statistically significant improvement with aspirin among people with diabetes for the prevention of major cardiovascular events (composite of cardiovascular death and nonfatal myocardial infarction and stroke, risk ratio, RR, 0.90, 95% CI 0.81 to 1.00), myocardial infarction (RR 0.86, 95% CI 0.61 to 1.21), stroke (RR 0.83, 95% CI 0.60 to 1.14) or all-cause mortality (RR 0.93, 95% CI 0.82 to 1.05).[73] There was also no statistically significant increase in gastrointestinal bleeding with aspirin among people with diabetes (RR 2.11, 95% CI 0.64 to 6.95).[73] Findings were "*not materially affected*" (no estimates supplied) when data from the Early Treatment of Diabetic Retinopathy Study were excluded.[73] De Berardis and colleagues found a significant reduction in the risk of myocardial infarction with aspirin among men (RR 0.57, 95% CI 0.34 to 0.94) but not in women with diabetes (RR 1.08, 95% CI 0.71 to 1.65).[73] Aspirin did not have a statistically significant effect on stroke among either men (RR 1.11, 95% CI 0.75 to 1.64) or women with diabetes (RR 0.75, 95% CI 0.37 to 1.53).[73] De Berardis and colleagues concluded that "*a clear benefit of aspirin in the primary prevention of major cardiovascular events in people with diabetes remains unproved*", that "*sex may be an important effect modifier*" and that "*toxicity is to be explored further*".

Pignone 2010

Pignone and colleagues conducted a meta-analysis of 11,787 patients with diabetes from nine randomised controlled trials.[74] All of the trials from Calvin and colleagues' meta-analysis were included with the following exceptions: Antiphospholipid Antibody-Acetylsalicylic Acid trial[78] excluded, British Doctors' Trial[64] and Thrombosis Prevention Trial[67] added (because of diabetes subgroup data provided by the Antithrombotic Trialists' Collaboration).[74] Pignone and colleagues found no statistically significant effect of aspirin on the risk of myocardial infarction among patients with diabetes (fatal and nonfatal, RR 0.91, 95% CI 0.79 to 1.05) or stroke (RR 0.85, 95% CI 0.66 to 1.11) and did not report any of their own analyses of bleeding outcomes.[74] They concluded that "*the effect of aspirin for primary prevention of cardiovascular disease events in adults with diabetes is currently unclear. Trials to date have reached mixed results, but overall suggest that aspirin modestly reduces risk of cardiovascular events*."[74] Pignone and colleagues recommended low-dose aspirin for adults with diabetes and no previous history of vascular disease with 10-year cardiovascular risk >10% and not at increased risk for bleeding.[74] This recommendation

was endorsed by the American Diabetes Association, American Heart Association and the American College of Cardiology Foundation.[74]

Zhang 2010

Zhang and colleagues included 11,618 patients in their meta-analysis from seven trials of aspirin in the primary prevention of cardiovascular disease.[75] As with the other meta-analyses of patients with diabetes, this meta-analysis included the following six trials: the Physicians' Health Study[65], the Early Treatment of Diabetic Retinopathy Study,[77], the Primary Prevention Project[83], the Women's Health Study[76], the Prevention of Progression of Arterial Disease and Diabetes trial[79] and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial[80].[75] Data from the Hypertension Optimal Treatment study[92] were also included,[75] as done by Calvin[72] and Pignone.[74] For patients with diabetes receiving aspirin, Zhang and colleagues found no statistically significant reduction of major cardiovascular events (cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke, RR 0.92, 95% CI 0.83 to 1.02) or major bleeding (not defined, RR 2.46, 95% CI 0.70 to 8.61).[75]

Summary of meta-analyses focusing on diabetes

Conclusions and limitations of the meta-analyses that were used as the basis of Australian and European guideline recommendations on the use of aspirin for primary prevention of cardiovascular events among patients with diabetes are summarised in Table 10 below. All of the meta-analyses are limited by their reliance on aggregate data, the inclusion of data from the Early Treatment of Diabetic Retinopathy Study (in which 49% of participants had established cardiovascular disease at baseline[77]) and the width of the confidence intervals associated with effect estimates. Data from Hypertension Optimal Treatment trial participants with diabetes were not included in the De Berardis meta-analysis.[73] The meta-analysis by Pignone[74] excluded data from participants receiving warfarin despite the lack of evidence of an interaction between aspirin and warfarin on the outcomes assessed.[67]

Table 10. Conclusions and limitations of meta-analyses used as the basis of Australian and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease among patients with diabetes

Meta-analysis (included trials)	**N**	**Conclusion**	**Limitations**
Calvin 2009[72] (PHS, ETDRS, HOT, PPP, WHS, APLASA, POPADAD, JPAD)‡	11,624	*"There are insufficient data among patients with diabetes to conclusively show a benefit for aspirin therapy for a primary prevention of cardiovascular events, our data suggest."*	-Based on aggregate data -Included ETDRS (49% of participants had CVD at baseline) -Wide confidence intervals
De Berardis 2009[73] (PHS, ETDRS PPP, WHS, POPADAD, JPAD)	10,117	*"A clear benefit of aspirin in the primary prevention of major cardiovascular events in the primary prevention of major cardiovascular events in people with diabetes remains unproved."*	-Based on aggregate data -Included ETDRS (49% of participants had CVD at baseline) -Wide confidence intervals -Following trial not included: HOT
Pignone 2010[74] (BDT, PHS, ETDRS, HOT, TPT, PPP, WHS, POPADAD, JPAD)	11,787	*"The effect of aspirin for primary prevention of cardiovascular disease events in adults with diabetes is currently unclear. Trials to date have reached mixed results, but overall suggest that aspirin modestly reduces risk of cardiovascular events."*	-Based on aggregate data -Included ETDRS (49% of participants had CVD at baseline) -Wide confidence intervals - Warfarin participants excluded despite no evidence of interaction
Zhang 2010[75] (PHS, ETDRS, HOT, PPP, WHS, POPADAD, JPAD)	11,618	*"In patients with diabetes, aspirin therapy did not significantly reduce the risk of cardiovascular events without an increased risk of major bleeding"*	-Based on aggregate data -Included ETDRS (49% of participants had CVD at baseline) -Wide confidence intervals

APLASA=Antiphospholipid Antibody-Acetylsalicylic Acid trial; BDT=British Doctors' Trial; CVD=cardiovascular disease; ETDRS=Early Treatment of Diabetic Retinopathy Study; HOT=Hypertension Optimal Treatment trial; JPAD=Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial; N=number of participants; PHS=Physicians' Health Study; POPADAD=Prevention of Progression of Arterial Disease and Diabetes trial; PPP=Primary Prevention Project; TPT=Thrombosis Prevention Trial; WHS=Women's Health Study

The findings of each of the meta-analyses for cardiovascular events are summarised in Table 11. The findings of the Antithrombotic Trialists' Collaboration for patients with diabetes are also included in the table because although their meta-analysis did not include the more recently published trials, they also did not include the Early Treatment of Diabetic Retinopathy Study (in which 49% of participants had established cardiovascular disease at baseline[77]).[43] None of the findings are statistically significant and the confidence intervals are wide. Across meta-analyses the point estimates of the relative effect of aspirin among people with diabetes ranged from 0.88 to 0.92 (cardiovascular events), 0.85 to 0.95 (coronary heart disease), 0.82 to 0.85 (stroke) and 0.93 to 0.97 (all-cause mortality). There is no obvious difference in the effect of aspirin according to diabetes status.

Table 11. Results for cardiovascular outcomes from meta-analyses used as the basis of Australian and European guideline recommendations on the use of aspirin in the primary prevention of cardiovascular disease among patients with diabetes

RR (95% CI)	**Calvin 2009**[72] (N=11,624)§	**De Berardis 2009**[73] (N=10,117)	**Pignone 2010**[74] (N=11,787)	**Zhang 2010**[75] (N=11,618)	**ATC 2009**[43] (N=3,906)
CVD*	NR	0.90 (0.81 to 1.00)	NR	0.92 (0.83 to 1.02)	0.88 (0.67 to 1.15)
CHD†	0.86 (0.67 to 1.11)	0.86 (0.61 to 1.21)	0.91 (0.79 to 1.05)	0.85 (0.65 to 1.11)	0.95 (0.64 to 1.32)
Stroke‡	NR	0.83 (0.60 to 1.14)	0.85 (0.66 to 1.11)	0.83 (0.63 to 1.10)	0.82 (0.52 to 1.28)
Mortality	0.97 (0.87 to 1.08)	0.93 (0.82 to 1.05)	NR	0.95 (0.85 to 1.06)	NR

CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; N=number of participants; NR=not reported; RR=risk ratio

*CVD defined as myocardial infarction, stroke (including haemorrhagic) and cardiovascular deaths.

†CHD defined as myocardial infarction (fatal or nonfatal).

‡Strokes defined as fatal or nonfatal strokes of ischaemic, haemorrhagic or unknown cause (unless otherwise specified).

§Data from text (discrepancy between data in text and Forest plots).

Hernandez-Diaz 2006

The final reference, by Hernandez-Diaz and Garcia Rodriguez,[81] was used to support United States guideline recommendations on the use of aspirin in primary prevention.[21] Hernandez-Diaz and Garcia Rodriguez estimated the number of additional people who would experience a serious upper gastrointestinal tract complication (bleeding, perforation or other serious upper gastrointestinal tract event resulting in hospitalisation or visit to a specialist) as a result of taking aspirin.[81] Separate estimates were provided for subgroups according to their age (20-60, 60-69, 70-79 and >80 years), sex, prior history of gastrointestinal disease (none, upper gastrointestinal pain, history of uncomplicated gastrointestinal ulcer and history of complicated gastrointestinal ulcer), and concomitant use of non-aspirin non-steroidal anti-inflammatory drugs.[81] Their estimates were based on a number of assumptions regarding the incidence of serious upper gastrointestinal tract complication (based on observational evidence), and their assumptions have been compared with the findings of the Antithrombotic Trialists' Collaboration meta-analysis (Table 12). As can be seen, there is a strong degree of concordance between the assumptions of Hernandez-Diaz and Garcia Rodriguez and the findings of the Antithrombotic Trialists' Collaboration, despite the differences in their methods. The Antithrombotic Trialists' Collaboration did not assess the effect of a history of gastrointestinal disorders or the concomitant use of a non-aspirin non-steroidal anti-inflammatory agents on bleeding rates so Hernandez-Diaz and Garcia Rodriguez's assumptions could not be tested against their findings in this regard. Hernandez-Diaz concluded that underlying gastrointestinal risk, as well as cardiovascular risk, need to be considered when balancing the benefits and harms of aspirin for an individual patient.[81]

Table 12. Assumptions of Hernandez-Diaz 2006 regarding the incidence of, and risk factors, for major bleeds, and comparison with findings of the Antithrombotic Trialists' Collaboration 2009 individual participant data meta-analysis of randomised controlled trials of aspirin in the primary prevention of cardiovascular disease

Hernandez-Diaz 2006[81]		**Findings of the ATC 2009 meta-analysis**[43] **for major non-cerebral, mainly GI, bleeds**
Assumptions	**Evidence**	
Baseline incidence approximately 1 per 1,000 person-years	Systematic review (observational studies 1980 to 2000)[93]	Mean incidence in control group 0.7 per 1,000 person-years
Incidence (per 1,000 person-years): <1 until 60 years, over 5 from 85 years	Case control study (2001, data from United Kingdom General Practice Research Database)[94]	Rate ratio for each additional decade 2.15 (95% CI 1.93 to 2.39) (after adjusting for aspirin allocation, age, diabetes, smoking, BP, cholesterol and BMI). Incidence 0.7 per 1,000 person-years for people aged 51 to 60 years (around the mean age of 56), incidence for older age groups would be (per 1,000 person-years): 61 to 70 years: 1.5; 71 to 80 years: 3.2; 81 to 90 years: 7.0
Incidence in men is double that among women		Rate ratio for men 1.99 (95% CI 1.45 to 2.73) (after adjusting for aspirin allocation, age, diabetes, smoking, BP, cholesterol and BMI)
GI history: none (RR 1), upper GI pain (RR 2), GI ulcer uncomplicated (RR 6), complicated (RR 10)		Not assessed
NSAID + GI history: no GI history (RR 4), upper GI pain (RR 3), GI ulcer (RR 2.5)	Systematic review (observational studies 1990 to 1999)[95]	Not assessed
Aspirin RR 2	Systematic review (observational studies 1990 to 1999)[95] and Case control study (2001, data from United Kingdom General Practice Research Database)[94]	Rate ratio 1.54 (95% CI 1.30 to 1.82) and no heterogeneity according to age, sex, history of diabetes, history of hypertension, smoking status, BP, cholesterol, BMI or predicted 5-year risk of CHD

ATC=Antithrombotic Trialists' Collaboration; BMI=body mass index; BP=blood pressure; CHD=coronary heart disease; CI=confidence interval; GI=gastrointestinal; NSAID=non-steroidal anti-inflammatory; RR=rate ratio

2.3.4. Balancing the benefits and harms of aspirin

New Zealand guidelines recommend aspirin for high-risk primary prevention people after "*taking into account harms and benefits*" but provide no specific guidance on how harms should be taken into account.[7] The 2005 guideline notes that aspirin <300 mg/day doubles the risk of upper gastrointestinal bleeding/perforation (attributed to Garcia Rodriguez 2001[96] in the 2003 guideline[36]), and is associated with an absolute excess of approximately two intracranial and one to two extracranial haemorrhages per 1000 people treated per year.[53] The 2003 guidelines states that "*the cardiovascular benefits of low-dose aspirin outweigh the harm in people with a 5-year cardiovascular risk greater than 15%"* and this statement is based on the meta-analyses by Sanmuganathan 2001[62] and Hayden 2002.[63] As noted, the assumption by Sanmuganathan and colleagues that absolute bleeding risk is independent of absolute cardiovascular risk does not appear to be valid. In the latest

guidelines the threshold for considering aspirin in primary prevention has been increased from 15 to 20% but the justification for this change has not been provided.[7]

The United States Preventive Services Task Force recommendation is to "*encourage men age 45 to 79 years* [women age 55 to 79 years] *to use aspirin when the potential benefit of a reduction in myocardial infarction* [ischemic strokes in women] *outweighs the potential harm of an increase in gastrointestinal hemorrhage*".[21] The lower age limits (45 years for men and 55 years for women) were selected because of limited evidence on the benefits of aspirin in younger people and their limited potential to benefit because of the strong association between absolute cardiovascular risk and age.[21] The upper age limit (79 years) was selected as although absolute cardiovascular increases with age, bleeding risk also increases with age.[21] The United States Preventive Services Task Force noted that the benefits of aspirin might outweigh harms in people aged 80 years and older without other risk factors for gastrointestinal bleeding (apart from age) and who could tolerate a gastrointestinal bleed (e.g. because of normal haemoglobin level and good kidney function).[21] In order to facilitate balancing the benefits and harms of aspirin among men aged 45 to 79 years and women aged 55 to 70 years, the United States Preventive Services Task Force produced tables of the likely number of cardiovascular events (myocardial infarctions for men and strokes for women) avoided and additional bleeds caused by aspirin in primary prevention, by age group and sex (Figure 8).[21]

The United States Preventive Services Task Force assumed that the proportional effect of aspirin on coronary heart disease in men (32% reduction) and strokes in women (17% increase) were as estimated by Berger and colleagues.[71] They noted that decisions regarding the use of aspirin in primary prevention would depend on how individuals valued the benefit of avoiding cardiovascular events and their level of concern regarding having a bleed, and therefore that shared decision making (between individuals and their health care provider) "*should be encouraged*" when the potential benefits and harms of aspirin are more closely balanced.[21] The applicability of these tables to other contexts is limited because they are stratified by absolute risk of coronary heart disease and stroke, rather than the composite of cardiovascular risk, which is the basis of management decisions in guidelines such as those from New Zealand[7] and Australia.[17]

Figure 8. United States Preventive Services Task Force tables comparing benefits and harms of aspirin in primary prevention

Variable	Estimated MIs Prevented (per 1000 Men), *n*		
	Age 45–59 Years	Age 60–69 Years	Age 70–79 Years
10-year CHD risk			
1%	3.2	3.2	3.2
2%	6.4	6.4	6.4
3%	9.6	9.6	9.6
4%	12.8	12.8	12.8
5%	16	16	16
6%	19.2	19.2	19.2
7%	22.4	22.4	22.4
8%	25.6	25.6	25.6
9%	28.8	28.8	28.8
10%	32	32	32
11%	35.2	35.2	35.2
12%	38.4	38.4	38.4
13%	41.6	41.6	41.6
14%	44.8	44.8	44.8
15%	48	48	48
16%	51.2	51.2	51.2
17%	54.4	54.4	54.4
18%	57.6	57.6	57.6
19%	60.8	60.8	60.8
20%	64	64	64
	Estimated Harms, *n*		
Type of event			
GI bleeding	8	24	36
Hemorrhagic stroke	1	1	1

Variable	Estimated Strokes Prevented (per 1000 Women), *n*		
	Age 55–59 Years	Age 60–69 Years	Age 70–79 Years
10-year stroke risk			
1%	1.7	1.7	1.7
2%	3.4	3.4	3.4
3%	5.1	5.1	5.1
4%	6.8	6.8	6.8
5%	8.5	8.5	8.5
6%	10.2	10.2	10.2
7%	11.9	11.9	11.9
8%	13.6	13.6	13.6
9%	15.3	15.3	15.3
10%	17	17	17
11%	18.7	18.7	18.7
12%	20.4	20.4	20.4
13%	22.1	22.1	22.1
14%	23.8	23.8	23.8
15%	25.5	25.5	25.5
16%	27.2	27.2	27.2
17%	28.9	28.9	28.9
18%	30.6	30.6	30.6
19%	32.3	32.3	32.3
20%	34	34	34
	Estimated Harm, *n*		
Type of event			
GI bleeding	4	12	18

CHD=coronary heart disease; GI=gastrointestinal; MI=myocardial infarction
Note: The shaded areas indicate the combinations of 10-year CHD risk, age and sex for which the number of harms (GI bleeding and haemorrhagic stroke, latter in men only) are greater than or approximately equal to the number of MIs (men) or strokes (women) prevented.
Assumptions: Aspirin associated with the following relative risk reduction: 32% (MI in men) and 17% (strokes in women, taking into account haemorrhagic strokes) (from Berger 2006[71]) and patients have no upper GI pain or history of GI ulcer and are not taking non-aspirin non-steroidal anti-inflammatory drugs.
Source: United States Preventive Services Task Force[21]

An individualised bleeding risk assessment tool has been developed by Lanas and colleagues (http://servidor.lya2.es/calculadora/).[97] After inputting requested risk factor information an individualised estimate of the absolute risks of a coronary event and gastrointestinal complication both with and without aspirin are provided.[97] Bleeding risk is estimated by age, sex, ulcer history and concomitant medications (clopidogrel, warfarin and proton pump inhibitor).[97] Estimates of the relative effect of individual risk factors on bleeding have been obtained from a variety of sources (observational and experimental).[97] The joint effect of combinations of risk factors is assumed to be product of the relevant risk ratios (i.e. a multiplicative effect[44])[97] but the validity of this assumption is unclear.

Cuzick and colleagues modelled the benefits (reduction in cardiovascular disease and cancer) and harms (bleeding) of taking aspirin for 10 years according to sex and age group.[98] They found that for 'average-risk' individuals aged 50-65 years the number of cardiovascular events and cancers averted was greater than major extracranial bleeds caused (incidence

model).[98] They also found that the number of deaths avoided (through a reduction in cancer and myocardial infarction mortality) exceeded the number of deaths caused (through an increase in fatal strokes, gastrointestinal bleeds and peptic ulcers) (mortality model).[98] For both models national (United Kingdom) collections were used as estimates of the untreated incidence and mortality of cardiovascular disease and cancer.[98] Sex and age group-specific 'untreated' rates for major extracranial bleeding were obtained from the control groups in the Antithrombotic Trialists' Collaboration 2009 meta-analysis (for the incidence model) and for gastrointestinal bleeding and peptic ulcer were obtained from observational data (for the mortality model).[98] Although Cuzick and colleagues have taken into account age and sex, bleeding estimates are for those of 'average-risk' within sex and age groups, and are therefore not able to estimate individual cardiovascular or bleeding risk.

2.3.5. Findings

A number of findings emerged regarding the effectiveness and safety of aspirin for primary prevention from this review of the evidence that underpins current international guidelines:

Benefits of aspirin for primary prevention

1. Aspirin is associated with a reduction in the risk of cardiovascular disease, coronary heart disease (in men) and ischaemic strokes (in women). The magnitude of this proportional reduction is in the order of 12% for cardiovascular disease, 23-32% for coronary heart disease in men and 23-24% for ischaemic strokes in women.
2. There is no evidence of heterogeneity in the proportional effect of aspirin on cardiovascular disease according to age, sex, history of vascular disease, history of diabetes, history of hypertension, smoking status, blood pressure, cholesterol, body mass index or estimated 5-year risk of coronary heart disease.
3. Absolute risk of a first cardiovascular event varies (independently and after adjusting for aspirin allocation) according to age, sex, smoking status, blood pressure, cholesterol and body mass index.
4. The absolute reduction in cardiovascular events therefore appears to depend primarily on baseline absolute risk of cardiovascular disease.

Harms of aspirin for primary prevention

1. Aspirin is associated with an increase in the risk of major non-cerebral (mainly gastrointestinal) bleeds and haemorrhagic strokes. The magnitude of this proportional

harm is in the order of 54% for major non-cerebral bleeds and 32% for haemorrhagic stroke.

2. There is no evidence of heterogeneity in the proportional effect of aspirin on major non-cerebral bleeding according to age, sex, history of vascular disease, history of diabetes, history of hypertension, smoking status, blood pressure, cholesterol, body mass index or estimated 5-year risk of coronary heart disease.
3. Absolute risk of a major non-cerebral bleed varies (independently and after adjusting for aspirin allocation) according to age, sex, smoking status, blood pressure and body mass index.
4. The absolute increase in major non-cerebral bleeds therefore appears to depend primarily on baseline absolute risk of a major non-cerebral bleed.

Given these findings, the current New Zealand guidelines[7] are difficult to implement because a method for estimating bleeding risk with aspirin is not provided. The United States recommendations[21] provide a method for estimating bleeding risk but that method is limited because of the number of risk factors considered. The Australian[8] and European[10] guidelines have taken a conservative position and decided not to recommend the use of aspirin in primary prevention, despite current evidence supporting benefits outweighing harms in some subgroups (according to absolute risk, age and sex).

With the variation in conclusions reached by the different meta-analyses and guidelines, it is important to systematically search for all existing meta-analyses and any subsequent randomised controlled trials to appraise if there are any changes to the current state of evidence around the use of aspirin for primary prevention. This systematic review and critical appraisal was conducted and is described in the first half of chapter 3.

Despite the preponderance of cardiovascular risk assessment tools, individualised bleeding risk assessment is less well developed.[7 21] Of the three tools described, only the United States Preventive Services Task Force tables are currently incorporated in national guidelines.[21] Lanas and colleagues calculator, while incorporating other important risk factors besides sex and age, has potential methodological limitations.[97] Cuzick and colleagues, while incorporating the benefits of aspirin in terms of reducing cancer, have provided an ‘average risk’ that does not support individualised assessment.[98] Ideally a validated clinical prediction model would be available for estimating an individual’s risk of bleed with aspirin, such as the QBleed tool recently published by Hippisley-Cox and

Coupland for anticoagulants.[99] In the absence of such a tool for aspirin in primary prevention, modelling 5-year cardiovascular risk and incorporating updated proportional estimates of the reduction in cardiovascular events and increase in major non-cerebral bleeds with aspirin, based on the methodology used by the United States Preventive Services Task Force, may assist in determining the balance of benefits and harms of aspirin in primary prevention in New Zealand. This modelling was conducted and is described in the second half of chapter 3.

2.4. Effectiveness of aspirin for the primary prevention of cancer

The situation is further complicated because there is a growing body of evidence regarding the potential benefit of aspirin in the prevention of cancer, an effect that becomes apparent over a longer time-frame than aspirin's effect on cardiovascular disease.[23] Rothwell and colleagues have conducted a series of meta-analyses of cancer outcomes from randomised controlled trials originally designed to assess the effect of daily aspirin on cardiovascular outcomes.[22-24]

One meta-analysis of trials including 14,033 people who were treated with aspirin over a mean duration of six years, found that aspirin was associated with a 35% reduction (95% CI 12% to 52%) in 20-year risk of death from colon cancer.[24] Another meta-analysis included 25,570 people from trials with mean duration of at least four years' of treatment with aspirin. This study found that aspirin was associated with a 21% reduction (95% CI 8% to 32%) in cancer mortality during trial follow-up.[22] A third meta-analysis including 69,224 people from trials with a duration of aspirin treatment of at least three months found that aspirin was associated with a 15% reduction (95% CI 4% to 24%) in cancer mortality during trial follow-up, with most benefit after five years' follow-up (33% reduction in cancer mortality, 95% CI 18% to 51%).[23]

The effect of aspirin on the primary prevention of cancer was not included in the modelling conducted in this thesis because cancer was not a pre-specified outcome in the trials included in the meta-analyses. Trials that have prospectively planned to assess the effect of aspirin on cancer are underway, and these will provide more robust evidence of the effect of aspirin on cancer over five years or more.[100-103]

2.5. Effectiveness and safety of a cardiovascular polypill

2.5.1. Concept

The term 'polypill' was popularised by Wald and Law in 2003 with the publication of their paper "*A strategy to reduce cardiovascular disease by more than 80%*".[27] A patent application for the polypill proposed by Wald and Law (aspirin, statin, three blood pressure lowering drugs [each at half standard dose] and folic acid) was filed in 2000.[27] The most well-known cardiovascular prevention strategy utilising a polypill, as proposed by Wald and Law, is for everyone above a certain age (e.g. 55 years) to receive a polypill, without the need for measuring risk factors such as low density lipoprotein cholesterol or blood pressure.[27] The other polypill cardiovascular prevention strategy is for its use among people with established cardiovascular disease.[27 28] This use of the polypill appears to have been first proposed in 2001, during a World Health Organization meeting of international experts to discuss strategies for the secondary prevention of non-communicable diseases.[28] One of ten recommendations arising from that meeting was the development of a daily fixed-dose combination pill containing aspirin, statin and two blood pressure lowering agents, for people with established cardiovascular disease.[28] The experts considered that such a pill could potentially help address suboptimal implementation of guidelines and poor patient adherence.[28] The focus of this thesis is on the use of the polypill among those with established cardiovascular disease, in addition to those at high risk of cardiovascular disease who are also recommended for treatment with the components of the polypill according to New Zealand guidelines.[7]

Potential advantages of a polypill-based strategy among people at high risk of cardiovascular disease include, as noted above, improved implementation of guidelines and patient adherence.[104] A 2009 survey of general practitioners from different regions in New Zealand identified simplicity and convenience, along with improved compliance, to be the major potential advantages of a polypill-based strategy.[105] Potential benefits of a polypill reported among patients from a random selection of Auckland pharmacies in 2010 were convenience (simple regimen, ease of use when travelling, time-saving), less confusion regarding medication regimen and fewer tablets to take.[106]

It has also been suggested that a polypill may reduce costs through the use of generic components, a reduction in packaging, distribution and marketing costs, and a reduction in

physician visits and laboratory tests.[104] Reduced cost would make the polypill very attractive to low-income countries, where the burden of cardiovascular disease is increasing and current access to many (patented) cardiovascular medications is limited due to their cost.[107] [108] [109] The use of off-patent multi-drug regimens including blood pressure lowering and statin therapy by individuals with established cardiovascular disease or at high absolute risk could potentially avert nearly 18 million deaths over 10 years in low- and middle-income countries.[110] The average cost per treated individual, including programme set-up, screening, risk assessment and medications (blood pressure lowering, statin and low dose aspirin), has been estimated to be US$55 per annum.[110] Cost is also an identified barrier to medication adherence in New Zealand, where 6.4% of respondents in a nationally representative survey conducted from 2004 to 2005 indicated that they had deferred paying for a prescription in the preceding 12 months because they could not afford it.[111] An Australian review of preventive health strategies included the polypill as one of a limited number of cost-effective strategies that could have a large impact on population health.[112]

Potential disadvantages of the polypill are the lack of ability to titrate doses of the different components, uncertainty regarding the cause of a side effect when different medications are initiated simultaneously, failure to achieve treatment targets in people with high levels of individual risk factors, and the risk that lifestyle behaviours will deteriorate if a polypill is perceived as a panacea.[113] New Zealand general practitioners surveyed regarding the polypill saw the main disadvantage of this intervention as the lack of choice regarding components and doses.[105] The following concerns were raised by Auckland patients interviewed regarding the polypill: the efficacy of the product (whether the polypill was supported by published evidence and their own practitioner, its equivalence to their current medications and the reputability of the manufacturer); inflexibility of formulation and dose; the size of the tablet; and its safety.[106]

Two main types of randomised controlled trials have assessed the effectiveness and/or safety of the polypill: (1) those that have compared the polypill with an inactive control, in people without indications for any of the components of the polypill, and (2) those that have compared the polypill with an active control, in people with indications for all of the components of the polypill.

2.5.2. Trials comparing polypill with inactive control

A 2012 meta-analysis by Elley and colleagues included randomised controlled trials of a polypill containing at least one statin and one blood pressure lowering agent compared with a placebo (or one active component) for at least six weeks.[114] Six trials (with a combined total of 2,218 participants) were identified: The Indian Polycap Study (TIPS),[115] Neutel 2009,[116] Malekzadeh 2010,[117] Grimm 2010,[118] Programme to Improve Life and Longevity (PILL) Collaborative Group 2011[51] and Wald 2012[119]. Compared with the control group, systolic blood pressure (-9.2 mm Hg, 95% CI -13.4 to -5 mm Hg) and low density lipoprotein cholesterol (-1.02 mmol/L, -1.37 to -0.67) were reduced in the polypill group.[114] While both of these outcomes were associated with high levels of heterogeneity, the authors of the meta-analysis considered that this was unsurprising given that, as with real life, there were a variety of clinical settings and populations in the included trials.[114] Further, effect sizes were similar in random-effects models (based on observed between-trial heterogeneity) and quality-effects models (based on measured methodological heterogeneity between studies).[114 120] Medication discontinuation was more frequent in the polypill than the control group (20% vs 14%, OR 1.5, 95% CI 1.2 to 1.9).[114] There was no statistically significant difference between the groups in reported adverse effects (36% polypill vs 28% control, OR 1.5, 95% CI 0.7 to 2.5).[114]

A 2013 Cochrane meta-analysis by de Cates and colleagues included randomised controlled trials of a polypill containing at least one statin and one blood pressure lowering agent compared with usual care, placebo or a single drug comparator.[121] Nine trials (with a combined total of 7,047 participants) were included: the same six trials as included in the Elley et al 2012 meta-analysis with the addition of three trials comparing a polypill with usual care: Soliman 2011,[122] Cluster Randomized Usual care vs. Caduet Investigation Assessing Long-term-risk (CRUCIAL) 2011[123] and Use of a Multi-drug Pill In Reducing cardiovascular Events (UMPIRE) 2013.[124] The trials comparing the polypill with usual care are discussed below. Three of the analyses did not include trials where the comparator was usual care: where the outcome was discontinuation, increased liver chemistries and bleeding.[121] The polypill was associated with more treatment discontinuation than control, but the effect was not as pronounced in the meta-analysis of de Cates et al (14% vs 11%, RR 1.26, 95% CI 1.02 to 1.55[121]) as in the meta-analysis of Elley et al (20% vs 14%, OR 1.5, 95% CI 1.2 to 1.9[114]). This was primarily because of differences between meta-analyses in how the numbers of participants that discontinued trial treatment from the Malekzadeh 2010

trial[117] were derived. De Cates found no difference between groups in elevated liver chemistries (RR 1.01, 95% CI 0.72 to 1.43).[121] Bleeding was more common in the polypill than the control group but this outcome was only reported by one trial and numbers were small (4 vs 1, RR 4.00, 95% CI 0.45 to 35.46).[121]

No additional trials comparing a polypill with an inactive control have been completed to date based on a search of clinicaltrials.gov on 18 October 2014 or according to recent polypill review articles.[121 125 126] The third International Polycap Study (TIPS-3) is currently recruiting participants to a randomised 2x2x2 factorial design placebo-controlled trial evaluating three interventions: Polycap, aspirin 75mg and vitamin D.[102 103] The Polycap is a polypill containing simvastatin 40mg and three blood pressure lowering agents (hydrochlorothiazide 25mg, atenolol 100mg and ramipril 10mg).[102] The recruitment target is 5,000 participants and results are expected in 2020.[103]

2.5.3. Trials comparing polypill with an active control

The Fixed Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) trial compared a polypill (aspirin 100mg, simvastatin 40mg, ramipril 2.5-10mg) with the three components separately for nine months among 695 patients who had experienced a myocardial infarction within the preceding two years.[127] The primary outcome was 'good adherence', defined as a score of 20 out of 20 on the Morisky-Green questionnaire as well as a pill count of 80-110%.[128] After nine months a greater proportion of polypill than control participants were classified as having good adherence (51% vs 41%, p=0.02).[128] There was no statistically significant difference between groups in blood pressure or low density lipoprotein cholesterol.[128] Serious adverse events were reported by 7% of polypill and 6% of control participants.[128]

Five randomised controlled trials have been completed to date in which a polypill (containing at least two of the following components: aspirin, statin, blood pressure lowering agent) has been compared with usual care: Soliman 2011,[122] Cluster Randomized Usual care vs. Caduet Investigation Assessing Long-term-risk (CRUCIAL) 2011,[123] Use of a Multi-drug Pill in Reducing Cardiovascular Events (UMPIRE) 2013,[124] Kanyini Guidelines Adherence with the Polypill (Kanyini GAP) 2014[129] and IMProving Adherence using Combination Therapy (IMPACT) 2014.[130] Key features of the trials are summarised in Table 13 below.

Table 13. Key features of randomised controlled trials that have compared a cardiovascular polypill with usual care

Trial	Location	Setting	Main inclusion criteria	Polypill components	N	Follow-up (months)
Soliman 2011[122]	Sri Lanka	Tertiary care	10-year CVD risk 20%+, no CVD	Aspirin 75mg, Simvastatin 20mg, Lisinopril 10mg, HCTZ 12.5mg	216	3
CRUCIAL 2011[123]	Asia, Europe, Latin America, Middle East	Primary or secondary care	4+ CVD risk factors including hypertension, no CHD	Amlodipine (5 or 10mg), Atorvastatin (10 or 20mg)	1,461	12
UMPIRE* 2013[124]	Europe, India	Mainly secondary care	5-year CVD risk 15%+, either with or without CVD	Aspirin 75mg, Simvastatin 40mg, Lisinopril 10mg, (HCTZ 12.5mg or Atenolol 50mg)	2,004	15 (median)
Kanyini-GAP* 2014[129]	Australia	Primary care			623	18 (median)
IMPACT* 2014[130]	New Zealand	Primary care			513	23 (median)

CHD=coronary heart disease; CRUCIAL=Cluster Randomized Usual care vs. Caduet Investigation Assessing Long-term-risk; CVD=cardiovascular disease; HCTZ=hydrochlorothiazide; IMPACT=IMProving Adherence using Combination Therapy; Kanyini GAP=Kanyini Guidelines Adherence to the Polypill; N=number of participants; UMPIRE= Use of a Multi-drug Pill in Reducing Cardiovascular Events

*Part of SPACE (Single Pill to Avert Cardiovascular Events) Collaboration, which has prospectively planned to undertake a meta-analysis of their combined results.[131]

Soliman 2011

The trial by Soliman and colleagues was a feasibility study that sought to assess the efficacy, safety and acceptability of the polypill among patients at high risk of a first cardiovascular event.[122] Participants were recruited from three tertiary hospital sites in Sri Lanka and received a polypill (containing aspirin 75mg, simvastatin 20mg, lisinopril 10mg and hydrochlorothiazide 12.5mg) or usual care for three months.[122] The trial found no statistically significant difference in estimated 10-year cardiovascular risk (the primary outcome), systolic blood pressure or total cholesterol between the polypill and usual care groups.[122] Between baseline and end of trial the investigators noted large improvements in systolic blood pressure (-29 mm Hg polypill vs -27 mm Hg usual care) and total cholesterol (-1.4 mmol/L vs -1.0 mmol/L) in both treatment groups.[122] They considered that usual care participants had "*received an unusually high level of care after randomization, which, in turn, raised this study group's level of risk factor intervention to the level of the Polypill group*".[122] Soliman and colleagues noted that over 80% of participants randomised to the polypill "*demonstrated >80% adherence to the pill*", although it is unclear how adherence was assessed.[122] The most commonly reported side effects were musculoskeletal pain (27% polypill vs 28% usual care), cough (26% vs 17%) and epigastric pain (19% vs 16%). The main difference between the groups in reported side effects was that more polypill than usual care participants reported cough, although this difference did not reach statistical

significance (p=0.14).[122] Most participants (86% polypill and 93% usual care) said they would 'definitely' or 'probably' take the polypill for life if it were shown to reduce cardiovascular risk.[122] Likewise, most physicians agreed ('yes, definitely' or 'yes, probably') that they would prescribe the polypill for primary (86%) or secondary (93%) prevention if it was shown to reduce cardiovascular risk in large clinical trials.[122]

CRUCIAL 2011

The Cluster Randomized Usual care vs. Caduet Investigation Assessing Long-term-risk (CRUCIAL) trial compared a polypill containing amlodipine (5 or 10mg) and atorvastatin (10 or 20mg) with usual care among patients with no history of coronary heart disease but at moderate cardiovascular risk (based on having at least four cardiovascular risk factors).[123] Some participants had cerebrovascular disease (stroke or transient ischaemic attack, 14%) or peripheral vascular disease (23%) at baseline.[123] The investigators found a greater reduction in mean Framingham 10-year coronary heart disease risk over one year (the primary outcome) in the polypill compared with the usual care group among participants included in the analysis (difference in least squares mean -27% , 95% CI -32 to -23%).[123] There were also statistically significant reductions in blood pressure, total cholesterol and low density lipoprotein cholesterol over a year in the polypill compared with the usual care groups among participants included in the analysis.[123] Serious adverse events were reported among 7% of polypill and 3% of usual care participants.[123] Investigators reported that 6.7% of polypill and 0.6% of usual care participants had a serious adverse event that resulted in permanent study discontinuation.[123] However, findings from this trial are at high risk of bias because the analysis did not use intention to treat principles (when all participants are analysed in the group to which they were randomised, regardless of any departures from randomised treatment[132]), large amounts of data were missing (14% of participants originally randomised did not complete the trial) and missing data were handled by carrying the last observation forward (an imputation method that may introduce bias[133]).

SPACE Collaboration

Use of a Multi-drug Pill in Reducing Cardiovascular Events (UMPIRE) 2013,[124] Kanyini Guidelines Adherence with the Polypill (Kanyini GAP) 2014[129] and IMProving Adherence using Combination Therapy (IMPACT) 2014[130] are part of the SPACE (Single Pill to

Avert Cardiovascular Events) Collaboration, which has prospectively planned to undertake a meta-analysis of their combined results[131] (results to be published). The three trials used very similar inclusion criteria and primary outcomes, and the same polypill. The main inclusion criteria were established cardiovascular disease or estimated 5-year risk of cardiovascular disease of 15% or greater.[131] The primary outcomes were self-reported use of the combination of an antiplatelet, statin and two or more blood pressure lowering agents, and change in blood pressure and cholesterol.[131] The polypill (called the Red Heart Pill) contained aspirin 75mg, simvastatin 40mg, lisinopril 10mg and either atenolol 50mg or hydrochlorothiazide 12.5mg.[131] Further information regarding the design and results of the UMPIRE and Kanyini-GAP trials is outlined below. The IMPACT trial forms part of this thesis and is discussed in detail in chapters 4-6.

UMPIPRE 2013

The UMPIRE trial randomised a total of 2004 participants from India (n=1000) and Europe (England, Ireland and the Netherlands) (n=1004) to polypill-based care or usual care for a median of 15 months.[124] Participants from India were recruited from hospital specialist clinics and participants from Europe were recruited from research databases, hospital clinics and general practice registries.[124] The polypill was dispensed six-monthly from the trial centre free of charge.[124] Participants in the usual care group continued to receive their medication according to local dispensing schedules (usually three-monthly) and payments.[124] Most participants (85%) had established cardiovascular disease, and 62% reported using combination medication (antiplatelet, statin and two or more blood pressure lowering agents) at baseline.[124] Self-reported use of combination medication increased to 86% in the polypill compared with 65% in the usual care group at trial end (RR 1.33, 95% CI 1.26 to 1.41, $p<0.001$).[124] Polypill-based care was associated with a reduction in both systolic blood pressure (-2.6 mm/Hg, 95% CI -4.0 to -1.1, $p<0.001$) and low density lipoprotein cholesterol (-0.11 mmol/L, 95% CI -0.17 to -0.05, $p<0.001$) over trial duration compared with usual care.[124] There was no statistically significant difference between the groups in the number of participants who experienced at least one serious adverse event during the trial (polypill 11.8% vs usual care 10.2%, p value not provided).[124]

Kanyini-GAP 2014

The Kanyini-GAP trial randomised 623 participants from Australian general practice to polypill-based care or usual care for a median of 18 months.[129] Half of the participants (51%) were of indigenous ethnicity.[129] The prescribing, dispensing and payment for the polypill were the same as if the polypill were to be marketed in Australia and subsidised through their Pharmaceutical Benefits Scheme.[129] At baseline, 61% of participants had established cardiovascular disease and 50% of participants reported use of combination medication (antiplatelet, statin and two or more blood pressure lowering agents).[129] At the end of the trial self-reported use of combination medication increased to 70% in the polypill group compared with 47% in the usual care group (RR 1.49, 95% CI 1.30 to 1.72, p<0001).[129] Between baseline and end of trial there was no statistically significant difference between the polypill and usual care groups in the mean change in systolic blood pressure (-1.5 mm Hg, 95% CI -4.0 to 1.0, p=0.24) or low density lipoprotein cholesterol (0.08 mmol/L, -0.06 to 0.22, p=0.26).[129] Trial authors noted that by the end of the trial 17% of people in the polypill group and 67% of those in the usual care group were taking atorvastatin or rosuvastatin, more potent statins than that contained within the polypill (simvastatin).[129] There was no difference between groups in the proportion of participants that experienced at least one serious adverse event during the trial (polypill 46% vs usual care 41%, p=0.16).[129]

2.5.4. Findings

The following findings have emerged regarding the effectiveness and safety of a polypill for the prevention of cardiovascular disease from this review of the randomised controlled trials completed to date.

Effectiveness

1. The polypill is associated with improved adherence but not consistently with improved systolic blood pressure and low density lipoprotein cholesterol among patients at high risk of their first or a subsequent cardiovascular disease when compared with usual care.
2. When compared with inactive control, the polypill is associated with reductions in systolic blood pressure and low density lipoprotein cholesterol similar to that expected with individual components.

Safety

1. No major safety concerns have emerged regarding the use of the polypill when compared with usual care or an inactive control.

While the polypill has been shown to improve adherence, its effect on blood pressure and cholesterol has ranged from no effect to some effect when compared with usual care. Although no major safety concerns have emerged to date, the safety of the polypill is unclear because of the relatively small number of trials conducted to date. Further randomised controlled trial evidence, particularly if conducted in New Zealand, would assist in understanding the potential role of a polypill in enhancing the implementation of guideline-recommended therapy in New Zealand.

2.6. Summary

Cardiovascular disease is a major cause of mortality, morbidity and inequalities in New Zealand and globally. Comprehensive strategies to reduce the burden of cardiovascular disease require a combination of prevention and treatment. International guidelines recommend basing decisions on the use of cardiovascular preventive medications on absolute risk of cardiovascular disease, but there is inconsistency regarding advice on the use of aspirin in primary prevention as well as the conclusions of meta-analyses on which these have been based. Individualised bleeding risk assessment, as well as cardiovascular risk assessment, is needed to determine in which people without cardiovascular disease the benefits of aspirin are likely to outweigh its harms. Modelling using the methodology of the United States Preventive Services Task Force could be undertaken, incorporating updated proportional estimates of the effect of aspirin and with a composite cardiovascular outcome to facilitate use in New Zealand. While the polypill has been shown to improve adherence, its effect on blood pressure and cholesterol has been inconsistent when compared with usual care, and there is only a relatively small evidence base from which to assess its safety among people with indications. A New Zealand randomised controlled trial could provide clarity on the potential role of a polypill in enhancing the implementation of guideline-recommended therapy in this country by providing local evidence. In addition, a trial could expand the international evidence base regarding the effect of polypill-based compared with usual care on blood pressure and cholesterol, as well as safety.

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Chapter 3. Systematic review and modelling of benefits and harms of aspirin in the primary prevention of cardiovascular disease

3.1. Introduction

Different meta-analyses and guidelines have reached different conclusions regarding the use of aspirin in the primary prevention of cardiovascular disease. The first part of this chapter describes a systematic review of meta-analyses of randomised controlled trials of aspirin to identify any updated estimates of the relative reduction in the risk of a first cardiovascular event and the relative increase in the risk of a major non-cerebral bleed with aspirin among people without established cardiovascular disease. Despite the preponderance of cardiovascular risk assessment tools, individualised bleeding risk assessment is less well developed. Such assessment is needed in order to determine the balance of benefits (cardiovascular events avoided) and harms (additional bleeds) of aspirin in primary prevention. In the second part of this chapter the benefits and harms of aspirin in primary prevention were modelled by sex and age group, using the methodology of the United States Preventive Services Task Force, and incorporating the updated proportional estimates of the benefits and harms of aspirin in primary prevention from the systematic review.

3.2. Systematic review

3.2.1. Aims, hypotheses and PECOT criteria

The aims of this systematic review were to:

1. Identify the most up to date meta-analyses of randomised controlled trials (and any subsequent randomised controlled trials) of aspirin in the primary prevention of cardiovascular disease
2. Critically appraise the meta-analyses and any subsequent randomised controlled trials of aspirin in the primary prevention of cardiovascular disease
3. Given the totality of evidence, identify the most robust estimates of the benefit (proportional reduction in total cardiovascular events) and harms (proportional increase in major non-cerebral bleeds) of aspirin in the primary prevention of cardiovascular disease

Aspirin is associated with a reduction in the risk of myocardial infarction and ischaemic stroke, and an increase in the risk of haemorrhagic stroke and non-cerebral (mainly

gastrointestinal) bleeds.[43] Ischaemic and haemorrhagic strokes were not able to be differentiated in some trials (e.g. the British Doctors' Trial investigators noted "*though information was sought about the likely aetiology of any strokes, the lack of computed tomography meant that a firm distinction between cerebral infarction and primary intracerebral haemorrhage was possible in only a minority of cases*"[64]). Therefore, in this systematic review, the effect of aspirin on haemorrhagic stroke was incorporated within the cardiovascular outcome (total cardiovascular events were defined as myocardial infarction, stroke [ischaemic or haemorrhagic] and fatal cardiovascular events) and not the bleeding outcome (major non-cerebral bleeds were defined as non-cerebral bleeds resulting in death or requiring hospitalisation or transfusion).

The hypotheses of this systematic review were that the:

1. Proportional reduction in total cardiovascular events with long-term use of aspirin among adults with no history of cardiovascular disease is approximately 12% (based on the estimate obtained by the Antithrombotic Trialists' Collaboration 2009 meta-analysis[43])
2. Proportional increase in major non-cerebral bleeds with long-term use of aspirin among adults with no history of cardiovascular disease is approximately 54% (based on the estimate obtained by the Antithrombotic Trialists' Collaboration 2009 meta-analysis[43])

Meta-analyses of randomised controlled trials (and any subsequent randomised controlled trials) were sought that met the criteria outlined in Table 14.

Table 14. Criteria for the systematic review of meta-analyses and randomised controlled trials of aspirin in the primary prevention of cardiovascular disease

Criteria*	**Description**
Population	Adults, men and women, with or without diabetes, with no history of established or symptomatic cardiovascular disease (coronary, cerebrovascular or peripheral vascular) and without atrial fibrillation or congestive heart failure
Exposure	Aspirin, oral, ≤500mg daily
Comparison	Placebo, no treatment or treatment with a medication that was unlikely to affect any of the outcomes of interest or, where the medication was likely to affect an outcome of interest, there was no evidence of an interaction between the effect of aspirin and the other intervention on the outcome(s) of interest
Outcomes	Total cardiovascular events (myocardial infarction, stroke [including haemorrhagic] or death from a cardiovascular cause) Major non-cerebral bleeds (bleed resulting in death or requiring hospitalisation or transfusion)
Time	At least 1 year

*PECOT (Population, Exposure, Comparison, Outcomes and Time) criteria.[134]

Randomised controlled trial evidence was sought because randomised controlled trials are the gold standard for evaluating an intervention,[135] and can assess both intended (such as a reduction in the rate of ischaemic cardiovascular events) and unintended (such as an increase

in the rate of major bleeds) effects.[136] When interventions are allocated at random, there is a greater degree of assurance regarding the validity of a result than any observational study design,[137] and there is greater confidence that the relationship observed between an exposure (such as an intervention) and outcome (intended or unintended) might be causal.[5]

Meta-analysis is a method of summarising similar trials by synthesizing their results into a single quantitative estimate of treatment effect.[136] The purpose of combining trial data in this way is that all relevant (even apparently conflicting) evidence can be incorporated into a single effect estimate, thereby increasing the precision of the estimate.[136] Meta-analyses that included data from both randomised controlled trials and observational studies were permitted only if the data from randomised controlled trials were analysed separately.

3.2.2. Methods

Search strategies (Table 15) were developed to identify potentially relevant meta-analyses (published up to 17 June 2014) and randomised controlled trials (published between September 2012 and 31 July 2014, to identify trials published after the meta-analyses had been conducted). The search for randomised controlled trials was limited to the period from September 2012 because comprehensive systematic searches of previously published randomised controlled trials had already been undertaken by other reviewers.[138 139]

Table 15. Search strategies for the systematic review of meta-analyses and randomised controlled trials of aspirin in the primary prevention of cardiovascular disease

Database	**Meta-analyses** (published up to 17 June 2014)	**Randomised controlled trials** (published September 2012 to 31 July 2014)
Cochrane	Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects	Cochrane Central Register of Controlled Trials
	1. Aspirin.mp. 2. Acetylsalicylic acid.mp. 3. Salicylate$.mp. 4. Salicylic$.mp. 5. 1 or 2 or 3 or 4	1. Exp aspirin/ 2. Aspirin.mp. 3. Acetylsalicylic acid.mp. 4. Salicylate$.mp. 5. Salicylic$.mp. 6. Or/1-5 7. Exp cardiovascular diseases/ 8. Exp stroke/ 9. Exp hemorrhage/ 10. Or/7-9 11. 6 and 10 12. Limit 11 to yr=”2012-Current”

Database	**Meta-analyses** (published up to 17 June 2014)	**Randomised controlled trials** (published September 2012 to 31 July 2014)
Medline	Basis: McMaster systematic review search strategy with highest specificity[140]	Basis: Cochrane randomised controlled trial search strategy; sensitivity-maximising[141]
	1. Exp Aspirin/ 2. Aspirin$.tw. 3. Acetylsalicylic acid$.tw. 4. Salicylate$.tw 5. Salicylic$.tw 6. Or/1-5 7. Exp Death/ 8. Death$.tw. 9. Exp Cardiovascular Diseases/ 10. Cardiovascular$.tw. 11. Myocardial infarction$.tw. 12. Coronary$.tw. 13. Heart disease$.tw. 14. Exp Stroke/ 15. Stroke$.tw. 16. Exp Death, Sudden/ 17. Sudden death$.tw. 18. Exp cerebral hemorrhage/ 19. Cerebral bleed$.tw. 20. Cerebral hemorrhage$.tw. 21. Cerebral haemorrhage$.tw. 22. Exp Hemorrhage/ 23. Gastrointestinal bleed$.tw. 24. Gastrointestinal hemorrhage$.tw. 25. Gastrointestinal haemorrhage$.tw. 26. Or/7-25 27. Medline.tw. 28. Systematic review.tw. 29. Meta-analysis.mp,pt. or meta analysis.mp,pt. 30. Or/27-29 31. 6 and 26 and 30	1. Exp Aspirin/ 2. Aspirin$.tw. 3. Acetylsalicylic acid$.tw. 4. Salicylate$.tw 5. Salicylic$.tw 6. Or/1-5 7. Exp Death/ 8. Death$.tw. 9. Exp Cardiovascular Diseases/ 10. Cardiovascular$.tw. 11. Myocardial infarction$.tw. 12. Coronary$.tw. 13. Heart disease$.tw. 14. Exp Stroke/ 15. Stroke$.tw. 16. Exp Death, Sudden/ 17. Sudden death$.tw. 18. Exp Cerebral hemorrhage/ 19. Cerebral bleed$.tw. 20. Cerebral hemorrhage$.tw. 21. Cerebral haemorrhage$.tw. 22. Exp Haemorrhage/ 23. Gastrointestinal bleed$.tw. 24. Gastrointestinal hemorrhage$.tw. 25. Gastrointestinal haemorrhage$.tw. 26. Or/7-25 27. Randomized controlled trial.pt. 28. Controlled clinical trial.pt. 29. Randomized.ab. 30. Randomised.ab. 31. Placebo.ab. 32. Drug therapy.fs. 33. Randomly.ab. 34. Trial.ab. 35. Groups.ab. 36. Or/27-35 37. Exp animals/ not humans.sh. 38. 36 not 37 39. 6 and 26 and 38 40. Limit 39 to yr=”2012-Current”
PubMed	Basis: PubMed clinical query function	Basis: PubMed clinical query function
	1. Aspirin 2. Cardiovascular Disease 3. Cerebrovascular Disorder 4. Hemorrhage 5. Or/2-4 6. 1 and 5 7. 6 and systematic review filter (Note: Supplementary search on 22 November 2014 for meta-analyses published in 2014)	1. Aspirin 2. Cardiovascular Disease 3. Cerebrovascular Disorder 4. Hemorrhage 5. Or/2-4 6. 1 and 5 7. 6 and therapy filter (broad) 8. 7 and Publication date from 2012/09/01 (Note: Supplementary search on 22 November 2014 for randomised controlled trials published in 2014)

Database	**Meta-analyses** (published up to 17 June 2014)	**Randomised controlled trials** (published September 2012 to 31 July 2014)
EMBASE	Basis: McMaster systematic review search strategy with highest specificity[142]	Basis: Cochrane randomised controlled trial search strategy[143]
	1. Exp Acetylsalicylic acid / 2. Exp Heart infarction/ 3. Exp Stroke/ 4. Exp Sudden Death/ 5. Exp bleeding / 6. Or/2-5 7. Meta-analysis.tw. 8. Systematic review.tw. 9. Or/7-8 10. 1 and 6 and 9	1. Exp Acetylsalicylic acid/ 2. Exp Heart infarction/ 3. Exp Stroke/ 4. Exp Sudden death/ 5. Exp Bleeding/ 6. Or/2-5 7. Random$ 8. Factorial$ 9. crossover$ or cross over$ or cross-over$ 10. Placebo$ 11. double$ adj blind$ 12. singl$ adj blind$ 13. Assign$ 14. Allocat$ 15. Volunteer$ 16. Crossover procedure.sh. 17. Double-blind procedure.sh. 18. Randomized controlled trial.sh. 19. Single-blind Procedure.sh. 20. Or/7-19 21. 1 and 6 and 20 Limit 21 to yr=”2012-Current”
CINAHL Plus	Basis: McMaster systematic review search strategy with highest specificity[144]	Basis: CINAHL Plus clinical query function
	1. Aspirin MH 2. Myocardial infarction+ MH 3. Stroke+ MH 4. Death, Sudden+ MH 5. Hemorrhage+ MH 6. Or/2-5 7. Meta analysis MH 8. Meta-analysis.tw. 9. Systematic review MH 10. Systematic review.tw. 11. Or/7-10 12. 1 and 6 and 11	1. Aspirin MH [cannot explode] 2. Myocardial infarction+ MH 3. Stroke+ MH 4. Death, Sudden MH or Death, Sudden, Cardiac MH 5. Hemorrhage+ 6. Or/2-5 7. 1 and 6 8. Limited to clinical queries: therapy – high sensitivity 9. Limited to Published Date from 20120901-current
PROS-PERO	1. “aspirin” in title 2. “primary prevention” in title 3. 1 and 2	Not applicable

ab=word in abstract; CINAHL=Cumulative Index to Nursing and Allied Health Literature; EMBASE=Excerpta Medica database; exp=explode (i.e. searches for that MeSH term and all MeSH terms that sit underneath it); MeSH=Medical Subject Heading; MH=exact subject heading (MeSH term not ‘exploded’); mp=(word in title, short title, abstract, full text, keywords, caption text); PROSPERO=International prospective register of systematic reviews; pt=publication type; sh=subheading; tiab or tw=word in title or abstract
/MeSH term.
+explode (i.e. searchers for that MH and all MHs that sit underneath it).
$truncation (i.e. searches for all occurrences that start with the specified root).

The candidate searched eight databases: the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials, Medline, PubMed, EMBASE (the Excerpta Medica database), Cinahl Plus (Cumulative Index to Nursing and Allied Health Literature) and PROSPERO (an international prospective register of systematic reviews). Search strategies for Medline,[140]

[141] EMBASE[142] [143] and Cinahl Plus[144] were based on those developed by the Health Information Research Unit at McMaster University (to identify systematic reviews) or the Cochrane Collaboration (to identify randomised controlled trials) (Table 15). Strategies and search terms with the highest specificity were used to identify meta-analyses because of the large number of potentially relevant articles returned, whereas strategies with the highest sensitivity were used to identify any recent randomised controlled trials. The search strategies for PubMed were based on clinical query functions, which include specific systematic review and therapy filters. Terms for aspirin were used in all databases interrogated. Additional database-relevant terms were used for cardiovascular disease, bleeding and systematic reviews for Medline, PubMed, EMBASE and Cinahl Plus.

A supplementary search of meta-analyses and randomised controlled trials published in 2014 was conducted by the candidate on 22 November 2014, just prior to submission of this thesis. This supplementary search was restricted to the PubMed database.

Flow diagrams were prepared by the candidate for the citations identified in the systematic searches of meta-analyses and randomised controlled trials (using the flow diagram of the Preferred Reporting Items for Systematic reviews and Meta-Analyses, PRISMA, Statement[145]). All identified citations were considered for inclusion, irrespective of whether they were for journal articles or grey literature (such as conference proceedings or reports). Reference lists of relevant trials and review articles were searched by the candidate for any additional relevant trials or meta-analyses. Only studies with the full text published in English were included, as the candidate did not have the resources to fund manuscript translation.

Each meta-analysis included in the qualitative synthesis was described by the candidate using the University of Auckland's GATE (Graphic Approach To Evidence based practice) CAT (Critically Appraised Topic) frame for systematic reviews of intervention studies (Appendix 1). The GATE CAT has been designed to assist in systematically describing the design of systematic reviews. Meta-analyses that met all criteria were critically appraised by two reviewers independently (the candidate and Associate Professor Raina Elley) using the University of Auckland's FAITH (Find, Appraise, Include, Total-up and Heterogeneity) tool (Appendix 2). The FAITH tool has been designed to assist in critically appraising systematic reviews and comprises a series of questions against which systematic reviews can be assessed and rated (good, poor, unclear, not applicable). Completed FAITH templates were collated by

the candidate. Any disagreements between reviewers in the quality score assigned to each meta-analysis for each of the FAITH criteria were resolved by consensus between the two reviewers and checked or adjudicated by a third reviewer, Dr Sue Wells.

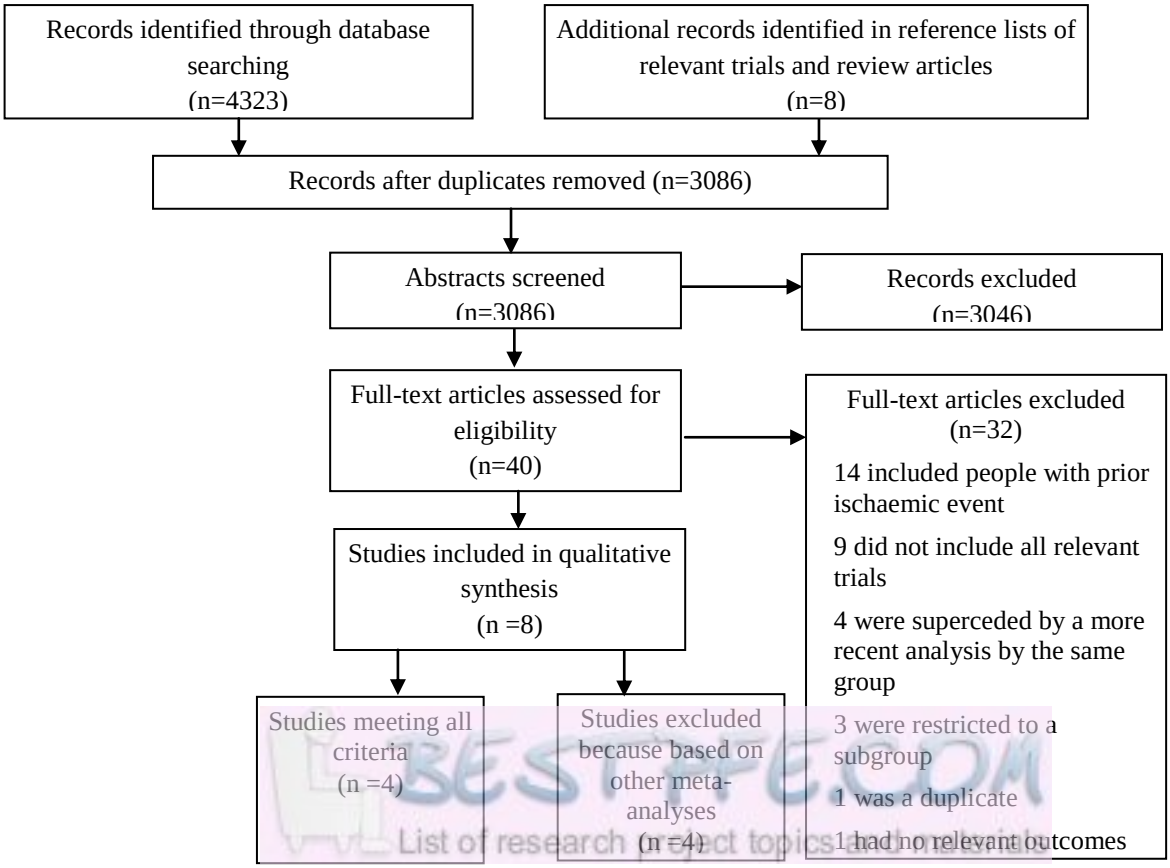
Each randomised controlled trial included in the qualitative synthesis (that had not already been included within eligible meta-analyses) was described and critically appraised by the candidate using the University of Auckland's GATE (Graphic Approach To Evidence based practice)-lite for randomised controlled trials and observational studies.

All data were extracted by the applicant.

3.2.3. Results

The flow diagram of the citations identified in the systematic searches of meta-analyses is provided below (Figure 9). Eight systematic reviews were included in the qualitative synthesis and are described below. Four met all inclusion criteria (Bartolucci 2011,[146] Berger 2011,[147] Raju 2011[139] and Seshasai 2012[148]) and the other four (Wolff 2009,[149 150] Raju 2012,[151] Sutcliffe 2013[138 152] and Puhan 2014[153]) were ultimately excluded as they were primarily based on other meta-analyses.

Figure 9. Citations identified in the systematic review of meta-analyses of aspirin in the primary prevention of cardiovascular disease trials



The meta-analyses included one additional relevant randomised controlled trial, not previously discussed in chapter 2, the Aspirin for Asymptomatic Atherosclerosis trial 2010.[154] That trial involved 3,350 Scottish men and women with low ankle brachial index (indicating atherosclerosis and an increased risk of cardiovascular disease) but without symptomatic peripheral or other cardiovascular disease.[154] Participants were randomised to aspirin or placebo for an average of 8.2 years.[154] There was no difference between the groups in the composite of fatal or nonfatal coronary event or stroke or revascularisation (hazard ratio, HR, 1.03, 95% confidence interval, CI, 0.84 to 1.27) and an increase in major haemorrhage that did not reach statistical significance (HR 1.71, 95% CI 0.99 to 2.97).[154]

In total, nine relevant randomised controlled trials were included in each of the included meta-analyses. These trials are summarised in Table 16. With the exception of the Aspirin for Asymptomatic Atherosclerosis trial 2010, all of the trials have been previously described in chapter 2.

Table 16. Key features of randomised controlled trials of aspirin in the primary prevention of cardiovascular disease from eligible meta-analyses identified by the systematic review

Trial	**N**	**%CVD**	**% Women**	**% Diabetes**	**Aspirin daily dose**	**Control**	**Additional randomly allocated treatment (trial design)**	**Follow-up, months**
BDT 1988[64]	5,139	8%†	0%	2%	500mg	No aspirin	Nil	66.1 (mean)
PHS 1989[65]	22,071	1%†	0%	2%	325 (alt days)	Placebo	Beta carotene (2x2)	60.2 (mean)
HOT 1998[66]	18,790	3%†	47%	8%	75	Placebo	BP-lowering agents, randomly assigned target BP (2x3)‡	45.6 (mean)
TPT 1998[67]	5,085	<1%†	0%	Not stated	75	Placebo	Warfarin (2x2)	76.3 (mean)
PPP* 2003[83]	4,784	4%†	57%	22%	100	No aspirin	Vitamin E (2x2)	44.4 (median)
WHS 2005[76]	39,876	<1%†	100%	2.6%	100 (alt days)	Placebo	Vitamin E and beta carotene§ (2x2x2)	121.2 (mean)
POPADAD 2008[79]	1,276	0%	56%	100%	100	Placebo	Antioxidant (2x2)	80.4 (median)
JPAD 2008[80]	2,539	0%	45%	100%	81 or 100	No aspirin	Nil	52.4 (median)
AAA 2010[154]	3,350	0%	72%	3%	100mg	Placebo	Nil	98.4 (mean)

AAA=Aspirin for Asymptomatic Atherosclerosis trial; alt=alternate; BDT=British Doctors' Trial; BP=blood pressure; HOT=Hypertension Optimal Treatment trial; JPAD=Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial; N=number of participants; PHS=Physicians' Health Study; POPADAD=Prevention of Progression of Arterial Disease and Diabetes trial; PPP=Primary Prevention Project; TPT=Thrombosis Prevention Trial; WHS=Women's Health Study

*Data in this table is from a 2003 trial report that included data from an additional 289 participants (all of whom had diabetes) than had been originally reported on in the main trial report published in 2001.[68]

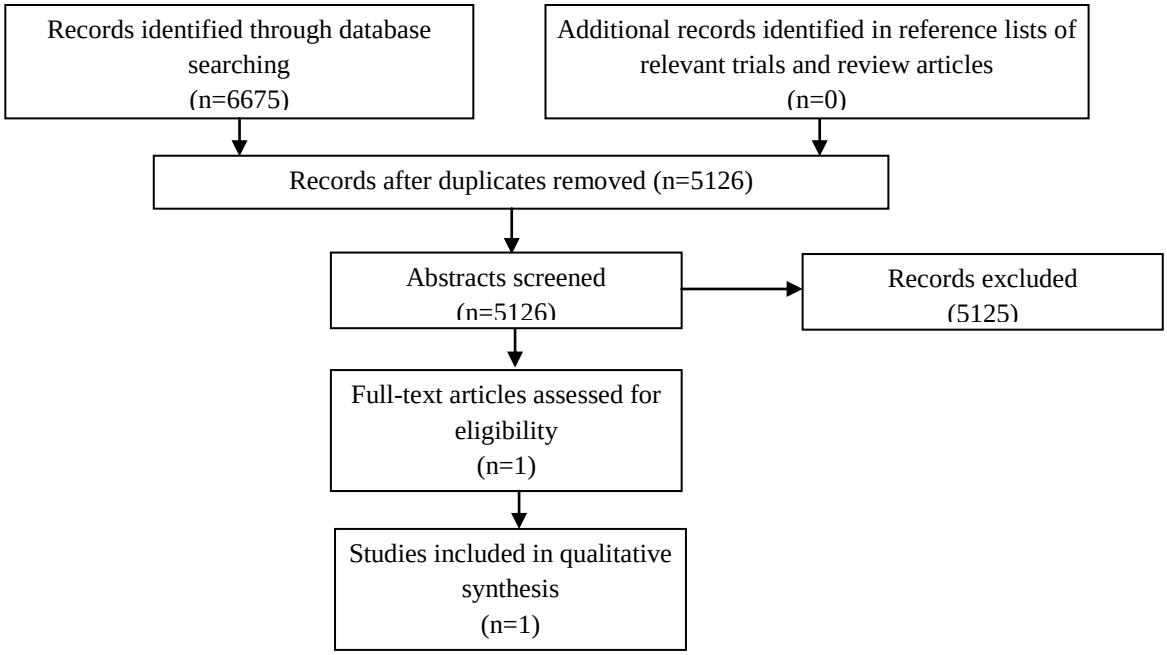
†CVD defined as myocardial infarction, cerebrovascular disease, angina, peripheral arterial disease or heart failure and obtained from Antithrombotic Trialists' Collaboration 2009 individual participant data meta-analysis.[43]

‡All participants received felodipine with the addition of other BP-lowering agents according to a five-step regimen to achieve the randomly allocated target diastolic BP (≤90, ≤85 or ≤80 mm Hg).[66]

§Beta carotene stopped after mean 22.8 months after PHS results published showing no effect on vascular outcomes.[84]

One further randomised controlled trial was identified in the systematic review of randomised controlled trials published from 2012 (Figure 10), the Japanese Primary Prevention Project.[155] The Japanese Primary Prevention Project trial is described and appraised in 3.2.6.

Figure 10. Citations identified in the systematic review of randomised controlled trials of aspirin in the primary prevention of cardiovascular disease



3.2.4. Review articles excluded because primarily based on other meta-analyses

Four review articles investigating the effect of aspirin on the primary prevention of cardiovascular disease (Wolff 2009,[149 150] Raju 2012,[151] Sutcliffe 2013[138 152] and Puhan 2014[153]) appeared to meet the criteria for this systematic review but were ultimately excluded because they were primarily based on other meta-analyses. The key features of the excluded reviews are summarised Table 17. The reviews by Sutcliffe[138 152] and Puhan[153] are discussed in more detail because they included additional analyses to evaluate the benefits and harms of aspirin.

Table 17. Key features of review articles that were excluded from the systematic review of meta-analyses of aspirin in the primary prevention of cardiovascular disease

	Wolff 2009[149 150]	**Raju 2012**[151]	**Sutcliffe 2013**[138 152]	**Puhan 2014**[153]
Methods	SR of RCTs, MAs and SRs	SR of RCTs and MAs	SR of RCTs, MAs and SRs + re-analyses of data from other MAs	Benefit/harm analysis (NNT/NNH and GNCI approaches)
Meta-analyses on which based (number of relevant RCTs included in each meta-analysis)	-ATC 2009 [43] (6/9 RCTs) -Berger 2006[71] (6/9 RCTs)	-ATC 2009[43] (6/9 RCTs) -Raju 2011[139] (9/9 RCTs) -Bartolucci 2011[146] (9/9 RCTs) -Seshasai 2012[148] (9/9 RCTs)	-ATC 2009[43] (6/9 RCTs) -Raju 2011[139] (9/9 RCTs) -Bartolucci 2011[146] (9/9 RCTs) -Seshasai 2012[148] (9/9 RCTs) -Berger 2011[147] (9/9 RCTs)	-Berger 2011[147] (9/9 RCTs)
Conclusions	Aspirin: - reduces CVD (MI in men and ischaemic stroke in women) - increases major bleeds in men and women - increases haemorrhagic stroke in men but not women	- In those at low risk, aspirin reduces the risk of MI, increases the risk of major bleeding and results in a modest and nominally significant reduction in total mortality - Recommendations should take into account the balance between benefits and harms, as well as individual values and preferences	- Small absolute effects of aspirin relative to the burden of these diseases - When aspirin is used for primary prevention of CVD the absolute harms exceed the benefits	-NNT and NNH reduced with increasing age (b/c baseline rates of benefits and harms increased with age) -GNCI approach: Aspirin caused slightly more benefit than harm in all age categories of men and women (weightings: MI 0.45, ischaemic stroke 0.89, haemorrhagic stroke 0.89, GI bleed 0.20)

ATC=Antithrombotic Trialists' Collaboration; CHD=coronary heart disease; CVD=cardiovascular disease; GI=gastrointestinal; GNCI= Gail/National Cancer Institute; MA=meta-analyses; MI=myocardial infarction; NNH=number needed to harm; NNT=number needed to treat; RCT=randomised controlled trials; SR=systematic reviews; US=United States

Sutcliff 2013

Sutcliffe and colleagues re-analysed data from three meta-analyses (Berger 2011,[147] Raju 2011[139] and Seshasai 2012[148]).[152] First, they re-analysed the proportional effect of aspirin on total coronary heart disease by ordering each trial chronologically in a cumulative random effects model.[152] They noted that over time the effect of aspirin on total coronary heart disease appears to have diminished, and consider that this could be a reflection of improvements in the prevention and treatment of cardiovascular disease.[152] Second, they constructed L'Abbé plots of the event rate in aspirin against those in the comparator arm of contributing trials for a number of outcomes using data from the meta-analyses.[152] They noted considerable heterogeneity between studies in outcome event rates.[152] Third, they assessed the effect of leaving out data from one trial at a time on a number of outcomes using

data from the meta-analyses, and found that several of the large studies (noting the Women's Health Study and the Physicians' Health Study) were highly influential in the results for some outcomes.[152] Finally, Sutcliffe and colleagues applied the updated proportional effect estimates from the three recent meta-analyses to absolute risk data from the Antithrombotic Trialists' Collaboration meta-analysis.[152] They estimated that treating 10,000 people with aspirin for 10 years would avert 33 to 46 deaths and 60 to 84 major cardiovascular events, and would cause 46 to 49 major bleeds.[152]

Puhan 2014

Puhan and colleagues compared two quantitative approaches to balance the benefits and harms of aspirin.[153] For both approaches, baseline (untreated) incidence of cardiovascular and bleeding events were obtained from United States and Spanish community cohort studies, and baseline (untreated) mortality rates were derived from United States national mortality statistics.[153] Proportional effects of aspirin on outcomes were obtained from the 2011 meta-analysis by Berger and colleagues.[153] The first approach compared the numbers needed to treat (NNT) to avert a myocardial infarction or an ischaemic stroke, with the numbers needed to harm (NNH) to cause an additional haemorrhagic stroke or gastrointestinal bleed with aspirin, by sex and age group.[153] They found that both the NNT and NNH with aspirin reduced with increasing age because the baseline incidence of both beneficial and harmful effects increased with age.[153] For example, for a man (women) the NNT for a myocardial infarction was 1,786 (5,953) at age 45-54 years and 511 (872) at age 75 to 84 years and the NNH for a major gastrointestinal bleed was 1,344 (2,688) at age 45-54 years and 202 (436) at age 75 to 84 years.[153] Their second approach (from the Gail/National Cancer Institute) weighted outcomes according to the preferences of patients without cardiovascular disease for those outcomes in a small (n=42), separate study.[153] These relative weights (with a higher weight representing a less desirable outcome) were 0.89, 0.45 and 0.20 for strokes, myocardial infarctions and gastrointestinal bleeds, respectively.[153] The weighted number of haemorrhagic strokes and major gastrointestinal bleeds caused by aspirin were subtracted from the weighted number of myocardial infarctions and ischaemic strokes averted with aspirin, by subgroups of sex and age.[153] They found that for both women and men, and in all age groups (between 45 and 84 years), the benefits of aspirin outweighed its harms.

3.2.5. Eligible meta-analyses

Four meta-analyses investigating the effect of aspirin on the primary prevention of cardiovascular disease met the criteria for this systematic review: Bartolucci 2011,[146] Berger 2011,[147] Raju 2011[139] and Seshasai 2012[148]. Each of these meta-analyses is described below in Table 18 .

Table 18. Key features of eligible meta-analyses identified by the systematic review of aspirin in the primary prevention of cardiovascular disease

Feature*	**Bartolucci 2011**[146]	**Berger 2011**[147]	**Raju 2011**[139]	**Seshasai 2012**[148]
Source of studies	Not specified	Medline, Cochrane and Embase (2005 to 'present' – article submitted 3 March 2011). Previous study searched 1966 to 2005.	Medline (from 1966), Embase (from 1980), Cinahl (from 1982) and Cochrane (all to May 2010). Bibliographies of journal articles hand searched. 'Related article' search done on PubMed. Clinicaltrials.gov searched. Experts contacted.	PubMed and Cochrane (to June 2011). Reference lists hand searched for additional studies.
Eligibility criteria: studies	RCTs. Exposure aspirin. Comparison not specified. Outcomes included cardiovascular events. Duration not specified. No exclusion criteria specified.	RCTs. Exposure aspirin along. Comparison placebo or control. Outcomes included cardiovascular events and bleeding. Duration not specified Exclusion criteria: not in English.	RCTs. Exposure aspirin (any dose). Comparison placebo or no aspirin. Outcomes included cardiovascular events and bleeding. Follow up duration not specified. Exclusion criteria: aspirin combined with second antithrombotic unless separate placebo and aspirin-only treatment groups	RCTs only. Exposure aspirin. Comparison placebo. Outcomes included cardiovascular events and bleeding. Duration at least 1 year. Exclusion criteria: <1000 participants, secondary prevention or mixed primary and secondary prevention, pilot studies, studies comparing aspirin with other antiplatelet agents.
Eligibility criteria: participants	Not specified	Patients without clinical CVD	Patients without a history of symptomatic CVD (>95% enrolled participants)	Patients with no prior CHD or stroke
Search strategy	Not specified	Not specified	Search terms: Aspirin, acetylsalicylic acid, cardiovascular disease, myocardial infarction, stroke, cerebrovascular disease, mortality, death, survival, randomized trial, controlled trial, random, prevent, primary prevention	Aspirin AND Primary prevention AND Cardiovascular disease AND Mortality

Feature*	**Bartolucci 2011**[146]	**Berger 2011**[147]	**Raju 2011**[139]	**Seshasai 2012**[148]
Studies screened	Not specified	Not specified	Two investigators independently evaluated studies for inclusion using predefined criteria. Relevance was assessed using a hierarchical approach based on title, abstract and full text publication. Disagreement on eligibility was resolved by discussion and third reviewer. Numbers screened, incl, excluded (with reasons) supplied.	Method of screening not specified. Numbers screened, included, excluded (with reasons) supplied.
Process of appraising study validity	Not specified	Not specified	Criteria adapted from Cochrane Methods Group Guidelines on Systematic Reviews of Interventions.	Quality of studies evaluated using a Delphi scoring system. How applied not specified
Data extraction methods	Not specified	Not specified	Two investigators independently extracted data on study design, participant characteristics, eligibility criteria, intervention and comparator, quality, and outcomes.	Three authors independently abstracted data and discrepancies resolved through discussion.
Studies included/ excluded in analyses	Number of appraised studies included/ excluded and reasons why – not supplied. Main characteristics of studies and participants supplied.	Number of appraised studies included/ excluded and reasons why – not supplied. Main characteristics of studies and participants supplied.	Numbers of appraised studies included/ excluded supplied. Main characteristics of studies and participants supplied.	Numbers of appraised studies included/ excluded supplied. Main characteristics of studies and participants supplied
Summary measures used	Odds ratios. Random effects model	Risk ratios. Random effects model.	Risk ratios. Random effects model. Compared with fixed effects model.	Odds ratios Random effects model. Compared with fixed effects model.
Summary tables of individual studies	Effect estimates and CIs supplied but neither outcome nor participant numbers.	Outcome numbers/ participant numbers for EG and CG, effect estimates and CIs provided for each outcome. Forest plots of each outcome provided.	Outcome numbers/participant numbers for EG and CG, effect estimates and CIs provided for each outcome. Forest plots of each outcome provided.	Outcome numbers/ participant numbers for EG and CG, effect estimates and CIs provided for each outcome. Forest plots of each outcome provided.
Measures of differences between studies and sensitivity analyses	Heterogeneity assessed by χ^2 test.	Heterogeneity assessed by Q statistic and I^2 test. Sensitivity analyses done.	Heterogeneity assessed by I^2 and χ^2 tests. Potential sources of heterogeneity explored. Sensitivity analyses done.	Heterogeneity assessed by I^2 test. Sensitivity analyses done.

CG=Control Group; CHD=coronary heart disease; CI=Confidence Interval; CVD=cardiovascular disease; EG=Exposure (i.e. aspirin) Group; RCT=Randomised Controlled Trial

*Based on the GATE (Graphic Approach To Evidence based practice) CAT (Critically Appraised Topic) frame for systematic reviews of intervention studies (Appendix 1).

Critical appraisal of eligible meta-analyses

Each of the meta-analyses was critically appraised by two independent reviewers, with any disagreements resolved by consensus or a third reviewer. The findings of the critical appraisal for each meta-analysis are provided in Appendix 3 and are summarised in Table 19. All of the meta-analyses included the same nine randomised controlled trials therefore the most significant aspect of the critical appraisal is their analysis of data. Bartolucci 2011 was the weakest of the four meta-analyses because the number of participants and numbers of outcomes in each group were not presented, and no sensitivity analyses were reported. The interpretation of some data by Raju 2011 was questionable because they reported that aspirin had reduced all-cause mortality and myocardial infarction despite the confidence intervals for these effect estimates including 1.00. Overall the highest quality meta-analyses were therefore Berger 2011 and Seshasai 2012.

Table 19. Summary of critical appraisal of eligible meta-analyses identified by the systematic review of aspirin in the primary prevention of cardiovascular disease

FAITH (Find, Appraise, Include, Total-up and Heterogeneity) tool features		**Bartolucci 2011** [146]	**Berger 2011** [147]	**Raju 2011** [139]	**Seshasai 2012** [148]
		Risk of errors (+, x, ?, na)			
Find studies	All appropriate information sources searched?	?	x	+	x
	Appropriate study eligibility criteria?	+	+	+	+
	Appropriate participant eligibility criteria?	?	+	+	+
	Search strategy/processes: explicit, comprehensive, systematic?	x	?	+	+
Appraise studies	How well were data on each study extracted (standardised, systematic, repeated)?	?	?	+	+
	How well were studies critically appraised?	?	x	+	+
Include studies	Clear rationale given for including / excluding studies based on individual study appraisal?	?	?	+	+
	Relevant prognostic characteristics reported and used to determine inclusion in analyses?	+	+	+	+
	Important benefits and harms assessed?	x	+	+	+
	Follow-up time sufficiently similar to combine?	+	+	+	+
Total-up (summary) of studies and **H**etero-geneity of studies	Was it reasonable to consider combining the studies based on their PECOT characteristics?	+	+	+	+
	Summary tables/forest plots of results sufficient to describe the findings of each included study?	x	+	+	+
	Effect estimates sufficiently similar for similar enough from study to study to undertake meta-analyses?	+	+	+	+
	Sensitivity analyses required?	?	+	+	+
	Were summary measures performed correctly?	+	+	+	+
	Precision of summary measures given?	+	+	+	+
	Summary effect estimates meaningful for practice?	+	+	+	+
Summary of review appraisal	Valid, systematic, reproducible review methodology?	x	?	+	?
	Was there likely to be important publication bias?	?	+	+	+
	Were studies summarised (and/or combined) appropriately?	?	+	+	+
	Confidence intervals sufficiently narrow for results to be meaningful?	+	+	x	+
	Findings applicable in practice?	+	+	+	+

Effect of aspirin on total cardiovascular events

Aspirin was associated with a 10% proportional reduction in the risk of total cardiovascular events (95% CI 4% to 15%) according to both Berger 2011 and Seshasai 2012 (Table 20), the highest quality meta-analyses. No statistically significant heterogeneity in this outcome was identified by any of the four meta-analyses.

Table 20. Results for total cardiovascular events from eligible meta-analyses identified by the systematic review of aspirin in the primary prevention of cardiovascular disease

	Bartolucci 2011[146]	**Berger 2011**[147]	**Raju 2011**[139]	**Seshasai 2012**[148]
Definition	CVD death, MI, stroke	CVD death, nonfatal MI, nonfatal stroke	CVD death, nonfatal MI, nonfatal stroke	Total CVD events, not further specified
Number of participants	Not reported	Aspirin: 52,145 Control: 50,476	Aspirin: 50,868 Control: 49,208	Aspirin: 52,145 Control: 50,476
Number of events	Not reported	Aspirin: 2029 Control: 2099	Aspirin: 1861 Control: 1957	Aspirin: 2107 Control: 2171
Method of analysis	Random-effects model	Random-effects model	Random-effects model	Random-effects model
Effect estimate	**OR 0.87**	**RR 0.90**	**RR 0.88**	**OR 0.90**
95% CI	**0.80 to 0.93**	**0.85 to 0.96**	**0.83 to 0.94**	**0.85 to 0.96**
Hetero-geneity	p=0.39 (χ^2)	Tau^2=0.00; χ^2=4.65, df=8, p=0.79; Q statistic did not indicate statistically significant heterogeneity; I^2=0%	Tau^2=0.00; χ^2=7.56, df=8, p=0.48; I^2=0%	I^2=0.0%
Additional analyses	Not reported	See text below	Not reported	See text below

CI=confidence interval; CVD=cardiovascular disease; MI=myocardial infarction; OR=odds ratio; RR=risk ratio
Statistically significant results in bold

Berger 2011 and Seshasai 2012 reported considerable additional analyses to test the robustness of their finding of the effect of aspirin on total cardiovascular events. Both meta-analyses found that the relative effect estimate (risk ratio in Berger and odds ratio in Seshasai) remained at 0.90 whether the analysis used random or fixed effects models.[147 148] Berger and Seshasai found that the effect of aspirin on total cardiovascular events remained statistically significant after the following:

- Systematically removing data from one trial at a time (risk ratio, RR, varied between 0.891 and 0.893)
- Excluding trials that used enteric-coated or controlled release aspirin (n=3)
- Excluding trials that were restricted to the following groups:
    - People with diabetes (n=2, RR 0.90, 95% CI 0.84 to 0.96)
    - People with subclinical atherosclerosis (n=2, RR 0.89, 95% CI 0.83 to 0.95)
    - Non-Western people
    - Healthcare professionals[147 148]

Berger and Seshasai found no relationship between the effect of aspirin on total cardiovascular events according to the following trial-level potential effect modifiers:

- Year of trial publication (pre 2000 or after 2000, as a surrogate for any changes in background cardiovascular preventive therapies)
- Number of trial participants (<5,000 or 5,000+)
- Number of events in the trial (<500 or 500+)
- Aspirin daily dose (<100mg or 100mg+)
- Aspirin schedule (daily or alternate day)
- Use of concomitant randomly allocated treatment
- Baseline cardiovascular risk (assessed by incidence of events in the control group)
- Mean age of trial participants
- Proportion of trial participants that were male
- Proportion of trial participants who were smokers
- Proportion of trial participants with diabetes
- Mean total cholesterol of trial participants
- Mean systolic blood pressure of trial participants[147 148]

Seshasai found a statistically significant difference in the effect of aspirin on total cardiovascular events when trial results from five of the trials with such data available in their published reports (n=39,876) were stratified according to whether participants were above or below the mean age of the trial in which they were included.[148] Aspirin had a greater proportional effect on people above the mean age (OR 0.78, 95% CI 0.59 to 1.04) than those below the mean age of their trial (OR 1.00, 95% CI 0.85 to 1.17).[148] However, the effect of age is assessed more robustly by the Antithrombotic Trialists' Collaboration 2009 individual participant data meta-analysis (n=95,456).[43] The 2009 Collaboration found that the effect of aspirin on total cardiovascular events was very similar (χ^2=0.0, p=0.9) in those <65 years (rate ratio 0.87, 95% CI 0.78 to 0.98) and 65 years or older (rate ratio 0.88, 95% CI 0.77 to 1.01).[43]

Effect of aspirin on major non-cerebral bleeds

Major non-cerebral bleeding was only assessed in the meta-analyses by Berger 2011[147] and Raju 2011[139] (Table 21 below). Aspirin was associated with a 62% (95% CI 31% to 100%)[147] to 66% (95% CI 41% to 95%)[139] proportional increase in major bleeds. No

statistically significant heterogeneity was identified in this outcome by either meta-analysis.[139 147]

Table 21. Results for major non-cerebral bleeds from eligible meta-analyses identified by the systematic review of aspirin in the primary prevention of cardiovascular disease

	Berger 2011[147]	**Raju 2011**[139]
Definition	Major bleeding (as defined by each trial)	Major bleeding (as defined by each trial)
Number of participants	Aspirin: 52145 Control: 50476	Aspirin: 48968 Control: 47244
Number of events	Aspirin: 458 Control: 278	Aspirin: 406 Control: 234
Method of analysis	Random-effects model	Random-effects model
Risk ratio	1.62	1.66
95% CI	1.31 to 2.00	1.41 to 1.95
Heterogeneity	Tau^2=0.03; χ^2=12.36, df=8, p=0.14; I^2=35%; Q statistic did not indicate statistically significant heterogeneity	Tau^2=0.00; χ^2=6.01, df=6, p=0.42 I^2=0%
Additional analyses	See text below	Not reported

CI=confidence interval; RR=risk ratio

No additional analyses on this effect estimate were undertaken by Raju.[139] Berger found no relationship between the effect of aspirin on major bleeds according to the following trial-level potential effect modifiers:

- Year of trial publication (as a surrogate for any changes in background preventive therapies)
- Aspirin daily dose
- Baseline cardiovascular risk (assessed by incidence of events in the control group)
- Mean age of trial participants
- Proportion of trial participants that were male[147]

Effect of aspirin on all-cause mortality

None of the meta-analyses found a statistically significant association between aspirin and a reduction in all-cause mortality (Berger RR 0.94 [95% CI 0.89 to 1.00], Seshasai OR 0.94 [95% CI 0.88 to 1.00], Raju RR 0.94 [95% CI 0.88 to 1.00], Bartolucci OR 0.95 [95% CI 0.88 to 1.01]).[139 146-148] There was no statistically significant heterogeneity in any of these estimates.

3.2.6. Eligible randomised controlled trial

In addition to randomised controlled trials included within the eligible meta-analyses, one further randomised controlled trial of aspirin in the primary prevention of cardiovascular disease has been published, the Japanese Primary Prevention Project trial.[155] The trial randomised 14,658 Japanese patients without established cardiovascular disease to aspirin 100mg or no aspirin. Participants were aged 60 to 85 years and had hypertension, dyslipidaemia or diabetes. The trial was discontinued prematurely after a median follow-up duration of just over 5 years because the trial's data monitoring committee considered that the trial was unlikely to show a difference between groups in the primary outcome (total cardiovascular events), were follow-up to be continued as planned for a maximum of 6.5 years.[155] Trial investigators had based sample size calculations on a total cardiovascular disease event rate of 1.5 to 2% per year, and a treatment effect of 20%.[155] The observed event rate for total cardiovascular disease in the trial's control group was much lower than expected (3% over 5 years), as was the observed proportional effect of aspirin on the total cardiovascular disease event rate (hazard ratio 0.94, 95% CI 0.77 to 1.15).[155]

The limitations of the study are:

- Open-label design (although endpoints were adjudicated by a blinded expert committee)
- Moderate loss to follow-up (10.5%)
- Compliance with aspirin in the intervention group suboptimal (89% in year 1, 76% by year 5)
- Low-to-moderate contamination of intervention (use of aspirin in the control group was 2% in year 1 and 10% by year 5)

The trial was therefore subject to some random and non-random error. Non-random error may have led to an underestimation of the true effect of aspirin. The full critical appraisal of the trial is provided in Appendix 4.

3.2.7. Discussion

The highest quality eligible meta-analyses were those by Berger 2011 and Seshasai 2012.[147 148] Both studies found that, when considering all nine relevant randomised controlled trials (n=102,621), aspirin was associated with a 10% proportional reduction in total cardiovascular events (95% CI 4% to 15%). This was a slight attenuation from the 12% proportional reduction estimated by the Antithrombotic Trialists' Collaboration meta-

analysis, based on six randomised controlled trials (n=95,456).[43] There was no statistically significant heterogeneity in this estimate; it remained statistically significant throughout sensitivity analyses and did not appear to be modified according to a number of potential effect modifiers.[147 148] It is therefore appropriate to use this updated estimate from Berger and Seshasai of the proportional reduction in total cardiovascular events to model the benefits and harms of aspirin in the primary prevention of cardiovascular disease.

Of the two highest quality eligible meta-analyses, only Berger 2011 assessed major bleeding. That study found a 62% proportional increase in major bleeding with aspirin (95% CI 31% to 100%).[147] Berger noted a reliance upon each contributing trial's definition of major bleeding,[147] but Seshasai noted variation between trials in their definitions of major bleeding.[148] The most reliable estimate of major bleeding is therefore most likely to be that from the 2009 Antithrombotic Trialists' Collaboration (proportional increase in major non-cerebral bleeding with aspirin 54%, 95% CI 30% to 82%) because they were able to reclassify individual events according to standard criteria.[43] It is therefore appropriate to use the 2009 Collaboration's estimate of the proportional increase in major non-cerebral bleeding to model the benefits and harms of aspirin.

The conclusions of Raju and colleagues were more positive towards the use of aspirin in the primary prevention of cardiovascular disease of the four meta-analyses.[139] They stated "*Our results demonstrate a consistent pattern of reduced mortality in all of the aspirin primary prevention trials and a significant, albeit modest, reduction in all-cause mortality when the data are pooled. This reduction in all-cause tilts the balance between the benefits and risks of treatment in favour of the use of aspirin*".[139] However, as previously noted, their interpretation of the all-cause mortality outcome is questionable because the confidence interval included 1.00 (RR 0.94, 95% CI 0.88 to 1.00).

Berger 2011 and Seshasai 2012 do not support the routine use of aspirin in primary prevention, and note the importance of weighing individual likely benefits and harms from aspirin before initiating its use in those without established disease. Berger 2011 stated "*the current totality of evidence provides only modest support for a benefit of aspirin in patients without clinical cardiovascular disease, which is offset by its risk*" and that "*the decision to use aspirin for the prevention of a first myocardial infarction or stroke remains a complex issue. Weighing the overall benefit and risk requires careful consideration by the physician and patient before initiating aspirin for preventive therapy in patients without clinical*

cardiovascular disease".[147] Seshasai stated that "*despite important reductions in nonfatal myocardial infarction, aspirin prophylaxis in people without prior cardiovascular disease does not lead to reductions in either cardiovascular death or cancer mortality. Because the benefits are further offset by clinically important bleeding events, routine use of aspirin for primary prevention is not warranted and treatment decisions need to be considered on a case-by-case basis*".[148] Bartolucci also acknowledges the need to balance benefits and harms on an individual basis in their conclusion: *"The overall size of our sample and the differing cohorts within each study lend convincing evidence to the advantage of aspirin over placebo or no aspirin for decreasing the risk for cardiovascular events in a range of patients. However, the benefits of primary prevention with aspirin must be considered in relation to the potential risks on a patient-by-patient basis"*.[146]

The Japanese Primary Prevention Project trial was published after the eligible meta-analyses had been conducted. The trial was subject to some non-random and random error, and was discontinued prematurely because it was considered unlikely to be able to demonstrate a difference between groups in the primary outcome (total cardiovascular events) were follow-up to be continued as planned.[155] Although the trial's observed proportional effect on total cardiovascular disease event rate (hazard ratio 0.94, 95% CI 0.77 to 1.15) was lower that estimated by the two highest quality meta-analyses described above (risk ratio or odds ratio 0.90, 95% CI 0.85 to 0.96[147 148]), the Japanese Primary Prevention Project trial was subject to non-random error that is likely to have led to an underestimation of the true effect of aspirin on total cardiovascular disease.

In the second part of this chapter, the updated effect estimates identified in this systematic review were applied to age group, sex and cardiovascular risk categories. This modelling enabled an individualised assessment of the benefits (number of cardiovascular events avoided) and harms (number of additional major bleeds) of aspirin among people without established cardiovascular disease and eligible for the IMProving Adherence using Combination Therapy (IMPACT) polypill trial.

3.3. Modelling

3.3.1. Aims and hypotheses

The aims of this modelling section were to:

1. Estimate, by sex and age group, the number of total cardiovascular events avoided and major non-cerebral bleeds caused by aspirin alone in primary prevention.
2. Estimate, by sex and age group, the number of total cardiovascular events avoided and major non-cerebral bleeds caused by adding aspirin to blood pressure lowering therapy and a statin in primary prevention.

The hypotheses of this modelling section were that:
1. The number of total cardiovascular events avoided would exceed major non-cerebral bleeds by aspirin for men and women aged 18 to 79 years without established cardiovascular disease but with estimated 5-year cardiovascular disease 15% or greater.
2. The number of total cardiovascular events avoided would exceed major non-cerebral bleeds by aspirin when added to blood pressure lowering therapy and a statin for men and women aged 18 to 79 years without established cardiovascular disease but with estimated 5-year cardiovascular disease 15% or greater.

The age group and cardiovascular risk level were selected because these were inclusion criteria for the IMProving Adherence using Combination Therapy (IMPACT) polypill trial.

3.3.2. Methods

The United States Preventive Services Task Force tables were identified in chapter 2 as the most useful tool to use as the basis for modelling the benefits and harms of aspirin at this stage as they: (1) are currently incorporated in national guidelines, (2) do not appear to have any serious methodological limitations and (3) are able to provide an individualised assessment.[21]

In order to optimise their relevance to the New Zealand setting, the expected number of cardiovascular events over 5 years for hypothetical populations of 1000 people by 5-year cardiovascular risk (in 1% increments from 5% to 25%) was calculated. For example, 50 cardiovascular events would be expected over 5 years for 1000 people with 5-year cardiovascular risk 5%. The cardiovascular outcomes predicted in Framingham-based prediction models, such as the model used in New Zealand, are myocardial infarction, angina, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, congestive heart failure and cardiovascular-related death.[40] The number of cardiovascular events avoided with aspirin over 5 years was estimated by applying the proportional reduction in total cardiovascular events obtained by the Berger and Seshasai meta-analyses (i.e. 10%[147 148])

to the expected number of cardiovascular events over 5 years, for each 5-year cardiovascular risk category. Total cardiovascular events were defined as nonfatal myocardial infarction, nonfatal stroke (including haemorrhagic) or cardiovascular death (including death due to myocardial infarction or stroke) by Berger, and not specifically defined by Seshasai.[147 148]

The expected number of major non-cerebral bleeds over 5 years for hypothetical populations of 1000 people by sex and age was based on estimates of the incidence of serious upper gastrointestinal tract events derived from observational data by Hernandez-Diaz and Rodriguez.[81] Serious upper gastrointestinal tract events were defined as bleeding, perforation or other upper gastrointestinal tract event resulting in death, hospitalisation or visit to a specialist.[93] The incidence rates were for people without a history of upper gastrointestinal pain or gastrointestinal ulcer and not receiving aspirin or non-aspirin non-steroidal anti-inflammatory agents. The number of additional major non-cerebral bleeds caused by aspirin over 5 years was estimated by applying the proportional increase in major non-cerebral bleeds from the Antithrombotic Trialists' Collaboration 2009 meta-analysis (i.e. 54%[43]). The 2009 Collaboration defined major non-cerebral bleeds as a bleed (mainly gastrointestinal) requiring transfusion or resulting in death.[43]

The modelling was undertaken separately for two scenarios: firstly adding aspirin as monotherapy (as described above), and secondly when aspirin was prescribed in addition to a statin and blood pressure lowering therapy. For the second scenario, the number of cardiovascular events avoided with aspirin over 5 years was estimated by applying the same proportional reduction in total cardiovascular events (i.e. 10%) but the 5-year cardiovascular risk for each category was first reduced by the expected proportional reduction in total cardiovascular events from adding a statin and then adding a blood pressure lowering agent. It was assumed that statin therapy would reduce the risk of a major cardiovascular event (fatal and nonfatal) by 25%, based on a Cochrane Collaboration meta-analysis of 56,934 primary prevention participants from randomised controlled trials comparing statin with control.[156] It was assumed that blood pressure lowering therapy would reduce the risk of major cardiovascular events (defined as fatal or nonfatal stroke, coronary heart disease, heart failure or cardiovascular morbidity) by 18%, 15%, 13% and 15% for people with 5-year cardiovascular risk <11%, 11-15%, 15-21% and >21%, respectively, based on the Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis of individual participant data from 67,475 participants of randomised controlled trials.[52] Finally, it was assumed

that the joint effect of multiple medications is likely to be multiplicative (i.e. when a joint effect is the product of the risk ratios[44]), based on evidence from major randomised controlled trials[43 45-49] and as indicated by several authors[27 43 50 51]

3.3.3. Results

Aspirin monotherapy

The number of additional bleeds with aspirin monotherapy was equal to or greater than the number of cardiovascular events avoided for men aged 60-69 years with 5-year cardiovascular risk less than 7% and for men aged 70-79 years with 5-year cardiovascular risk less than 11% (Table 22).

Table 22. Modelled number of cardiovascular events averted and additional major non-cerebral bleeds with aspirin among men without cardiovascular disease, by cardiovascular risk and age group

5-year CVD risk	For 1000 men over 5 years							
	CVD events		Major non-cerebral bleeds					
	Expected	Avoided with aspirin	18-60 years		60-69 years		70-79 years	
			Expected	Extra with aspirin	Expected	Extra with aspirin	Expected	Extra with aspirin
5%	50	5	4	2	12	6	18	10
6%	60	6	4	2	12	6	18	10
7%	70	7	4	2	12	6	18	10
8%	80	8	4	2	12	6	18	10
9%	90	9	4	2	12	6	18	10
10%	100	10	4	2	12	6	18	10
11%	110	11	4	2	12	6	18	10
12%	120	12	4	2	12	6	18	10
13%	130	13	4	2	12	6	18	10
14%	140	14	4	2	12	6	18	10
15%	150	15	4	2	12	6	18	10
16%	160	16	4	2	12	6	18	10
17%	170	17	4	2	12	6	18	10
18%	180	18	4	2	12	6	18	10
19%	190	19	4	2	12	6	18	10
20%	200	20	4	2	12	6	18	10
21%	210	21	4	2	12	6	18	10
22%	220	22	4	2	12	6	18	10
23%	230	23	4	2	12	6	18	10
24%	240	24	4	2	12	6	18	10
25%	250	25	4	2	12	6	18	10

CVD=cardiovascular disease; GI=gastrointestinal; MI=myocardial infarction

Assumptions: 1. CVD events are MI, angina, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, congestive heart failure and CVD-related deaths.[40] 2. Proportional reduction in CVD events with aspirin is 10% and is the net effect of aspirin on fatal and nonfatal MI and stroke (including haemorrhagic).[147 148] 3. Major non-cerebral bleeds are GI bleeds, perforation or other upper gastrointestinal tract event resulting in death, hospitalisation or visit to a specialist.[93]

4. Age and sex-specific incidence of major non-cerebral bleeds is that derived from observational data and there is no history of upper GI pain or GI ulcer and no concomitant use of a non-aspirin non-steroidal anti-inflammatory agent.[81] 5. Proportional increase in major non-cerebral bleeds with aspirin is 54% and is the effect of aspirin on bleeds (mainly GI) requiring transfusion or resulting in death.[43]

Note: Area in grey is where the number of additional bleeds is equal to or greater than the number of CVD events

The number of additional bleeds with aspirin monotherapy was equal to or greater than the number of cardiovascular events avoided for women aged 70-79 years with 5-year cardiovascular risk less than 6% (Table 23).

Table 23. Modelled number of cardiovascular events averted and additional major non-cerebral bleeds with aspirin among women without cardiovascular disease, by cardiovascular risk and age group

5-year CVD risk	For 1000 women over 5 years							
	CVD events		Major bleeds					
	Expected	Avoided with aspirin	18-60 years		60-69 years		70-79 years	
			Expected	Extra with aspirin	Expected	Extra with aspirin	Expected	Extra with aspirin
5%	50	5	2	1	6	3	9	5
6%	60	6	2	1	6	3	9	5
7%	70	7	2	1	6	3	9	5
8%	80	8	2	1	6	3	9	5
9%	90	9	2	1	6	3	9	5
10%	100	10	2	1	6	3	9	5
11%	110	11	2	1	6	3	9	5
12%	120	12	2	1	6	3	9	5
13%	130	13	2	1	6	3	9	5
14%	140	14	2	1	6	3	9	5
15%	150	15	2	1	6	3	9	5
16%	160	16	2	1	6	3	9	5
17%	170	17	2	1	6	3	9	5
18%	180	18	2	1	6	3	9	5
19%	190	19	2	1	6	3	9	5
20%	200	20	2	1	6	3	9	5
21%	210	21	2	1	6	3	9	5
22%	220	22	2	1	6	3	9	5
23%	230	23	2	1	6	3	9	5
24%	240	24	2	1	6	3	9	5
25%	250	25	2	1	6	3	9	5

CVD=cardiovascular disease; GI=gastrointestinal; MI=myocardial infarction

Assumptions: 1. CVD events are MI, angina, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, congestive heart failure and CVD-related deaths.[40] 2. Proportional reduction in CVD events with aspirin is 10% and is the net effect of aspirin on fatal and nonfatal MI and stroke (including haemorrhagic).[147 148] 3. Major non-cerebral bleeds are GI bleeds, perforation or other upper gastrointestinal tract event resulting in death, hospitalisation or visit to a specialist.[93]

4. Age and sex-specific incidence of major non-cerebral bleeds is that derived from observational data and there is no history of upper GI pain or GI ulcer and no concomitant use of a non-aspirin non-steroidal anti-inflammatory agent.[81] 5. Proportional increase in major non-cerebral bleeds with aspirin is 54% and is the effect of aspirin on bleeds (mainly GI) requiring transfusion or resulting in death.[43]

Note: Area in grey is where the number of additional bleeds is equal to or greater than the number of CVD events

Aspirin in combination therapy

When adding aspirin to combination treatment with a statin and blood pressure lowering agent, the number of additional bleeds was equal to or greater than the number of cardiovascular events avoided for the men aged 60-69 years with untreated 5-year cardiovascular risk less than 11% and men aged 70-79 years with untreated 5-year cardiovascular risk less than 17% (Table 24).

Table 24. Modelled number of cardiovascular events averted with aspirin and additional major non-cerebral bleeds with aspirin when added to statin and blood pressure lowering therapy among men without cardiovascular disease, by cardiovascular risk and age group

Un-treated 5-year CVD risk	5-year CVD risk on statin	5-year CVD risk on statin and BP lowering	For 1000 men over 5 years							
			CVD events		Major bleeds					
			Expected	Avoided with aspirin	18-60 years		60-69 years		70-79 years	
					Expected	Extra with aspirin	Expected	Extra with aspirin	Expected	Extra with aspirin
5%	4%	3%	31	3	4	2	12	6	18	10
6%	5%	4%	37	4	4	2	12	6	18	10
7%	5%	4%	43	4	4	2	12	6	18	10
8%	6%	5%	49	5	4	2	12	6	18	10
9%	7%	6%	55	6	4	2	12	6	18	10
10%	8%	6%	62	6	4	2	12	6	18	10
11%	8%	7%	68	7	4	2	12	6	18	10
12%	9%	7%	74	8	4	2	12	6	18	10
13%	10%	8%	80	8	4	2	12	6	18	10
14%	11%	9%	89	9	4	2	12	6	18	10
15%	11%	10%	96	10	4	2	12	6	18	10
16%	12%	10%	102	10	4	2	12	6	18	10
17%	13%	11%	108	11	4	2	12	6	18	10
18%	14%	11%	115	11	4	2	12	6	18	10
19%	14%	12%	121	12	4	2	12	6	18	10
20%	15%	13%	131	13	4	2	12	6	18	10
21%	16%	14%	137	14	4	2	12	6	18	10
22%	17%	14%	144	14	4	2	12	6	18	10
23%	17%	15%	150	15	4	2	12	6	18	10
24%	18%	16%	157	16	4	2	12	6	18	10
25%	19%	16%	163	16	4	2	12	6	18	10

CVD=cardiovascular disease; GI=gastrointestinal; MI=myocardial infarction

Assumptions: 1. CVD events are MI, angina, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, congestive heart failure and CVD-related deaths.[40] 2. Proportional reduction in CVD events with aspirin is 10% and is the net effect of aspirin on fatal and nonfatal MI and stroke (including haemorrhagic).[147 148] 3. Major non-cerebral bleeds are GI bleeds, perforation or other upper gastrointestinal tract event resulting in death, hospitalisation or visit to a specialist.[93]

4. Age and sex-specific incidence of major non-cerebral bleeds is that derived from observational data and there is no history of upper GI pain or GI ulcer and no concomitant use of a non-aspirin non-steroidal anti-inflammatory agent.[81] 5. Proportional increase in major non-cerebral bleeds with aspirin is 54% and is the effect of aspirin on bleeds (mainly GI) requiring transfusion or resulting in death.[43] 6. Proportional reduction in CVD events (fatal and nonfatal) with statins is 25%.[156] 7. Proportional reduction in CVD events (fatal and nonfatal stroke, coronary heart disease, heart failure or cardiovascular morbidity) with blood pressure lowering agents is 18% (5-year CVD risk <11%), 15% (5-year CVD risk 11-15%), 13% (5-year CVD risk 15-21%), 15% (5-year CVD risk >21%).[52] 8.Joint effects of multiple medications multiplicative (i.e. the product of the risk ratios).[43]

Note: Area in grey is where the number of additional bleeds is equal to or greater than the number of CVD events

When adding aspirin to combination treatment with a statin and blood pressure lowering agent, the number of additional bleeds was equal to or greater than the number of cardiovascular events avoided for women aged 60-69 years with untreated 5-year cardiovascular risk less than 6% and women aged 70-79 years with untreated 5-year cardiovascular risk less than 9% (Table 25).

Table 25. Modelled number of cardiovascular events averted with aspirin and additional major non-cerebral bleeds with aspirin when added to statin and blood pressure lowering therapy among women without cardiovascular disease, by cardiovascular risk and age group

Un-treated 5-year CVD risk	5-year CVD risk on statin	5-year CVD risk on statin and BP lowering	For 1000 women over 5 years							
			CVD events		CVD events					
			Expected	Avoided with aspirin	18-60 years		60-69 years		70-79 years	
					Expected	Extra with aspirin	Expected	Extra with aspirin	Expected	Extra with aspirin
5%	4%	3%	31	3	2	1	6	3	9	5
6%	5%	4%	37	4	2	1	6	3	9	5
7%	5%	4%	43	4	2	1	6	3	9	5
8%	6%	5%	49	5	2	1	6	3	9	5
9%	7%	6%	55	6	2	1	6	3	9	5
10%	8%	6%	62	6	2	1	6	3	9	5
11%	8%	7%	68	7	2	1	6	3	9	5
12%	9%	7%	74	8	2	1	6	3	9	5
13%	10%	8%	80	8	2	1	6	3	9	5
14%	11%	9%	89	9	2	1	6	3	9	5
15%	11%	10%	96	10	2	1	6	3	9	5
16%	12%	10%	102	10	2	1	6	3	9	5
17%	13%	11%	108	11	2	1	6	3	9	5
18%	14%	11%	115	11	2	1	6	3	9	5
19%	14%	12%	121	12	2	1	6	3	9	5
20%	15%	13%	131	13	2	1	6	3	9	5
21%	16%	14%	137	14	2	1	6	3	9	5
22%	17%	14%	144	14	2	1	6	3	9	5
23%	17%	15%	150	15	2	1	6	3	9	5
24%	18%	16%	157	16	2	1	6	3	9	5
25%	19%	16%	163	16	2	1	6	3	9	5

CVD=cardiovascular disease; GI=gastrointestinal; MI=myocardial infarction

Assumptions: 1. CVD events are MI, angina, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, congestive heart failure and CVD-related deaths.[40] 2. Proportional reduction in CVD events with aspirin is 10% and is the net effect of aspirin on fatal and nonfatal MI and stroke (including haemorrhagic).[147 148] 3. Major non-cerebral bleeds are GI bleeds, perforation or other upper gastrointestinal tract event resulting in death, hospitalisation or visit to a specialist.[93]

4. Age and sex-specific incidence of major non-cerebral bleeds is that derived from observational data and there is no history of upper GI pain or GI ulcer and no concomitant use of a non-aspirin non-steroidal anti-inflammatory agent.[81] 5. Proportional increase in major non-cerebral bleeds with aspirin is 54% and is the effect of aspirin on bleeds (mainly GI) requiring transfusion or resulting in death.[43] 6. Proportional reduction in CVD events (fatal and nonfatal) with statins is 25%.[156] 7. Proportional reduction in CVD events (fatal and nonfatal stroke, coronary heart disease, heart failure or cardiovascular morbidity) with blood pressure lowering agents is 18% (5-year CVD risk <11%), 15% (5-year CVD risk 11-15%), 13% (5-year CVD risk 15-21%), 15% (5-year CVD risk >21%).[52] 8.Joint effects of multiple medications multiplicative (i.e. the product of the risk ratios).[43]

Note: Area in grey is where the number of additional bleeds is equal to or greater than the number of CVD events

3.3.4. Discussion

For people without a history of upper gastrointestinal pain or gastrointestinal ulcer and not receiving concomitant non-aspirin non-steroidal anti-inflammatory agents, the benefits of aspirin (number of cardiovascular events avoided) outweighed its harms (additional major gastrointestinal bleeds) for men and women aged 18 to 79 years with estimated 5-year cardiovascular risk greater than 10% (as monotherapy) or greater than 16% (when added to statin and blood pressure lowering therapy), using modelled data. This finding is supportive of current New Zealand guidelines that recommend aspirin for people without established

cardiovascular disease but with 5-year cardiovascular risk greater than 20%.[7] Further, the tables allow individualised assessment of the balance of benefits and harms.

The modelling enabled consideration of the appropriateness of the inclusion criteria for the IMProving Adherence using Combination Therapy (IMPACT) polypill trial. The IMPACT trial included men and women aged 18 to 79 years without established cardiovascular disease but with estimated 5-year cardiovascular risk 15% or greater. For people aged 70 to 79 years and with 5-year cardiovascular risk 15%, the number of cardiovascular events avoided with aspirin (when added to statin and blood pressure lowering therapy) was estimated to be twice the number of additional bleeds with aspirin for women, but the same as the number of additional bleeds with aspirin for men. The IMPACT trial therefore excluded men aged 70 years or more without established cardiovascular disease.

The modelled tables are an advance on what is currently available in New Zealand, but have two major limitations. First, there are differences in the event definitions used for absolute and relative risks that will limit the accuracy of the model. For example, the New Zealand 5-year risk equation (based on the Framingham equation) predicts a broader range of cardiovascular events (myocardial infarction, angina, ischaemic stroke, transient ischaemic attack, peripheral vascular disease, congestive heart failure and cardiovascular deaths[40]) than were used in meta-analyses by Berger or Seshasai when they estimated the effect of aspirin on total cardiovascular events (fatal and nonfatal myocardial infarction, stroke and cardiovascular death[147 148]). There is also a slight mismatch in that the 5-year risk equation does not include haemorrhagic stroke, whereas the estimate of the effect of aspirin on total cardiovascular events is a net effect, taking into account an increase in haemorrhagic strokes and a reduction in ischaemic strokes.[147 148]

Secondly, although sex and age are taken into account, a number of other important bleeding risk factors are not. The bleeding incidence data are for people with no history of upper gastrointestinal pain or ulcer, and not using concomitant non-aspirin non-steroidal anti-inflammatory agents.[81] The 2009 Antithrombotic Trialists' Collaboration found in their individual participant data meta-analysis that in addition to age, sex and aspirin, other independent risk factors for major bleeds were: diabetes, smoking, higher blood pressure and higher body mass index.[43] Bleeding estimates in this model are therefore likely to underestimate the number of additional bleeds with aspirin because they underestimate 'baseline' bleeding risk, especially for people with multiple comorbidities.

In the future, proportional estimates of the benefits and harms of aspirin in primary prevention will be further refined, particularly for those at high risk of their first event, with a number of large trials due to present their results over the next 5 years (Table 26). The average absolute risk of cardiovascular disease among control group participants in the first six trials was 0.57% per year, and only 2% of participants had an estimated 5-year risk of coronary heart disease of 10% of more at baseline, which limited the reliability of findings in this subgroup.[43] Given the similarity in the magnitude of the proportional reduction in cardiovascular disease with aspirin in the low risk primary prevention (RR 0.88, 95% CI 0.82 to 0.94) and secondary prevention populations (RR 0.81, 95% CI 0.75 to 0.87),[43] it is unlikely that the proportional reduction in cardiovascular disease with aspirin in intermediate or high risk primary prevention populations is different. These upcoming trials will test this assumption, and will also contribute to the expanding evidence base on bleeding with aspirin, as well as non-cardiovascular benefits of aspirin, such as cancer prevention.

Table 26. Key features of randomised controlled trials in progress that are assessing aspirin for the primary prevention of cardiovascular disease

Trial	**Inclusion criteria**	**Aspirin (mg)**	**Control**	**Additional treatment**	**N**	**Follow-up (years)**	**Primary outcome**	**Other relevant outcomes**	**Results due**
ASPREE [157 158]	≥70 years without CVD	100	Placebo	Nil	19,000	5	Death, dementia or physical disability	Bleeds	2018
ACCEPT-D[159 160]	Diabetes without CVD	100	No aspirin	Simva-statin (all)	5,170	5	CVD	Bleeds, death	Un-known
ASCEND [161 162]	Diabetes without CVD	100	Placebo	Omega-3 fatty acid (2x2 trial)	15,480	7.5	CVD	Bleeds	2017
ARRIVE[100 101]	Moderate risk of CVD (20-30% 10-year risk) and no CVD	100	Placebo	Nil	12,000	6	CVD	Cancer, death	2016
CVD prevention in chronic kidney disease [163]	45-79 years (55-79 for women) and chronic kidney disease (stage 3 or 4) and no CVD	100	No aspirin	Nil	97	5	CVD	Bleeds	2015
TIPS-3 [102 103]	≥55 years (≥60 for women) and INTERHEART risk score* ≥10 and no CVD	75	Placebo	Polycap DS†, Vitamin D (2x2x2 trial)	5,000	5	CVD, cancer, fractures		2020

ACCEPT-D=Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes; ASCEND=A Study of Cardiovascular Events In Diabetes; ASPREE=ASPirin in Reducing Events in the Elderly; CVD=cardiovascular disease; N=number of participants; TIPS=The International Polycap Study

*The INTERHEART risk score estimates the risk of a first myocardial infarction for an international population.[164]

†Polycap DS contains (hydrochlorothiazide 25mg, atenolol 100mg, ramipril 10mg and simvastatin 40mg).

Note: compiled from articles reviews and a search of clinicaltrials.gov (using the search terms "aspirin" and "primary prevention" and restricted to intervention studies) on 18 October 2014)

3.4. Summary

In this chapter, meta-analyses of randomised controlled trials of aspirin in primary prevention and any subsequent randomised controlled trials were systematically reviewed and critically appraised. Robust, up to date estimates were obtained for the proportional effect of aspirin on major cardiovascular events (10% decrease) and major non-cerebral bleeds (54% increase). These proportional effects of aspirin were applied to absolute rates of major cardiovascular events and bleeds to balance the benefits (reduction in major cardiovascular events) and harms (additional major bleeds) in groups by sex and age. The benefits of aspirin outweighed its harms for men and women aged 18 to 79 years with estimated 5-year cardiovascular risk greater than 10% (as monotherapy) or greater than 16% (when added to statin and blood pressure lowering therapy), using modelled data. These estimates are applicable to people without a history of upper gastrointestinal pain or gastrointestinal ulcer and not receiving concomitant non-aspirin non-steroidal anti-inflammatory agents, and without any other contraindication to aspirin.

The modelling enabled consideration of the appropriateness of the inclusion criteria for the IMProving Adherence using Combination Therapy (IMPACT) trial, which is described in the next chapter. The IMPACT trial evaluated a polypill containing a statin, blood pressure lowering agents and aspirin, and included men and women aged 18 to 79 years either with established cardiovascular disease, or without established cardiovascular disease but with estimated 5-year cardiovascular risk of 15% or more. For people aged 70 to 79 years and with 5-year cardiovascular risk 15%, the number of cardiovascular events avoided with aspirin (when added to statin and blood pressure lowering therapy) was estimated to be twice the number of additional bleeds with aspirin for women, but the same as the number of additional bleeds with aspirin for men. The IMPACT trial therefore excluded men aged 70 years or more without established cardiovascular disease.

Chapter 4. IMProving Adherence using Combination Therapy (IMPACT) randomised controlled trial: Methods

4.1. Introduction

Although the polypill has been shown to improve adherence, its effect on blood pressure and cholesterol has been inconsistent when compared with usual care and there is only a relatively small evidence base from which to assess its safety among people with indications. A New Zealand randomised controlled trial could provide clarity on the potential role of a polypill in enhancing the implementation of guideline-recommended therapy in this country by providing local evidence. In addition, a trial could expand the international evidence base regarding the effect of polypill-based compared with usual care on blood pressure and cholesterol, as well as safety. Such a trial was conducted, the IMProving Adherence using Combination Therapy (IMPACT) trial, and forms the second part of this thesis.

This chapter describes the methods of the IMPACT trial. The aims and hypotheses of the IMPACT trial are presented first. The design of the trial is described with sections on the trial population, sample size, randomisation, allocation concealment, the intervention and control, blinding, outcomes, data collection, analyses and trial governance and management. Trial processes are described including training, recruitment, baseline and follow-up assessments and pharmacovigilance. The rationale for key design elements is then provided, ending with a particular emphasis on the way in which the trial implemented an indigenous right-based perspective.

4.2. Aims and hypotheses

The aims of the trial were to investigate the following.

1. Does polypill-based care increase the proportion of people at high risk of cardiovascular disease who are adherent to guideline-recommended medication over a one-year period, compared with usual care?
2. Does polypill-based care reduce blood pressure and low density lipoprotein cholesterol in people at high risk of cardiovascular disease over a one-year period, compared with usual care?

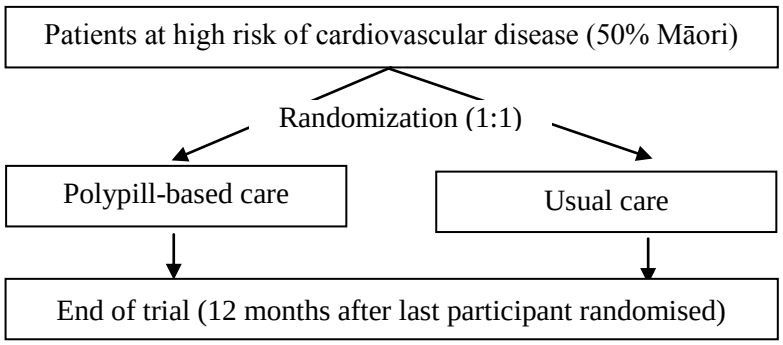
The hypotheses of the trial were that, compared with usual care:

1. A greater proportion of people at high risk of cardiovascular disease receiving polypill-based care are adherent to guideline-recommended medication over a one-year period.
2. The reduction in blood pressure and low density lipoprotein cholesterol is greater in people at high risk of cardiovascular disease receiving polypill-based care over a one-year period.

4.3. Design

IMPACT was an open-label, parallel, randomised controlled trial (Figure 11). The trial sought to randomise equal numbers of Māori and non-Māori to polypill-based care or usual care. Follow-up for each participant was to continue until 12 months after the last participant had been randomised.

Figure 11. Overall IMPACT trial design



IMPACT=IMProving Adherence using Combination Therapy

4.3.1. Trial population

Primary Health Organisation

Primary Health Organisations are groups of providers working with their communities to improve health and reduce health inequalities by coordinating and providing essential primary health care services, including general practice services, to an enrolled population in New Zealand.[165]

Primary Health Organisations were eligible for inclusion in the trial if they met ALL of the following criteria:

- Located within the Auckland or Waikato regions of New Zealand
- Likely to have high enrolment of Māori

    - Primary Health Organisations were sought that were Māori-led, had a large enrolled population or that were located within an area in which a high proportion of Māori resided.
    - The trial aimed to randomise equal numbers of Māori and non-Māori so that information about Māori would be obtained to at least the same depth and breadth as that obtained for non-Māori. This meant oversampling of Māori who comprise just 15% of the total New Zealand population.[32]
- Endorsed the IMPACT trial
- Supported the IMPACT trial team approaching general practices affiliated with the Primary Health Organisation

General practices and general practitioners

General practices were eligible for inclusion in the trial if they met ALL of the following criteria:

- Affiliated with an eligible Primary Health Organisation
- Had practice electronic records accessible to trial staff
- Had the capacity for at least one general practitioner to participate in the trial

General practitioners were eligible for inclusion in the trial if they met ALL of the following criteria:

- Working (either part-time or full-time) at a participating general practice
- Had completed training on the trial and trial procedures
- Agreed to abide by the trial protocol
- Were willing to prescribe the polypill to participants randomised to polypill-based care and to notify trial staff of any serious adverse events in any trial participant
- Had signed a contract regarding their responsibilities on the trial

Pharmacies

Pharmacies were eligible for inclusion in the trial if they met ALL of the following criteria:

- At least one pharmacist in the pharmacy had completed training on the trial and trial procedures
- Agreed to abide by the trial protocol
- Agreed to stock the polypill and store it at <25°C

- Were willing to dispense the polypill only to participants randomised to polypill-based care (according to their trial identification card) and on receipt of a prescription for the polypill
- Had signed a contract regarding their responsibilities on the trial

Participants

Patients were eligible for inclusion in the trial if they met ALL of the following criteria.

- Were aged 18-79 years
- Were at high risk of cardiovascular disease (as defined in Table 27)
- Their usual general practitioner considered that all of the medications in at least one of two polypills available for the trial were indicated for them
- Their usual general practitioner was uncertain as to whether therapy would be best provided as a polypill or with usual care (i.e. 'clinical equipoise', see below)
- Were able to give informed consent

The definition of 'high risk' of cardiovascular disease (Table 27) was based on New Zealand cardiovascular guidelines from 2003.[36] These were the most up to date guidelines when the trial was initially designed and electronic case record forms with an integrated cardiovascular risk calculator developed, in 2006. The guidelines were updated in 2009,[39] just prior to the initiation of trial recruitment. The definition used in the IMPACT trial is largely consistent with the 2009 update with some minor exceptions. For example, the trial definition includes metabolic syndrome as an adjustment factor in line with 2003 guidelines, whereas this was dropped in the 2009 update.

Table 27. Definition of 'high risk' of cardiovascular disease for the IMPACT trial

Category (5-year CV risk)	**Definition**
Clinical (20%+)	• Previous history of CVD (coronary artery, cerebrovascular or peripheral vascular) OR • Familial hypercholesterolaemia, familial ApoB or familial combined dyslipidaemia OR • Diabetes and renal disease (diabetic nephropathy or other)
Extreme risk factor levels (>15%)	• Total cholesterol greater than 8 mmol/L OR • Total cholesterol:HDL cholesterol ratio greater than 8 OR • Blood pressure consistently greater than 170/100 mm Hg
Framingham-based estimate (15%+)	1. Estimate risk with Framingham-based cardiovascular risk calculator 2. Multiply risk by 1.15 for each of the following treatments being taken by the patient: antiplatelet, blood pressure lowering, cholesterol lowering* 3. Add 5% if the patient meets any one of the following: • Ethnicity Māori, Pacific or Indian subcontinent • Diabetes + microalbuminuria • Type 2 diabetes greater than or equal to 10 years • Diabetes + HbA1c consistently greater than 8% • Family history of heart disease or ischaemic stroke in a first degree relative (father or brother less than 55 years, or mother or sister less than 65 years) • Metabolic syndrome; three or more of the following: (1) Abdominal obesity (waist circumference $\geq$ 100cm [men] or 90cm [women]), (2) Fasting triglycerides $\geq$ 1.7 mmol/L, (3) HDL cholesterol < 1.0 mmol/L (men) or 1.3 mmol/L (women), (4) Blood pressure $\geq$ 130 mm Hg (systolic) or 85 mm Hg (diastolic), (5) Fasting glucose $\geq$ 6.1 mmol/L

CV=cardiovascular; CVD=cardiovascular disease; IMPACT=IMProving Adherence using Combination Therapy
*Adjustment for current preventive medications not part of the NZ guidelines.
Note: categories and criteria based on the 2003 New Zealand cardiovascular guidelines[36] except where indicated.

'Clinical equipoise' (when there is no clear advantage or disadvantage of one treatment option over the other) is a requirement for the ethical conduct of clinical trials.[166] For the IMPACT trial, this requirement was met according to the published literature and for provider-patient decision making. In terms of the literature, there is currently uncertainty about the actual (as opposed to potential) benefits and harms of a polypill-based strategy. At the level of the patient, general practitioners were asked to confirm that they were uncertain whether therapy for each individual patient was best provided as a polypill or with usual care.

Patients were excluded if ANY of the following criteria were met.

- Male and aged 70 years or more and without established cardiovascular disease (because of the increased risk of bleeding with aspirin, as discussed in chapter 3)
- Contraindication to any of the components of the relevant polypill
- Confirmed clinical diagnosis of congestive heart failure (e.g. by echocardiography, because New Zealand heart failure guidelines[167] recommend higher dosages of angiotensin-converting enzyme inhibitors for people with heart failure than were included within the trial polypill)
- Currently treated for congestive heart failure
- Documented haemorrhagic stroke
- Active stomach or duodenal ulcer

- Receiving treatment with warfarin or dabigatran
- Their usual general practitioner considered that changing the patient's cardiovascular medications would put the patient at risk (e.g. if on a high dose beta-blocker that was required to manage angina or for rate control in atrial fibrillation)
- There was a known situation where the medication regimen was likely to change for a significant length of time (e.g. planned coronary bypass graft operation)
- Patient was unlikely to complete the trial or the trial procedures (e.g. due to a life-threatening condition other than cardiovascular disease or because they were planning to move to a different part of the country)

4.3.2. Sample size

The trial statistician estimated that 600 participants would provide 95% power at 2p = 0.05 to detect a 0.25 mmol/L difference in low density lipoprotein cholesterol and 4 mm Hg difference in systolic blood pressure between the intervention and control groups, assuming standard deviations around the change from baseline score of 0.8 mmol/L and 14 mm Hg respectively. This would also provide over 95% power to detect a 30% relative improvement in adherence (e.g. from 50% to 65% adherence). The recruitment target was revised down to 500 participants given available funding resources, which provided 89-93% power to detect the same risk factor differences and 92% power to detect a 30% relative improvement in adherence (see rationale for reduction in sample size in 4.9.2). Recruitment of equal numbers of Māori and non-Māori was planned to assess the consistency of effects across these group (rationale for equal recruitment provided in 4.9.1).

4.3.3. Randomisation and allocation concealment

Participants were randomised to either polypill-based care or usual care (1:1). Randomisation was activated by the general practitioner via the trial website. As randomisation was performed by a centralised online system, participants, general practitioners and trial staff had no way of knowing in advance whether a particular participant would be allocated to polypill-based or usual care. Likewise, participants, general practitioners and trial staff had no way of influencing allocation to polypill-based or usual care during the randomisation process.

Randomisation used a minimisation algorithm with the following factors: Primary Health Organisation, history of cardiovascular disease (yes/no), level of baseline medication adherence (whether or not the participant self-reported current use of antiplatelet, statin and

combination [≥ 2] blood pressure lowering agents) and ethnicity (Māori/non-Māori). As each successive patient was randomised, the minimisation algorithm calculated any imbalance within each of these factors. The probability that the patient was allocated to the treatment group with the lowest count was 0.9. This meant that the randomisation process minimised any imbalances between the numbers of patients in each treatment group (i.e. polypill vs usual care) according to Primary Health Organisation, history of cardiovascular disease, baseline medication adherence and ethnicity.

4.3.4. Intervention and control

The intervention was access to a once-daily polypill, called the 'Red Heart Pill' (developmen described below). Two versions were available with the following components:

- Version 1 contained aspirin 75mg, simvastatin 40mg, lisinopril 10mg and atenolol 50mg
- Version 2 contained aspirin 75mg, simvastatin 40mg, lisinopril 10mg and hydrochlorothiazide 12.5mg

The rationale for the components of the polypills is provided in 4.8.5.

Following randomisation, the participant's cardiovascular medication was reviewed by their usual general practitioner, who was encouraged to manage participants irrespective of treatment allocation in accordance with New Zealand Cardiovascular Risk Assessment and Management Guidelines.[36 39] The polypill had been manually added to the formulary within the electronic practice management system of all participating general practitioners, as choosing e-prescribing items via this electronic list is the usual method of prescribing among New Zealand general practitioners. General practitioners could then choose which version of the polypill to prescribe, and were able to prescribe additional medications (including cardiovascular medications) that they considered appropriate.

The polypill was dispensed by community pharmacists, along with usual medications, on presentation of a prescription. Participants were required to pay the standard co-payment for a single government-subsidised medicine thus mimicking real practice were the polypill to be funded by New Zealand's Pharmaceutical Management Agency (PHARMAC). The standard co-payment was $3 per item (up to a maximum of 20 items per family per year, after which time there was no patient co-payment for the rest of the year). From 1 January 2013 the standard co-payment increased to $5 per item (again, up to a maximum of 20 items per family per year).

The control was usual management, without access to the Red Heart Pill. As with the intervention group, the participant's cardiovascular medication was reviewed by their usual general practitioner, who was encouraged to manage participants irrespective of treatment allocation in accordance with New Zealand Cardiovascular Risk Assessment and Management Guidelines.[36 39] Usual care medications were also dispensed on presentation of a prescription to a community pharmacist with payment of the standard co-payment for each government-subsidised medicine.

Development of the Red Heart Pill

The Red Heart Pill was developed by Dr Reddy's Laboratories Ltd, the largest pharmaceutical company in India, in consultation with Professor Anthony Rodgers and other senior physicians. Feasibility studies for pill development began in late 2002 and the polypill was eventually approved for use in the IMPACT trial in 2009. The Red Heart Pill was manufactured in a centre approved by the United States Food and Drug Administration and in accordance with Good Manufacturing Practice standards. Dr Reddy's Laboratories Ltd supplied the two polypill versions at no cost to the trial. While the components of the Red Heart Pill are registered medicines in New Zealand, the Red Heart Pill itself is not. Approval under Section 30 of the Medicines Act 1981 was therefore obtained for both versions of the Red Heart Pill to enable their use in the trial.

In order to meet regulatory, as well as clinical and ethical, requirements, the Red Heart Pill needed to be bioequivalent to its separate components prior to being used in the trial. Achieving adequate bioequivalence and stability (which affects product shelf-life) proved to be a significant challenge because of the inclusion of aspirin in the Red Heart Pill. Unlike the other components of the Red Heart Pill, aspirin is pharmaceutically unstable.[168] Degradation of aspirin can also make other drugs more reactive, causing interaction products to be formed.[168]

The first formulation (developed between 2002 and 2007) was a bi-layered tablet, in which aspirin was separated from the antihypertensives (Figure 12). This formulation did not ultimately meet bioequivalence or stability requirements.

Figure 12. Red Heart Pill formulated as a bi-layered tablet

White layer: aspirin and simvastatin; pink layer: antihypertensives

The second formulation (developed between 2008 and 2009) was a capsule containing an antihypertensive tablet (pink), a simvastatin caplet and an aspirin tablet (Figure 13). This formulation did meet bioequivalence and stability requirements and was the formulation approved for, and used in, the IMPACT trial.

Figure 13. Red Heart Pill formulated as a single capsule

Capsule contents (left to right): antihypertensive tablet (pink), simvastatin caplet, aspirin tablet

4.3.5. Blinding

Blinding of participants, research nurses and general practitioners to trial medication allocation was not possible. Given that participants were at high risk of cardiovascular disease and were indicated for cardiovascular preventive medication it would have been unethical to have a no treatment or placebo comparator. The polypill is a fixed dose combination treatment and the potential benefits of this approach (e.g. easier to prescribe /

take) necessitated an open-label design, and a usual care comparator with currently available medications, to determine the efficacy and safety of a polypill-based approach.

A number of strategies were used in order to reduce the risk of bias associated with the open-label design. Blood pressure was obtained by an automated sphygmomanometer and all recordings were logged, to ensure that selective measures were not used for individual participants. Low density lipoprotein cholesterol was obtained by community laboratories blind to participation in the trial and treatment allocation. Self-reported medication use was compared with biological measures (blood pressure and low density lipoprotein cholesterol) and dispensing data. Pre-specified cardiovascular, renal and bleeding events were adjudicated by a Clinical Adjudication Committee blind to treatment allocation and independent of trial researchers (Prospective Randomised Open Blinded End-point, PROBE, design[169]). During the review of the results within the trial team, investigators were blinded to treatment allocation and all results presented as treatment A and B. The results were unblinded only after the final statistical report had been completed.

4.3.6. Primary outcomes

The primary outcomes investigated the *effectiveness* of polypill-based care. The primary outcomes were:

- Proportion that self-reported use of an antiplatelet, statin and two or more blood pressure lowering agents at 12 months
- Change in blood pressure over 12 months
- Change in low density lipoprotein cholesterol over 12 months

The reason for selecting each of these outcomes is provided below, along with how each outcome was measured. All primary outcomes were defined prior to the commencement of the trial and recorded in the Australian New Zealand Clinical Trial Registry (ACTRN12606000067572).

Proportion that self-reported use of an antiplatelet, statin and two or more blood pressure lowering agents at 12 months

Adherence to aspirin, statin and blood pressure lowering therapy was chosen to reflect contemporaneous guidelines[39] that recommended concomitant use of all three recommended medication modalities in trial participants. The use of two or more blood

pressure lowering agents was specified in this outcome for a number of reasons. First, two or more blood pressure lowering agents are specifically indicated in some situations (e.g. a beta-blocker and an angiotensin converting enzyme [ACE] inhibitor for people with significant left ventricular impairment following a myocardial infarction; a thiazide diuretic and an ACE inhibitor for people who have had a stroke or transient ischaemic attack).[39] Second, more than one blood pressure lowering agent is frequently required to lower blood pressure to optimum levels.[39] Third, low dose combinations of blood pressure lowering therapies can achieve greater reductions in blood pressure and reduced side effects than single blood pressure lowering therapies at maximal dose.[39]

Adherence is defined by the World Health Organization as "*the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*".[26] As there is no established gold standard for measuring adherence[26 170 171] the advantages and disadvantages of different methods of measuring adherence were considered prior to determining which would be the most suitable for the IMPACT trial.

Adherence can be measured directly or indirectly.[172] Direct measures include observing patients taking medication (directly observed therapy) and blood tests for the drug or a metabolite.[172] If a patient is observed to put their medication in their mouth, there is a high degree of certainty that they will swallow it and can therefore be regarded as being adherent to it. Disadvantages to this approach are that it would be very expensive and intrusive in this setting.[170] Cardiovascular medications are taken at least once a day, hundreds of patients were to be recruited and the follow up duration was to be at least 12 months. Cardiovascular medications are detectable in the blood stream therefore a blood test can prove that a patient has taken a particular medication. However given that there were no restrictions on the kind of cardiovascular medications taken it would have been very expensive and therefore not feasible to test every participant's blood for every possible antiplatelet, blood pressure lowering agent and statin. Further, this method provides no information about adherence between blood tests.

Indirect measures include self-report, pill counts, electronic medication devices, prescription data and dispensing data. Self-report is a practical and valid way to measure adherence in clinical practice according to a review of measures of adherence.[173] Further, self-reported non-adherence has been associated with an increase in cardiovascular events in a cohort of

patients with stable coronary heart disease.[174] However, self-reported measures are prone to bias by inaccurate recall or social desirability, when an overly optimistic estimation of adherence is provided to a healthcare provider.[170] Counting remaining pills seems to provide a potential solution to understanding adherence over time, but this method can easily be manipulated[170] (e.g. any missing medication might have been taken all at once or discarded prior to the pill count). Electronic medication devices are more difficult to manipulate than pill counts because the times they have been opened can be recorded.[172] Such devices are expensive and would have been difficult to use on this trial given that there was likely to be a lot of variation between patients in their treatment regimens with a usual care comparator and use of concomitant medication.

Prescription and dispensing data have become an attractive option for measuring adherence with the increasing availability of electronic records and databases.[170] In New Zealand there is near 100% use of electronic prescribing in general practice. The limitation of using prescription data is that these data are not collected centrally in New Zealand, meaning that it needs to be accessed from the general practice directly. This is logistically difficult, and still does not ensure complete coverage of prescription data because patients can change the general practice with which they are enrolled and are able to attend a practice in which they are not enrolled. Further, even if a patient receives a prescription for a medication, they may not necessarily have the prescription dispensed or take it as prescribed.

Dispensing data have the advantage of being more proximal to the patient actually taking their medication than prescription data and such data are collected nationally. This means that even if the patient moves practice, any medication dispensed to them in New Zealand is recorded within the national dispensing database. The main limitation of measuring adherence in the IMPACT trial with dispensing data was uncertainty regarding the extent to which aspirin would be underrepresented because it is available over the counter as well as on prescription.

On balance the most suitable measure of adherence for the IMPACT trial was considered to be self-report. Medications were classified as antiplatelets, statins or blood pressure lowering medications (Appendix 15). The risk of recall bias was minimised by asking patients for their current (rather than past) use, and the risk of social desirability bias was minimised by having research nurses, who had nothing to do with the ongoing care of patients, collecting this data. Dispensing of combination medication was included as a secondary outcome.

Change in blood pressure over 12 months

Mean change in blood pressure over 12 months was included as a primary outcome to provide a direct measure of the effect of blood pressure lowering agents, and to enable triangulation with the indirectly measured self-reported use of medication outcome. A meta-analysis of randomised controlled trials of thousands of participants has demonstrated that a reduction in blood pressure with blood pressure lowering drugs is associated with a reduction in cardiovascular events.[41] All classes of blood pressure lowering drugs largely have a similar effect in reducing coronary heart disease events and strokes for a given reduction in blood pressure.[41] The proportional reduction in cardiovascular events is similar regardless of pre-treatment blood pressure and the presence or absence of existing cardiovascular disease.[41]

Blood pressure was measured by research nurses using the OMRON model T9P automatic blood pressure monitor. Three seated measures were taken, at least three minutes apart. The mean of the second and third measures was used. Baseline blood pressure was subtracted from blood pressure at the 12 month visit for each participant for the primary outcome. All recordings were logged and subject to audit by the trial monitor to ensure that selective measures were not used for individual participants.

Change in low density lipoprotein cholesterol over 12 months

Mean change in low density lipoprotein cholesterol over 12 months was included as a primary outcome to provide a direct measure of the effect of statins, and to enable triangulation with the indirectly measured self-reported use of medication outcome. A meta-analysis of randomised controlled trials of thousands of participants has demonstrated that a reduction in low density lipoprotein cholesterol is associated with a reduction in cardiovascular events.[42] The reduction of low density lipoprotein cholesterol with a statin reduces the risk of cardiovascular events, largely irrespective of age, sex, baseline low density lipoprotein cholesterol and previous cardiovascular disease.[42]

Fasting low density lipoprotein cholesterol concentration was measured from serum samples obtained by community laboratories blind to participation in the trial and treatment allocation. The laboratory form was signed by the participant's general practitioner, so results were sent directly to the general practitioner and then obtained by research nurses. The blood test was required to have been taken in the period from one month prior to 14 days after the

associated visit date. Research nurses gave participants instructions for fasting. Participants were asked to fast overnight (at least 8 hours) and to have the blood test the following morning. Participants were advised that no food or drink apart from water was allowed during the fasting period, and that medication should not be stopped. All laboratories held ISO 15189 (2003 or later) accreditation. Low density lipoprotein was estimated, and not calculated directly. At baseline, any patient who did not have a measurable low density lipoprotein (because their triglyceride levels were too high) was excluded from the trial. Baseline low density lipoprotein was subtracted from low density lipoprotein at 12 months for each participant for the primary outcome.

4.3.7. Secondary outcomes

The secondary outcomes investigated other aspects of *effectiveness, safety, quality of life, acceptability* and *cost* of polypill-based care. The secondary outcomes are listed below, and have been categorised according to the main aspect of polypill-based care that they investigated. Trial end was pre-specified as 12 months after the last participant had been randomised.

Effectiveness

- Proportion that were dispensed an antiplatelet, statin and two or more blood pressure lowering agents at 12 months
- Proportion that self-reported use of an antiplatelet, statin and two or more blood pressure lowering drugs at trial end
- Change in blood pressure over trial duration
- Change in low density lipoprotein cholesterol change
- Change in other lipid fractions (high density lipoprotein cholesterol, total cholesterol, triglycerides) over 12 months and over trial duration
- Cardiovascular events over trial duration

Safety

- Serious adverse events over trial duration
- Polypill discontinuation over trial duration

Quality of life, acceptability and cost

- Quality of life (EQ-5D) at 12 months
- Barriers to adherence at 12 months

- General practitioner acceptability of polypill-based care at end of trial
- Healthcare resource consumption and cost-effectiveness at 12 months (results not reported in this thesis as economic analysis outside of scope)

Secondary outcomes were defined prior to the commencement of the trial and recorded in the Australian New Zealand Clinical Trial Registry (ACTRN12606000067572). The reason for selecting each of these outcomes is now provided, along with how they were measured.

Secondary outcomes (effectiveness)

Dispensing data were collected as an alternative measure of adherence. Dispensing data are more objective and less likely to be subject to recall or social desirability bias. The pre-specified definition of the dispensing outcome did not include antiplatelet agents because, as aspirin is available over the counter (i.e. without a prescription) in New Zealand, there was a risk that dispensing data would underestimate antiplatelet use. In fact this was not the case so the outcome was amended to dispensing of an antiplatelet, statin and two or more blood pressure lowering agents at 12 months.

Polypill dispensing data were obtained from paper-based polypill dispensing logs (Appendix 17) and electronic pharmacy records of any dispensing of the polypill by trial pharmacists. Dispensing of publicly funded pharmaceuticals was obtained from the national pharmaceutical dispensing database via data linkage using participants' National Health Index (NHI). The NHI is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand. NHIs were obtained from participant's general practices at the baseline assessment. Consent to allow data linkage to national records was specifically obtained from participants as part of the informed consent process for the trial (Consent form, Appendix 10).

Trial end was 12 months after the last participant had been randomised. It was recognised from the outset that trial recruitment would take at least 12 months because of the pragmatic nature of the trial, its primary care setting and the aim of equal recruitment of Māori and non-Māori. Rather than discontinuing follow-up for all participants at the 12 month time point when the primary outcomes had been assessed, this was considered a valuable opportunity to obtain longer-term follow up on key outcomes. Further, continuing all participants up until the same time point made it possible for participants that were randomised to the polypill and

for whom it was suitable, to continue this treatment at the end of the trial were it to be registered in New Zealand at that time.

All three of the primary outcomes were measured in the same way at end of trial as at 12 months.

Reduction in low density lipoprotein is the major action of statins[36] and hence was one of the primary outcomes for this trial. The other lipid fractions (total cholesterol, high density lipoprotein and triglycerides) were also measured as they are independently associated with cardiovascular disease[36] and were measured at the same time using the same test and for the same cost as low density lipoprotein.

The IMPACT trial was not sufficiently powered to detect a difference in cardiovascular events between polypill and usual care participants. Cardiovascular events were pre-specified and adjudicated by an independent and blinded Clinical Adjudication Committee so that IMPACT events could contribute to any future meta-analyses that would have the power to assess this outcome. The pre-specified events were: stroke, transient ischaemic attack, subarachnoid haemorrhage, myocardial infarction, unstable angina, heart failure and new onset claudication. The following procedures were also pre-specified and adjudicated: coronary artery bypass graft, percutaneous coronary intervention, amputation due to ischaemia and peripheral arterial revascularisation procedure. Events and procedures were identified and reported to the trial team by research nurses (during follow up encounters with participants) and general practitioners (throughout the trial). The criteria for events and procedures are provided in Table 28.

Table 28. Criteria for pre-specified cardiovascular events for the IMPACT trial

Type	**Event**	**Criteria**
Death	Cardiovascular	Proximate or any underlying causes of death cardiovascular
	Other	Neither proximate nor any underlying causes of death cardiovascular
Cerebro-vascular	Non-fatal stroke	Sudden onset, focal neurological impairment or deficit, lasting more than 24 hours (or if less than 24 hours with evidence of acute infarction on imaging studies consistent with the neurological deficit) and of presumed vascular origin Classified as haemorrhagic, non-haemorrhagic or of unknown type
	Transient ischaemic attack	Typical clinical history with symptoms less than 24 hours with no evidence of acute infarction on imaging studies (if performed) and presumed to be of vascular origin
	Subarachnoid haemorrhage	Typical symptoms and/or signs and evidence of blood in the subarachnoid space
Coronary heart disease	Non-fatal myocardial infarction	Change in cardiac biomarkers associated with: symptoms of ischaemia, ECG changes indicative of new ischaemia, development of pathological Q waves on the ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Type	Event	Criteria
Coronary heart disease	Coronary artery bypass graft	Evidence of a surgical procedure, either emergency or elective, during which a graft vessel is used to shunt an occluded segment of the coronary artery
	Percutaneous coronary intervention	Evidence of a procedure (non-surgical) during which a narrowed coronary artery is mechanically widened percutaneously
	Unstable angina	Hospitalisation for unstable angina and typical ischaemic symptoms that: occur at rest and last for more than 10 minutes, are severe and of new onset, or that occur with a crescendo pattern Criteria for myocardial infarction not fulfilled
Heart failure	Heart failure	Administration of intravenous diuretic, escalation of diuretic dose and/or inotropes for heart failure with heart failure on chest x-ray resulting in either hospitalisation or death
Peripheral arterial disease	New onset claudication	Typical symptoms and signs with at least one test abnormality (ankle brachial pressure index less than 0.9 in either leg, ultrasound or angiographic evidence of stenosis) in the absence of any other cause
	Amputation due to ischaemia	Surgical amputation of at least one toe due to arterial insufficiency
	Peripheral arterial revascularisation procedure	Evidence of a procedure where arterial revascularisation (carotid endarterectomy or stenting, open repair or endoluminal stenting of thoracic, thoracoabdominal or abdominal aortic aneurysm or dissection, limb revascularisation procedure) is undertaken

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Secondary outcomes (safety)

A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, a malignancy, an overdose, or another medically important event.[175-177] Serious adverse events were monitored during the trial to determine the safety of polypill-based care. Collection of serious adverse events was also required to meet clinical trial ethical[176] and regulatory[177 178] requirements. The method of collecting and recording as well as reporting serious adverse events is described in 4.7.8.

Only serious (and not all) adverse events were collected for a number of reasons. First, the level of risk to participants receiving the polypill was considered to be relatively low. Participants had indications for all of the medications in the polypill, and the medications and their side effect profiles are very well known as they have been in use, both singly and in combination with each other, for many years. Second, general practitioners knew exactly what trial medication their patients had been prescribed (as they retained responsibility for prescribing and knew to which treatment arm trial participants had been randomised) and so were able to manage adverse effects to these known medications in the usual way, including reporting any suspected reaction of clinical concern to the national Centre for Adverse Reactions Monitoring (CARM).[179] Third, there was a risk that adverse events in the

polypill arm would be more likely to be reported than adverse events in the usual care arm because of the open-label nature of the trial.[136] The risk of this bias can be reduced by maximising the objectivity of the measurement of adverse events,[136] such as by requiring adverse events to meet the threshold for a serious adverse event.

It was planned to summarise the number of participants discontinuing treatment with cardiovascular medications by treatment group and by reasons for discontinuation. The candidate did not consider it to be valid to compare this outcome between treatment arms because participants in the polypill arm were required to have their medication changed, whereas people in the usual care arm were not. Instead, polypill discontinuation over trial discontinuation was reported, along with the main reason the polypill had been stopped.

Secondary outcomes (quality of life, acceptability and cost)

Quality of life was included as an outcome to investigate any broader effect of polypill-based care on participants. The EuroQol 5D (EQ-5D) was chosen over more sensitive instruments such as the Short Form (36) Health Survey (SF-36) because it was less complex, and therefore less likely to adversely affect recruitment. In addition, the EQ-5D has social tariffs (population-based weightings) for New Zealand[180] and for Māori[181]. These social tariffs enable each of the 243 possible health states of the EQ-5D to be converted to a single utility score. The utility score can be used to compare incremental cost per quality-adjusted life year (QALY) gained, which can be used in full economic evaluations. The EQ-5D consists of a descriptive system and a visual analogue scale. The descriptive system has five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each of these dimensions is assessed across three levels (no problems, some problems, extreme problems).[182]

In order to better understand why the polypill might improve adherence, differences in previously identified barriers to adherence that may theoretically be addressed by a polypill, were compared in the polypill and usual care groups. These barriers included treatment side effects, belief in the benefit of treatment, regimen complexity, practical barriers, economic barriers, forgetfulness and changes to daily routines.[172] Participants were asked (via self-completed questionnaire, Appendix 11): "*Over the last month, how often have you missed taking your prescribed medication for each of the following reasons?*" and indicated their response on a five-point Likert scale ranging from 1 (never) to 5 (always).

General practitioner acceptability is an important aspect of the potential role of polypill-based care as, even if primary outcomes are improved, concerns with the 'usability' of the intervention by the prescribers would be likely to limit the implementation and potential impact of this intervention. The IMPACT trial was ideally placed to assess the acceptability of polypill-based care to general practitioners given the pragmatic nature of the trial. The general practitioner of each participant randomised to the polypill was invited to complete a post-trial survey on the acceptability of polypill-based care. General practitioners with more than one participant randomised to the polypill completed a separate survey for each participant in the polypill arm. General practitioners were asked to rate different aspects of polypill-based care (initiation, blood pressure control, cholesterol control, tolerability, guidelines implementation) and to indicate the most important advantage and disadvantage of polypill-based care for their patients (Appendix 20).

Health resource consumption data were collected to enable economic evaluation of polypill-based care. The following costs were collected: primary care consultations (general practitioner and practice nurse), hospitalisations, emergency department attendances, outpatient specialist consultations, laboratory tests and medications. Where practical, these costs were limited to those relevant to the management of cardiovascular disease. Economic evaluation was outside of the scope of this thesis.

4.3.8. Other outcomes

This section describes outcomes (including some that were pre-specified) where the analyses had not been pre-specified. These outcomes investigate some further aspects of *effectiveness*, *safety* and *acceptability* of polypill-based care. The other outcomes are listed below, and have been categorised according to the main aspect of polypill-based care that they investigated.

Effectiveness

- Proportion that self-reported use of the following medications at 12 months :
    - Antiplatelet, statin and one or more blood pressure lowering drugs
    - Individual components
- Change in blood pressure over 12 months and trial duration, adjusted by baseline blood pressure and pre-specified covariates
- Change in low density lipoprotein cholesterol over 12 months and trial duration, adjusted by baseline low density lipoprotein cholesterol and pre-specified covariates

Safety

- Non-cardiovascular adjudicated events over trial duration (renal, major bleeding)
- Smoking, alcohol consumption, physical activity duration and body mass index at 12 months
- Change in other laboratory tests over 12 months (creatinine, uric acid, sodium, potassium, alanine transaminase, aspartate transaminase, glucose, glycosylated haemoglobin and urinary albumin to creatinine ratio)

Acceptability

- Participant-reported ease of taking all prescribed medications (including the polypill) at 12 months
- Participant-reported advantages and disadvantages of taking the polypill at trial end

Other outcomes (effectiveness)

Self-reported use of the combination of antiplatelet, statin and at least *one* blood pressure lowering agent was assessed to increase understanding of changes in the more restrictive combination for the primary outcome (self-reported use of the combination of antiplatelet, statin and *two* or more blood pressure lowering agents). Self-reported use of the following individual modalities was also assessed: antiplatelet, statin, at least one blood pressure lowering agent, and two or more blood pressure lowering agents.

Additional analyses were undertaken for both change in blood pressure and low density lipoprotein cholesterol in which baseline values (blood pressure and low density lipoprotein cholesterol, respectively, as undertaken in the UMPIRE trial[124]) were included in analyses adjusted by pre-specified covariates.

Other outcomes (safety)

In addition to cardiovascular events, renal events and major bleeds were also pre-specified (Table 29) and adjudicated by the Clinical Adjudication Committee. These events were included to provide information on the safety of a polypill-based treatment strategy. The renal events were: microalbuminuria, macroalbuminuria, 50% loss of estimated glomerular filtration rate and commencement of renal replacement therapy. Events and procedures were identified and reported to the trial team by research nurses (during follow up encounters) and general practitioners (throughout the trial). In addition, occurrence of most of the renal events

(microalbuminuria, macroalbuminuria and 50% loss of estimated glomerular filtration rate) was actively sought by comparing baseline and follow-up laboratory values in all participants. Information about the events and procedures was collected on Form X as with other serious adverse events (4.7.8 and Appendix 18).

Table 29. Criteria for pre-specified renal events and major bleeds for the IMPACT trial

Type of event	**Event**	**Criteria**
Renal	New onset of microalbuminuria	Baseline: Urine ACR less than 3mg/mmol AND During trial: Urine ACR equal to or greater than 3mg/mmol AND less than or equal to 33.9 mg/mmol
	Progression to macroalbuminuria	Baseline: Urine ACR less than or equal to 33.9 mg/mmol AND During trial: Urine ACR greater than 33.9 mg/mmol
	50% loss of estimated glomerular filtration rate	Reduction of estimated glomerular filtration rate (eGFR) of 50% or more from baseline and eGFR less than 60mLs/min/1.73m^2 eGFR calculated using Modification of Diet in Renal Disease (MDRD) formula
	Commencement of renal replacement therapy for end-stage renal disease	Requirement for renal replacement therapy (dialysis or transplantation) due to end-stage kidney disease
Major bleeding	Major bleeding	Active bleeding that results in a reduction of haemoglobin of at least 20g/l, or requires transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ.

ACR=albumin:creatinine ratio; eGFR=estimated glomerular filtration rate; IMPACT=IMProving Adherence using Combination Therapy; MDRD=Modification of Diet in Renal Disease

One concern about the use of polypill-based care has been that patients might perceive the polypill as a 'magic bullet' and reduce attention on addressing risk factor behaviours. In order to determine whether or not this was the case, the following outcomes were assessed: smoking, alcohol consumption, duration of physical activity and body mass index at 12 months. Smoking status, alcohol consumption and the duration and intensity of physical activity were obtained from participants by self-report.

A current smoker was defined as someone who smoked ready-made or roll-your-own cigarettes on most days. Alcohol consumption was measured by units of alcohol per week. The New Zealand Ministry of Health recommends that, in any one week, no more than 21 units of alcohol should be consumed by men and 14 by women.[183] Physical activity was measured by determining the number of minutes of moderate and vigorous intensity physical activity in the preceding 7 days.[184] The World Health Organization recommends that adults should undertake at least 150 minutes of moderate (or 75 minutes of vigorous) intensity physical activity during each week.[185] Body mass index (weight in kilograms divided by [height in metres]^2) was calculated by the trial website after measurement and entry of weight and height by research nurses. Weight was measured by electronic, calibrated

scales (Salter model 9175). Height was measured using mobile stadiometers (Seca model 214). A body mass index of 25 mg/m^2 or greater was classified as overweight, and obesity was defined as a body mass index of 30 mg/m^2 or greater.[183]

In addition to lipids, the following laboratory tests were requested: creatinine, uric acid, sodium, potassium, alanine transaminase, aspartate transaminase and glucose. General practitioners were also asked to check glycosylated haemoglobin and urinary albumin to creatinine ratio, although as these were not considered to be part of routine clinical care the research nurses advised general practitioners that these were optional. These tests were included in analyses to ascertain whether polypill-based care might be associated with any additional safety concerns compared with usual care.

Other outcomes (acceptability)

All participants were asked: 'During the study, how easy did you find it to take all of the medicines prescribed by your doctor? (including the polypill)'. Participants could respond: very easy, easy, average, difficult or very difficult. (Form C, Appendix 16).

At the end of the trial all participants were posted a self-completion survey regarding their experience on the trial. This survey included questions on the advantages and disadvantages of taking the polypill for participants randomised to polypill-based care (Appendix 21).

4.3.9. Data collection

Participants were assessed at baseline and four time points following randomisation: 1 month, 6 months, 12 months and end of trial. End of trial was defined as 12 months after the final participant had been randomised. Data collected at each trial contact are summarised in Table 30.

Table 30 Data collected for the IMPACT trial, by follow-up time point

Data source	Baseline	1 month	6 months	12 months	End of trial*
Participant					
Currently used medications	X	X	X	X	X
Blood pressure	X			X	X
Fasting cholesterol	X			X	X
Barriers to adherence	X			X	X
Serious adverse events†		X	X	X	X
Events to be adjudicated†		X	X	X	X
Quality of life (EuroQol-5D)	X			X	X
Symptoms causing medication discontinuation		X	X	X	X
Risk factor behaviour	X			X	X
Participant acceptability of medicines				X	X
General practice					
Serious adverse events†		X	X	X	X
Events to be adjudicated†		X	X	X	X
Prescriber acceptability					X
General practitioner and practice nurse visits					X
Pharmacy					
Polypill dispensing					X
National databases					
Cardiovascular medication dispensing					X
Accident and Emergency attendances					X
Cardiovascular laboratory tests					X
Hospitalisations					X
Deaths					X

IMPACT=IMProving Adherence using Combination Therapy
*End of trial was 12 months after the last participant had been randomised.
†Events could be reported by participants or general practitioners at any time.

4.4. Statistical analyses

Analyses were led by the candidate and undertaken by the trial statistician (Ms Varsha Parag). The candidate specified how analyses were to be conducted, defined all outcomes and checked all code. The candidate independently checked primary outcomes and conducted some analyses. Means and standard deviations or proportions were calculated for baseline characteristics. For each of the continuous outcomes, the change from baseline to follow-up was compared between the polypill and usual care arms using 2-sample t-tests. Binary outcomes were compared using the χ^2 test. Primary outcomes were analysed by intention to treat (i.e. all participants to be included in the group to which they were randomised, regardless of any departures from randomised treatment[132]). Where 12 month adherence was missing, the participant was assumed to be non-adherent, and where change in systolic blood pressure or low density lipoprotein cholesterol from baseline to 12 months was missing, the change was assumed to be zero. These assumptions were made because it was not considered appropriate to assume that data were missing at random.[132]

Adjusted analyses were conducted for adherence at 12 months (logistic regression) and change in systolic blood pressure and low density lipoprotein cholesterol from baseline to 12 months (linear regression) and included pre-specified covariates (treatment group, stratification factors, age and sex). The likelihood ratio $\chi 2$ test between unadjusted and adjusted models was used to assess whether the covariates in the adjusted model significantly improved goodness of fit of the model. Where the goodness of fit for the adjusted analysis was significantly better than the unadjusted analysis, the adjusted analysis was also reported. Pre-specified subgroup analyses for the primary outcomes were conducted if the results were highly significant ($p<0.005$) using tests of heterogeneity for stratification factors, age and sex.

4.5. Registration and approvals

The trial methods, including primary and secondary outcomes, were prospectively registered by the candidate on the Australian New Zealand Clinical Trial Registry (trial ID ACTRN12606000067572) on 16 February 2006 and updated on 18 June 2010 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=1101).

Approval of the Director General Health was obtained via the Standing Committee on Therapeutic Trials (SCOTT) to use the polypills in this trial, under Section 30 of the Medicines Act 1981 (approval number TT50-7895 [692]) originally on 2 February 2007 , and again, following reformulation, on 20 November 2009. Such approval was required as the polypills were not registered for use in New Zealand at the time the trial was undertaken.

The trial was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Ethical approval of the trial protocol and participant information documents was obtained from the New Zealand Northern X Regional Ethics Committee (Ethics reference NTX/06/06/072) originally on 15 November 2006 and again, following amendments, on 8 January 2010.

4.6. Governance, management and committees

The trial was overseen by a Steering Committee, which was chaired by each current principal investigator. The Steering Committee was responsible for providing strategic guidance for the trial including developing the trial design, approving the trial protocol and statistical analysis plan, informing recruitment strategies and publishing trial results.

Current members of the Steering Committee are: Associate Professor Chris Bullen (principal investigator), Dr Sue Crengle (co-principal investigator), Dr Vanessa Selak (senior research fellow), Ms Angela Wadham (senior project manager), Ms Varsha Parag (statistician), Professor Bruce Arroll, Dr Dale Bramley, Dr Linda Bryant, Professor Robert Doughty, Associate Professor Raina Elley, Dr Matire Harwood, Professor Rod Jackson, Associate Professor Richard Milne, Dr Natasha Rafter and Professor Anthony Rodgers.

Previous members of the Steering Committee members are: Professor Jennie Connor, Dr Robert Cook, Professor Valery Feigin, Professor Tim Maling, Professor Bruce Neal, Professor Anushka Patel, Mr Avinesh Pillai, Professor David Simmons, and Mr Stephen Vander Hoorn.

The daily operation of the trial was undertaken by a Management Committee, which reported to the Steering Committee. The Management Committee was responsible for developing trial materials, undertaking the trial, monitoring recruitment and data quality and analysing results.

The trial was independently monitored by the Health Research Council's Data Monitoring Core Committee. The role of the Data Monitoring Committee was to monitor emerging safety and efficacy data, review trial conduct and make recommendations to the Steering Committee, in order to safeguard the interests of study participants, and to preserve the integrity and credibility of the study.

Pre-specified events were adjudicated by a Clinical Adjudication Committee, blinded to treatment allocation and were independent of trial researchers. Each member had to review the events against pre-specified criteria contained within a manual of procedures (Appendix 19) to determine whether or not the criteria for the event had been met.

4.7. Processes

4.7.1. Healthcare provider recruitment and training

Endorsement of Primary Health Organisations was obtained by attending relevant Primary Health Organisation meetings and presenting on the trial. Most of these presentations were undertaken by the candidate. Other presentations were undertaken by Associate Professor Raina Elley and Dr Sue Crengle. Once endorsement of a Primary Health Organisation had been obtained, the candidate contacted affiliated practices and arranged to attend the practice

to provide training if at least one general practitioner in the practice was interested in the trial. Participating general practitioners were asked to identify the local pharmacies most frequently used by their patients. Those pharmacies were approached by the project manager, asked to stock and dispense the polypill for the trial, and provided with training if they agreed to participate.

Prior to trial commencement, research nurses and participating general practitioners and pharmacists received training on the rationale for the trial, recruitment procedures, the trial protocol, participant inclusion and exclusion criteria, polypill components, prescribing and dispensing of the polypill, the reporting of serious adverse events and events to be adjudicated. Training on role-specific responsibilities was provided, as well as training on Good Clinical Practice (GCP). GCP is the internationally recognised standard for the ethical and scientifically rigorous conduct of clinical trials.[175]

General practitioners were reimbursed for training ($150) and provided a payment ($150) for each patient that was randomised. This payment compensated the general practitioner for the time involved in assessing their patients, enrolling them and monitoring their treatment, as well as reporting of, and providing medical information about, any serious adverse events experienced by their trial participants during the trial. Trial participants were not charged for their initial trial visit with their general practitioner. They were also not charged at the end of the trial when they were transferred off the polypill to currently available medications.

Pharmacists were reimbursed for training ($100) and received $9.14 per dispensing of the polypill (minus any patient co-payment). This dispensing fee was 50% greater than the standard dispensing fee, to account for the additional trial paperwork. Pharmacists were asked to charge patients any applicable co-payments equivalent to the charge per dispensed item usually charged, to mimic actual general practice and dispensing conditions and patient charges.

4.7.2. Identification of potentially eligible patients

The candidate signed a confidentiality agreement with eligible general practices and interrogated their practice management systems on their behalf to identify potentially eligible patients. Queries were developed to ensure that the records were interrogated systematically and consistently across practices despite differences in practice management system and coding practices (Table 31). The simplest way to identify potentially eligible patients was if

they had already had a documented 5-year cardiovascular risk assessment and the risk was 15% or greater, or if they had a recorded history of cardiovascular disease. Additional queries were performed to identify Māori who, despite not having a documented cardiovascular risk assessment or history cardiovascular disease, might still have been at high cardiovascular risk (Table 31). A lower threshold for screening Māori was used because of the aim of recruiting equal numbers of Māori and non-Māori onto the trial. Trial eligibility criteria were the same for all participants irrespective of ethnicity.

Table 31. Electronic queries used to screen for inclusion criteria in the IMPACT trial

Category	**Inclusion criteria**	**Ethnicity**
Risk assessment	Documented 5-year cardiovascular risk at least 15%	All
History of cardiovascular disease	Documented history of cardiovascular disease*	All
	Prescription for glyceryl trinitrate in last 6 months (an indicator that may have ischaemic heart disease)	Māori only
Smoker*	Male smokers aged 55-69	Māori only
	Female smokers aged 65-79	Māori only
Diabetes*	Men with diabetes aged 60-69	Māori only
	Women with diabetes aged 65-79	Māori only

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*Identified using Read codes (Appendix 5), the coding system used by most general practitioners in New Zealand.[186]

Those identified as potentially eligible were then checked for exclusion criteria by the candidate prior to the final list of potentially eligible patients being considered by the general practitioner (Table 32). Only patients that were enrolled in the practice were considered, so patients who visited the practice 'casually' were not eligible. This was because it was considered that the most appropriate person to confirm participant eligibility and potentially change the participant's medication if they were randomised to the polypill was the general practitioner responsible for the ongoing care of the patient (not a health care provider that they only attended intermittently).

Table 32. Electronic queries used to screen for exclusion criteria in the IMPACT trial

Category	**Exclusion criteria**
Enrolment status	Not enrolled in the practice
Age	Women or men aged over 80 years
	Men aged over 70 with no history of cardiovascular disease
Heart failure	Documented history of heart failure
Warfarin	Prescription for warfarin in the preceding 6 months
Allergies	Allergy or alert to aspirin, angiotensin converting enzyme inhibitor or statin
Angiotensin receptor blocker	Prescription for candesartan or losartan (because likely to have intolerance to angiotensin converting enzyme inhibitors)
Atorvastatin	Prescription for atorvastatin in the last 6 months (because likely to have intolerance or inadequate response to simvastatin)

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For patients that met at least one of the inclusion criteria and none of the exclusion criteria, the candidate extracted specific information from the practice records (Table 33). The main purpose of the information was to facilitate general practitioner review of the list of their patients potentially eligible for the trial (as, using this list, the general practitioners confirmed which of their patients would be invited onto the trial). The information was also used to facilitate communication between the trial team (acting on behalf of the general practitioner) and patients. Finally, data on ethnicity were collected to enable the trial team to differentially sample patients according to practice-recorded ethnicity (self-reported ethnicity was collected following informed consent for use in the actual trial by trial staff as outlined in 4.7.4).

Table 33. Information extracted electronically from practice records of patients potentially eligible for the IMPACT trial

Information	**Reason**
National Health Index	General practitioner review / If need to review individual patient record
Name	General practitioner review / Invitation letter
Date of birth	Age an exclusion criterion
Phone number	Follow up re: invitation letter
Address	Invitation letter
Patient's general practitioner	So that the general practitioners reviewed their own patients for trial eligibility (in the setting of a group practice)
Ethnicity	To allow differential sampling of Māori and non-Māori

IMPACT=IMProving Adherence using Combination Therapy

Initially all potentially eligible patients were included in the list of patients to be reviewed by the general practitioner. The recruitment of Māori lagged behind that of non-Māori, therefore Māori were oversampled by including all potentially eligible Māori patients, but only a random sample of the same number of non-Māori, in the lists to be reviewed by general practitioners. Despite this, recruitment of non-Māori still reached the target of 250 participants first. Once the target of 250 participants had been reached for non-Māori, only Māori were recruited.

The list of potentially eligible patients from each practice was reviewed by the corresponding general practitioner, who deleted patients that did not meet trial inclusion criteria or who met any of the exclusion criteria. The people remaining on the list were invited onto the trial by their general practitioner, facilitated by the designated trial staff member. The project manager entered their initials, date of birth, sex and ethnicity (Māori or non-Māori) onto the trial screening log (on the trial website, Appendix 6). Other fields on the screening log could not be entered until after the trial team had had direct contact with the patient and they had given their informed consent.

4.7.3. Invitation and registration

Letters of invitation (for template see Appendix 7) were signed by the general practitioner and posted to patients along with information about the trial. If trial staff did not receive any contact from the patient they phoned them directly to check that they had received the letter. If patients indicated that they were not interested or unavailable they were not contacted again. If they were interested, they progressed to the next (registration) stage.

Interested patients were registered by research nurses (Form A, Appendix 8), usually over the telephone, and data were entered onto the trial website. Research nurses obtained verbal consent from patients at this stage to double check their trial eligibility by reviewing (in detail) their records at their general practice. The nurse confirmed the patient's full name and sex, and obtained their date of birth. Patient identifiers for the website were an automatically generated unique trial registration number, date of birth and initials (patient names were not used on the trial website).

4.7.4. Baseline

If the patient remained potentially eligible, the research nurse arranged a time to undertake the baseline assessment. Patients were asked to have a fasting blood test prior to the baseline visit, and had the laboratory request form (signed by their general practitioner) posted to them by the research nurse. It was considered to be safer and more clinically appropriate for these tests to be requested and therefore reviewed by the patient's own general practitioner.

Baseline assessments were conducted by the research nurse at a location of the patient's choosing. Most baseline visits were conducted at the patient's home, but some were conducted at their general practice or work place. Patients were encouraged to have family or support people with them during the baseline visit. At baseline, written informed consent was obtained (Appendix 10) and the following forms were completed: Form Z (Participant details, Appendix 9), Participant Questionnaire (Appendix 11), Form B1 (Baseline, Appendix 12) and Form M (Medications, Appendix 13).

Participants received a $30 voucher as compensation for the time taken to complete the baseline assessment.

Written informed consent

At the start of the baseline visit the research nurse discussed the trial with the patient and any family or support people present, and answered any of their questions. If the patient wanted to go ahead with the trial, the research nurse obtained their written informed consent to participate (Appendix 10). As part of the informed consent process, patients were specifically asked to provide consent for trial staff to access their medical records for information relevant to the trial (from general practice, hospitals, specialists, national databases) and for trial data to be audited and published.

Form Z: Participant details and ethnicity

After receiving written informed consent, research nurses asked patients to self-complete a contact details form (Form Z, Appendix 9). This form also collected self-reported ethnicity using the standard written New Zealand Census ethnicity questions. Ethnicity was collected and recorded in accordance with New Zealand ethnicity data protocols.[187] Patients were asked to self-identify their ethnicity, could select as many ethnic groups as they wanted to, and were able to write in any ethnicity/ethnicities not specifically listed. Research nurses transcribed ethnicity data from Form Z onto Form A. No other patient details from Form Z were entered onto the trial website.

Participant questionnaire

Patients were asked to self-complete the participant questionnaire (Appendix 11), which contained the EuroQol-5D health state questionnaire and questions about barriers to medications.

Form B1: Baseline

Nurses completed Form B1 (Baseline, Appendix 12) directly on the trial website. This comprised questions about exclusion criteria, other relevant aspects of medical history and questions about socioeconomic status. For the latter, patients were asked whether or not they had a Community Services Card (this is available for people on low to middle incomes and can reduce the cost of some health services and prescriptions), their highest completed educational qualification, whether they were currently in paid employment and their total gross household income. Research nurses measured patient's blood pressure, along with their heart rate, weight and waist circumference.

Form M: Medications

Fifth, research nurses entered the patient's current medication onto the trial website (Form M, Appendix 13). Prior to the baseline visit patients were asked to bring (or collect if the visit was at their home) all of their current medications. The research nurse asked the patient to tell them the names and dosages of all of the medications they were currently taking. The patient and nurse were able to refer to the medications for confirmation of names and/or dosages if there was any confusion. For example, if the patient only knew the trade name and the nurse was unfamiliar with it, they could refer to the medication packaging to ascertain the generic name. Likewise, if the patient said they took two tablets a day, the nurse could look at the medication packaging to ascertain what each of the tablets contained. Nurses were specifically asked to obtain from the patients what they were actually taking, as opposed to what they had been prescribed or dispensed.

The Form M was designed to be like an inpatient medication chart, in that it was an up to date 'running sheet' with a separate row for each medication. Therefore, in addition to drug name and dosage, patients were asked for a start date for the medication, and to indicate whether it was ongoing and, if not, a 'stop date'. The latter two fields enabled nurses in subsequent visits to indicate that a medication was no longer being taken and when it had been stopped. When only partial start or stop dates were know (e.g. just a year or month), the middle point was used (e.g. if the patient said they had started a medication sometime in February 2010, 15 February 2010 was entered). It was important to have a start and stop date for each medication as the primary outcome of adherence was assessed according to whether or not a patient was taking specific medications at a specific point in time.

When a cardiovascular medication had been stopped, participants were asked for the main reason. Nurses were asked to select a relevant response from a drop-down menu on the website (pre-specified options were: abdominal pain, bradycardia, bronchospasm, cold extremities, constipation, cough, dizziness/hypotension, fatigue, flatulence, gastritis/ dyspepsia, gout, hyperglycaemia, hyperkalaemia, hypoglycaemia, muscle pain or weakness, nausea, tinnitus, warfarin started, other side effect, patient choice, unknown). If the patient's response did not fit any of the pre-specified options the nurse could select 'other' and type the response into a free text field.

4.7.5. General practitioner approval and randomisation

After the baseline assessment, if the patient had provided written informed consent, the research nurse obtained their baseline laboratory results from the general practice and entered these onto the trial website (in Form B1). If patients were eligible and did not have any exclusion criteria, the research nurse arranged for the patient to meet with the general practitioner at the general practice to confirm eligibility prior to randomisation. The general practitioner was provided with a summary of trial information about their patient (cardiovascular risk category, current medications, blood pressure and laboratory test results) to ensure that there were no discrepancies in understanding between the patient, general practitioner and research nurse. The general practitioner was also provided with patient-specific medication contraindications, cautions and indications based on trial information (Table 34).

Table 34. Medication contraindications, cautions and indications supplied to general practitioners for individual patients prior to randomisation in the IMPACT trial

Medication	Contraindications	Cautions	Indications
Beta blocker	If history of asthma, heart block or allergy to beta blocker	If history of peripheral vascular disease or chronic obstructive pulmonary disease	If history of coronary artery disease and no contraindications or cautions with beta blocker
Thiazide	If allergy to thiazide	If history of gout, urate >0.36 mmol/L (women) or >0.42 mmol/L (men), sodium <135 mmol/L, or potassium <3.5 mmol/L	If history of cerebrovascular disease and no contraindications or cautions with thiazide
Aspirin	(NA – any contraindications to these medications would mean that the patient was ineligible for the trial as both versions of the polypill contain these components)	If already taking a non-steroidal anti-inflammatory agent	Not applicable
Angiotensin converting enzyme inhibitor		If creatinine >90 µmol/L (women) or >105 µmol/L (men), or potassium >5.2 mmol/L	Not applicable
Statin		Alanine or aspartate transaminase $\geq$ 135 IU	Not applicable

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If the general practitioner and patient still wanted to proceed with randomisation, the general practitioner logged onto the trial website and confirmed that they believed that each of the polypill components was indicated, that they were unsure as to whether a polypill-based strategy or usual care were better, and that they approved randomisation (Form B2, Appendix 14). The general practitioner was also asked which version of the polypill they would prescribe if their patient was randomised to the polypill group (to ensure that at least one of the versions would be suitable).

4.7.6. Follow-up

One month and six months

Research nurses assessed participants one month and six months following randomisation. These assessments were usually undertaken over the telephone, unless the participant specifically requested that they be done in person. Form M was updated by asking participants what medication they were currently taking. Any medication that had been discontinued from baseline had the 'ongoing' field changed from 'yes' to 'no' and a stop date entered. If a cardiovascular medication had been discontinued, nurses were prompted to ascertain the main reason for stopping. When a participant discontinued the polypill, the research nurse asked them the main reason it had been stopped using the options from a dropdown box previously described (4.7.4).

Research nurses also completed relevant sections of Form C (Appendix 16). Nurses asked participants how many times they had seen specific health practitioners since their last trial assessment (practice nurse, general practitioner who enrolled them into the trial, any other general practitioner, a doctor at a private accident and medical centre, a doctor in a public hospital, a specialist in an outpatients' clinic [public or private] for their heart, blood pressure, diabetes or stroke care). Participants were asked whether they were currently in paid employment, whether they had had a serious adverse event since their last assessment (in which case nurses were reminded about the need to complete Form X) and at what time of the day they took their polypill (if randomised to it).

12 months and end of trial

The 12 month and end of trial assessments were undertaken by the research nurse but arrangements were made to undertake these assessments in person, at a location suitable to the participant. As with the baseline assessment, most of these assessments took place at the participant's home. All of the questions asked at the one and six month follow-up assessments were repeated. In addition, research nurses asked questions about lifestyle behaviours (physical activity, smoking and alcohol), gout (number of episodes in the preceding 12 months for those with gout), whether they had a community services card and how easy they found taking all of their medicines. Research nurses measured blood pressure, heart rate, weight and waist circumference.

Participants were also asked to repeat laboratory tests at 12 months and end of trial. As with baseline, research nurses obtained laboratory request forms from the participant's general practitioner, posted them to the participant (usually prior to the face-to-face assessment), obtained the results from the general practice, and entered results onto the trial website.

Participants received a voucher as compensation for the time taken to complete the 12 month assessment ($30) and the end of trial assessment ($30).

Trial follow-up continued until 12 months after the last participant had been randomised. The last participant was randomised on 13 July 2012. For the last 11% of participants randomised, where 12 month and end of trial visits were less than 6 months apart, only one assessment was undertaken, and this occurred at the 12 month time-slot.

4.7.7. Clinical care of participants during the trial

The participant's usual general practitioner remained responsible for their clinical care during the entire trial, irrespective of treatment allocation. This involved managing participants according to best clinical practice, including obtaining additional blood tests, monitoring treatment, managing adverse events, providing repeat prescriptions and managing lifestyle risk factors. When new medications (such as the polypill) were initiated, it was the responsibility of the participant's general practitioner to manage participants as they normally would with the introduction of such medications. For example, if the participant was to be started on an angiotensin converting enzyme inhibitor (whether this was as a single compound or as part of a polypill), renal function and electrolytes should be checked before initiation and monitored during treatment.[188] General practitioners were not specifically asked to do this because (1) the trial was unblinded, (2) they were making the prescribing decisions and (3) the ingredients of the polypill were well known and had been in use in clinical practice for many years.

4.7.8. Pharmacovigilance and safety reporting

A process of safety reporting for serious adverse events, serious adverse drug reactions and suspected unexpected serious adverse reactions, was developed in order to protect the safety of trial participants. This process was designed to meet the safety reporting requirements of the Northern X Regional Ethics Committee, the Standing Committee on Therapeutic Trials (SCOTT) and the Data Monitoring Committee. Further, it was consistent with the

International Conference on Harmonization (ICH) Good Clinical Practice (GCP). GCP is an internationally recognised standard for conducting clinical trials in an ethically and scientifically rigorous manner.[175]

Serious adverse events were reported to the trial team by research nurses (during follow up encounters with participants) and general practitioners (as soon as possible after being made aware of a potential serious adverse event, throughout the trial). Information about the events was collected on Form X (Appendix 18). The Form X was completed by the candidate and signed off by the general practitioner or medical practitioners on the research team.

For each event, at least one diagnosis was required. Where a diagnosis was not known signs and/or symptoms were to be entered. Relevant procedures were also able to be reported on Form X. All diagnoses and procedures were coded using the Medical Dictionary for Regulatory Activities (MedDRA) by a clinical coder. MedDRA is an internationally accepted medical terminology for biopharmaceutical regulatory purposes, developed under the auspices of the International Conference on Harmonisation (ICH).[189] Although the coder was not blinded to treatment allocation, she was independent of the trial research group. The trial research group had no influence on the coding process, other than to provide additional information at the request of the coder if clarification was required.

For each diagnosis, the following information was also collected:

- Onset date
- Event type (death, life-threatening, hospitalisation or prolongation of hospitalisation, persistent or significant disability, congenital abnormality, malignancy, overdose, other medically important event [such as a pre-specified event that did not fit into any of the other categories])
- Severity (mild, moderate, severe)
- Likely relationship to polypill (definitely, probably, possibly, unlikely, not related)
- Outcome status (resolved, ongoing, death, unknown/lost to follow-up)
- Resolution date

Severity was classified by the candidate as mild (awareness of event but easily tolerated and causing no limitations of usual activities), moderate (discomfort enough to cause some interference with usual activity) or severe (inability to carry out usual activity).[190]

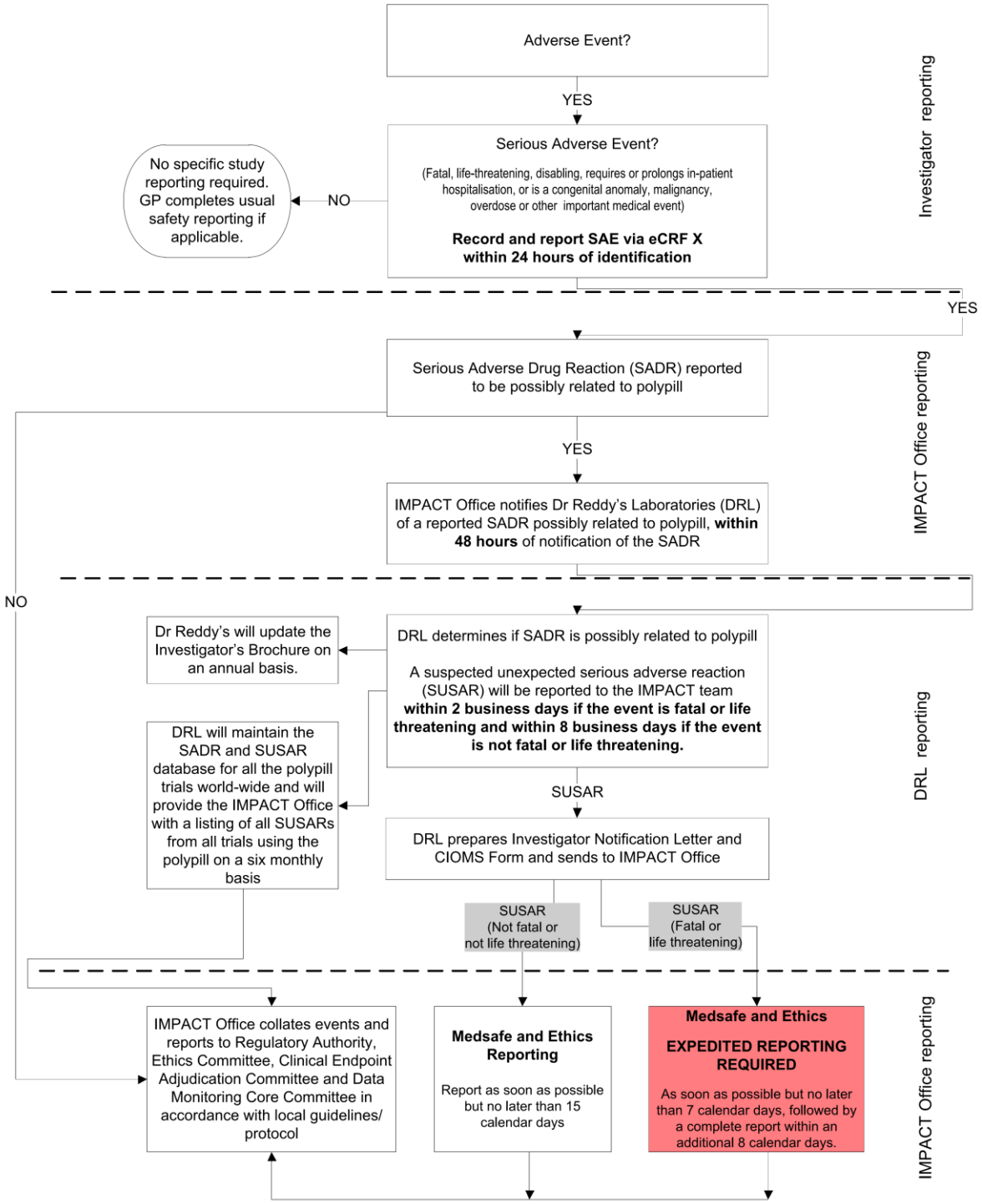
Likely relationship to the polypill was classified by the candidate as 'definitely' (clearly related to the polypill and other contributing factors can be ruled out), 'probably' (likely to be related to the polypill and the influence of other factors is unlikely), 'possibly' (may be related to trial treatment, however, the influence of other factors may have contributed to the event, e.g. the participant's clinical condition or other concomitant treatments), 'unlikely' (doubtfully related to the trial treatment, there is another reasonable explanation for the event, e.g. the participant's clinical condition or other concomitant treatments), 'not related' (clearly not related to trial treatment) or the participant was not in the polypill group.[191]

Serious adverse drug reactions were defined, by the candidate, as a serious adverse event that was 'possibly', 'probably' or 'definitely' related to the polypill. These could therefore only be reported for participants in the polypill arm. Serious adverse drug reactions were to be reported to the trial team by the participant's general practitioner within 24 hours, and the trial team was required to notify Dr Reddy's Laboratories Ltd within 48 hours. Dr Reddy's Laboratories Ltd required specific information regarding the reaction, which the candidate completed (according to the template in Appendix 22).

Dr Reddy's Laboratories Ltd had an internal committee that determined, within 2 days if fatal or life threatening, or 8 days otherwise, whether the serious adverse drug reaction was 'expected' or 'unexpected' according to the Investigator's Brochure. If the event was determined to be 'unexpected' by Dr Reddy's Laboratories Ltd (i.e. a suspected unexpected serious adverse reaction), Dr Reddy's Laboratories Ltd prepared an Investigator Notifications letter and Council for International Organisations of Medical Science (CIOMS) adverse drug reaction reporting form for the trial team. The trial team in turn was responsible for reporting the suspected unexpected adverse reaction with the documentation from Dr Reddy's Laboratories Ltd to the ethics committee and Medsafe (within 8 days if fatal or life threatening; otherwise within 15 days), as well as trial general practitioners.

Safety reporting for the trial is summarised in Figure 14 below.

Figure 14. Safety reporting for the IMPACT trial



Abbreviations: CIOMS = Council for International Organisation of Medical Sciences, DRL = Dr Reddy's Laboratories Ltd, SADR = serious adverse drug reaction, SAE =serious adverse event, SUSAR = suspected unexpected serious adverse reaction

Other information collected on Form X was any procedures undertaken as part of the serious adverse event, whether the participant was hospitalised (and if so, dates of admission and discharge) and whether the participant died (and if so, date of death and immediate and underlying causes of death recorded on the death certificate).

A medical practitioner from the research team classified each diagnosis and procedure recorded on the Form X according to whether or not it was a potentially a pre-specified event for adjudication. When a potentially pre-specified event for adjudication was identified, the relevant Form X and any additional information required to enable adjudication was de-identified, blinded to treatment group and adjudicated by the adjudication committee. The committee provided final, independent and blinded verification of the event or procedure against pre-specified criteria (Table 28).The full process for adjudication is outlined in Appendix 19, the manual of mrocedures for the Clinical Adjudication Committee.

4.7.9. Monitoring

The trial was monitored by an independent Clinical Trials Research Unit monitor. Monitoring activities were conducted according to the Clinical Trial Research Unit's standard operating procedures and Good Clinical Practice.[175]

4.8. Rationale for key design elements

4.8.1. Randomised controlled trial

The randomised controlled trial is the gold standard for evaluating an intervention, when properly designed, conducted and reported.[135] This is because when interventions are allocated at random, there is a greater degree of assurance regarding the validity of a result than any observational study design.[137] The randomised controlled trial gives greater confidence that the relationship observed between an exposure (such as an intervention) and outcome might be causal.[5]

4.8.2. The use of surrogate endpoints (blood pressure and cholesterol)

The ideal endpoint for a clinical trial assessing effectiveness is an outcome that is relevant to patients. In the case of an intervention aimed at reducing cardiovascular disease, it would therefore be preferable to have cardiovascular events as endpoints, as opposed to surrogate or intermediate markers such blood pressure or cholesterol. From a patient's perspective a

reduction in blood pressure or cholesterol is likely to have much less importance than a reduction in their risk of having a heart attack or stroke. Further, from a scientific point of view using surrogate markers can be problematic. For example, the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial compared the combination of torcetrapib and atorvastatin with atorvastatin alone.[189] The combination was associated with a significant reduction in low density lipoprotein cholesterol but was also associated with a significant increase in all-cause mortality and major cardiovascular events. Had the trial only considered change in cholesterol, the findings may have been misleading.

The problem with using cardiovascular events as an endpoint is that these events are relatively infrequent, even among those at high risk. For instance, a 15% risk of cardiovascular disease over 5 years (the lowest level of risk required for entry into the IMPACT trial) equates to a 3% risk every year. The problem is confounded by the use of usual care as a comparator because the potential size of the benefit (in terms of reduction in cardiovascular events) is lower than if the comparator were no treatment.[192] This means that in order to provide enough power a very large sample size and/or very long duration of follow up would be required.[192] Such a trial would therefore be very difficult to carry out in a country with New Zealand's population and health research funding.

IMPACT used blood pressure and cholesterol as primary outcomes, along with self-reported use of medication. There is very strong evidence from individual participant data meta-analyses of thousands of participants demonstrating that reductions in low density lipoprotein with statins and blood pressure with blood pressure lowering agents reduce cardiovascular events in both primary and secondary prevention, across strata of baseline cardiovascular risk.[42 52] Should polypill-based care reduce blood pressure and/or cholesterol, it is therefore highly likely that, over time, cardiovascular events and mortality are also likely to decrease, providing that serious adverse events do not outweigh the benefit.

While IMPACT was not powered to assess the effect of polypill-based care on cardiovascular outcomes directly, events were adjudicated by an independent and blinded committee so they can contribute to any future meta-analyses that are powered to assess this outcome.

4.8.3. Usual care comparator

Two of the inclusion criteria for trial participants were that (1) they were at high risk of having a cardiovascular event and (2) that their general practitioner considered that all of the medications in at least one of the two polypills available for the trial were indicated. This meant that a non-active control group (such as a placebo or no treatment) would have been unethical for these participants. Ideally all trial participants should receive best available care.[166] However, clinical care is heterogeneous and in order to understand how new strategies are likely to affect actual clinical care, it is important to test such strategies in realistic conditions. There was therefore a need to balance the ethical requirement for providing trial participants with 'best available care' and the desire to obtain a good understanding of how a polypill-based strategy was likely to perform if available. In order to try to achieve this balance, general practitioners were encouraged to manage all of their participants (irrespective of treatment allocation) according to New Zealand cardiovascular guidelines and their own best clinical judgement. The only difference between the two groups was that for participants randomised to polypill-based care, general practitioners were able to use a trial polypill. Further, general practitioners were encouraged to make any changes to participants' medication that they considered to be in the best interests of their patients during the trial, again irrespective of treatment allocation.

4.8.4. Primary health care setting

Primary health care is generally the first point of contact people have with the health system in New Zealand.[193] It includes generalist first-level services (such as general practice, mobile nursing, community health and pharmacy) as well as health improvement and preventive services such as health education and counselling, disease prevention and screening.[193] Participants were recruited directly from primary health care as this is the setting in which most medical management of cardiovascular disease occurs.[194] The purpose of the trial was to understand the likely effectiveness of polypill-based care were the polypill to be made available to medical practitioners in New Zealand. The trial was therefore designed to be as integrated with current primary care as possible. General practitioners confirmed the eligibility of potential participants, prescribed the polypill (to those randomised to it) in the same way they prescribe other medications (i.e. electronically) and remained responsible for monitoring their patients and changing their medications as required throughout the trial. Further, participants had the polypill dispensed in the same way as it

would be were it to be available and funded in New Zealand. Pharmacists stocked the polypill and dispensed it on receipt of a prescription, and participants paid what they would normally pay to receive a single medication.

4.8.5. Components of the Red Heart Pill

The Red Heart Pill was developed by Dr Reddy's Laboratories Ltd, in consultation with Professor Anthony Rodgers and other senior physicians, from 2002. Both versions of the Red Heart Pill contained aspirin 75mg, simvastatin 40mg and lisinopril 10mg. Red Heart Pill 1C also contained 50mg atenolol, while Red Heart Pill 2C also contained 12.5mg hydrochlorothiazide. The guiding principles in choosing these agents at these doses in 2002 were to:

- Ensure the affordability of the polypill (e.g. by using off-patent medications)
- Allow once-daily administration
- Include low-to-moderate doses so that most of the potential benefits of each agent would be realized, while most of the side effects would be avoided (given the generally shallow dose response for benefits, and steep dose response for side effects).

Aspirin

The dose of aspirin was chosen on the basis of evidence indicating that the benefits of 75-150mg of aspirin are at least as great as those obtained with higher doses, and adverse effects are less at lower doses.[63] The Antithrombotic Trialists' Collaboration 2009 meta-analysis was published just prior to initiation of the trial,[43] so a systematic review and modelling were conducted (chapter 3) to determine the balance of benefits and harms of aspirin in patients without a history of cardiovascular disease, but at high risk. The modelling found that for people aged 70 to 79 years and with 5-year cardiovascular risk 15%, the number of cardiovascular events avoided with aspirin (when added to statin and blood pressure lowering therapy) was estimated to be twice the number of additional bleeds with aspirin for women, but the same as the number of additional bleeds with aspirin for men. Men aged 70 years or more without established cardiovascular disease were therefore excluded from the trial.

Simvastatin

At the time of development, evidence suggested that all statins had similar effectiveness in terms of coronary risk reduction per mmol/L of cholesterol reduction.[195] Simvastatin is

still the first line statin in New Zealand (2012) guidelines.[40] For most people statins are safe and well-tolerated.[196] A recent Cochrane systematic review of the use of statins in primary prevention found a reduction in all-cause mortality (risk ratio, RR, 0.83, 95% confidence interval, CI, 0.73 to 0.95), combined fatal and non-fatal cardiovascular endpoints (RR 0.70, 95% CI 0.61 to 0.79) and revascularisation rates (RR 0.66, 95% CI 0.53 to 0.83) with no excess adverse events; although there were also indications of selective reporting of outcomes.[156]

Blood pressure lowering agents

Two blood pressure lowering drugs at less than full dose were included to maximise blood pressure reduction (as greater risk reductions are produced with more intensive blood pressure lowering), while reducing risks of side effects from any one drug.[36 197-199] New Zealand guidelines note that "*low dose combination therapies can maximise effectiveness and help minimise side effects*".[40] A meta-analysis of 354 trials (n=60,000) found that: (1) blood pressure reductions achieved by the major classes of blood pressure lowering drugs were similar, independent and additive, and that (2) using half-standard-dose reduced efficacy by only 20% while more than halving adverse effects.[198]

An angiotensin converting enzyme (ACE) inhibitor was included in the polypill because New Zealand guidelines note similar efficacy in lowering blood pressure with thiazide diuretics and calcium channel blockers.[40] ACE inhibitors are also specifically indicated in diabetes and following myocardial infarction, particularly if there is any significant left ventricular impairment.[40]

A thiazide was included because New Zealand guidelines note similar efficacy in blood pressure lowering with ACE inhibitors and calcium channel blockers.[40] Thiazides are recommended for people without indications for another antihypertensive class (first line) and for diabetes (second line).[40]

A beta-blocker was included because New Zealand guidelines specifically recommend this class of antihypertensive following myocardial infarction,[40] because in the first few years following a myocardial infarction, beta blockers are associated with greater reductions in coronary heart disease than other classes of antihypertensives.[41] Atenolol has been shown to have a similar protective effect to other beta blockers, such as metoprolol,[41] is available off-patent and is easily given once-daily.

4.9. Implementing an indigenous right-based perspective

As the indigenous people of New Zealand, Māori have rights under the United Nations Declaration of the Rights of Indigenous Peoples and the Treaty of Waitangi (signed between representatives of Māori and the British Crown).[189 200] These include the rights to self-determination and health comparable to that enjoyed by others in New Zealand. Despite these rights, Māori are disproportionately affected by cardiovascular disease compared with non-Māori,[201 202] as described in the 2.2.1. Other countries also experience inequalities in cardiovascular disease between indigenous and non-indigenous peoples.[203 204]

The Steering Committee sought to develop the trial from an indigenous-rights based perspective. Priority was therefore placed on supporting indigenous rights to self-determination to the extent feasible throughout the trial. The trial Steering Committee included experienced Māori researchers who were involved in every stage of trial design (Dr Sue Crengle and Dr Dale Bramley) and conduct (Dr Sue Crengle and Dr Matire Harwood). The Steering Committee sought to recruit equal numbers of Māori and non-Māori (even though Māori only comprise 15% of the total population of New Zealand[32]) so that the trial could assess the effectiveness of a polypill-based strategy in Māori as well as non-Māori. Trial aims and design was informed by advice from Raukura Hauora O Tainui, Tāmaki Healthcare Primary Health Organisation and the Clinical Trials Research Unit Māori Research Advisory Committee. All of these groups provided formal endorsement of the trial prior to its initiation.

Research nurses were employed to undertake most trial procedures including baseline assessments (face-to-face) on behalf of trial primary care physicians. Māori research nurses were sought to optimise recruitment of Māori participants.[205] Additional funding and research nurse time were allocated for the recruitment of Māori participants to allow for extra face-to-face time (face-to-face contact is essential for Māori participants), the development of trust and rapport, whakawhanaungatanga (culturally-specific process of establishing relationships with people), more family involvement prior to enrolment and continuity of the research nurse-participant relationship over the course of the trial.[205 206] It was estimated that twice the research nurse time would be needed to recruit Māori compared with non-Māori (estimated randomisation rate of seven Māori and 14 non-Māori participants per full time research nurse per month).

The trial team sought the endorsement of the Māori-led and mainstream Primary Health Organisations affiliated with the practices in Auckland and the Waikato regions of New Zealand likely to have high enrolment of Māori. Practices likely to have high enrolment of Māori, based on geographical location and Primary Health Organisation data, were approached first. Over-sampling of potentially eligible Māori patients and lower thresholds for screening of Māori were used although actual trial eligibility criteria were the same for all participants. Data on ethnicity were obtained initially from practice records, and then directly from patients as part of the informed consent process, according to NZ guidelines.[187] The non-Māori group included all other ethnic groups as recommended by NZ guidelines for ethnicity statistics.[207]

4.9.1. Equal recruitment of Māori and non-Māori

If a polypill-based treatment strategy is demonstrated to be effective at improving adherence and risk factors in a randomised controlled trial among New Zealand patients at high risk of cardiovascular disease, assuming that a polypill-based treatment strategy would be effective at improving adherence and risk factors among Māori patients at high risk of cardiovascular disease is problematic for two reasons. Firstly, indigenous populations are often under-represented in trials so the effect of interventions is often unable to be specifically assessed for them. Secondly, interventions shown in trials to be effective do not necessarily reduce ethnic disparities, and may in fact widen them.[208 209] Therefore, the IMPACT trial aimed to recruit as many Māori as non-Māori so that information about Māori would be obtained to at least the same depth and breadth as that obtained for non-Māori. This meant oversampling of Māori who comprise just 15% of the total New Zealand population.[32] Given that researchers have often found it challenging to recruit sufficient numbers of indigenous participants to intervention trials, including Māori,[205 210 211] an indigenous rights-based perspective (as outlined above) was taken to achieve equal recruitment of Māori and non-Māori participants.

4.9.2. Reduction in recruitment target to maintain 50% recruitment of Māori

Despite the numerous strategies to support recruitment of Māori onto the trial, it became apparent that it would not be possible to achieve the recruitment target of 600 participants and 50% recruitment of Māori within available resources. As the trial team had already sought additional funding to enhance recruitment of Māori, it was unlikely that further

funding to support recruitment of Māori would have been secured. The trial team therefore had to decide whether to maintain the target of 600 participants knowing that the recruitment of Māori would be significantly less than 50%, or to reduce the overall recruitment target and achieve the aim of 50% recruitment of Māori.

The trial team decided that recruiting 50% Māori was more important that recruiting 600 participants. A number of factors contributed to this decision. First, sample size re-calculations indicated that despite a reduction in total sample size from 600 to 500 participants there would still be sufficient power to demonstrate any statistically significant differences in the primary outcomes between treatment groups. Second, the Steering Committee had committed to Māori organisations, researchers as well as funders that they would recruit equal numbers of Māori. To go back on this commitment would have seriously undermined those relationships. Third, a meta-analysis of trials using IMPACT's protocol and the same polypills was planned as part of the SPACE (Single Pill to Avert Cardiovascular Events) collaboration. This meta-analysis would provide some compensation for a reduction in the total number of IMPACT participants by combining all data from the IMPACT, Australian (Kanyini-GAP, n=623), Indian and UK (UMPIRE, n=2004) trials.

4.10. Summary

The IMPACT trial was an open-labelled randomised controlled trial in New Zealand general practice that compared polypill-based care with usual care among people at high risk of cardiovascular disease. Participants remained under the care of their general practitioner, who prescribed the polypill to those thus randomised, throughout the trial. Community pharmacists dispensed the polypill and charged participants what they would normally pay for a single, subsidised prescription. The trial was designed to determine the effectiveness of polypill-based care (in Māori and non-Māori) in improving adherence to guidelines-recommended cardiovascular medication as well as blood pressure and low density lipoprotein cholesterol control over a one-year period.

Chapter 5. IMProving Adherence using Combination Therapy (IMPACT) randomised controlled trial: Results

5.1. Introduction

This chapter describes the results of the IMProving Adherence using Combination Therapy (IMPACT) trial. Of particular interest to this thesis was the effect of the polypill on blood pressure and cholesterol (given inconsistency in trial evidence to date), and its safety (given the relative paucity of trial data to date). A trial timeline is presented first because of the considerable delays in completing the trial. Next, recruitment, retention and baseline characteristics are described. Primary, secondary and other outcomes are then presented.

5.2. Trial timeline

The IMPACT trial timeline is summarised in Table 35. There were considerable delays between when the trial was designed (2003) and randomisation initiated (2010) because of challenges with the development of the polypill.

Table 35. Timeline for the IMPACT trial from initial design through to completion of follow-up

Year	Event
2002	DRL initiated polypill development
2003	IMPACT trial designed
2004	Trial awarded funding from the New Zealand Health Research Council
2005	Polypill development delayed due to bioequivalence and stability challenges
2006	Candidate began to work on the trial Trial materials finalised (protocol, statistical analysis plan, case record forms, trial website) Primary Health Organisations, practices, project managers and research nurses recruited
2007	March: Polypill approved for use in trial under Section 30 of the Medicines Act July: Trial put on hold because of inadequate stability on further testing by DRL
2008	DRL reformulated polypill
2009	Reformulated polypill approved for use in trial under Section 30 of the Medicines Act Trial materials updated (protocol, statistical analysis plan, case record forms, trial website)
2010	January: Ethics approval updated June: Trial registration updated July: First participant randomised December: 132 participants randomised
2011	May: 267 participants randomised (including 99 Māori)
2012	July: Recruitment completed (513 participants randomised, including 257 Māori)
2013	August: Final follow-up visit completed

DRL=Dr Reddy's Laboratories Limited; IMPACT=IMProving Adherence using Combination Therapy

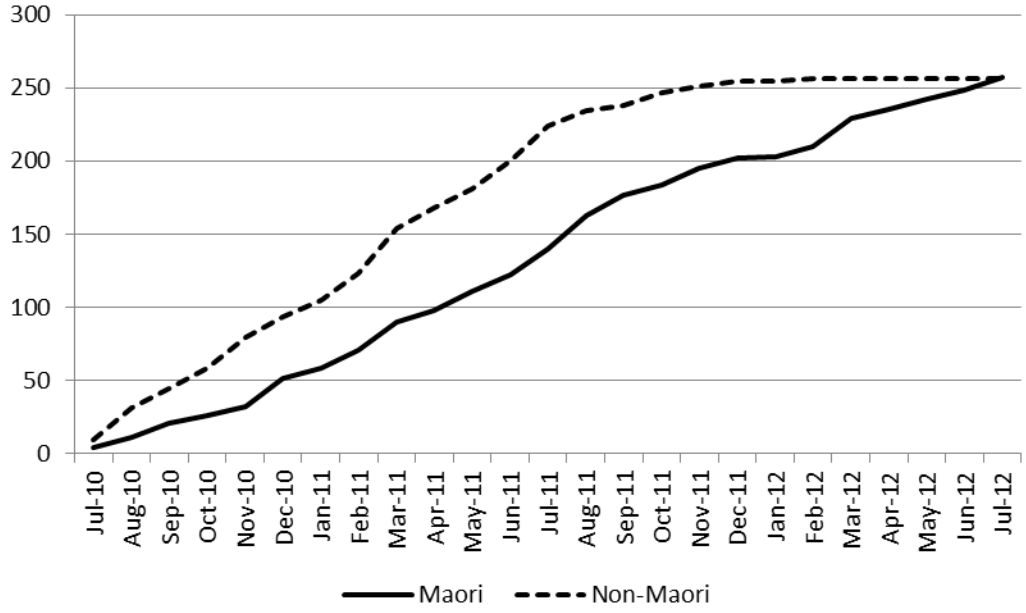
5.3. Participant recruitment and retention

Participants were recruited from 10 Primary Health Organisations (PHOs), 46 general practices and 90 general practitioners. Of the 10 PHOs, four were Māori-led (Raukura Hauora O Tainui, Te Hononga O Tāmaki Me Hoturoa, Toiora PHO, Waiora Healthcare PHO) and six were not (Auckland PHO, HealthWEST, Midland Health Network, Procare, Total Healthcare Otara, and Health Rotorua PHO). Fifty one pharmacies dispensed the polypill at least once during the trial period.

Eight hundred and fourteen potentially eligible patients who had been invited by their general practitioner to participate in the IMPACT trial provided written informed consent and were screened. Between July 2010 and July 2012, 513 of these patients met eligibility criteria and were randomised. The numbers and reasons patients were excluded are outlined in Figure 16. The most common reason people were excluded was that their 5-year cardiovascular risk at baseline was less than 15%.

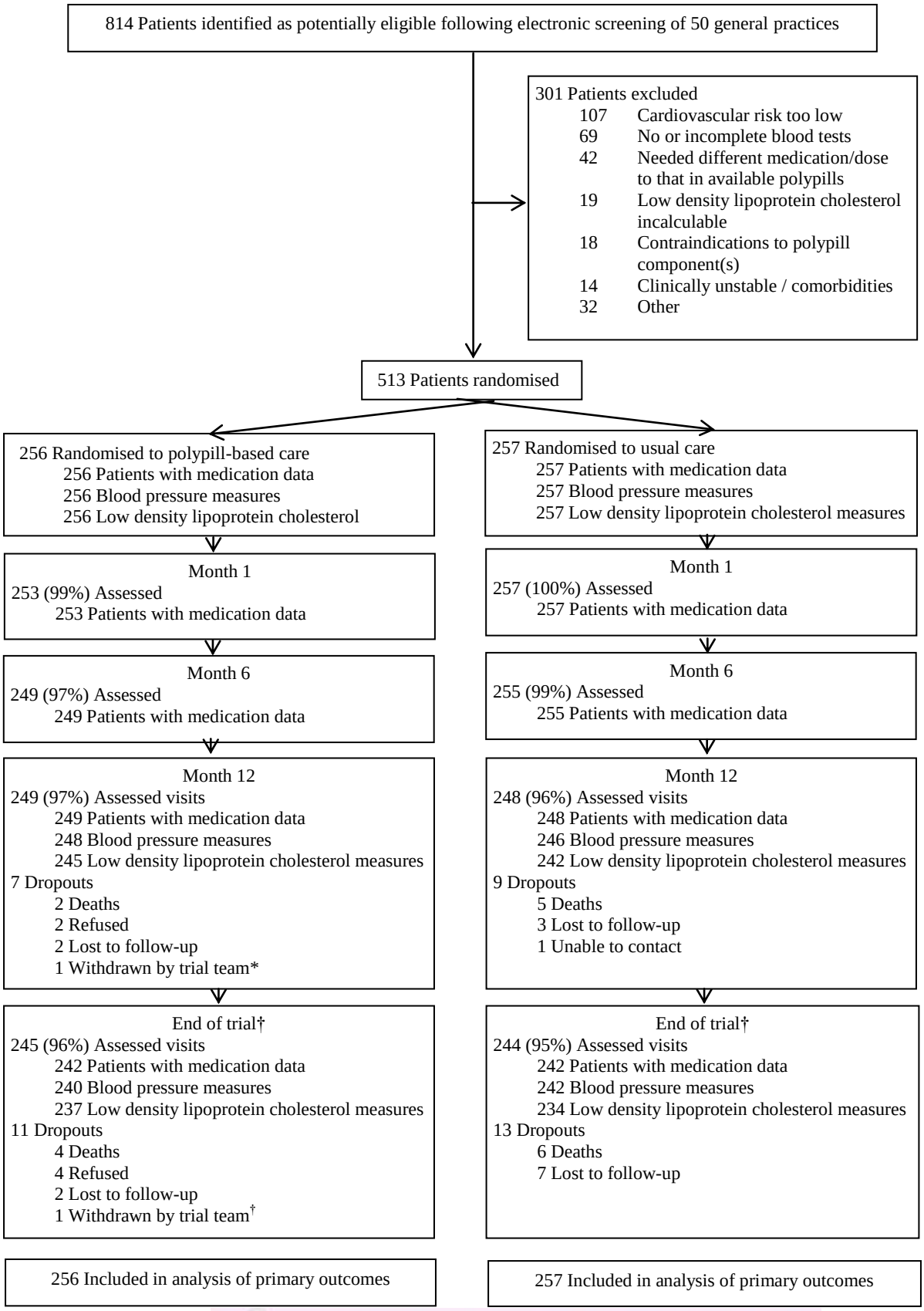
The mean recruitment rate was 20.5 patients per month. Māori were recruited over the entire recruitment period, from July 2010 until July 2012 (mean recruitment rate 10.3 patients per month). Non-Māori were recruited from July 2010 until December 2011 (mean recruitment rate 14.2 patients per month). Cumulative recruitment by month is shown in Figure 15.

Figure 15. IMPACT trial cumulative recruitment of Māori and non-Māori by month



IMPACT=IMProving Adherence using Combination Therapy

Figure 16. IMPACT trial CONSORT diagram



CONSORT= Consolidated Standards of Reporting Trials, IMPACT=IMProving Adherence using Combination Therapy
*Withdrawn by trial team because cardiovascular risk <15% but included in primary outcomes which were analysed by intention to treat
†Median follow-up duration in both groups was 23 months (interquartile range 21 to 27 months for both groups).

As planned, follow-up was undertaken at 1 month (obtained from 99% of participants), 6 months (98%), 12 months (97%) and at the end of the trial (95%) (Figure 16). The end of the trial was 12 months after the last participant had been randomised. Follow-up duration therefore varied by participant, with a median duration of 23 months in both the polypill and usual care groups. Follow-up concluded in August 2013.

5.4. Baseline characteristics

The mean age of IMPACT trial participants was 62 years, 50% were Māori and 36% were female (Table 36). Forty-five percent (n=233) had established cardiovascular disease and the remainder (55%, n=280) had an estimated 5-year adjusted Framingham cardiovascular risk of at least 15% and no history of cardiovascular disease. Forty-two percent (n=218) of participants had a history of diabetes mellitus, mean body mass index was 33 kg/m2 and 30% (n=154) of participants were current cigarette smokers. Forty-three percent (n=233) of participants reported taking recommended medications (antiplatelet, statin and two or more blood pressure lowering agents) at baseline. The polypill and usual care groups were similar at baseline with no obvious imbalances in major characteristics, including stratification factors. The only obvious difference between groups at baseline was the median reported duration of moderate intensity physical activity per week (polypill 180 vs usual care 210 minutes), but this difference was unlikely to have affected primary or secondary outcomes.

Table 36. Baseline characteristics of IMPACT trial participants, total and by treatment group

Characteristic	**Polypill-based care (n=256)**	**Usual care (n=257)**	**TOTAL (n=513)**
Socio-demographic			
Age, years, mean (SD)	62 (8)	62 (8)	62 (8)
Female, number (%)	99 (39)	88 (34)	187 (36)
Māori ethnicity, number (%)	129 (50)	128 (50)	257 (50)
Paid employment, number (%)	117 (46)	112 (44)	229 (45)
Medical history, number (%)			
Coronary artery disease	89 (35)	97 (38)	186 (36)
Cerebrovascular disease	27 (11)	27 (11)	54 (11)
Peripheral vascular disease	11 (4)	8 (3)	19 (4)
CVD (coronary, cerebral and/or peripheral)	116 (45)	117 (46)	233 (45)
Diabetes mellitus	113 (44)	105 (41)	218 (42)
Self-reported medication, number (%)			
Antiplatelet + statin + two or more BP lowering drugs	107 (42)	116 (45)	223 (43)
Antiplatelet + statin + one or more BP lowering drug	167 (65)	174 (68)	341 (66)
One or more BP lowering drug	229 (89)	232 (90)	461 (90)
Two or more BP lowering drugs	145 (57)	146 (57)	291 (57)
Statin	208 (81)	214 (83)	422 (82)
Antiplatelet	195 (76)	199 (77)	394 (77)

Characteristic	Polypill-based care (n=256)	Usual care (n=257)	TOTAL (n=513)
Cardiovascular risk factors, mean (SD) unless specified otherwise			
Systolic blood pressure, mm Hg	143 (20)	145 (20)	144 (20)
Diastolic blood pressure, mm Hg	83 (12)	83 (11)	83 (12)
Total cholesterol, mmol/L	4.5 (1.0)	4.4 (1.0)	4.4 (1.0)
Low density lipoprotein cholesterol, mmol/L	2.6 (0.8)	2.5 (0.8)	2.5 (0.8)
High density lipoprotein cholesterol, mmol/L	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)
Triglycerides, mmol/L	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)
Fasting glucose, mmol/L	6.8 (2.4)	6.7 (2.3)	6.7 (2.4)
Glycated haemoglobin (HbA1c), mmol/mol	53 (17)	52 (16)	52 (16)
Urine albumin:creatinine ratio, mg/mmol, median (IQR)	1.2 (1 to 5.1)	1.0 (1 to 3.2)	1.1 (1 to 3.6)
Creatinine, µmol/L	85 (45)	84 (23)	84 (36)
Current tobacco smoker, number (%)	73 (29)	81 (32)	154 (30)
Body mass index, kg/m^2	33 (7)	33 (7)	33 (7)
Moderate physical activity, minutes in the last week, median (IQR)	180 (1 to 420)	210 (20 to 420)	180 (2 to 420)
Vigorous physical activity, minutes in the last week, median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Alcohol (standard units per week), median (IQR)	0 (0 to 5)	0 (0 to 6)	0 (0 to 6)

BP=blood pressure; CVD=cardiovascular disease; IMPACT=IMProving Adherence using Combination Therapy; IQR=interquartile range; SD=standard deviation

5.5. Primary outcomes

5.5.1. Proportion that self-reported use of recommended medications at 12 months

Self-reported use of recommended medications (antiplatelet, statin and two or more blood pressure lowering drugs) at 12 months was 75% greater in participants randomised to polypill-based compared with usual care (95% confidence interval, CI, 52% to 103%, Table 37).

Table 37. IMPACT trial primary outcome results, by treatment group

Outcome	Polypill (n=256)	Usual care (n=257)	Treatment effect (95% CI)	
			Unadjusted	Adjusted*
Proportion that self-report adherence to recommended medications at 12 months, n (%)	208 (81%)	119 (46%)	**RR 1.75 (1.52-2.03), p<0.0001 OR 5.03 (3.37-7.48), p<0.0001**	**OR 8.93 (5.47-14.56), p<0.0001**
Mean change in systolic BP over 12 months, mm Hg (SD)	-4.5 (21.0)	-2.3 (18.1)	Difference -2.2 (-5.6 to 1.2), p=0.21	Difference -2.2 (-5.6 to 1.2), p=0.21
Mean change in diastolic BP over 12 months, mm Hg (SD)	-2.1 (11.8)	0.9 (11.2)	Difference -1.2 (-3.2 to 0.8), p=0.22	Difference -1.2 (-3.2 to 0.8), p=0.22
Mean change in LDL cholesterol over 12 months, mmol/L (SD)	-0.20 (0.73)	-0.15 (0.72)	Difference -0.05 (-0.17 to 0.08), p=0.46	Difference -0.04 (-0.17 to 0.08), p=0.48

BP=blood pressure; CI=confidence interval; IMPACT=IMProving Adherence using Combination Therapy; LDL=low density lipoprotein; OR=odds ratio; RR=risk ratio; SD=standard deviation

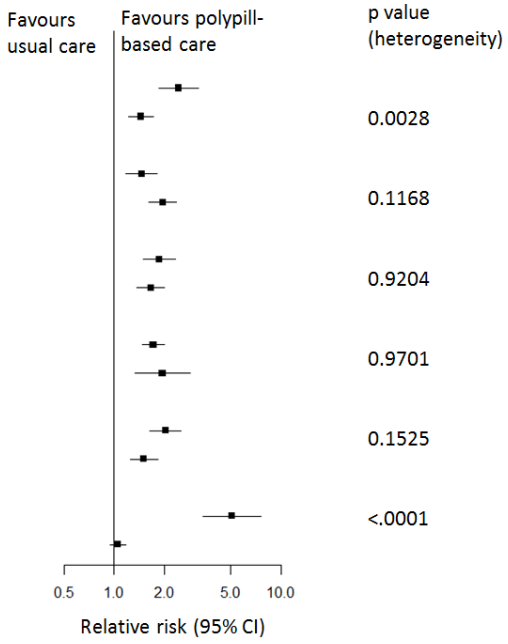
*Pre-specified covariates: treatment allocation, age, sex, ethnicity, history of cardiovascular disease, self-reported use of recommended medications at baseline and Primary Health Organisation

Statistically significant results in bold

Adjustment with pre-specified covariates (Table 37) improved the goodness of fit of the model ($p<0.0001$ for the likelihood ratio $\chi 2$ test between unadjusted and adjusted models). The absolute difference in self-reported use of recommended medications (35%) gave a number needed to treat (NNT) of 2.9 patients (95% CI 2.3 to 3.7 patients). The effect of polypill-based care on self-reported use of recommended medications at 12 months was significantly greater in participants not adherent to recommended medications at baseline ($p<0.0001$) and those aged <60 years ($p=0.003$), but there was no heterogeneity of treatment effect on adherence by sex, ethnicity, Primary Health Organisation or history of cardiovascular disease (Figure 17).

Figure 17. Proportion that self-reported use of recommended medications in the IMPACT trial, by pre-specified subgroups, by treatment group

	Adherence, number (%)		
	Polypill-based care	Usual care	Relative risk (95%CI)
Age			
<60 years	90 (86)	37 (35)	2.43 (1.86-3.19)
≥ 60 years	118 (78)	82 (54)	1.45 (1.22-1.72)
Sex			
Female	79 (80)	48 (55)	1.46 (1.18-1.81)
Male	129 (82)	71 (42)	1.96 (1.61-2.37)
Ethnicity			
Māori	102 (79)	54 (42)	1.87 (1.50-2.34)
Non-Māori	106 (83)	65 (50)	1.66 (1.37-2.00)
Primary Health Organisation			
Mainstream	171 (82)	100(48)	1.72 (1.47-2.01)
Māori	37 (77)	19 (40)	1.95 (1.33-2.85)
History of CVD			
No	114 (81)	56 (40)	2.04 (1.64-2.53)
Yes	94 (81)	63 (54)	1.50 (1.25-1.82)
Adherence to indicated medications at baseline			
No	113 (76)	21 (15)	5.09 (3.40-7.63)
Yes	95 (89)	98 (84)	1.05 (0.95-1.17)



IMPACT=IMProving Adherence using Combination Therapy
Note: Recommended medications: antiplatelet, statin and two or more blood pressure lowering agents.

5.5.2. Change in blood pressure over 12 months

The mean reduction in systolic blood pressure between baseline and 12 months was 4.5 mm Hg (SD 21.0) in the polypill group compared with 2.3 mm Hg (SD 18.1) in the usual care group (Table 37). Neither the unadjusted nor unadjusted differences were statistically significant (for both analyses: treatment difference -2.2 mm Hg, 95% CI 5.6 to 1.2, p=0.21, Table 37).

The mean reduction in diastolic blood pressure between baseline and 12 months was 2.1 mm Hg (SD 11.8) in the polypill group compared with 0.9 mm Hg (SD 11.2) in the usual care

group (Table 37). This difference was not statistically significantly different between the polypill and usual care groups whether unadjusted or adjusted (Table 37).

5.5.3. Change in low density lipoprotein cholesterol over 12 months

The mean change in low density lipoprotein cholesterol between baseline and 12 months was -0.20 mmol/L (SD 0.73) among polypill participants compared with -0.15 (SD 0.72) in usual care participants (Table 37). Neither the unadjusted nor the adjusted treatment differences were statistically significant (Table 37).

5.6. Secondary outcomes

5.6.1. Secondary outcomes - effectiveness

Polypill-based care was associated with a 67% increase (95% CI 44% to 93%) in the proportion of participants dispensed recommended medications (an antiplatelet, statin and two or more blood pressure lowering agents) compared with usual care at 12 months (Table 38).

Table 38. IMPACT trial results for secondary effectiveness outcomes, by treatment group

Outcome		Polypill	Usual care	Treatment effect, unadjusted (95% CI) and/or p value
Effectiveness				
Proportion that were dispensed recommended medications at 12 months, n/N (%)		196/249 (79%)	117/248 (47%)	**Risk ratio 1.67 (1.44 to 1.93), p<0.0001**
Proportion that self-reported use of recommended medications at end of trial, n/N (%)		185/256 (72%)	119/257 (46%)	**Risk ratio 1.56 (1.34 to 1.82), p<0.0001**
Mean change in systolic BP over trial duration, mm Hg (SD)		-5.9 (20.6)	-4.6 (20.9)	Difference -1.3 (-4.9 to 2.3), p=0.48
Mean change in diastolic BP over trial duration, mm Hg (SD)		-2.5 (11.9)	-1.9 (12.2)	Difference -0.7 (-2.7 to 1.4), p=0.54
Mean change in LDL cholesterol over trial duration, mmol/L (SD)		-0.21 (0.68)	-0.16 (0.64)	Difference -0.05 (-0.17 to 0.06), p=0.35
Change in other lipid fractions over 12 months, mmol/L	Total cholesterol, mean (SD)	-0.16 (0.88)	-0.09 (0.85)	Difference -0.07 (-0.22 to 0.08), p=0.37
	HDL cholesterol, mean (SD)	0.04 (0.16)	0.05 (0.17)	Difference -0.01 (-0.04 to 0.02), p=0.52
	Triglycerides, median (IQR)	0.0 (-0.3 to 0.3)	0.0 (-0.3 to 0.4)	p=0.66
Proportion with at least one cardiovascular event during trial, n (%)		16/256 (6%)	18/257 (7%)	p=0.73

BP=blood pressure; CI=confidence interval; HDL=high density lipoprotein; IMPACT=IMProving Adherence using Combination Therapy; IQR=interquartile range; LDL=low density lipoprotein; NA=not applicable; SD=standard deviation
Statistically significant results in bold

There was a high degree of concordance between dispensing and self-report data in the use of recommended medications (Table 39).

Table 39. IMPACT trial participant use of recommended medications at 12 months, by data source and by treatment group

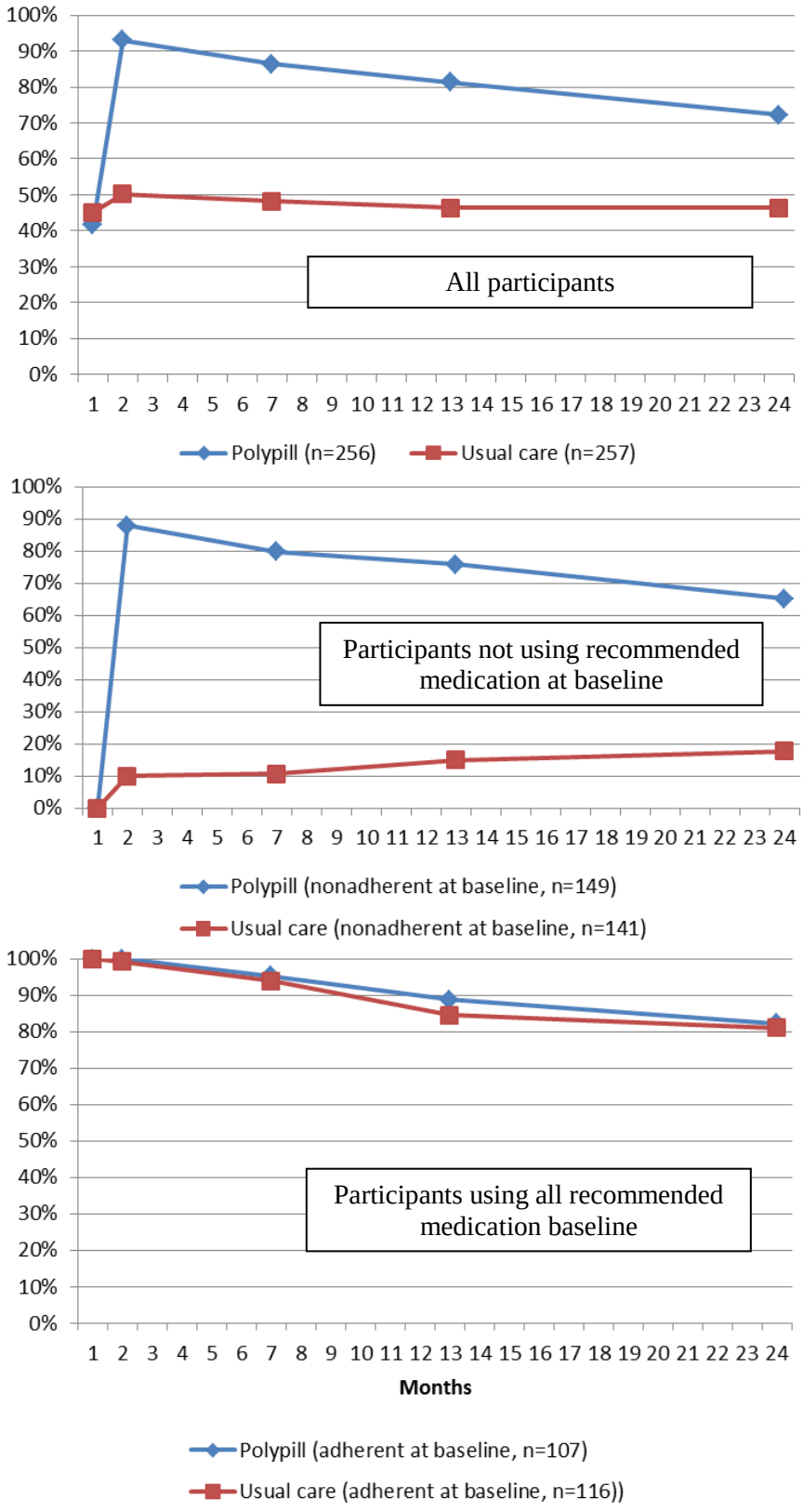
Data source	**Polypill n/N (%)**	**Usual care n/N (%)**
Self-report	208/256 (81%)	119/257 (46%)
Dispensing data	196/249 (79%)	117/248 (47%)
Difference	2%	1%

IMPACT=IMProving Adherence using Combination Therapy
Note: Recommended medications were an antiplatelet, statin and two or more blood pressure lowering agents.

Self-reported use of recommended medications remained greater in the polypill compared with the usual care group at the end of the trial (72% vs 46%, risk ratio, RR, unadjusted 1.56, 95% CI 1.34-1.82, Table 38). Adjusting self-reported use of recommended medications at the end of trial with pre-specified covariates (treatment allocation, age, sex, ethnicity, history of cardiovascular disease, self-reported use of recommended medications at baseline and Primary Health Organisation) improved the goodness of fit of the model (OR [unadjusted] 3.02, 95% CI 2.09-4.36, $p<0.0001$; OR [adjusted] 4.24, 95% CI 2.77-6.50, $p<0.0001$; $p<0.0001$ for the likelihood ratio $\chi 2$ test between unadjusted and adjusted models).

Self-reported use of recommended medications, by treatment allocation, is demonstrated over time: for all participants, and for those non-adherent and adherent to recommended medications at baseline in Figure 18.

Figure 18. Proportion that self-reported use of recommended medications in the IMPACT trial over time (months), by treatment group, among: all participants; participants not using recommended medication at baseline; and participants using recommended medication at baseline



IMPACT=IMProving Adherence using Combination Therapy
Recommended medications: antiplatelet, statin and two or more blood pressure lowering agents

At trial end, the mean reduction in systolic blood pressure from baseline was 5.9 mm Hg (SD 20.6) in the polypill group compared with 4.6 mm Hg (SD 20.9) in the usual care group (Table 38). There was no statistically significant difference in this reduction between the polypill and usual care groups, whether analyses were unadjusted (-1.3 mm Hg, 95% CI -4.9 to 2.3, p=0.48) or adjusted by pre-specified covariates (as defined above, -1.3 mm Hg, 95% CI -4.8 to 2.2, p=0.47).

The mean reduction in diastolic blood pressure between baseline and trial end was 2.5 mm Hg (SD 11.9) in the polypill group compared with 1.9 mm Hg (SD 12.2) in the usual care group (Table 38). There was no statistically significant difference in this reduction between the polypill and usual care groups, whether analyses were unadjusted (-0.7 mm Hg, 95% CI -2.7 to 1.4, p=0.54) or adjusted by pre-specified covariates (as defined above, -0.6 mm Hg, 95% CI -2.7 to 1.4, p=0.55).

At trial end, the mean reduction in low density lipoprotein cholesterol from baseline was 0.21 mmol/L (SD 0.68) in the polypill group compared with 0.16 mmol/L (SD 0.64) in the usual care group (Table 38). There was no statistically significant difference in this reduction between the polypill and usual care groups, whether analyses were unadjusted (-0.05 mmol/L, 95% CI -0.17 to 0.06, p=0.35) or adjusted by pre-specified covariates (as defined above, -0.05 mmol/L, 95% CI -0.16 to 0.06, p=0.37).

There was also no statistically significant difference between polypill and usual care groups in the mean change in total cholesterol, high density lipoprotein cholesterol or triglycerides between baseline and 12 months (Table 38).

Cardiovascular events

Sixteen polypill (6%) and 18 (7%) usual care participants experienced at least one cardiovascular event that met pre-specified criteria by an independent and blinded expert adjudication committee. Fifty cardiovascular events (24 polypill vs 26 usual care) met pre-specified criteria by the committee (Table 40). Six strokes were confirmed. Of these one was a haemorrhagic stroke (in a polypill participant), and one was an infarct with haemorrhagic transformation (in a usual care participant). The other strokes were ischaemic (n=3) and of undetermined type (n=1).

Table 40. Cardiovascular events in the IMPACT trial, by treatment group

Type of cardiovascular event	Polypill, n	Usual care, n
Cardiovascular death	1	0
Percutaneous coronary intervention	7	8
Non-fatal myocardial infarction	5	6
Hospitalisation for unstable angina	4	0
Coronary artery bypass graft	1	3
Hospitalisation for heart failure	0	2
Non-fatal stroke	2	4
Transient ischaemic attack	0	1
Peripheral arterial revascularisation	3	2
Amputation due to ischaemia	1	0
TOTAL	24	26

IMPACT=IMProving Adherence using Combination Therapy
Note: Patients could contribute only once to each row, but more than once to each column.

5.6.2. Secondary outcomes - safety

During the trial 285 serious adverse events (including all adjudicated outcomes) were experienced by trial participants, as reported by participants, trial staff and general practitioners. Of these events, 158 occurred in participants in the polypill group and 127 in the usual care group. The difference in the incidence of serious adverse events between the two groups did not reach statistical significance (0.03 polypill vs 0.02 usual care serious adverse events per person-month, rate ratio 1.24, 95% CI 0.98-1.57, p=0.07).

Ten serious adverse events resulted in death (4 polypill vs 6 usual care). Of the remainder, 196 events resulted in hospitalisation (107 polypill vs 89 usual care) and 79 did not (47 polypill vs 32 usual care). Ninety-nine polypill participants (39%) reported at least one serious adverse event during the trial, compared with 93 (36%) of usual care participants. The difference between the polypill and usual care groups in the incidence of a participant experiencing at least one serious adverse event during the trial was also not statistically significant (0.02 first serious adverse event per person-month in the polypill and usual care groups, rate ratio 1.06, 95% CI 0.80-1.41, p=0.679).

Serious adverse events were coded by Medical Dictionary for Regulatory Activities (MedDRA) system order class,[212] and are provided in Table 41. The most commonly reported diagnoses were renal and urinary disorders (72 participants had at least one such diagnosis), infections and infestations (n=43), cardiac disorders (n=31) and musculoskeletal and connective tissue disorders (n=24). The reported renal and urinary disorders were predominately new onset microalbuminuria (23 polypill vs 24 usual care) and progression to macroalbuminuria (12 polypill vs 4 usual care). Nine polypill participants had vascular

serious adverse events (mostly hypotension; n=6), compared with two among usual care participants.

Table 41. Serious adverse events in the IMPACT trial, by treatment group

Medical Dictionary for Regulatory Activities (MedDRA) system organ class	**Polypill, n***	**Usual care, n***
Blood and lymphatic system disorders	1	0
Cardiac disorders	13	18
Ear and labyrinth disorders	1	0
Endocrine disorders	1	0
Gastrointestinal disorders	12	9
General disorders and administration site conditions	1	3
Hepatobiliary disorders	3	3
Infections and infestations	22	21
Injury, poisoning and procedural complications	7	2
Investigations	4	3
Metabolism and nutrition disorders	6	1
Musculoskeletal and connective tissue disorders	14	10
Neoplasms benign, malignant and unspecified	14	7
Nervous system disorders	8	4
Psychiatric disorders	0	1
Renal and urinary disorders	40	32
Reproductive system and breast disorders	2	5
Respiratory, thoracic and mediastinal disorders	4	6
Skin and subcutaneous tissue disorders	1	0
Surgical and medical procedures	1	0
Vascular disorders†	9	2

IMPACT=IMProving Adherence using Combination Therapy
*Number of participants with at least one one serious adverse event by MedDRA system organ class.
†Vascular disorders reported among polypill participants: aortic aneurysm(1), arterial insufficiency(1), arteriosclersosis(1), hypotension(6); vascular disorders reported among usual care participants: intermittent claudication(1), hypertension(1).

Over a third (n=94, 37%) of participants initiated on the polypill discontinued it during the trial, with similar numbers discontinuing each version (49 discontinued version 1; 45 discontinued version 2). The main reported reasons for discontinuing the polypill were: medical practitioner decision, not further specified (n=15), dizziness/hypotension (n=13), cough (n=10), patient choice (n=9), deterioration in renal function (n=6), fatigue (n=6), inadequate risk factor control (n=5), unknown reason (n=4), bleed (n=3), gastritis/dyspepsia/ulcer (n=3), other side effect (n=13), and other reason (n=7) (Table 42).

Table 42. Main reason for discontinuing the polypill among the IMPACT trial participants who were randomised to polypill-based care and who discontinued the polypill during the trial

Main reason	Number (% of those that discontinued)
GP decision, not further specified	15 (16%)
Dizziness/hypotension	13 (14%)
Cough	10 (11%)
Patient choice	9 (10%)
Deterioration in renal function	6 (6%)
Fatigue	6 (6%)
Inadequate risk factor control	5 (5%)
Study discontinuation	5 (5%)
Bleed*	3 (3%)
Gastritis/dyspepsia/ulcer	3 (3%)
Unknown reason	4 (4%)
Other side effect	13 (14%)
Discontinued pre-surgery	1 (1%)
Withdrawn	1 (1%)
TOTAL	94

GP=general practitioner; IMPACT=IMProving Adherence using Combination Therapy
*Haemorrhagic stroke (1), gastrointestinal bleed (1), epistaxis (1).

5.6.3. Secondary outcomes – quality of life and acceptability

Quality of life measures at 12 months were not statistically significantly different between the polypill and usual groups. The median visual analogue scale score for health state (EQ-5D) was 80 for both groups (p=0.23, Mann-Whitney test). There was no statistically significant difference in EuroQol-5D domain scores between groups (Table 43)

Table 43. EuroQol-5D domain scores at 12 months for IMPACT trial participants, by treatment group

Domain	Polypill	Usual care	p value*
Mobility	*n=249*	*n=248*	0.75
No problems	192 (77%)	195 (79%)	
Some problems	57 (23%)	53 (21%)	
Confined to bed	0 (0%)	0 (0%)	
Self-care	*n=249*	*n=248*	0.90
No problems	239 (96%)	240 (97%)	
Some problems	9 (4%)	7 (3%)	
Unable	1 (0%)	1 (0%)	
Usual activities	*n=249*	*n=241*	0.36
No problems	214 (86%)	209 (84%)	
Some problems	30 (12%)	37 (15%)	
Unable	5 (2%)	2 (1%)	
Pain/discomfort	*n=238*	*n=241*	0.09
No pain/discomfort	168 (68%)	169 (68%)	
Moderate pain/discomfort	70 (28%)	76 (31%)	
Extreme pain/discomfort	11 (4%)	3 (1%)	
Anxiety/depression	*n=249*	*n=238*	0.26
Not anxious/depressed	204 (82%)	215 (87%)	
Moderate anxious/depressed	37 (15%)	28 (11%)	
Extremely anxious/depressed	8 (3%)	4 (2%)	

IMPACT=IMProving Adherence using Combination Therapy
*Fishers Exact test.

At 12 months, the most commonly reported reasons participants reported missing any prescribed medication in the preceding month were that they forgot (polypill 29% vs usual care 30%), had a change in their daily routine (polypill 16% vs usual care 18%) or ran out of pills (polypill 11% vs usual care 11%) (Table 44). There was no statistically significant difference in the proportion of participants who reported missing prescribed medications in the preceding month at 12 months due to any of the possible barriers to adherence.

Table 44. Barriers to adherence at 12 months for IMPACT trial participants, by treatment group

Participants that reported missing taking any prescribed medication in the preceding month for the following reasons	**Polypill, n (%)**	**Usual care, n (%)**	**p value**
Wanted to avoid side effects	7 (3%)	9 (4%)	0.61†
Felt that you didn't need to take the medication	7 (3%)	7 (3%)	1.00†
Felt sick or ill	9 (4%)	9 (4%)	1.00†
Had too many pills to take at once	6 (2%)	5 (2%)	0.76†
Had to take pills too many times during the day	4 (2%)	4 (2%)	1.00*
Were unclear what pills you were supposed to take when	4 (2%)	1 (0%)	0.37*
The print on the medication was difficult to read	1 (0%)	1 (0%)	1.00*
The medication was hard to get out of the packet/bottle	1 (0%)	4 (2%)	0.37*
Visiting the doctor to get a prescription was too expensive	7 (3%)	7 (3%)	1.00†
Filling a prescription from the pharmacy was too expensive	8 (3%)	5 (2%)	0.40†
It was too hard to get to the doctor	8 (3%)	5 (2%)	0.40†
It was too hard to get to the pharmacy	3 (1%)	5 (2%)	0.72*
Ran out of pills	27 (11%)	28 (11%)	0.89†
Forgot or weren't reminded to take the pills	71 (29%)	74 (30%)	0.77†
Had a change in your daily routine (eg went on holiday)	40 (16%)	44 (18%)	0.63†

IMPACT=IMProving Adherence using Combination Therapy
*Fishers Exact test.
†χ^2 test.

Each participant's general practitioner was asked to rate the acceptability of the polypill on different aspects of care for that participant. If general practitioners had randomised more than one participant, they were asked to rate the polypill for each participant separately. Four participants' general practitioners were not approached as the participant had changed general practice and a relationship with the new practice had not been established. Fifty six general practitioners (of 64, 88%) responded to the survey for the remaining 252 participants. Of the eight non-responding general practitioners, one was on leave (responsible for 2 participants), four had changed practice (responsible for 13 participants), and three were contacted but did not respond (responsible for 6 participants). This meant that there was a response from a general practitioner for the remaining 231 (of 252, 92%) participants.

Ninety percent of participants' general practitioners said that if they had another patient like their patient who was a trial participant, they would start them on the polypill if it were available. General practitioners rated various aspects of polypill-based care as 'very

satisfactory' or 'satisfactory' for 78-91% of their participants randomised to the polypill (Table 45).

Table 45. Prescriber-rated satisfaction with polypill-based care for their patients randomised to polypill-based care in the IMPACT trial

Aspect of polypill-based care	Very satis-Factory, n (%)	Satis-factory, n (%)	OK, n (%)	Unsatis-factory, n (%)	Very unsatis-factory, n (%)	Total responses, N
Starting the polypill	126 (56%)	80 (35%)	8 (4%)	13 (6%)	0	227
Blood pressure control	114 (52%)	66 (30%)	13 (6%)	27 (12%)	0	220
Cholesterol control	107 (49%)	63 (29%)	34 (16%)	14 (6%)	0	218
Tolerability	137 (61%)	44 (20%)	7 (3%)	35 (16%)	0	223
Guideline adherence	127 (58%)	58 (26%)	28 (13%)	6 (3%)	0	219

IMPACT=IMProving Adherence using Combination Therapy
Note: 56 (of 64; 88%) of general practitioners responded; responses relate to 231 (of 252, 92%) of participants. Each participant's general practitioner was asked to rate the acceptability of polypill-based care on different aspects of care for that participant. If general practitioners had randomised more than one participant, they were asked to rate the polypill for each participant separately.

Improved medication adherence was considered to be the most important advantage of the polypill by general practitioners (for 57% of participants), and for 50% of participants no important disadvantage was reported by their general practitioner (Table 46).

Table 46. Prescriber-rated advantages and disadvantages with the polypill for their patients randomised to polypill-based care in the IMPACT trial

Most important advantage, n (%)	
Improved medication adherence	127 (57%)
No important advantage	40 (18%)
Reduced cost	28 (13%)
Patient preference	13 (6%)
Multiples of the above options selected	8 (4%)
Reduced length of consultation time	3 (1%)
Other	2 (1%)
Most important disadvantage, n (%)	
No important disadvantage	111 (50%)
Lack of flexibility	82 (37%)
More adverse effects	23 (10%)
Increased length of consultation time	4 (2%)
Increased cost	1 (0%)

IMPACT=IMProving Adherence using Combination Therapy
Note: 56 (of 64; 88%) of general practitioners responded; responses relate to 221 (of 252, 88%) of participants. Each participant's general practitioner was asked to name the most important disadvantage and most important advantage of polypill-based care for each of their participants randomised to the polypill. If general practitioners had randomised more than one participant, they were asked to rate the polypill for each participant separately.

5.7. Other outcomes

5.7.1. Other outcomes - effectiveness

Self-reported use of an antiplatelet, statin and at least one blood pressure lowering agent at 12 months was greater in the polypill than in the usual care group (88 v 73%, RR[unadjusted] 1.20, 95% CI 1.10-1.31, p<0.0001) (Table 47) Self-reported use of each medication type at

12 months were high in both groups, especially in the polypill group. For antiplatelet therapy they were 93% polypill vs 83% usual care (p<0.001), for statin 94% vs 89% (p=0.06), for combination blood pressure lowering 89% vs 59% (P<0.001) and for any blood pressure lowering 96% vs 91% (p=0.02) (Table 47).

Table 47. Other self-reported use of medication outcomes at 12 months in the IMPACT trial, by treatment group

Medication(s)	**Polypill, n/N (%)**	**Usual care, n/N (%)**	**Risk ratio, unadjusted (95% CI)**
Antiplatelet, statin and BP lowering agent	219/249 (88%)	187/248 (73%)	**1.20 (1.10-1.31) p<0.0001**
BP lowering agent	240/249 (96%)	226/248 (91%)	**1.06 (1.01-1.11), p=0.02**
Two or more BP lowering agents	222/249 (89%)	147/248 (59%)	**1.50 (1.34-1.68), p<0.0001**
Statin	233/249 (94%)	220/248 (89%)	1.05 (1.00-1.11), p=0.06
Antiplatelet	231/249 (93%)	205/248 (83%)	**1.12 (1.05-1.20), p=0.0006**

BP=blood pressure; CI=confidence interval; IMPACT=IMProving Adherence using Combination Therapy
Statistically significant results in bold

The mean reduction in systolic blood pressure between baseline and 12 months was not statistically significant between polypill and usual care groups whether or not analyses were adjusted by pre-specified covariates (sex, age, ethnicity, Primary Health Organisation, history of cardiovascular disease and self-reported use of recommended medications at baseline). After adding baseline systolic blood pressure to the adjusted analysis, the difference in the mean reduction in systolic blood pressure between baseline and 12 months became statistically significantly greater in the polypill compared with the usual care group (-3.2 mm Hg, 95% CI -6.1 to -0.3, p=0.03).

There was no statistically significant difference between polypill and usual care groups when analyses were adjusted for baseline values in addition to pre-specified covariates in any of the following outcomes:

- Mean reduction in systolic blood pressure between baseline and end of trial (-2.4 mm Hg, 95% CI -5.4 to 0.6, p=0.12)
- Mean reduction in low density lipoprotein cholesterol between baseline and 12 months (-0.03 mmol/L, 95% CI -0.14 to 0.07, p=0.54).
- Mean reduction in low density lipoprotein cholesterol between baseline and end of trial (-0.04 mmol/L, 95% CI -0.15 to 0.06, p=0.40)

5.7.2. Other outcomes – safety

The Clinical Adjudication Committee confirmed 70 ‘renal events’ (polypill 40 vs usual care 30) and four polypill participants (no usual care participants) had major extracranial bleeds.

The excess of renal events in the polypill group was primarily due to greater progression to macroalbuminuria (polypill 12 vs usual care 4, Table 48).

Table 48. Renal events, major bleeds and non-cardiovascular deaths in the IMPACT trial, by treatment group

Type of non-cardiovascular event	**Polypill, n***	**Usual care, n***
Renal		
New onset microalbuminuria	23	24
Progression to macroalbuminuria	12	4
50% loss of estimated glomerular filtration rate	4	2
Commencement of renal replacement therapy for ESRD	1	0
TOTAL	40	30
Major bleed (extracranial)	4	0
Non-cardiovascular death	3	6

ESRD=end stage renal disease; IMPACT=IMProving Adherence using Combination Therapy
*Patients can contribute only once to each row, but more than once to each column

There was no difference in the proportion of current smokers among polypill and usual care participants at 12 months (28% polypill vs 28% usual care, p=0.943). There was also no difference between the groups in the mean change in body mass index or duration of activity (of moderate or vigorous intensity) between baseline and 12 months (Table 49). There was a borderline significant reduction in the mean change in units of alcohol consumed per week between baseline and 12 months in the polypill compared with the usual care groups (mean difference -2.2 vs 0.1 units/week, p=0.049) (Table 49).

Table 49. Alcohol consumption, body mass index and duration of physical activity among IMPACT trial participants, by treatment group

Risk factor	**Mean change between baseline and 12 months**		**p value**
	Polypill	**Usual care**	
Alcohol consumption (units/week)	-2.2 (Median change 0) (SD 16.2, IQR -1 to 0) (n=249)	0.1 (Median change 0) (SD 7.3, IQR 0-0) (n=248)	**0.049***
Body mass index (kg/m^2)	0.17 (SD 1.87) (n=248)	0.06 (SD 1.56) (n=245)	0.49
Moderate activity (minutes/week)	-43 (Median change 0) (SD 353, IQR -180 to 100) (n=249)	-27 (Median change 0) (SD 360, IQR -210 to 130) (n=248)	0.64*
Vigorous activity (minutes/week)	14 (Median change 0) (SD 186, IQR 0 to 0) (n=249)	15 (Median change 0) (SD 206, IQR 0-0) (n=248)	0.57*

IMPACT=IMProving Adherence using Combination Therapy
*Mann-Whitney test (non-normal data).
Statistically significant result in bold

Mean serum uric acid remained unchanged between baseline and 12 months in the usual care group, but increased by a mean of 0.01 mmol/L in the polypill group. The difference in the mean change in uric acid between polypill and usual care groups was statistically significant (p=0.01, Table 50). Mean serum sodium increased by 0.08 mmol/L in the polypill group and by 0.62 mmol/L in the usual care group; this difference was also statistically significant

(p=0.01). There were no other statistically significant differences between polypill and usual care groups in the mean change from baseline to 12 months in laboratory values (Table 50).

Table 50. Results of other laboratory tests in the IMPACT trial, by treatment group

Laboratory test	Mean change from baseline to 12 months		p value
	Polypill	Usual care	
Creatinine (µmol/L)	5.23 (Median change 3) (SD 26.05, IQR -5 to 9) (n=243)	3.32 (Median change 1) (SD 31.25, IQR -5 to 7) (n=246)	0.10*
Uric acid (mmol/L)	0.01 (Median change 0.01) (SD 0.08, IQR -0.03 to 0.05) (n=228)	0.00 (Median change 0) (SD 0.06, IQR -0.03 to 0.03) (n=227)	**0.01***
Sodium (mmol/L)	0.08 (SD 2.46) (n=241)	0.62 (SD 2.28) (n=239)	**0.01**
Potassium (mmol/L)	0.06 (SD 0.46) (n=240)	0.05 (SD 0.45) (n=238)	0.87
Alanine amino-transferase (IU/L)	-1.00 (Median change -1.00) (SD 10.08, IQR -6 to 4)) (n=231)	-0.26 (Median change 1.00) (SD 17.95, IQR -4 to 5) (n=230)	0.11*
Aspartate amino-transferase (IU/L)	-0.54 (Median change 0) (SD 7.99, IQR -3 to 2) (n=89)	0.32 (Median change 0) (SD 6.1, IQR -3 to 3) (n=79)	0.57*
Fasting glucose (mmol/L)	-0.07 (Median change 0) (SD 2.05, IQR -0.6 to 0.5) (n=232)	0.00 (Median change 0) (SD 1.76, IQR -0.5 to 0.6) (n=231)	0.29*
Glycosylated haemoglobin (%)	-0.13 (Median change -0.1) (SD 0.84, IQR -0.4 to 0.2) (n=231)	-0.17 (Median change -0.1) (SD 0.82, -0.4 to 0.1) (n=235)	0.56*
Urinary ACR (mg/mmol)	0.11 (Median change 0) (SD 57.97, IQR -0.6 to 0.4) (n=209)	1.08 (Median change 0) (SD 20.15, IQR -0.3 to 0.7) (n=218)	0.36*

ACR=albumin:creatinine ratio; IMPACT=IMProving Adherence using Combination Therapy; IQR=interquartile range, SD=standard deviation
*Mann-Whitney test (non-normal data).
Statistically significant result in bold

5.7.3. Other outcomes – acceptability

When asked how easy they found taking all of their prescribed medicines at 12 months, 224 (91%) of polypill participants responded ‘very easy’ or ‘easy’, compared with 212 (86%) of usual care participants (Table 51). Four (2%) of polypill participants responded ‘difficult’ or ‘very difficult’ to this question at 12 months, compared with 9 (4%) of usual care participants.

Table 51. IMPACT trial participant-reported ease of taking all prescribed medications (including the polypill) at 12 months, by treatment group

Ease of use	Polypill, n (%) N=246	Usual care, n (%) N=246
Very Easy	136 (55%)	117 (48%)
Easy	88 (36%)	95 (39%)
Average	18 (7%)	25 (10%)
Difficult	4 (2%)	6 (2%)
Very Difficult	0	3 (1%)

IMPACT=IMProving Adherence using Combination Therapy
Note: Fisher’s exact test p=0.19.

All participants were sent a post-trial survey regarding their experience on the trial. The survey included questions on polypill-based care for those randomised to the polypill. Eighty percent (205/256) of participants randomised to polypill-based care returned their surveys. In

response to the question 'Were there any advantages with taking the polypill?', 88% (177 of 203 that responded to that question) said 'Yes' and 12% (25/203) said 'No'. Those that responded 'Yes' were asked to specify the advantages of the polypill. They could select pre-specified advantages ('fewer pills to take', 'cheaper prescription costs', 'fewer side effects to medication', 'fewer visits to the general practitioner required') as well as specifying any other advantages. Participants could provide multiple responses. The most commonly reported advantage to taking the polypill was 'fewer pills to take' (83%, 169/203). All reported advantages are listed in Table 52.

Table 52. Advantages of the polypill according to IMPACT trial participants who were randomised to polypill-based care and who responded to a post-trial survey

Advantages	**n* (%†)**
Fewer pills to take	169 (83%)
Cheaper prescription costs	46 (23%)
Fewer visits to the GP required	25 (12%)
Fewer side effects	23 (11%)
Better risk factor control	3 (1%)
Other	1 (0%)

GP=general practitioner; IMPACT=IMProving Adherence using Combination Therapy
*Multiple responses allowed for each responding participant.
†Denominator is the number of participants that responded 'Yes' or 'No' to the question 'Were there any advantages with taking the polypill?', i.e. 203.

In response to the question 'Were there any disadvantages with taking the polypill?', 25% (46 of 186 that responded to that question) said 'Yes' and 75% (140/186) said 'No'. Those that responded 'Yes' were asked to specify the disadvantages of the polypill. They could select pre-specified disadvantages ('more pills to take', 'more expensive prescription costs', 'more side effects to medication', 'extra visits to general practitioner required') as well as specifying any other disadvantages. Participants could provide multiple responses. The most commonly reported disadvantage to taking the polypill was 'more side effects' (16%, 29/186). All reported disadvantages are listed in Table 53.

Table 53. Disadvantages of the polypill according to IMPACT trial participants who were randomised to polypill-based care and who responded to a post-trial survey

Disadvantages	**n* (%†)**
More side effects	29 (16%)
Inadequate risk factor control	4 (2%)
More pills to take	4 (2%)
Lack of flexibility	2 (1%)
Extra visits to GP required	2 (1%)
Not available outside trial	2 (1%)
Didn't like formulation	2 (1%)
More expensive prescription costs	1 (1%)
If forget pill miss 4 meds not 1	1 (1%)
Other	1 (1%)

GP=general practitioner; IMPACT=IMProving Adherence using Combination Therapy
*Multiple responses allowed for each responding participant.
†Denominator is the number of participants that responded 'Yes' or 'No' to the question 'Were there any disadvantages with taking the polypill?', i.e. 186.

5.8. Summary

Five hundred and thirteen participants were randomised to polypill-based (n=257) or usual care (n=256) over a recruitment period of 24 months. As planned, the trial continued until 12 months after the last participant had been randomised. The median duration of follow-up was 23 months. At baseline, polypill and usual care participants were similar overall, although the median duration of moderate intensity physical activity was slightly lower among polypill than usual care participants. Primary outcome data were available for 97% of trial participants at 12 months. Self-reported use of an antiplatelet, statin and two or more blood pressure lowering drugs was 75% greater among polypill than usual care participants at 12 months. Differences in blood pressure and low density lipoprotein cholesterol between treatment groups did not reach statistical significance, but medication use was high in both treatment arms. There was no statistically significant difference between groups in the incidence of serious adverse event during the trial; however 37% in the intervention group discontinued the polypill during the study period (median trial duration 23 months).

Chapter 6. IMProving Adherence using Combination Therapy (IMPACT) randomised controlled trial: Discussion

6.1. Introduction

This chapter discusses the effectiveness of a polypill-based treatment strategy in improving blood pressure and cholesterol (given inconsistency in trial evidence to date), and its safety (given the relative paucity of trial data to date), among New Zealand patients at high risk of cardiovascular disease. The key findings from the IMPACT trial are summarised, the strengths and limitations of the trial are discussed, and the results of the trial are compared with those of previous studies.

6.2. Summary of key findings

The IMPACT trial found that polypill-based care improved the use of recommended combination therapy at 12 months among New Zealand participants at high risk of cardiovascular disease. The effect of polypill-based care on the use of recommended combination therapy was significantly greater in participants not adherent to recommended medications at baseline and those under 60 years of age. Over 12 months, the mean reduction in systolic blood pressure was modestly greater in the polypill compared with the usual care group, but this difference was only statistically significant in an additional (not pre-specified) analysis that adjusted for baseline systolic blood pressure. This adjustment is likely to have changed the result from not statistically significant to significant because at baseline mean systolic blood pressure was slightly higher in the usual care group (145mm Hg) than the polypill-based care group (143 mm Hg). The expected reduction in systolic blood pressure with antihypertensives increases with increasing pre-treatment systolic blood pressure.[41] Low density lipoprotein cholesterol reduction over 12 months was not statistically significantly different between the polypill and usual care groups.

Serious adverse events were reported in over a third of trial participants. There was a trend towards more serious adverse events in the polypill group compared with the usual care group, although the number of individuals in each group who had at least one serious adverse event was similar. There was also the same number of serious cardiovascular events in each group and a greater number of deaths occurred in the usual care group. In the polypill compared with the usual care group, more serious bleeds (4 vs 0) and significant hypotensive

events (6 vs 0) were reported, and more progression to macroalbuminuria (12 vs 4) was identified.

Serious bleeds were adjudicated by a blinded endpoint committee independent of trial researchers, and were pre-specified as active bleeding that resulted in a reduction of haemoglobin of at least 20 g/L, or required transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ. The expected number of serious bleeds was estimated using the modelling in chapter 3, and compared with the observed number of serious bleeds (Table 54). While 2.5 more bleeds than expected were observed in the polypill group, 1.6 fewer bleeds than expected were observed in the usual care group. The use of an antiplatelet was higher in the polypill than the usual care group (at trial end, 90% vs 81%) but this increase is unlikely to explain the observed result. Possible alternative explanations are chance (because the trial was not powered to assess differences between groups in serious bleeds), greater daily use of antiplatelets over time in polypill compared with usual care participants (not captured by self-reported or dispensed use at a single time point), and increased vigilance and/or reporting of bleeds in polypill compared with usual care participants because of the open-label nature of the trial.

Table 54. Number of expected and observed serious bleeds in the IMPACT trial, by treatment group

	Polypill, n	**Usual care, n**
Expected*	1.5	1.6
Observed	4	0
Difference	+2.5	-1.6

IMPACT=IMProving Adherence using Combination Therapy
*Expected estimated from modelling in chapter 3.

Unlike serious bleeding, significant hypotensive events were neither defined in advance nor independently adjudicated. Of the six participants that experienced significant hypotension, five required hospitalisation for this serious adverse event. At trial end, more polypill than usual care participants were taking two or more blood pressure lowering agents (83% vs 61%); a similar proportion were taking at least one blood pressure lowering agent (94% vs 92%). However, the magnitude of the difference in blood pressure between the two groups was modest and did not reach statistical significance at either 12 months or end of trial. The only exception was in an additional analysis, which adjusted for baseline systolic blood pressure (difference, adjusted by baseline systolic blood pressure and pre-specified covariates, -3.2 mm Hg, 95% confidence interval, CI, -6.1 to -0.3, p=0.03). Possible explanations for the increase in significant hypotensive events are that lack of titration of

medication was harmful to some participants or that hypotension was more likely to be reported in polypill than usual care participants because the trial was not blinded.

Progression from microalbuminuria to macroalbuminuria was a pre-specified endpoint that was adjudicated by a blinded committee independent of trial researchers. Differential reporting between polypill and usual care arms was possible (particularly because this test was optional), although no more polypill than usual care participants had their urinary albumin:creatinine ratio tested (at 12 months, 209 polypill participants vs 218 usual care participants, at end of trial 186 vs 206). Urinary albumin:creatinine ratio was slightly higher in polypill than usual care participants at baseline (mean 15.4 vs 10.1 mg/mmol, median 1.2 vs 1.0 mg/mmol). At 12 months, the mean increase in the urinary albumin:creatinine ratio was 0.11 mg/mmol in the polypill compared with 1.08 mg/mmol in the usual care group (median increase 0 in both groups, p=0.36 using the Mann-Whitney test as data were not normally distributed). At end of trial, the mean increase was 8.26 mg/mmol in the polypill compared with 3.58 in the usual care group (median increase 0 in both groups, p=0.87 using the Mann-Whitney test). What further complicates the interpretation of this finding is that angiotensin converting enzyme inhibitors (such as lisinopril, included in both versions of the polypill used in the IMPACT trial) are specifically indicated for patients with diabetes and microalbuminuria, irrespective of whether or not hypertension is present, to reduce progression of microalbuminuria.[40]

Over a third (n=94, 37%) of participants initiated on the polypill discontinued it during the trial. The main reasons for discontinuing the polypill were a side effect (n=54, of which 13 were for dizziness/hypotension, and 10 were for cough), but other reasons were medical practitioner decision, not further specified (n=15), patient choice (n=9), inadequate risk factor control (n=5), other reason (n=7) and unknown reason (n=4).

There was no difference between polypill and usual care groups in the proportion of participants smoking cigarettes at 12 months (p=0.94) or in the mean change in duration of physical activity (moderate intensity p=0.64, vigorous intensity p=0.57) or body mass index (p=0.49) over 12 months. There was a borderline significant reduction between baseline and 12 months in the mean number of units of alcohol consumed per week in the polypill compared with the usual care group (p=0.049). Also there were no significant differences between the groups in the mean changes of most laboratory tests over 12 months (creatinine, potassium, alanine aminotransferase, aspartate aminotransferase, fasting glucose,

glycosylated haemoglobin and urinary albumin:creatinine ratio). There were minor but statistically significant differences between the two groups in mean change over 12 months in uric acid and sodium. These findings are unlikely to be clinically significant and may have been found by chance due to the number of statistical tests performed.

Participant acceptability of medicines (including the polypill for those randomised to it) was high in both polypill and usual care groups, and there was no difference between the two groups in quality of life measures or possible barriers to adherence. The most frequent advantage of the polypill reported by participants in the intervention arm was 'fewer pills to take' (82%). The most frequently reported disadvantage was 'more side effects' (14%). Over two thirds of polypill participants reported that there were no disadvantages with taking the polypill. General practitioners rated the polypill highly on different aspects of care for individual participants randomised to the polypill, and 90% said that if they had another patient like their patient who was a trial participant, they would start them on the polypill if it were available.

6.3. Trial strengths and limitations

A major strength of the IMPACT trial is that it tested the strategy of polypill-based care in a pragmatic primary care setting. The trial mimicked usual practice in three key ways: (1) participants were recruited, randomised and had trial treatment initiated by their usual general practitioner who retained responsibility for the participant's medical care, including on-going prescribing of the polypill; (2) the polypill was dispensed by community pharmacists and; (3) participants were required to pay what they would normally pay to receive a single government-subsidised medication. These features will also improve generalisability of results to real practice if a polypill were to be registered and fully subsidised by PHARMAC (New Zealand's Pharmaceutical Management Agency). It will also make any subsequent economic analysis likely to reflect real costs both to the patient and health provider.

Potential participants were identified by systematic screening through general practice electronic medical records, which reduced the possible bias of general practitioners choosing participants opportunistically. This aids the generalisability of results to usual general practice. While general practitioners decided which patients were suitable to proceed to randomisation, this non-random selection process reflects what would happen in clinical practice were such a polypill available. Participants who agreed to participate may have been

more likely to adhere to their medication already. However this may make it more difficult to improve adherence, so any bias is likely to be conservative.

Selection bias may occur in randomised controlled trials when allocation to the intervention or control group is predictable and may therefore influence the decision of whether or not to enter a participant into a trial.[192] In the IMPACT trial, the allocation sequence was protected right up to the point of randomisation, thereby minimising the risk of selection bias, by having randomisation (once activated by the general practitioner) performed by a centralised online randomisation system. Further, there was no evidence of allocation bias[213] as polypill and usual care groups were similar at baseline with no major imbalances in assessed risk factors. Random allocation to polypill and usual care groups minimised the risk of confounding by randomly distributing both known and unknown confounding variables between treatment groups.[5] The risk of confounding was further reduced by analysing primary outcomes on an intention to treat basis, as confounding may influence follow-up.

Attrition bias can occur when loss to follow up is different in the experimental and control arm of a trial.[214] This bias can be minimised by ensuring that follow-up is as complete as possible and undertaking intention to treat analyses. Follow-up in the IMPACT trial was very good, with 97% of polypill and 96% of usual care participants followed up to 12 months, and 96% of polypill and 95% of usual care participants followed up to the end of trial. Primary outcomes for the IMPACT trial made conservative assumptions where data were not available (i.e. assumptions of non-adherence or no change in systolic blood pressure and low density lipoprotein cholesterol where data were missing) to mitigate the effects of any attrition bias, thereby reducing the chance of type I error (rejecting the null hypothesis when it should be accepted).

The trial initially sought to recruit 600 participants but this was revised down to 500 participants given available funding resources. Although it was estimated that power would be sufficient for all three primary outcomes, the observed non-significant ‘differences’ in systolic blood pressure and low density lipoprotein cholesterol between polypill and usual care groups at 12 months (-2.2 mm Hg and -0.05 mmol/L, respectively) were much lower than those expected and used for power calculations (-4 mm Hg and -0.25 mmol/L, respectively). The trial was therefore underpowered to confirm the differences in these outcomes as statistically significant between the polypill and usual care groups, i.e. these

outcomes were potentially subject to type II error. The trial was not specifically powered to detect differences in serious adverse effects.

Multiple comparisons were made between polypill and usual care groups in secondary and other outcomes, increasing the risk of falsely significant results (i.e. type I errors).[215] Adjustment for multiple comparisons (such as the Bonferroni and Holm methods[215]) was not undertaken because many of these comparisons were performed specifically to identify possible safety concerns of polypill-based care. Further, there is the potential to compare findings from the IMPACT trial with other, similar, trials to assess the robustness and consistency of findings.

The unblinded design was unavoidable given the intervention being assessed. Lack of blinding increases the risk of bias; particularly performance bias and measurement bias. Performance bias, which is often also called co-intervention, is when treatment or exposures differ between the groups, other than the intervention itself.[141] The IMPACT trial was particularly susceptible to performance bias because all participants were entered onto the trial and prescribed cardiovascular preventive medications (including the polypill for those randomised to it) by their usual general practitioner. As the general practitioners knew which of their patients participating in the trial and whether participants had been randomised to the polypill or usual care, this may have affected the care received by trial participants beyond the effect of the trial intervention. Although general practitioners were encouraged to manage all of their participants according to current New Zealand guidelines, it was only those randomised to the polypill who in effect had to change their medication (as they were being offered something previously unavailable). This may have resulted in additional visits to the general practitioner for polypill participants, leading to additional care from their general practitioner compared with usual care participants. However, the trial only funded baseline, end of trial and a small number of additional general practitioner visits on a case-by-case basis (e.g. if a polypill participant had a side effect and had to be put back onto usual care), so this was very close to mimicking usual practice conditions. The unblinded nature of the trial may have influenced participant adherence to medication during the trial independent of the effect of the intervention itself, although both polypill and usual care groups had the same number of research visits and measurements, to limit the potential for co-intervention.

Measurement bias occurs when measurement or classification of an exposure or outcome are inaccurate.[5] When measurement bias occurs equally in groups being compared (non-

differential bias), it tends to underestimate the true strength of any identified relationships (i.e. increasing the chance of type II error [accepting the null hypothesis when it should be rejected]). The risk of non-differential measurement bias was minimised in IMPACT for the systolic blood pressure and low density lipoprotein cholesterol outcomes because systolic blood pressure was measured using a validated and calibrated automatic sphygmomanometer with automatic printout (Omron T9P) and low density lipoprotein cholesterol was measured by accredited laboratories. Measurement bias can also be differential, when measurement or classification is influenced by treatment allocation, thereby increasing the chance of type I error. For the IMPACT trial, systolic blood pressure and low density lipoprotein cholesterol outcomes were at risk of differential measurement bias because treatment allocation was not blinded. The risk of differential measurement bias in the systolic blood pressure measurements was reduced by using an automatic sphygmomanometer and auditing printouts from these machines to ensure that only the requested number of blood pressure measurements (three) was taken for each participant. The risk of differential measurement bias in low density lipoprotein cholesterol measurement was low because it was measured by technicians at accredited laboratories who were blind to treatment allocation.

The self-reported use of medication outcome was at risk of both non-differential and differential measurement bias as it was assessed by self-report. The risk of non-differential measurement bias (e.g. participants being unfamiliar with the names of the medication they were taking) was decreased by asking participants to have all of the medications they were currently taking available during trial assessments or visits, so that they could read these out to the research nurse. This would also have reduced the risk of recall bias, a type of differential measurement bias when past exposure is recalled differentially.[5] However, there may still have been systematically different ways polypill and usual care participants reported their current medications to research nurses because they were not blinded to treatment allocation. While medication use may have been assessed more objectively with pill counts or electronic pill bottles, these were not used because of their cost and inconvenience for participants (which may in itself have affected medication use) and their potential for manipulation.[172] Ultimately, dispensing data were obtained and these demonstrated close concordance with self-reported medication use. Measurement bias is therefore unlikely to have had a substantial effect on the self-reported use of medication outcome.

The findings from the IMPACT trial are unlikely to have been affected by selection bias (because of robust allocation sequence concealment prior to randomisation), attrition bias (because of comprehensive follow-up and use of intention to treat analysis) or confounding. The fact that differences between polypill and usual care groups in systolic blood pressure and low density lipoprotein cholesterol control did not reach statistical significance may have been because the trial was underpowered to detect the observed differences and are therefore potentially subject to type II error. This was because larger differences were expected and the usual care arm was well treated.

Performance bias may also have been a factor in the trial given that participants' general practitioners were not able to be blinded to treatment allocation. The trial is likely to be generalisable through its systematic identification of potentially eligible participants and integration with usual clinical practice, although ultimately decisions about whether participants should proceed to randomisation were made by their general practitioner.

6.4. Comparison with literature

The effect of the polypill compared with usual care on the use of cardiovascular medications in trials published to date that have assessed this outcome, including IMPACT, has been summarised in Table 55. Polypill-based care was associated with a 33% to 56% relative and a 21% to 26% absolute improvement in the use of recommended medications compared with usual care. Absolute and relative improvements in the use of recommended medications with polypill-based compared with usual care was greatest in the IMPACT trial, which also had the lowest level of recommended medication use among usual care participants.

Table 55. Polypill compared with usual care – effect on use of recommended medications in randomised controlled trials completed to date that have assessed this outcome

Trial	**Time point (median)**	**Self-reported use of recommended* cardiovascular medications, n/N (%)**		**Risk ratio (95% CI)**	**Absolute improvement in adherence**
		Polypill	**Usual care**		
UMPIRE 2013[124]	15 months	829/961 (86%)	621/960 (65%)	**1.33 (1.26 to 1.41)**	21%
Kanyini GAP 2014[129]	18 months	213/304 (70%)	143/305 (47%)	**1.49 (1.30 to 1.72)**	23%
IMPACT 2014[130]	23 months	185/256 (72%)	119/257 (46%)	**1.56 (1.34 to 1.82)**	26%

CI=confidence interval; EOT=end of trial; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; SD=standard deviation; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events
*Antiplatelet, statin and two or more BP lowering medications.
Statistically significant results in bold

The ‘improvement’ in systolic blood pressure was greater in the intervention than control arms in all trials comparing polypill with usual care published to date (Table 56). However, this ‘improvement’ was only statistically significant in UMPIRE (the largest trial) and CRUCIAL (at high risk of bias because the analysis did not use intention to treat principles, large amounts of data were missing and missing data were handled by carrying the last observation forward). The magnitude of the ‘improvement’ in trials other than CRUCIAL was modest (ranging from 1.3 mm Hg [IMPACT] to 2.6 mm Hg [UMPIRE]).

Table 56. Polypill compared with usual care – effect on systolic blood pressure in randomised controlled trials completed to date that have assessed this outcome

Trial	**Time point**	**Difference in mean systolic BP, mm Hg , between baseline and EOT (SD or 95% CI)**		**Difference (95% CI)**
		Polypill	**Usual care**	
Soliman 2011[122]	3 months	-28.8 (24.9) [n=99]	-26.9 (25.7) [n=104]	-1.9 (-8.9 to 5.1)
CRUCIAL 2011*[123]	12 months	-19.8 (17.1) [n=760]	-10.0 (16.4) [n=657]	LSM: **-5.8 (-8.0 to -3.5)**
UMPIRE 2013[124]	15 months (median)	Mean SBP at EOT 129.2 (128.1 to 130.2) [n=1002]	Mean SBP at EOT 131.7 (130.7 to 132.8) [n=1002]	**-2.6 (-4.0 to -1.1)**
Kanyini GAP 2014[129]	18 months (median)	Mean SBP at EOT 139.0 (0.9) [n=311]	Mean SBP at EOT 140.5 (0.9) [n=312]	-1.5 (-4.0 to 1.0)
IMPACT 2014[130]	23 months (median)	-5.9 (20.6) [n=256]	-4.6 (20.9) [n=257]	-1.3 (-4.9 to 2.3)

CI=confidence interval; CRUCIAL=Cluster Randomised Usual care vs Caduet Investigation Assessing Long-term-risk; EOT=end of trial; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; LSM=least squares mean; SBP=systolic blood pressure; SD=standard deviation; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events
*High risk of bias.
Statistically significant results in bold

The ‘improvement’ in cholesterol was greater in the intervention than control arms in all trials apart from Kanyini GAP (no absolute difference) comparing polypill with usual care (Table 57). As with systolic blood pressure, this ‘improvement’ was only statistically significant in UMPIRE (the largest trial) and CRUCIAL (at high risk of bias as outlined above), and the magnitude of any ‘improvement’ in trials other than CRUCIAL was modest.

Table 57. Polypill compared with usual care – effect on cholesterol in randomised controlled trials completed to date that have assessed this outcome

Trial	Time point	Cholesterol outcome, mmol/L* (SD or 95% CI)	Polypill	Usual care	Difference (95% CI)
Soliman 2011[122]	3 months	Total cholesterol, difference in mean between baseline and EOT	-1.4 (1.2) [n=99]	-1.0 (1.6) [n=104]	-0.4 (-0.8 to 0.0)
CRUCIAL 2011[123]*	12 months	LDL-C, difference in mean between baseline and EOT	-25.6% (27.4) [n=760]	2.7% (31.3) [n=657]	**LSM -27.1% (-30.9 to -23.4)**
UMPIRE 2013[124]	15 months (median)	LDL-C, mean at EOT	2.18 (2.13 to 2.22) [n=1002]	2.29 (2.24 to 2.33) [n=1002]	**-0.11 (-0.17 to -0.05)**
Kanyini GAP 2014[129]	18 months (median)	LDL-C, mean at EOT	2.23 (0.04) [n=311]	2.24 (0.04) [n=312]	-0.00 (-0.12 to 0.11)
IMPACT 2014[130]	23 months (median)	LDL-C, difference in mean between baseline and EOT	-0.21 (0.68) [n=256]	-0.16 (0.64) [n=257]	-0.05 (-0.17 to 0.06)

CI=confidence interval; CRUCIAL=Cluster Randomised Usual care vs Caduet Investigation Assessing Long-term-risk; EOT=end of trial; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; LDL=low density lipoprotein; LSM=least squares mean; SD=standard deviation; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events
*High risk of bias.
Statistically significant results in bold

More polypill than usual care participants experienced at least one serious adverse event during the trials that reported this outcome, although none of these differences were reported to be statistically significant (Table 58). Across trials there was considerable variation in the proportion of usual care participants experiencing a serious adverse event – from 3% in CRUCIAL to 41% in Kanyini GAP. This variation could reflect the differences between trial settings, participant characteristics, reporting practices and duration.

Table 58. Polypill compared with usual care – serious adverse events in randomised controlled trials completed to date that have assessed this outcome

Trial	Duration (median)	Participants with at least one serious adverse events, %		p value
		Polypill	Usual care	
CRUCIAL 2011[123]*	12 months	7%	3%	Not reported
UMPIRE 2013[124]	15 months	12%	10%	Not significant but p value not provided
Kanyini GAP 2014[129]	18 months	46%	41%	0.16
IMPACT 2014[130]	23 months	39%	36%	0.68

CRUCIAL=Cluster Randomised Usual care vs Caduet Investigation Assessing Long-term-risk; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events
*High risk of bias.
Statistically significant results in bold

The number of deaths in polypill and usual care groups were similar in the trials that reported this outcome (IMPACT 4 vs 6, UMPIRE 17 vs 15), and the CRUCIAL investigators noted no treatment-related deaths during their trial. There was also no statistically significant difference between groups in the number of people experiencing a fatal or nonfatal cardiovascular event in the trials that reported this outcome (IMPACT polypill 24 vs usual

care 26, Kanyini GAP 26 vs 22, UMPIRE 50 vs 35). None of the trials were powered to assess the effect of the polypill on death or cardiovascular events.

The polypill discontinuation rate in UMPIRE and Kanyini GAP was lower than that observed in IMPACT (Table 59).[124] These differences may reflect differences in trial duration, as trial annual polypill discontinuation rates were similar (18 to 19%). The reasons for discontinuation of the polypill were similar across the trials (Table 59). The main reasons were medical practitioner decision not further specified, patient choice and adverse event. The most commonly reported adverse events across trials were cough and dizziness/hypotension.

Table 59. Polypill compared with usual care – polypill discontinuation in randomised controlled trials completed to date that have assessed this outcome

Trial	Duration (median)	Discontinuation during trial, %	Discontinuation per year, %	Reasons for discontinuation (in descending order of frequency)
UMPIRE 2013[124]	15 months	22%	18%	Patient choice, cough, medical practitioner decision NFS, non-serious adverse event, dizziness, serious adverse event, other adverse event, other reason
Kanyini GAP 2014[129]	18 months	29%	19%	Medical practitioner decision NFS, patient choice, cessation by a specialist or during hospitalisation, cough, dizziness / hypotension
IMPACT 2014[130]	23 months	37%	19%	Medical practitioner decision NFS, dizziness or hypotension, cough, patient choice, deterioration in renal function, fatigue, inadequate risk factor control, unknown reason, bleed, gastritis / dyspepsia / ulcer, other side effect, other reason

Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; NFS=not further specified; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events

As previously noted, an excess of serious bleeds (4 vs 0), significant hypotensive events (6 vs 0) and progression to macroalbuminuria (12 vs 4) was identified in the polypill compared with the usual care group in IMPACT. In addition, a small but statistically significant increase in uric acid was observed in the polypill compared with the usual care group (median increase of 0.01 mmol/L). Soliman reported a similar frequency of epigastric pain in polypill and usual care groups (16% vs 19%) and did not specifically note any bleeds, hypotension, albuminuria or elevations in uric acid levels. CRUCIAL investigators did not specifically note any serious bleeds, albuminuria or elevations in uric acid levels, but the frequency of dizziness was 2.2% in the polypill arm compared with 1.3% in the usual care arm. As noted in Table 59 above, dizziness or hypotension was reported as a major reason for polypill discontinuation in UMPIRE and Kanyini GAP (9% and 6% of those that discontinued, respectively) as well as IMPACT (14% of those that discontinued). Neither

UMPIRE nor Kanyini GAP reported any serious bleeds or serious adverse events associated with hypotension.

UMPIRE did not note any albuminuria, but did identify small but statistically significant increases in uric acid (0.01 mmol/L) and creatinine (3 µmol/L) levels in polypill compared with usual care participants. Neither IMPACT nor Soliman found a statistically significant difference between groups in creatinine levels and this outcome was not reported in the other trials. Kanyini GAP found no statistically significant differences between polypill and usual care groups in new-onset microalbuminuria (55 vs 45, p=0.39) or progression to macroalbuminuria (22 vs 22 p=0.81). There was an almost statistically significant increase in polypill compared with usual care participants whose estimated glomerular filtration rate reduced by at least 50% from baseline in Kanyini GAP (11 vs 3, p=0.05), although the mean estimated glomerular filtration rate at end of trial was similar between groups (77.1 vs 77.0 ml/min).

6.5. Summary

When considered collectively, trials that have compared polypill-based care with usual care for participants with indications for cardiovascular preventive medications such as IMPACT have demonstrated an improvement in self-reported use of medication and small benefits in systolic blood pressure and low density lipoprotein cholesterol that have only been found to be statistically significant in the largest trials. Polypill-based care was acceptable to participants and their doctors. Neither the IMPACT nor the Kanyini GAP trial (in which half of the participants were indigenous) found any evidence of heterogeneity of treatment effect according to indigeneity. There was no evidence that polypill-based care adversely affected smoking, alcohol consumption, physical activity or weight. There is some evidence that polypill-based care was associated with increased bleeding (IMPACT trial) and hypotension (IMPACT and other trials) compared with usual care. The increased bleeding observed in IMPACT might have been a reflection of greater use of aspirin in polypill compared with usual care participants, in which case the most important issue is ensuring that, irrespective of whether aspirin is formulated separately or as part of a fixed dose combination, it is only prescribed to those for whom the benefits are likely to outweigh its harms. Although the increased hypotension identified in polypill compared with usual care participants in IMPACT might be a consequence of the unblinded nature of the trial, dizziness / hypotension was consistently reported across trials comparing polypill with usual care as a reason for

discontinuing the polypill. As with any cardiovascular prevention strategy that includes antihypertensive medication, any polypill-based strategy would need to mitigate against the potential harms of hypotension. There was no consistent evidence across trials of any other clinically relevant excess harm of polypill-based care compared with usual care. Polypill-based care was not suitable for all trial participants, and was associated with an annual discontinuation rate of approximately 20%, primarily due to side effects, personal choice and medical advice.

Chapter 7. Thesis conclusions

7.1. Rationale of the thesis

Globally, cardiovascular disease is the leading cause of death[1] and a major contributor to the overall burden of disease.[2] Cardiovascular disease is preventable and observed reductions in mortality rates in high-income countries have been attributed to both primary prevention (e.g. reducing smoking and the consumption of saturated fat) and secondary prevention (e.g. providing aspirin, statins and blood pressure lowering agents to people following a myocardial infarction.).[3] While the focus of this thesis was on the primary and secondary prevention of cardiovascular disease using medication, comprehensive strategies to reduce the burden of cardiovascular disease span the disease continuum by incorporating policy and environmental change through to end of life care.[6]

Three primary prevention strategies are of particular relevance to reducing the burden of cardiovascular disease: (1) the 'population' strategy (lowering the mean level of a risk factor), (2) the 'high risk' strategy (targeting those with elevations of a single risk factor) and (3) the 'high cardiovascular risk' strategy (treating people with high absolute risk of a cardiovascular event, estimated using data from multiple risk factors). [12] [15] The high cardiovascular risk strategy has been estimated to prevent more deaths than either the population or high risk strategy.[13]

For people with established cardiovascular disease and without contraindications, the combination of antiplatelet, statin and blood pressure lowering therapy is recommended by New Zealand, Australian, European and the United States guidelines.[7-11] International guidelines are also broadly consistent in recommending higher intensity treatment with cardiovascular preventive medications (statins and blood pressure lowering agents) the higher the individual's risk of a first cardiovascular event (i.e. in accordance with the 'high cardiovascular risk' strategy).[10 17-20] However, there is inconsistency across guidelines regarding the use of antiplatelet therapy for the primary prevention of cardiovascular disease.

Internationally, many people do not receive guideline-recommended cardiovascular preventive medications even when guidelines clearly and consistently indicate that benefits outweigh harms.[25] Even if cardiovascular preventive medications are prescribed and dispensed, their preventive potential is dependent on adherence to them.[26] Less than 50% of those prescribed medications for chronic conditions are estimated to be adherent long-

term.[26] One strategy that has the potential to improve the use of guideline-recommended medications and adherence to those medications is a fixed dose combination of medications, or 'polypill'.[27] A key recommendation of a 2001 World Health Organization meeting was that such a pill be developed for, and evaluated in, people with established cardiovascular disease.[28]

This thesis reported the results of two pieces of work. The first was a systematic review and modelling of the benefits and harms of aspirin in the primary prevention of cardiovascular disease. The second was the IMProving Adherence using Combination Therapy (IMPACT) trial, which compared polypill-based care with usual care among New Zealand patients at high risk of cardiovascular disease in a primary care setting.

7.2. Objectives of the thesis

The overall aim of this thesis was to investigate the safety and effectiveness of a cardiovascular polypill containing aspirin.

There were two objectives:

1. To investigate the benefits (reduction in cardiovascular events) and harms (increase in major bleeds) of treatment with aspirin when added to statin and blood pressure lowering medication in different age, sex and cardiovascular risk subgroups among people without established cardiovascular disease (systematic review and modelling).
2. To investigate the effectiveness of a polypill-based treatment strategy in improving the use of recommended medications and cardiovascular risk factors, and to assess its safety, in a trial of New Zealand patients at high risk of cardiovascular disease (the IMProving Adherence using Combination Therapy, IMPACT, trial).

7.3. Summary of key findings of the thesis

7.3.1. Effectiveness and safety of aspirin in the primary prevention of cardiovascular disease

A review of the evidence that underpins current international guidelines regarding the use of aspirin for the primary prevention of cardiovascular disease found that:

1. Aspirin is associated with a reduction in the risk of cardiovascular disease, coronary heart disease (in men) and ischaemic strokes (in women), and an increase in the risk of major non-cerebral (mainly gastrointestinal) bleeds and haemorrhagic strokes

2. There is no evidence of heterogeneity in the proportional effect of aspirin on either cardiovascular disease or major non-cerebral bleeding according to major characteristics
3. Absolute risk of both a first cardiovascular event and major non-cerebral bleed varies according to age, sex, smoking status, blood pressure and body mass index
4. The absolute reduction in cardiovascular events and increase in major non-cerebral bleeds therefore appears to depend primarily on baseline absolute risk of these events

Different meta-analyses and guidelines reached different conclusions regarding the use of aspirin in primary prevention, therefore it was considered appropriate to systematically search for all up to date meta-analyses, and any subsequent randomised controlled trials, to appraise if there are any changes to the current state of evidence around the use of aspirin for the primary prevention of cardiovascular disease.

In order to determine the balance of benefits and harms of aspirin for individual patients, both absolute cardiovascular risk and bleeding risk need to be assessed. Despite the preponderance of cardiovascular risk assessment tools, individualised bleeding risk assessment is less well developed. It was considered that modelling 5-year cardiovascular risk and incorporating updated proportional estimates of the reduction in cardiovascular events and increase in major non-cerebral bleeds with aspirin, based on the methodology used by the United States Preventive Services Task Force, would assist in determining the balance of benefits and harms of aspirin in primary prevention in New Zealand.

A review of the randomised controlled trials assessing a cardiovascular polypill for the prevention of cardiovascular disease found that:

1. The polypill is associated with improved use of medications but not consistently with improved systolic blood pressure and low density lipoprotein cholesterol among patients at high risk of their first or a subsequent cardiovascular disease when compared with usual care
2. When compared with inactive control, the polypill is associated with reductions in systolic blood pressure and low density lipoprotein cholesterol similar to that expected with individual components
3. No major safety concerns have emerged regarding the use of the polypill when compared with usual care or an inactive control, although this was based on a relatively small number of trials

Further randomised controlled trial evidence would therefore assist in understanding the effect of polypill-based care on blood pressure and cholesterol, and also its safety.

In chapter 3, meta-analyses of randomised controlled trials of aspirin in primary prevention were systematically reviewed and critically appraised. One additional randomised controlled trial was identified that had been published after the meta-analyses had been conducted, but that trial was subject to random and non-random error. Robust, up to date estimates were obtained for the proportional effect of aspirin on major cardiovascular events (10% decrease) and major non-cerebral bleeds (54% increase). These proportional effects of aspirin were applied to absolute rates of major cardiovascular events and bleeds to balance the benefits (reduction in major cardiovascular events) and harms (additional major non-cerebral bleeds) in groups by sex and age. The benefits of aspirin outweighed its harms for men and women aged 18 to 79 years with estimated 5-year cardiovascular risk greater than 10% (as monotherapy) or greater than 16% (when added to statin and blood pressure lowering therapy), using modelled data. These findings are restricted to people without a history of upper gastrointestinal pain or gastrointestinal ulcer and not receiving concomitant non-aspirin non-steroidal anti-inflammatory agents, and without any other contraindication to aspirin. The modelling enabled consideration of the appropriateness of the inclusion criteria for the IMPACT trial. The IMPACT trial evaluated a polypill containing a statin, blood pressure lowering agents and aspirin, and included men and women aged 18 to 79 years either with established cardiovascular disease, or without established cardiovascular disease but with estimated 5-year cardiovascular risk of 15% or more. For people aged 70 to 79 years without established cardiovascular disease but with 5-year cardiovascular risk 15%, the number of cardiovascular events avoided with aspirin (when added to statin and blood pressure lowering therapy) was estimated to be twice the number of additional bleeds with aspirin for women, but the same as the number of additional bleeds with aspirin for men. The IMPACT trial therefore excluded men aged 70 years or more without established cardiovascular disease.

7.3.2. Effectiveness and safety of a cardiovascular polypill

Five hundred and thirteen participants were randomised to polypill-based (n=257) or usual care (256) over a recruitment period of 24 months. As planned, the end of trial was 12 months after the last participant had been randomised. The median duration of follow-up was 23 months. At baseline polypill and usual care participants were largely similar. Primary outcome data were available for 97% of trial participants at 12 months. Self-reported use of

an antiplatelet, statin and two or more blood pressure lowering drugs was 75% greater among polypill than usual care participants at 12 months. Differences in blood pressure and low density lipoprotein cholesterol between treatment groups did not reach statistical significance, but medication use was high in both treatment arms. There was no statistically significant difference between groups in the number of participants who experienced a serious adverse event during the trial; however 37% in the intervention group discontinued the polypill during the study period (median trial duration 23 months).

7.4. Implications of the thesis

The focus of this thesis was on the primary and secondary prevention of cardiovascular disease using medication, which is an important component of a comprehensive strategy to reduce the burden of cardiovascular disease.

7.4.1. Effectiveness and safety of aspirin in the primary prevention of cardiovascular disease

The first part of this thesis focused on the use of aspirin in the primary prevention of cardiovascular disease, because of the different conclusions reached by different guidelines and meta-analyses. This thesis found consistent evidence of the benefit of aspirin in reducing cardiovascular disease and harm in increasing bleeds. The challenge for guideline developers, clinicians and patients, as reflected in the different conclusions reached, is in how to balance the benefits and harms of aspirin. This thesis found that in addition to assessing individual cardiovascular risk, individual bleeding risk also needs to be assessed in order to determine for which primary prevention patients the benefits of aspirin are likely to outweigh its harms. However, while many tools are available to assess cardiovascular risk, bleeding risk assessment is much more rudimentary. Calculators that automatically estimate cardiovascular risk and bleeding risk are recommended to assist in shared decision making regarding the use of aspirin in primary prevention. These could be implemented using current computerised decision support tools that are widely distributed in routine general practice in New Zealand. This thesis did not include the effect of aspirin on the primary prevention of cancer because the evidence supporting the association between aspirin and cancer is not as robust as that supporting the association between aspirin and cardiovascular disease. However, given that the evidence of aspirin's protective effect on cancer is growing, this additional benefit of aspirin should also be taken into account in the future.

7.4.2. Effectiveness and safety of a cardiovascular polypill

The second part of this thesis focused on the effectiveness and safety of a polypill containing aspirin compared with usual care for the prevention of cardiovascular disease among patients with indications for component medications. The IMProving Adherence using Combination Therapy (IMPACT) trial was conducted and found, as with other similar trials, an improvement in self-reported use of recommended medications but (as with other, similarly sized trials) was unable to demonstrate a statistically significant improvement in either systolic blood pressure or low density lipoprotein cholesterol. The evidence to date indicates that the benefits of a polypill-based treatment strategy are likely to be modest at an individual level within settings where treatment levels are already high. The greatest potential of polypill-based care appears to be in undertreated people (within well treated populations) and undertreated populations. The IMPACT and Kanyini GAP trials have demonstrated that there is no heterogeneity in treatment effect by indigenous ethnicity. However, polypill-based care is not without harms and evidence to date does not prove the safety of this strategy relative to usual care.

The advantages and disadvantages of a polypill-based treatment strategy from the perspectives of patients, clinicians and the health service, based on trial evidence to date, are summarised in Table 60.

Table 60.Advantages and disadvantages of a polypill-based treatment strategy from the perspective of patients, clinicians and health services, based on the findings of randomise controlled trials to date that have compared polypill-based care with usual care

Perspective	Advantages	Disadvantages
Patients	- Improved use of medications, BP and cholesterol - Overall acceptability to patients	- Does not suit all patients - Side effects like hypotension may be more common - Little benefit for those already taking recommended medications
Clinicians	- Improved use of medications, BP and cholesterol - Overall acceptability to clinicians	- Lack of ability to titrate may lead to an increase in side effects like hypotension - Limited options with components and dosages will limit applicability
New Zealand health service (and that of other rich countries)	- Small absolute benefits in BP and cholesterol that are likely to lead to reduced CVD if targeted to those undertreated - No indication that any less effective in indigenous patients	- Potential for increases in hospitalisations and associated costs due to side effects like hypotension - Limited benefit for those already taking recommended medications
Health services of low and middle income countries	- Large absolute benefits in BP and cholesterol that are likely to lead to significant reductions in CVD	- Dependent on skilled and relatively well funded health service to assess and manage high risk patients

BP=blood pressure; CVD=cardiovascular disease

The projected effect of polypill-based care (compared with usual care) on cardiovascular outcomes was modelled using the statistically significant improvements in risk factor levels observed in the UMPIRE trial (Table 61). Almost twice the number of cardiovascular events would be avoided with polypill-based compared with usual care using risk factor level estimates from participants who were not taking all four recommended medications at baseline. Neither of these estimates takes into account the benefits of aspirin.

Table 61. Projected effect of polypill-based care compared with usual care on cardiovascular outcomes based on the observed effect on blood pressure and low density lipoprotein cholesterol in the UMPIRE trial, by baseline treatment

	Estimated effect of polypill-based care compared with usual care					
	Risk factor level change*		**Relative risk reduction in CVD**		**Number of CV events averted for 1000 people with 5-year CV risk of 20% treated for 5 years**	
	Irrespective of baseline treatment	Undertreated* at baseline	Irrespective of baseline treatment	Undertreated* at baseline	Irrespective of baseline treatment	Undertreated* at baseline
SBP lowering†	-2.6 mm Hg	-4.9 mm Hg	5.5%	11%	11	22
LDL-C lowering‡	-0.11 mmol/L	-0.17 mmol/L	2.3%	3.6%	5	7
Combined effect §			7.7%	14.2%	15	28

CV=cardiovascular; CVD=cardiovascular disease; LDL-C=low density lipoprotein cholesterol; RRR=relative risk reduction; SBP=systolic blood pressure; UMPIRE= Use of a Multidrug Pill in Reducing Cardiovascular Events

*Based on observed statistically significant changes in the UMPIRE trial.[124] The 'undertreated at baseline' column is based on findings for the subgroup of trial participants who did not report being on all four recommended medications (antiplatelet, statin and two or more BP lowering drugs) at baseline.

†Based on RRR in CVD for people with 5-year CVD risk >21% and standardised to a 5 mm Hg SBP reduction from BP Lowering Treatment Trialists' Collaboration 2014 meta-analysis.[52] Full RRR applied for those not adherent at baseline and half RRR irrespective of baseline adherence (actual reductions in SBP 4.9 and 2.6 mm Hg, respectively).

‡Based on RRR in major vascular events and standardised to a 1.00mmol/L reduction in LDL-C from Cholesterol Treatment Trialists' Collaboration 2012 meta-analysis.[42] 11% and 17% of full RRR (actual reduction in LDL-C 0.11 mmol/L) applied irrespective of baseline adherence and for those not adherent at baseline, respectively.

§ It was assumed that the joint effect of multiple medications is likely to be multiplicative (i.e. when a joint effect is the product of the risk ratios[44]), based on major randomised controlled trials[43 45-49] and as indicated by several authors.[27 43 50 51]

These estimated benefits of a polypill-based treatment strategy are modest at an individual level but could have a significant impact at a population level. Further, these estimates are based on a trial where treatment levels were already high. At baseline, 62% of UMPIRE trial participants (most of whom had established cardiovascular disease) were taking an antiplatelet, statin and two or more blood pressure lowering agents.[124] In contrast, the Prospective Urban Rural Epidemiology (PURE) study found that use of at least three of four recommended preventive medications (aspirin, statin, angiotensin-converting enzyme inhibitor [or angiotensin-receptor blocker] and another blood pressure lowering drug) by patients with established cardiovascular disease was 44% in high-income, 13% in upper-middle and 3% in lower-middle and low-income countries.[25]

Adherence to cardiovascular preventative medications remains low, and in some populations, they are inaccessible or unaffordable. The use of a cardiovascular polypill combining generic

preventative medications into one capsule or pill could help improve accessibility, affordability and adherence. In settings with low treatment levels, a polypill-based treatment strategy could have a significant impact on the burden of cardiovascular disease at both individual and population levels. The availability of a wider range of polypills, with different components (e.g. atorvastatin instead of simvastatin, angiotensin-receptor blockers instead of angiotensin-converting enzyme inhibitors) and different dosages, may enhance the effectiveness and reduce the risks of a polypill-based treatment strategy, thereby increasing the potential of a polypill-based treatment strategy to reduce the burden of cardiovascular disease in a broader range of settings.

7.5. Unanswered questions and future research

The following additional research is recommended to address questions unable to be answered by this thesis.

7.5.1. Effectiveness and safety of aspirin in primary prevention

- Effect of aspirin on cardiovascular and bleeding outcomes among people without established cardiovascular disease but at high risk. The following major trials are underway and will provide this evidence over the next few years:
    - ASPirin in Reducing Events in the Elderly (ASPREE)[157 158]
    - Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D)[159 160]
    - A Study of Cardiovascular Events In Diabetes (ASCEND)[161 162]
    - Aspirin to Reduce Risk of Initial Vascular Events study (ARRIVE)[100 101]
    - The International Polycap Study (TIPS)-3[102]
- Development and validation of a clinical prediction model for estimating an individual's risk of bleed with aspirin, such as the QBleed tool recently published by Hippisley-Cox and Coupland for anticoagulants.[99] The candidate is leading work on the development of such a model using New Zealand data.
- Consideration of the effect of aspirin on the primary prevention of cancer when balancing the benefits and harms of aspirin, given the growing body of evidence for aspirin's protective effect of aspirin.[22-24]

7.5.2. Effectiveness and safety of a cardiovascular polypill

Prior to implementing a polypill-based treatment strategy for reducing the burden of cardiovascular disease, the following additional pieces of work (outside the scope of this thesis) would be required:

- Meta-analysis of the effect of the polypill compared with usual care on systolic blood pressure and low density lipoprotein cholesterol (to obtain more precise effect estimates and to ascertain whether differences are statistically significant). The SPACE (Single Pill to Avert Cardiovascular Events) Collaboration has undertaken an individual participant meta-analysis of IMPACT, Kanyini-GAP and UMPIRE (submitted for publication).[131]
- Meta-analysis of the effect of the polypill compared with usual care on systolic blood pressure and low density lipoprotein cholesterol in the subgroup of patients undertreated at baseline (to obtain more precise effect estimates and to ascertain whether differences are statistically significant in this subgroup with the greatest potential to benefit from polypill-based care). The SPACE Collaboration meta-analysis will assess the effect of the polypill on this subgroup (submitted for publication).[131]
- Meta-analysis of the effect of the polypill compared with usual care on systolic blood pressure and low density lipoprotein cholesterol in the subgroup of indigenous patients (to obtain more precise effect estimates and to ascertain whether differences are statistically significant in this subgroup, which currently experiences a disproportionate burden of cardiovascular disease). The SPACE Collaboration is planning to undertake a meta-analysis of the effect of the polypill on indigenous participants from IMPACT and Kanyini GAP.
- Meta-analysis of the effect of the polypill compared with usual care on serious adverse events (to obtain more precise effect estimates and to ascertain whether differences are statistically significant). The SPACE meta-analysis will assess the effect of the polypill on serious adverse events (submitted for publication).[131]
- Economic evaluation of polypill-based care compared with usual care using trial data. Economic evaluations to date have been based on estimates as opposed to observed effects of a polypill-based treatment strategy.[110 112 216 217] Economic evaluation was not included within the scope of this thesis, but will be undertaken for the IMPACT trial, and is also placed for the SPACE Collaboration.
- Implementation research[218] to guide appropriate uptake among patients currently receiving little or no treatment. Most cardiovascular deaths occur in high risk patients[13

219] and most of these patients globally receive few or no recommended medications.[25]

Polypill trials in progress will provide further evidence regarding the potential role of this intervention. The Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill (PolyIran) trial will assess the effect of a polypill compared with 'minimal' usual care on cardiovascular outcomes among 7,000 participants, with or without established cardiovascular disease and aged 50 to 79 years (results due 2018).[220] The Heart Outcomes Prevention and Evaluation (HOPE)-4 trial will compare usual care with a strategy of cardiovascular management implemented by non-physician health workers and incorporating the use of a polypill among 9500 participants and assess cardiovascular outcomes.[221]

7.6. Summary

Cardiovascular disease remains a leading cause of avoidable disability and mortality around the world. Besides lifestyle changes, cardiovascular medications have been shown to greatly reduce the risk of cardiovascular events in those at high risk. While aspirin can increase the risk of a major bleed, the benefits of aspirin have been shown to outweigh the harms among certain people without established disease. Adherence to cardiovascular preventative medications remains low, and in some populations, they are inaccessible or unaffordable. The use of a cardiovascular polypill combining generic preventative medications into one capsule or pill could help improve accessibility, affordability and adherence. This thesis has summarised the evidence for the benefits and harms of aspirin among those at high risk of cardiovascular disease. The thesis has also presented the findings from a pragmatic randomised controlled trial of a cardiovascular polypill administered in every-day practice to Māori and non-Māori patients at high risk in New Zealand primary care. Although results show adherence is improved with the polypill, more research is needed to confirm the clinical benefits and consistency of benefit across a range of populations.

Appendices

Appendix 1 GATE CAT frame

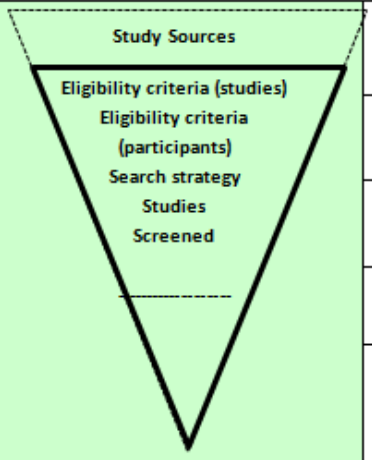
GATE: a Graphic Approach To Evidence based practice

GATE CAT- Systematic Reviews: Intervention studies

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

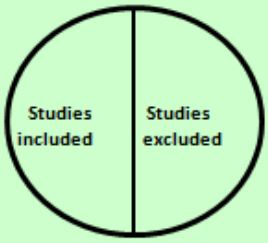
updates from previous version in red

Systematic Reviews of Intervention Studies
Step 3: Appraise Study
3a. Describe the design of the review by hanging it on the GATE frame (no separate excel GATE calculator for SRs)



Source of studies	List information sources for search (e.g. databases with dates of coverage, reference lists, contact with study authors to identify additional studies) & dates searched.
Eligibility criteria: studies	List types of studies included. Only RCTs? Cohort studies? Length of follow-up? Languages? Publication status?
Eligibility criteria for participants	List eligibility criteria for participants using PECOT: participants, exposure, comparison, outcomes and follow-up times. List any exclusion criteria.
Search strategy	List electronic search terms used for main database searched, including limits (if provided)
Studies screened	State number of studies/abstracts identified by search & screened. How screened (e.g. reading titles, abstracts, whole papers) How many included/excluded and why? Done by one or more screeners?

Studies appraised



Process of appraising study validity	State methods used to assess bias in each study. How were studies appraised (e.g. using standardised process like RAMboMAN, Jadad scale)?
Data extraction methods	State how data extracted from study reports (e.g. piloted forms), number of independent reviewers. Was any data obtained or confirmed from individual study investigators?
Studies included / excluded in analyses	Give the number of appraised studies included/excluded and reasons why. Give main characteristics of studies and participants e.g study size. PECOT.

Forest plot (or equivalent)

Summary measures used	List principal summary measures used (i.e. Risk Ratio or Odds ratio for dichotomous outcomes, differences in means for continuous outcomes) How calculated (e.g. with standard meta-analysis software like Revman)?
Summary tables of individual studies	For each outcome, attach a table or Forest plot of included study results. Ideally include outcome numbers/ participant numbers for EG & CG, effect estimates & CIs.
Measures of differences between studies & sensitivity analyses	Was there evidence of differences (i.e. heterogeneity) between studies? (E.g. by 'eyeballing' forest plots, formal tests of heterogeneity test). Note: Heterogeneity tests – 'Cochrane Q': if p< 0.1 significant heterogeneity present. 'I square value': 0 if no heterogeneity, if >50% combining studies questionable

Reported Results

Enter the main reported results (including sensitivity analyses) ➔

Outcome	Summary Effect (RR, OR)	Confidence Interval

Appendix 2 FAITH tool

Systematic Reviews of Intervention Studies Step 3: Appraise Study 3b. Assess risk of errors using FAITH		
Appraisal questions (FAITH)	**Risk of errors +, x, ?, na**	Notes
Recruitment/Applicability '**errors**': questions on risks to application of results in practice are in blue boxes		
Internal study design **errors**: questions on risk of errors within study (design & conduct) are in pink boxes		
Analyses **errors**: questions on errors in analyses are in orange boxes		
Random **error**: questions on risk of errors due to chance are in the green box		
Key for scoring risk of errors: + = low; x = of concern; ? = unclear; na = not applicable		
Find studies: was the search likely to find all the best evidence?		
All appropriate information sources searched?	Score risk of error as: +, x, ? or na (key above)	Were all relevant information sources searched? Relevant: time periods; languages; grey literature; reference lists of papers; Conference abstracts? Were investigators of original papers contacted about unpublished studies?
Eligibility criteria for the study characteristics appropriate?		Were only appropriate study types (e.g. RCTs), length of follow-up, etc included?
Eligibility criteria for the participant characteristics appropriate?		Were inclusion/exclusion criteria for participants explicit and appropriate given the review's objectives?
Search strategy and processes explicit, comprehensive and systematic?		Was the search strategy: explicit; comprehensive, used appropriate terms and limits? Was it done by more than one person? Were numbers included/excluded in initial screen documented and reasons for incl/excl given?
Appraise studies: were each of the studies meeting initial screening criteria critically appraised?		
How well were data on each study extracted (standardised, systematic, repeated)?		Was data extracted onto a standardised form? Was it extracted independently by more than one reviewer?
How well were studies critically appraised?		Were studies appraised using a systematic and standardised method? e.g. RAMMbo, Jadad score. Did at least 2 independent appraisers assess each study?
Include studies: were the appropriate studies included in the analyses?		
Clear rationale given for including / excluding studies based on individual study appraisal?		Did the investigators only include quality studies in their main analyses/summary of studies?
Relevant personal (prognostic) characteristics of participants reported and used to determine inclusion in analyses?		Was sufficient information given about personal characteristics of participant populations to determine whether included studies could be combined and to determine applicability of findings?
All important outcomes (including benefit and harm) assessed?		Were both benefits and harms considered? Were patient oriented outcomes measured, not just surrogate or intermediate outcomes?
Follow-up time in included studies sufficiently similar to combine?		Did follow-up vary between included studies? If so, was it appropriate to combine study results?
Total-up (summary) of studies : were results summarised appropriately? **Heterogeneity** of studies: was consistency between studies sufficient to justify pooling results (if meta-analysis)?		
Was it reasonable to consider combining the studies based on their PECOT characteristics?		Was there enough similarity between studies wrt participants, exposures, comparisons, outcomes and follow up times to consider pooling the studies in a meta-analysis?
Were summary tables/forest plots of results sufficient to describe the findings of each included study?		Was there a succinct summary of results of each included study showing numbers of subjects in EG and CG, number of outcomes in each group, effect estimates with 95% CIs? Ideally this will be presented graphically as forest plots

Were effect estimates similar enough from study to study to undertake meta-analyses?		Was assessment of heterogeneity sufficient to determine if it was present? Was it based just on 'eyeballing' the forest plots or formal tests?
Were sensitivity analyses required to test the robustness of the results?		Sensitivity analyses undertaken with/without lower quality studies? If heterogeneity present were sensitivity analyses presented without outlier studies?
Were summary measures (if meta-analysis performed) performed correctly?		Were summary measures (RR, OR, mean differences) generated using appropriate software (e.g. Revman) with each study weighted is according to size?
Precision of summary measures (if meta-analysis) given?		Were 95% CIs given for the summary measures?
Were reported summary effect estimates meaningful for practice?		Were summary results presented in a format that had meaning in practice? e.g. a clinically relevant measure of effect rather than a change in an abstract scale.
Summary of Review Appraisal		
Was a valid, systematic, reproducible review methodology followed?		Was the risk of error due to internal study design & conduct low enough for the results to be reasonably unbiased? Use responses to questions in pink boxes above
Was there likely to be important publication bias?		Did the investigators take any steps to formally analyse whether there was a likelihood of publication bias (disproportionate reporting of positive results)? e.g funnel plot, any other analysis?
Were studies summarised (and/or combined) appropriately?		Was the approach to summarising findings (i.e. qualitative description versus quantitative meta-analysis) reasonable?
Random error in estimates of intervention effects: were CIs sufficiently narrow for results to be meaningful?		Use responses to questions in green box above. Would you make a different decision if the true effect was close to the upper confidence limit rather than close to the lower confidence limit?
Applicability: are these findings applicable in practice?		Use responses to questions in blue boxes above

Appendix 3 Critical appraisals of systematic reviews

Bartolucci 2011

GATE: a Graphic Approach To Evidence based practice GATE CAT- Systematic Reviews: Intervention studies THE UNIVERSITY OF AUCKLAND FACULTY OF MEDICAL AND HEALTH SCIENCES updates from previous version in red				
Critically Appraised Topic (CAT): Applying the 5 steps of Evidence Based Practice **Using evidence about interventions from randomised controlled trials (RCTs) & non-randomised cohort studies**				
Assessed by: Raina Elley			**Date: 24/09/14**	
Assessed by: Vanessa Selak			**Date: 08/08/14**	
Evidence Selected				
Meta-Analysis of Multiple Primary Prevention Trials of Cardiovascular Events Using Aspirin. By Alfred A. Bartolucci, Michal Tendera, George Howard, Am J Cardiol 2011;107:1796–1801				
Systematic Reviews of Intervention Studies **Step 3: Appraise Study** **3b. Assess risk of errors using FAITH**				
Appraisal questions (FAITH)	**Risk of errors +, x, ?, na**		Notes	
	RE	**VS**	RE	VS
Recruitment/Applicability '**errors**': questions on risks to application of results in practice are in blue boxes				
Internal study design **errors**: questions on risk of errors within study (design & conduct) are in pink boxes				
Analyses **errors**: questions on errors in analyses are in orange boxes				
Random **error**: questions on risk of errors due to chance are in the green box				
Key for scoring risk of errors: + = low; x = of concern; ? = unclear; na = not applicable				
Find studies: was the search likely to find all the best evidence?				
All appropriate information sources searched?	?	?		Not specified
Eligibility criteria for the study characteristics appropriate?	+	+	Although included open label	Only RCTs included
Eligibility criteria for the participant characteristics appropriate?	**?**	**+**		Only primary prevention population included
Search strategy and processes explicit, comprehensive and systematic?	**x**	**?**		Not specified
Appraise studies: were each of the studies meeting initial screening criteria critically appraised?				
How well were data on each study extracted (standardised, systematic, repeated)?	?	?		Not specified
How well were studies critically appraised?	?	?		Not specified
Include studies: were the appropriate studies included in the analyses?				
Clear rationale given for including / excluding studies based on individual study appraisal?	?	?		Not specified although relevant trials included
Relevant personal (prognostic) characteristics of participants reported and used to determine inclusion in analyses?	+	+		See Table 1
All important outcomes (including	x	x		Benefits and harms considered but no meta-analysis for
V4: 2014: Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz 1				

benefit and harm) assessed?				harms
Follow-up time in included studies sufficiently similar to combine?	+	+		Follow up 3.6-10 years
Total-up (summary) of studies : were results summarised appropriately? **Heterogeneity** of studies: was consistency between studies sufficient to justify pooling results (if meta-analysis)?				
Was it reasonable to consider combining the studies based on their PECOT characteristics?	+	+		Enough similarity between studies with respect to participants, exposures, comparisons, outcomes and follow up times to consider pooling the studies in a meta-analysis
Were summary tables/forest plots of results sufficient to describe the findings of each included study?	X	+	CG and EG outcome numbers not presented	Succinct summary of results of each included study showing effect estimates with 95% CIs and presented graphically as forest plots. Numbers of subjects and numbers of outcomes in each group not presented
Were effect estimates similar enough from study to study to undertake meta-analyses?	?	+		Formal tests of heterogeneity performed
Were sensitivity analyses required to test the robustness of the results?	?	+		No sensitivity analyses undertaken. Authors note "overall difference between aspirin and placebo, as shown in this meta-analysis, is not affected by significant heterogeneity, because similar results were obtained with the random-effects model, which accounts for the randomness of the effects across studies."
Were summary measures (if meta-analysis performed) performed correctly?	+	+		Unsure how summary measures (OR) were generated. Each study was weighted according to its size: Authors note "A weighting factor was also used that depended in part on the size of the study, which in turn affected the inverse variance formula that the Mantel-Haenszel procedure uses to calculate heterogeneity." And "The standard procedure for the assessment of small study effects (i.e., a trend for relatively smaller studies to show larger treatment effects) has been the use of funnel plots using Egger's test. There has been considerable discussion regarding the properties of this test. The technique of Macaskill et al was used to adjust for this shortcoming."
Precision of summary measures (if meta-analysis) given?	+	+		95% CIs given for the summary measures
Were reported summary effect estimates meaningful for practice?	+	+	Only ORs. NNTs and NNHs would have been useful	Summary results presented in a format that had meaning in practice
Summary of Review Appraisal				
Was a valid, systematic, reproducible review methodology followed?	?	x		Relevant trials included but method of obtaining them not specified.
Was there likely to be important publication bias?	?	+	Funnel and Eggers done but not presented	No formal analysis to look for publication bias but relevant trials included.
Were studies summarised (and/or combined) appropriately?	?	+	Lacking detail	Approach to summarising findings reasonable?
Random error in estimates of intervention effects: were CIs	+	+		Yes for main benefit of interest (total cardiovascular events).
sufficiently narrow for results to be meaningful?				
Applicability: are these findings applicable in practice?	+	+	Although limited by quality of review	Findings applicable in practice

Discrepancies between reviewers and their resolution (Bartolucci 2011)

	RE 24/09	VS 08/08	RE 24/09	VS 08/08	VS notes 30/09	RE notes 01/10	VS notes 1/10	Consen-sus between RE and VS	Dec-ision required by SW
Eligibility criteria for the participant characteristics appropriate?	?	+		Only primary prevention population included	Agree with RE that probably should be '?' as, apart from primary prevention population, characteristics not explicitly stated	NA	NA	Yes – '?'	No
Search strategy and processes explicit, comprehensive and systematic?	x	?		Not specified	Agree with RE that, as not specified, should be 'x'	NA	NA	Yes – 'x'	No
Were summary tables/forest plots of results sufficient to describe the findings of each included study?	x	+	CG and EG outcome numbers not presented	Succinct summary of results of each included study showing effect estimates with 95% CIs and presented graphically as forest plots. Numbers of subjects and numbers of outcomes in each group not presented	Agree with RE that, as numbers not presented, should be 'x'	NA	NA	Yes – 'x'	No
Were effect estimates similar enough from study to study to undertake meta-analyses?	?	+		Formal tests of heterogeneity performed	Disagree with RE as formal tests of heterogeneity performed and, for outcome of interest (total cv events) – p value for heterogeneity 0.387 (calculated using chi-square test)	Agree with VS as heterogeneity was assessed and presented as VS notes	NA	Yes – '+'	No
Were sensitivity analyses required to test the robustness of the results?	?	+		No sensitivity analyses undertaken. Authors note "overall difference between aspirin and placebo, as shown in this meta-analysis, is not affected by significant heterogeneity, because similar results were obtained with the	Disagree with RE as, per adjacent note	Ok will accept this although statistical heterogeneity is not the only reason to undertake sensitivity analyses or subgroup analyses – e.g. clinical reasons/differenc es	As per RE's note now agree that should be '?'	Yes – '?'	No

				random-effects model, which accounts for the randomness of the effects across studies."					
Was a valid, systematic, reproducible review methodology followed	?	x		Relevant trials included but method of obtaining them not specified.	Disagree with RE- as not specified, should be 'x'	They may have followed it but not reported it However, I probably agree that the search should be stated so ok to have 'x'	NA	Yes – 'x'	No
Was there likely to be important publication bias?	?	+	Funnel and Eggers done but not presented	No formal analysis to look for publication bias but relevant trials included.	Agree with RE that, as results not presented, should be '?'	NA		Yes – '?'	No
Were studies summarised (and/or combined) appropriately?	?	+	Lacking detail	Approach to summarising findings reasonable	Agree with RE that, given lack of detail, should be '?'	NA		Yes – '?'	No

Berger 2011

GATE: a Graphic Approach To Evidence based practice

GATE CAT- Systematic Reviews: Intervention studies

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FACULTY OF MEDICAL AND HEALTH SCIENCES

updates from previous version in red

Critically Appraised Topic (CAT): Applying the 5 steps of Evidence Based Practice
Using evidence about interventions from randomised controlled trials (RCTs) & non-randomised cohort studies

Assessed by: Raina Elley	**Date: 17/09/2014**
Assessed by: Vanessa Selak	**Date: 08/08/2014**

Evidence Selected

Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: A meta-analysis of randomized trials. Jeffrey S. Berger, Anuradha Lala, Mori J. Krantz, Gizelle S. Baker, William R. Hiatt. Am Heart J, 2011

Systematic Reviews of Intervention Studies
Step 3: Appraise Study
3b. Assess risk of errors using FAITH

Appraisal questions (FAITH)	**Risk of errors +, x, ?, na**		Notes	
	RE	**VS**	RE	VS
Recruitment/Applicability '**errors**': questions on risks to application of results in practice are in blue boxes				
Internal study design **errors**: questions on risk of errors within study (design & conduct) are in pink boxes				
Analyses **errors**: questions on errors in analyses are in orange boxes				
Random **error**: questions on risk of errors due to chance are in the green box				
Key for scoring risk of errors: + = low; x = of concern; ? = unclear; na = not applicable				
Find studies: was the search likely to find all the best evidence? Score risk of error as: +, x, ? or na (key above)				
All appropriate information sources searched?	**?**	**x**	Medline, CCRCT and Embase only	No but all relevant RCTs included
Eligibility criteria for the study characteristics appropriate?	+	+	RCTs but no length F/U specified. English only	Only RCTs included
Eligibility criteria for the participant characteristics appropriate?	+	+	Although no age or co-morbid characteristics specified	Only primary prevention population included
Search strategy and processes explicit, comprehensive and systematic?	?	?		Not specified
Appraise studies: were each of the studies meeting initial screening criteria critically appraised?				
How well were data on each study extracted (standardised, systematic, repeated)?	?	?		Not specified
How well were studies critically appraised?	**x**	**?**		Not specified
Include studies: were the appropriate studies included in the analyses?				
Clear rationale given for including / excluding studies based on individual study appraisal?	?	?		Not specified although relevant trials included
Relevant personal (prognostic) characteristics of participants	+	+		See Tables I and II

reported and used to determine inclusion in analyses?				
All important outcomes (including benefit and harm) assessed?	+	+		Both benefits and harms considered
Follow-up time in included studies sufficiently similar to combine?	+	+		Follow up 3.7-10 years
Total-up (summary) of studies : were results summarised appropriately? **Heterogeneity** of studies: was consistency between studies sufficient to justify pooling results (if meta-analysis)?				
Was it reasonable to consider combining the studies based on their PECOT characteristics?	+	+		Enough similarity between studies with respect to participants, exposures, comparisons, outcomes and follow up times to consider pooling the studies in a meta-analysis
Were summary tables/forest plots of results sufficient to describe the findings of each included study?	+	+		Succinct summary of results of each included study showing numbers of subjects in EG and CG, number of outcomes in each group, effect estimates with 95% CIs, presented graphically as forest plots
Were effect estimates similar enough from study to study to undertake meta-analyses?	+	+	Used Tau2 and I2	Formal tests of heterogeneity performed
Were sensitivity analyses required to test the robustness of the results?	+	+		No difference in results between fixed effect or random-effect model for the primary outcome of major cardiovascular event. RR varied between 0.891 and 0.893 when each study was systematically removed. Primary outcome largely unchanged when: - trials that just recruited people with diabetes excluded RR 0.90 (0.84-0.96) trials that just recruited people with subclinical atherosclerosis were excluded RR 0.89 (0.83-0.95).
Were summary measures (if meta-analysis performed) performed correctly?	+	+		RR generated using Revman
Precision of summary measures (if meta-analysis) given?	+	+		95% CIs given for the summary measures
Were reported summary effect estimates meaningful for practice?	+	+	NNTs	Summary results presented in a format that had meaning in practice
Summary of Review Appraisal				
Was a valid, systematic, reproducible review methodology followed?	+	x		Relevant trials included but method of obtaining them insufficiently specified
Was there likely to be important publication bias?	+	+	Funnels conducted but not presented	Investigators said that they would do a funnel plot but this was not reported in results. However, relevant trials included.
Were studies summarised (and/or combined) appropriately?	+	+		Approach to summarising findings reasonable
Random error in estimates of intervention effects: were CIs	+	+		Yes for main benefits and harms of interest (major cardiovascular event and major bleed)
sufficiently narrow for results to be meaningful?				
Applicability: are these findings applicable in practice?	+	+		Findings applicable in practice

Discrepancies between reviewers and their resolution (Berger 2011)

	RE 17/09	VS 08/08	RE 17/09	VS 08/08	VS notes 30/09	RE notes 01/10	VS notes 01/10	Consensus between RE and VS	Decision required by SW
All appropriate information sources searched?	?	x	Medline, CCRCT and Embase only	No but all relevant RCTs included	Disagree with RE – still think it should be 'x' – as would expect more databases to have been checked given that it is a systematic review	Prisma checklist says "Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated." We only used CCRCT, Medline, and PubMed databases in our polypill sys rev. Although agree search could have been better/broader.	Given Prisma checklist, now agree with RE that should be '?'	7/10/14Further discussion between RE, SW and VS and agreement that these sources insufficient therefore should be rated as 'x'	No
How well were studies critically appraised?	x	?		Not specified	Agree with RE that as not specified should be 'x'	NA		Yes – 'x'	No
Was a valid, systematic, reproduce-ible review method-ology followed?	+	x		Relevant trials included but method of obtaining them insufficiently specified				Yes – '?'	No

Raju 2011

GATE: a Graphic Approach To Evidence based practice

GATE CAT- Systematic Reviews: Intervention studies

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Assessed by: Raina Elley	**Date: 24/09/14**
Assessed by: Vanessa Selak	**Date: 11/08/14**

Evidence Selected

Effect of Aspirin on Mortality in the Primary Prevention of Cardiovascular Disease. By Nina Raju, Magdalena Sobieraj-Teague, Jack Hirsh, Martin O'Donnell, John Eikelboom *The American Journal of Medicine (2011) 124, 621-629*

Systematic Reviews of Intervention Studies
Step 3: Appraise Study
3b. Assess risk of errors using FAITH

Appraisal questions (FAITH)	**Risk of errors +, x, ?, na**		Notes	
	RE	**VS**	RE	VS
Recruitment/Applicability '**errors**': questions on risks to application of results in practice are in blue boxes				
Internal study design **errors**: questions on risk of errors within study (design & conduct) are in pink boxes				
Analyses **errors**: questions on errors in analyses are in orange boxes				
Random **error**: questions on risk of errors due to chance are in the green box				
Key for scoring risk of errors: + = low; x = of concern; ? = unclear; na = not applicable				
Find studies: was the search likely to find all the best evidence?				
All appropriate information sources searched?	+	+		Yes as outlined above
Eligibility criteria for the study characteristics appropriate?	+	+		Only RCTs included
Eligibility criteria for the participant characteristics appropriate?	+	+		Only primary prevention population included
Search strategy and processes explicit, comprehensive and systematic?	+	+		Yes as outlined above
Appraise studies: were each of the studies meeting initial screening criteria critically appraised?				
How well were data on each study extracted (standardised, systematic, repeated)?	+	+		Standardised, systematic and repeated
How well were studies critically appraised?	+	+		Studies appraised using a systematic and standardised method. Two independent appraisers assessed each study.
Include studies: were the appropriate studies included in the analyses?				
Clear rationale given for including / excluding studies based on individual study appraisal?	+	+	Although some were open label, some early stop	Only relevant RCTs included. Sensitivity analysis excluded lesser quality studies.
Relevant personal (prognostic) characteristics of participants reported and used to determine	+	+	Although TPT trial included patients on warfarin	See Table 1

V4: 2014: Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz 1

inclusion in analyses?				
All important outcomes (including benefit and harm) assessed?	+	+		Benefits and harms considered.
Follow-up time in included studies sufficiently similar to combine?	+	+	(3.6 to 10.1 years)	Follow-up 3.6-10.1 years
Total-up (summary) of studies : were results summarised appropriately? **Heterogeneity** of studies: was consistency between studies sufficient to justify pooling results (if meta-analysis)?				
Was it reasonable to consider combining the studies based on their PECOT characteristics?	+	+	Although I^2 was 70% for MI, so PHS trial removed (early stop) for sensitivity analysis	Enough similarity between studies with respect to participants, exposures, comparisons, outcomes and follow up times to consider pooling the studies in a meta-analysis.
Were summary tables/forest plots of results sufficient to describe the findings of each included study?	+	+		Succinct summary of results of each included study showing numbers of subjects in EG and CG, number of outcomes in each group, effect estimates with 95% CIs? Presented graphically as forest plots
Were effect estimates similar enough from study to study to undertake meta-analyses?	+	+		Formal tests of heterogeneity performed
Were sensitivity analyses required to test the robustness of the results?	+	+		Sensitivity analyses undertaken as outlined above. Heterogeneity investigated as outlined above.
Were summary measures (if meta-analysis performed) performed correctly?	+	+		RR generated using Revman with each study weighted according to size
Precision of summary measures (if meta-analysis) given?	+	+		95% CIs given for the summary measures
Were reported summary effect estimates meaningful for practice?	+	+	Although NNTs would have been useful	Summary results presented in a format that had meaning in practice.
Summary of Review Appraisal				
Was a valid, systematic, reproducible review methodology followed?	+	+		Risk of error due to internal study design & conduct low enough for the results to be reasonably unbiased.
Was there likely to be important publication bias?	+	+	Begg's adj-rank corr test	Begg's adjusted-rank correlation test provided no evidence of publication bias for any of the outcomes examined
Were studies summarised (and/or combined) appropriately?	+	+		Approach to summarising findings reasonable
Random error in estimates of intervention effects: were CIs sufficiently narrow for results to be meaningful?	**X**	**+**	Some 95%CIs included 1	Yes for main benefit (total cv events) and harm (major bleeds) of interest
Applicability: are these findings applicable in practice?	+	+		

Discrepancies between reviewers and their resolution (Raju 2011)

	RE 24/09	VS 11/08	RE 24/09	VS 11/08	VS notes 30/09	RE notes 01/10	VS notes 08/10	Consen-sus between RE and VS	Decision required by SW
Random error in estimates of intervention effects: were CIs sufficiently narrow for results to be meaningful?	x	+	Some 95%CIs included 1	Yes for main benefit (total cv events) and harm (major bleeds) of interest	Disagree with RE as 95% CIs did not include 1 for specific outcomes of interest	Not sure I agree – e.g. in abstract: "Aspirin reduced all-cause mortality (RR 0.94; 95% CI, 0.88-1.00), myocardial infarction (RR 0.83; 95% CI, 0.69-1.00)…." However, I agree most outcomes did not include '1'. I would be willing to change to '?'	As per discussion with RE, issue is with authors' interpretation that if CI including 1 interpreted as being statistically significant. Agree with RE that this interpretation (even if not for primary outcome of interest) is not correct and therefore relevant to assessment of quality of meta-analysis.	Yes – 'x'	No

Seshasai 2012

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Assessed by: Raina Elley	**Date: 24/09/14**
Assessed by: Vanessa Selak	**Date: 11/08/2014**

Evidence Selected

Effect of Aspirin on Vascular and Nonvascular Outcomes: Meta-analysis of Randomized Controlled Trials. By *Sreenivasa Rao Kondapally Seshasai, Shanelle Wijesuriya, Rupa Sivakumaran, Sarah Nethercott, Sebhat Erqou, Naveed Sattar, Kausik K. Ray. Arch Intern Med. 2012;172(3):209-216.*

Systematic Reviews of Intervention Studies
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3b. Assess risk of errors using FAITH

Appraisal questions (FAITH)	**Risk of errors +, x, ?, na**		Notes	
	RE	**VS**	RE	VS
Recruitment/Applicability **'errors'**: questions on risks to application of results in practice are in blue boxes				
Internal study design **errors**: questions on risk of errors within study (design & conduct) are in pink boxes				
Analyses **errors**: questions on errors in analyses are in orange boxes				
Random **error**: questions on risk of errors due to chance are in the green box				
Key for scoring risk of errors: + = low; x = of concern; ? = unclear; na = not applicable				
Find studies: was the search likely to find all the best evidence?				
All appropriate information sources searched?	**?**	**+**	Only Cochrane, pubmed and ref lists	Relevant information sources searched
Eligibility criteria for the study characteristics appropriate?	+	+		Only RCTs
Eligibility criteria for the participant characteristics appropriate?	+	+		Only primary prevention population included
Search strategy and processes explicit, comprehensive and systematic?	+	+		Explicit, comprehensive and systematic Method of screening not specified. Numbers included/excluded in Figure 1
Appraise studies: were each of the studies meeting initial screening criteria critically appraised?				
How well were data on each study extracted (standardised, systematic, repeated)?	+	+		Data extracted independently by 3 authors
How well were studies critically appraised?	+	+	A Delphi method	Quality of studies evaluated using a Delphi scoring system, based on relevant characteristics. Scores provided in supplementary material. Ranged from 16-18. Who and how many applied not specified.
Include studies: were the appropriate studies included in the analyses?				
Clear rationale given for including / excluding studies based on	**+**	**?**		Not specified

individual study appraisal?				
Relevant personal (prognostic) characteristics of participants reported and used to determine inclusion in analyses?	+	+		See Table
All important outcomes (including benefit and harm) assessed?	+	+	Although many of non-vascular outcomes derived from various sources	Benefits and harms considered
Follow-up time in included studies sufficiently similar to combine?	+	+	Sensitivity analyses done	Follow-up 3.6-10.1 years
Total-up (summary) of studies: were results summarised appropriately? **Heterogeneity** of studies: was consistency between studies sufficient to justify pooling results (if meta-analysis)?				
Was it reasonable to consider combining the studies based on their PECOT characteristics?	+	+	Although aspirin dose, other meds and F/U varied	Enough similarity between studies with respect to participants, exposures, comparisons, outcomes and follow up times to consider pooling the studies in a meta-analysis
Were summary tables/forest plots of results sufficient to describe the findings of each included study?	**?**	**+**	Only summary forest plot. Perhaps individual studies forests are online	Outcome numbers/ participant numbers for EG & CG, effect estimates & CIs provided for each outcome. Forest plots for all outcomes in supplementary material
Were effect estimates similar enough from study to study to undertake meta-analyses?	+	+	I^2 and Meta-regression done to explore	Formal tests of heterogeneity performed
Were sensitivity analyses required to test the robustness of the results?	+	+	Although not for diff duration or some quality features	Effect of aspirin on total CVD events and nontrivial bleeds no different according to: period of publication, number of participants per study, number of events per study, average daily dose of aspirin, schedule of aspirin treatment and concomitant treatment. (NB some p values <0.05 for nontrivial bleeds but CIs overlapping so p values assumed to be incorrect) Results broadly similar (for total CVD and nontrivial bleed) when fixed effect meta-analysis done, and when following excluded: - non-western populations - diabetes only trials - PAD only trials - healthcare professional trials
Were summary measures (if meta-analysis performed) performed correctly?	+	+		Study-specific unadjusted ORs combined using random-effects meta-analysis (fixed effect meta-analysis conducted for comparison). Analyses performed using Stata Assume that each study weighted according to size
Precision of summary measures (if meta-analysis) given?	+	+		95% CIs given for the summary measures
Were reported summary effect estimates meaningful for practice?	+	+	NNTs and NNHs	Summary results presented in a format that had meaning in practice
Summary of Review Appraisal				
Was a valid, systematic, reproducible review methodology followed?	**?**	**+**	Critical appraisal done but not presented	Risk of error due to internal study design & conduct low enough for the results to be reasonably unbiased
Was there likely to be important publication bias?	+	+	Egger test	No evidence of publication bias (Egger test p value > 0.05 for all major outcomes)
Were studies summarised (and/or combined) appropriately?	+	+		Approach to summarising findings reasonable
Random error in estimates of intervention effects: were CIs sufficiently narrow for results to be meaningful?	+	+	As txt not recommended	Yes for total CVD events and nontrivial bleeds
Applicability: are these findings applicable in practice?	+	+		Findings applicable in practice

Discrepancies between reviewers and their resolution (Seshasai 2012)

	RE 24/09	VS 11/08	RE 24/09	VS 11/08	VS notes 30/09	RE notes 01/10	VS notes 01/10	Consen-sus between RE and VS	Decis-ion require-ed by SW
All appropriate information sources searched?	?	+	Only Cochrane PubMed and ref lists	Relevant information sources searched	As per comments on previous meta-analyses, think this should be 'x' as insufficien t databases checked for systematic review	Prisma checklist says "Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated." We only used CCRCT, Medline, and PubMed	Given Prisma check-list, now agree with RE that should be '?'	7/10/14 Further discussion between RE, SW and VS and agreement that these sources insufficient therefore should be rated as 'x'	No
Clear rationale given for including / excluding studies based on individual study appraisal?	+	?		Not specified	Disagree with RE as unable to locate critical appraisal of individual studies.	In Methods: "Quality of studies was evaluated using a Delphi scoring system,23 which is based on the following: adequacy of randomization; allocation concealment; balance between randomized groups at baseline; a priori identification of inclusion criteria; presence or absence of blinding; use of ITT analyses; and reporting of point estimates and measures of variability for main outcomes." Results in Supplementary table	Now agree with RE	Yes – '+'	No
Were summary tables/forest plots of results sufficient to describe the findings of each included study?	?	+	Only summary forest plot. Perhaps individ-ual studies forests are online	Outcome numbers/ participant numbers for EG & CG, effect estimates & CIs provided for each outcome. Forest plots for all outcomes in suppl. material	Disagree with RE. See adjacent note.	All included in supplementary material – so agree with you	NA	Yes – '+'	No
Was a valid, systematic, reproducible review methodology followed?	?	+	Critical appraisal done but not presented	Risk of error due to internal study design & conduct low enough for the results to be reasonably unbiased	Given limitations above agree with RE that should be '?'	NA		Yes – '?'	NA

Appendix 4 Critical appraisal of randomised controlled trial

Ikeda 2014

GATE-lite for RCTs & Observational (risk, prognosis, x-sectional) Studies 2013

Study details : Ikeda Y et al. Low-dose aspirin for primary prevention of CV events in Japanese patients 60 years or older with atherosclerotic risk factors. JAMA 2014

STUDY QUESTION & DESIGN - describe with **PECOT**

P = Participants

Briefly describe -
Setting: 1007 primary care clinics in Japan
Eligibility criteria: 60 to 85 years and (hypertension or dyslipidaemia or diabetes) and not diagnosed with atherosclerotic disease
Recruitment process: Screened on attendance at local clinic on routine visit
% of invited eligibles who participated: Not reported

EG = Exposed Group [Intervention / Risk factor]

Describe Exposure (how measured if not RCT): Aspirin 100mg (enteric-coated)

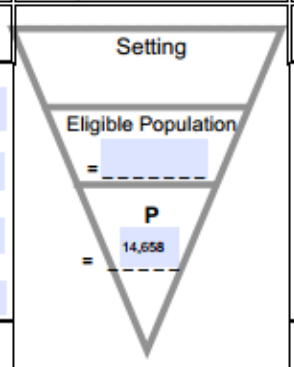
CG = Comparison Group [Control / comparison intervention / factor]

Describe Comparison (how measured if not RCT): No aspirin

O =Outcomes Primary (& 2° / adverse)
T = Time when outcomes counted (at what point in time or over what time period)

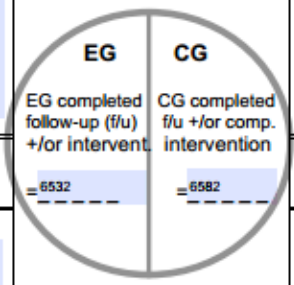
Describe O & T - how / when measured: Primary outcome - major cardiovascular events
Secondary outcomes included serious extra-cranial haemorrhage (requiring transfusion or hospitalisation)
Medial trial duration 5.02 years (stopped early due to futility)

STUDY NUMBERS - hang on **GATE frame**



How allocated: randomly or by measurement?

EG Allocated =7,323 **CG Allocated** = 7,335



EG incomplete f/u = 791 CG incomplete f/u = 753

+	a = 193	b = 207
-	c 7027	d 7037

STUDY ERROR - assess using **RAMBOMAN**

Recruitment appropriate to study goals / able to define who findings applicable to?

Setting & eligible population appropriate to goals & well described? Yes

Participants likely to be similar to all Eligibles? Not reported

Participant risk/prognostic profiles well described? Yes

Allocation to EG & CG done appropriately?

If allocated randomly: Was process concealed? Were EG&CG similar at baseline? Process concealed EG and CG similar at baseline

If allocated by measurement: Was it done accurately? Done before outcomes? Were differences between EG&CG documented? NA

Maintenance in allocated grps & on allocated interventions/exposures during study sufficient?

Completeness of follow-up high? High: Loss to follow-up 10.5%

Compliance high, Contamination low? EG: aspirin adherence 88.9% in year 1, 76.0% in year 5
CG: aspirin 1.5% in year 1, 9.8% in year 5

Co-interventions similar in EG&CG? Not reported although proportion of participants with hypertension, dyslipidaemia and diabetes similar between groups

Participants/Investigators blind to EG/CG status? Neither blinded

Blind and Objective Measurements?

Outcomes measured accurately? Endpoints adjudicated by a central and blinded expert committee

STUDY ANALYSES

Outcomes (categorical or numerical) & Time	EGO=a/EG or mean= Σa/EG	CGO=b/CG or mean= Σb/EG	RR = EGO/CGO ± 95% CI	RD = EGO-CGO ± 95% CI	NNT = 1/RD ± 95% CI
Major cardiovascular events	2.77% (event rate over 5 years)	2.96% (event rate over 5 years)	HR=0.97 (0.77 to 1.15)	0.19% over 5 years (95% CI not provided)	526 people over 5 years (no CI)
Serious extra-cranial haemorrhage	0.86% (event rate over 5 years)	0.51% (event rate over 5 years)	HR=1.85 (1.22 to 2.81)	0.35% over 5 years (95% CI not provided)	286 people over 5 years (no CI)

ANalyses: Intention to treat (if RCT)? No Adjusted if EG & CG different? NA **95% CIs** or p-values given? Yes

Summary:

1. **Non-random error sufficiently low?** (AMBOM: amount & direction of bias)
   Following causes of non-random bias: unblinded, high loss to follow-up, reducing compliance and increasing contamination over time). Direction of bias: against aspirin.
2. **Analytical error sufficiently low?** (AN: ITT /adjusted analyses)
   Yes although 1.5%, approx equal between groups, excluded from analysis, mainly due to protocol violations and failure to meet entry criteria.
3. **Random error sufficiently low?** (95% CIs: and if no statistically significant effects demonstrated was study power/sample size sufficiently high)
   No. Observed event rate and treatment effect lower than expected therefore trial may have been underpowered.
4. **Size of effects sufficient to be meaningful?** (RR &/or RD)
   No but low risk population. Risk of major cardiovascular event 3% in control group over 5 years.

Appendix 5 Read codes

Cardiovascular disease

Read Code	Read Term	Read Code	Read Term
G3.00	Ischaemic heart disease	G713.00	Abdom.aortic aneurysm+rupture
G3.11	Arteriosclerotic heart disease	G714.00	Abdom.aortic aneurysm-no rupt.
G3.13	IHD - Ischaemic heart disease	G715.00	Ruptured aortic aneurysm NOS
G30.00	Acute myocardial infarction	G7220.00	Aneurysm of common iliac art.
G30.15	MI - acute myocardial infarct	G73.00	Other peripheral vascular dis.
G300.00	Acute anterolateral infarction	G73.11	Periph ischaemic vascular dis.
G301.00	Anterior myocard. infarct OS	G73.12	Ischaemia of legs
G3011.00	Acute anteroseptal infarction	G73y0.00	Diabetic peripheral angiopathy
G301z.00	Anterior myocard.infarct NOS	G73z.00	Peripheral vascular dis. NOS
G302.00	Acute inferolateral infarction	G73z0.00	Intermittent claudication
G308.00	Inferior myocard. infarct NOS	G73z0.11	Claudication
G30z.00	Acute myocardial infarct. NOS	G73zz.00	Peripheral vasc.disease NOS
G311.13	Unstable angina	G74.00	Arterial embolism/thrombosis
G311z.00	Preinfarction syndrome NOS	G742.00	Embolus/thromb.arm/leg artery
G31yz.00	Other acute/subacute IHD NOS	G7425.00	Embolus/thromb.popliteal art.
G32.00	Old myocardial infarction		
G33.00	Angina pectoris		
G330.00	Angina decubitus		
G330z.00	Angina decubitus NOS		
G331.00	Prinzmetal's angina		
G33z.00	Angina pectoris NOS		
G33zz.00	Angina pectoris NOS		
G34.00	Other chr.ischaemic heart dis.		
G340.12	Coronary artery disease		
G3410.00	Ventricular cardiac aneurysm		
G34y1.00	Chronic myocardial ischaemia		
G3z.00	Ischaemic heart disease NOS		
G631.00	Carotid artery occlusion		
G632.00	Vertebral artery occlusion		
G634.00	Carotid artery stenosis		
G64.00	Cerebral arterial occlusion		
G64.11	CVA- cerebral artery occlusion		
G64.12	Infarction - cerebral		
G64.13	Stroke - cerebral art occlus		
G640.00	Cerebral thrombosis		
G64z.00	Cerebral infarction NOS		
G65y.00	Other transient cerebral isch.		
G66.00	Stroke/CVA unspecified		
G66.11	CVA unspecified		
G66.12	Stroke unspecified		
G67.00	Other cerebrovascular disease		
G70.00	Atherosclerosis		
G700.00	Aortic atherosclerosis		
G702.00	Extremity artery atheroma		
G70z.00	Arteriosclerotic vasc.dis.NOS		
G71.00	Aortic aneurysm		
G710.00	Dissecting aortic aneurysm		

Diabetes

Read Code	Read Term	Read Code	Read Term
1434.00	H/O: diabetes mellitus	9OL8.00	Diabetes monitor.phone invite
42W.00	Hb. A1C - diabetic control	9OL9.00	Diabetes monitoring deleted
42WZ.00	Hb. A1C - diabetic control NOS	9OLA.11	Diabetes monitored
44V3.00	Glucose tol. test diabetic	9OLA.00	Diabetes monitor. check done
66A.00	Diabetic monitoring	9OLZ.00	Diabetes monitoring admin.NOS
66A1.00	Initial diabetic assessment	C10.00	Diabetes mellitus
66A2.00	Follow-up diabetic assessment	C1000.11	Insulin dependent diab mellit
66A3.00	Diabetic on diet only	C1001.00	Diab.mell. no comp - adult
66A4.00	Diabetic on oral treatment	C1001.11	Maturity onset diabetes
66A5.00	Diabetic on insulin	C1001.12	Non-insulin depend.diabet.mell
66A8.00	Has seen dietician - diabetes	C101.00	Diab.mell. with ketoacidosis
66A9.00	Understands diet - diabetes	C102z.00	Diabetes+hyperosmolar coma NOS
66AA.11	Injection sites - diabetic	C104.00	Diab.mell. with nephropathy
66AD.00	Fundoscopy - diabetic check	C104.11	Diabetic nephropathy
66AG.00	Diabetic drug side effects	C104z.00	Diab.mell.+nephropathy NOS
66AH.00	Diabetic treatment changed	C106.11	Diabetic amyotrophy
66AI.00	Diabetic - good control	C106.00	Diab.mell. with neuropathy
66AJ.00	Diabetic - poor control	C106.12	Diab.mell. with neuropathy
66AJ.11	Unstable diabetes	C107.12	Diabetes with gangrene
66AJ1.00	Brittle diabetes	C1072.00	Diabetic gangrene - adult
66AJz.00	Diabetic - poor control NOS	C108.00	IDDM
66AK.00	Diabetic - cooperative patient	C108.11	IDDM
66AL.00	Diabetic-uncooperative patient	C1080.00	IDDM + renal comp
66AM.00	Diabetic - follow-up default	C109.00	NIDDM
66AN.00	Date diabetic treatment start	C109.11	NIDDM
66AO.00	Date diabetic treatment stopped	C1090.00	NIDDM + renal comp
66AP.00	Diabetes; practice programme	C1094.00	NIDDM + ulcer
66AQ.00	Diabetes: shared care programme	C1096.00	NIDDM + retinopathy
66AS.00	Diabetes annual review	C1097.00	NIDDM – poor control
66AT.00	Annual diabetic blood test	C314.11	Renal diabetes
66AZ.00	Diabetic monitoring NOS	C3500.11	Bronzed diabetes
6872.00	Diabetes mellitus screen	F1711.00	Autonomic neuropathy-diabetes
8A12.00	Diabetic crisis monitoring	F3450.00	Diabet mononeuritis multiplex
8A13.00	Diabetic stabilisation	F35z0.00	Diabetic mononeuritis NOS
8CA41.00	Pt advised re diabetic diet	F372.00	Polyneuropathy in diabetes
8H2J.00	Admit diabetic emergency	F372.12	Diabetic neuropathy
8H3O.00	Non-urgent diabetic admission	F372.11	Diabetic polyneuropathy
8H4F.00	Referral to diabetologist	F3813.11	Diabetic amyotrophy
8H7C.00	Refer, diabetic liaison nurse	F3813.00	Myasthenic syndrome+diabetes
8H7f.00	Referral to diabetes nurse	F420.00	Diabetic retinopathy
8HKE.00	Diabetology D.V. requested	F4200.00	Background diabetic retinopath
8HLE.00	Diabetology D.V. done	F4201.00	Proliferative diabetic retinop
8HME.00	Listed for Diabetology admissn	F4202.00	Preproliferative diabetic ret
9OL.11	Diabetes clinic administration	F4203.00	Advanced diabetic maculopathy
9OL.00	Diabetes monitoring admin.	F4204.00	Diabetic maculopathy
9OL1.00	Attends diabetes monitoring	F420z.00	Diabetic retinopathy NOS
9OL3.00	Diabetes monitoring default	F4407.00	Diabetic iritis
9OL4.00	Diabetes monitoring 1st letter	F4640.00	Diabetic cataract
9OL5.00	Diabetes monitoring 2nd letter	F6.00	Diabetic ketoacidosis
9OL6.00	Diabetes monitoring 3rd letter	F8.00	Diabetic neuropathy treatment
9OL7.00	Diabetes monitor.verbal invite	G73y0.00	Diabetic peripheral angiopathy
K01x1.00	Nephrotic syndrome+diabetes M.		
M0372.00	Cellulitis in diabetic foot		

M2710.00	Ischaemic ulcer diabetic foot		
M2711.00	Neuropathic diab ulcer - foot		
M2712.00	Mixed diabetic ulcer - foot		
N0300.00	Diabetic cheiroarthropathy		
N0300.11	Diabetic cheiropathy		
N0301.00	Diabetic Charcot arthropathy		
R0542.00	[D]Gangrene of toe in diabetic		
R0543.00	[D]Widespread diab foot gangr		
SL23.00	Insulin/antidiabetic poisoning		
SL23z.00	Insulin/antidiabetic pois.NOS		
TJ23.00	Adverse reaction to - insulins/antidiabetic ag.		
TJ23z.00	Adverse reaction to - insulins/antidiabetic NOS		

Current cigarette smoking

Read Code	Read Term
137.11	Smoker – amount smoked
1373.00	Light smoker – 1-9 cigs/day
1374.00	Moderate smoker – 10-19 cigs/d
1375.00	Heavy smoker – 20-39 cigs/day
1376.00	Very heavy smoker – 40+cigs/d
137C.00	Keeps trying to stop smoking
137G.00	Trying to give up smoking
137P.00	Cigarette smoker
137P.11	Smoker
137Q.00	Smoking started
137Q.11	Smoking restarted
137R.00	Current smoker

Heart failure

Read Code	Description
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G581.00	Left ventricular failure
G581.11	Asthma - cardiac
G581.12	Pulmonary oedema - acute
G581.13	Impaired left ventricular function
G58z.00	Heart failure NOS
G58.00	Heart failure
G58.11	Cardiac failure

Appendix 6 Screening log

IMPACT
Improving Adherence using Combination Therapy

Screening Log

Centre number

Complete a separate row for every patient who has been invited to participate in the study. Update the last 2 questions when the data are available.

Row number (auto generated)	Initials	Date of birth			Sex		Ethnicity		Registered		If not registered, Reason			
		Day	Month	Year	M	F	Maori	Non Maori	Yes	No	Not interested	Ineligible	Unable to contact	Other
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○
				1 9	○	○	○	○	○	○	○	○	○	○

IMPACT: Improving Adherence using Combination Therapy • Screening Log

DF03

Appendix 7 Patient invitation letter

Print on GP letterhead

[Insert patient name]
[Insert patient address]
[Insert patient address]
[Insert patient address]
[Insert patient address]

[Insert date]

Dear [insert patient name]

I am working with researchers at the University of Auckland on a study called IMPACT and would like to invite you to take part if you are interested. The lead researcher is [insert name] and the Study Manager is [insert name]. There is a team of research nurses working on the study: [insert names]

The study is comparing a "polypill", a capsule containing several heart medicines, with the usual medicines taken separately. We want to find out if taking a polypill helps people to take their medicine and lowers their blood pressure, cholesterol and risk of heart attack and stroke.

I have included some information about the study for you to read. The research nurse, on behalf of the practice, will ring you to follow up on this letter and can provide more information about what is involved if you are interested. You can also ring [insert Study Manager's name] the Study Manager for more information [insert Study Manager's number].

Taking part in this study is entirely voluntary (you do not have to take part) and whatever your decision, it will not affect the quality of the care that you receive from me or the team at [insert practice name].

Yours sincerely

Dr [insert GP name]

IMPACT GP initial patient contact letter. Version 7 dated 5 April 2011

Appendix 8 Form A: Registration

IMPACT
Improving Adherence using Combination Therapy

Form A: Registration

Registration number |_|_|_|_|_|-|_|_|

- The purpose of this form is to assess the person's eligibility for and interest in participating in the study.
- Complete this form for all people who have indicated an interest in participating in IMPACT.

1. Date of assessment

1.01 |_|_|_|_|2|0|_|_| Date of assessment
day month year

2. Participant characteristics

	Yes	No	
2.01	○	○	Verbal consent to check eligibility (this will include looking at your medical records)

→ **If No, person is ineligible. Stop here. Go to section 4 (signature). Update the Screening Log.**

2.02 |_|_|_|_| Initials

2.03 |_|_|_|_|1|9|_|_| Date of birth
day month year

2.04 Sex

○ Male or ○ Female

	Yes	
2.E	○	As per Manual of Procedures, confirm that ethnicity has **not** been collected prior to obtaining written informed consent.

Which ethnic group(s) does the participant belong to? Please indicate Yes or No to each of the following options:

	Yes	No	
2.05	○	○	New Zealand European
2.06	○	○	Maori
2.07	○	○	Samoan
2.08	○	○	Cook Island Maori
2.09	○	○	Tongan
2.10	○	○	Other Pacific Island ethnicity (e.g. Niuean, Tokelauan, Fijian [not Fijian Indian])
2.11	○	○	Chinese
2.12	○	○	Indian subcontinent ethnicity (i.e. Indian, Fijian Indian, Sri Lankan, Sinhalese, Afghani, Bangladeshi, Nepalese, Pakistani or Tibetan)
2.13	○	○	Other (such as Dutch, Japanese)

2.14 → If Other, specify _____ |_|_|_|_| office use

IMPACT
Improving Adherence using Combination Therapy

Form A: Registration

Registration number

3. Exclusion Criteria

	Yes	No	
3.01	○	○	Is there any reason that you know of why you cannot take: aspirin, or cholesterol lowering medication, or blood pressure lowering medication?
3.02	○	○	Are you taking Warfarin or Dabigatron [Pradaxa] (blood thinning medication)?
3.03	○	○	Are you pregnant, breastfeeding, had a recent pregnancy (within the last 3 months) or might become pregnant within the next 3 years?
3.04	○	○	In the next 12 months, is there any reason why your medication may be changed often, or for a significant length of time? (eg symptomatic or uncontrolled heart failure, planned major surgery)
3.05	○	○	Is there any reason or medical condition that would prevent you completing this trial (for at least 12 months follow-up)?

→ **If Yes to any of 3.01 – 3.05 then the person is ineligible. Go to section 4 (Signature) and then update the Screening Log.**

Research Nurse instructions

- Arrange baseline visit.
- Ask the participant to have a fasting blood test prior to the baseline visit.
- Ask the participant to bring all the medications they are currently taking to the baseline visit (including prescription and over-the-counter medicines).
- Send the GP signed laboratory form to the participant.
- Update Screening Log.

4. Signature of Research Nurse

4.01 _____ (signature) _____ (printed name) _____ (day) _____ (month) 2 0 _____ (year)

Appendix 9 Form Z: Participant details

IMPACT
Improving Adherence using Combination Therapy

Form Z: Participant Details

Participant initials

Participant date of birth
day month year 1 9

Registration number

Participant to complete this form after consent has been obtained at the baseline visit. Answer as many questions as possible. If the data are unavailable, put an asterisk (*).

Participant

Title: First name(s):

Last name:

Address:

Suburb:

City: Postal code:

Home phone number: ( ) area code

Work phone number: ( ) area code

Mobile phone number:

Email address:

Preferred phone contact for follow-up phone visits:

Comments (free text):

Which ethnic group do you belong to?
Mark the space or spaces that apply to you.

- ○ New Zealand European
- ○ Māori
- ○ Samoan
- ○ Cook Island Māori
- ○ Tongan
- ○ Niuean
- ○ Chinese
- ○ Indian
- ○ Other (such as Dutch, Japanese, Tokelauan)

If Other, specify:

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Improving Adherence using Combination Therapy

Form Z: Participant Details

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number -

Alternate Contact (1) (friend or relative not living with the participant)

Title: First name(s):

Last name:

Address:

Suburb:

City: Postal code:

Home phone number: ( ) (area code) Work phone number: ( ) (area code)

Mobile phone number:

Email address:

Relationship to Participant:

Comments (free text):

Alternate Contact (2) (friend or relative not living with the participant)

Title: First name(s):

Last name:

Address:

Suburb:

City: Postal code:

Home phone number: ( ) (area code) Work phone number: ( ) (area code)

Mobile phone number:

Email address:

Relationship to Participant:

IMPACT
Improving Adherence using Combination Therapy

Form Z: Participant Details

Participant initials

Participant date of birth
1 9
day month year

Registration number
-

Comments (free text):

General Practitioner

First name(s): Last name:

Practice name:

Pharmacy (Usual)

Pharmacy name(s):

Address:

Suburb:

City:

Pharmacy (Polypill dispensing if different from above)

Pharmacy name(s):

Address:

Suburb:

City:

Signature of Research Nurse

signature printed name
2 0
day month year

Please ensure that the contact details are correct for the participant at each study contact (phone call or visit). This form should be filed in the participant's study file.

Appendix 10 Consent form

Consent Form

IMPACT
Improving Adherence using Combination Therapy

We invite you to join a trial to test the use of fixed-dose combination medication (a "polypill") compared to usual care medication in people at high risk of cardiovascular disease.

This form and the accompanying participant information sheet outline what the trial involves and requests your consent to be part of the trial.

Request for an interpreter

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai

I understand that the trial involves:

- An initial visit with the Research Nurse (lasting about 1 hour). This will include taking a medical history, blood pressure, height & weight measurements, completing questionnaires about my quality of life, asking about my medication and checking my blood and urine results.
- If I am eligible being randomised to either the polypill group or the usual care group. This means that half the people in the trial will be in the polypill group and half in the usual care group. It is completely by chance which group I would be in if I joined the trial.
- A review of my medication by my General Practitioner.
- Taking either my usual medication or polypill, as prescribed by my General Practitioner, for at least 12 months.
- Having follow up telephone calls by the Research Nurse at 1, 6, 12 months and at the end of the trial, lasting about 15-20 minutes each.
- At 12 months and possibly at the end of the trial having a urine and fasting blood test at my local laboratory.
- A visit at 12 months and possibly at the end of the trial by the Research Nurse, at a convenient location for me, to take my blood pressure & weight and complete the quality of life questionnaire.
- Being invited to an additional interview about my thoughts and experiences around my health and medications (some participants only).
- Agreeing, that even if I stop taking the prescribed medication, I will continue to have the follow-up phone calls and trial visits.

Clinical Trials Research Unit • The University of Auckland • Level 4 • School of Population Health Building
Tamaki Campus • Morrin Road • Glen Innes • Auckland • Private Bag 92019 • Auckland • NEW ZEALAND
Telephone: 64 9 373 7999 • Facsimile: 64 9 373 1710 • Email: ctru@ctru.auckland.ac.nz • www.ctru.auckland.ac.nz

I understand and am satisfied:

- I have read and I understand the information sheet dated 18 February 2010 for volunteers taking part in the IMPACT trial.
- I have had the opportunity to invite whanau support or a friend to help me ask questions and understand the trial.
- I have had the opportunity to discuss this trial and I am satisfied with the answers I have been given.
- I have had time to consider whether to take part.
- I have been made aware of the procedures involved in the trial, including any known or expected inconvenience, risk, discomfort or potential side effects and of their implications as far as they are currently known by the researchers.
- I understand that taking part in this trial is voluntary (my choice) and that I may withdraw from the trial at any time and this will in no way affect my continuing health care.
- I understand that my participation in this trial is confidential and that no material which could identify me will be used in any reports on this trial.
- I understand that the treatment will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this trial.
- I know who to contact if I have any questions about the medication, side effects or the trial.

The following questions must be answered yes to participate in the trial.

Yes	No	
○	○	I agree for the Research Nurse to have access to my GP medical records and to obtain hospital / specialist reports or results of events related to this trial.
○	○	I agree to an approved auditor appointed by either the Clinical Trials Research Unit, ethics committee, or the medicines regulatory authority or their approved representative, reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the trial.
○	○	I agree to the researchers accessing New Zealand national databases, as outlined in the participant information sheet.
○	○	I understand that the results of the trial will be published in medical journals, including a combined analysis with other similar trials, but none of these publications will contain information about me personally.

Participant to complete:

I _____ (print full name) hereby consent to take part in this trial.

Signature: _____ Date: _____ (day month year)

Investigator or Delegated Person explaining the trial and conducting the Consent Process:
Investigator or Delegated Person Details:

Full name of Researcher: _____ Role in Project: _____

Researcher's contact phone number: _____

Signature: _____ Date: _____ (day month year)

One signed consent form is to be given to the participant and the second signed consent form is to be placed in the trial record file.

Appendix 11 Participant questionnaire

Participant initials	Participant date of birth	Registration number
	day month 1 9 year	-

Participant Questionnaire

Research Nurse to complete

0.1 day month 2 0 year Date of assessment

0.2 Assessment occasion **(tick ONE only)**

○ Baseline *or* ○ 12 months *or* ○ End of study

signature printed name day month 2 0 year

EQ-5D Health Questionnaire

English version for New Zealand

1. By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today**.

(tick ONE circle only)

	Mobility		
	I have no problems in walking about	I have some problems in walking about	I am confined to bed
1.01	○	○	○

2.	**Self-Care**		
	I have no problems with self-care	I have some problems washing or dressing myself	I am unable to wash or dress myself
2.01	○	○	○

3.	**Usual Activities** (eg. work, study, housework, family or leisure activities)		
	I have no problems with performing my usual activities	I have some problems with performing my usual activities	I am unable to perform my usual activities
3.01	○	○	○

4.	**Pain/Discomfort**		
	I have no pain or discomfort	I have moderate pain or discomfort	I have extreme pain or discomfort
4.01	○	○	○

5.	**Anxiety/Depression**		
	I am not anxious or depressed	I am moderately anxious or depressed	I am extremely anxious or depressed
5.01	○	○	○

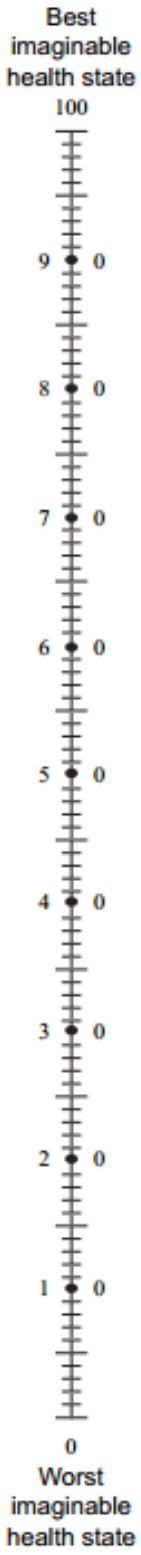
6.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

6.01 We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

For trial researcher to complete



Barriers to taking medications

1. Thinking about the last 7 days, on how many days have you missed taking any of your prescribed medication?

(Missed means taking your medication 6 or more hours late or not at all)

	None	1 day	2 days	3 days	4 days	5 days	6 days	7 days
1.01	○	○	○	○	○	○	○	○

2. **For the following questions please choose the number between 1 and 5 that best describes your answer to the following questions, where 1 is never and 5 is always**

Over the last month, how often have you missed taking your prescribed medication for each of the following reasons?

		1 (never)	2	3 (sometimes)	4	5 (always)
2.01	Wanted to avoid side effects	○	○	○	○	○
2.02	Felt that you didn't need to take the medication	○	○	○	○	○
2.03	Felt sick or ill	○	○	○	○	○
2.04	Had too many pills to take at once	○	○	○	○	○
2.05	Had to take pills too many times during the day	○	○	○	○	○
2.06	Were unclear what pills you were supposed to take when	○	○	○	○	○
2.07	The print on the medication was difficult to read	○	○	○	○	○
2.08	The medication was hard to get out of the packet/bottle	○	○	○	○	○
2.09	Visiting the doctor to get a prescription was too expensive	○	○	○	○	○
2.10	Filling a prescription from the pharmacy was too expensive	○	○	○	○	○
2.11	It was too hard to get to the doctor	○	○	○	○	○
2.12	It was too hard to get to the pharmacy	○	○	○	○	○
2.13	Ran out of pills	○	○	○	○	○
2.14	Forgot or weren't reminded to take the pills	○	○	○	○	○
2.15	Had a change in your daily routine (eg went on holiday)	○	○	○	○	○
	Other reasons (please state):					
2.16		○	○	○	○	○
2.17		○	○	○	○	○
2.18		○	○	○	○	○

Appendix 12 Form B1: Baseline

IMPACT
Improving Adherence using Combination Therapy

Form B1: Baseline Visit

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number

1. Date of visit

1.01 (day / month / year) 2 0 Date of baseline visit

2. Informed consent

	Yes	No	
2.01	○	○	Signed informed consent to participate in study obtained

→ **If No, the participant is INELIGIBLE. Do not complete the rest of this form. Go to Section 12 (Signature) and submit the data.**

3. NHI Number

3.01 ___ - ___ National Health Index (NHI) number

4. Eligibility Criteria

Does the participant have, or have they ever had **(if unsure after checking medical notes and/or discussing with GP, tick yes)**:

	Yes	No	
4.01	○	○	An active stomach or duodenal ulcer
4.02	○	○	A bleeding disorder (e.g. haemophilia)
4.03	○	○	Haemorrhagic stroke
4.04	○	○	Asthma
4.05	○	○	Liver disease or severe liver function impairment/liver failure or unexplained persistent elevation of serum transaminases (ALT/AST)
4.06	○	○	Heart block (except isolated first degree heart block)
4.07	○	○	Heart failure (confirmed clinical diagnosis of Congestive Heart Failure [CHF] or currently being treated for CHF)
4.08	○	○	An allergy or other reaction or contraindication to aspirin [e.g. Aspec or Cartia]
4.09	○	○	An allergy or other reaction or contraindication to a statin (for lowering cholesterol) (e.g. atorvastatin [Lipitor] or simvastatin [Lipex, Zocor])
4.10	○	○	An allergy or other reaction or contraindication to an ACE inhibitor (for treating high blood pressure) (e.g. perindopril [Coversyl], trandolapril [Gopten or Odrik], lisinopril [Prinivil], captopril [Capoten], cilazapril [Inhibace or Inhibace Plus], quinapril [Accupril])
4.11	○	○	An allergy or other reaction or contraindication to a beta-blocker (e.g. metoprolol [Lopresor, Betaloc], atenolol [Loten], carvedilol [Dilatrend], nadolol [Apo-nadolol], propranolol [Cardinol], timolol [Apo-timolol])
4.12	○	○	An allergy or other reaction or contraindication to a thiazide (also called water tablets or diuretics) (e.g bendrofluazide [Neo-Naclex], indapamide [Napamide], cyclopentiazide [Navidrex], chlorthalidone [Hygroton])
4.13	○	○	Is the participant currently taking Warfarin or Dabigatron [Pradaxa]?

IMPACT
Improving Adherence using Combination Therapy

Form B1: Baseline Visit

Participant initials | Participant date of birth (day / month / year) 1 9 | Registration number

5. Other relevant medical history

Has the participant ever had **(if unsure tick no)**:

	Yes	No	
5.01	○	○	Coronary artery disease (eg angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, stent)
5.02	○	○	Atrial fibrillation
5.03	○	○	Familial hypercholesterolaemia, familial defective ApoB or familial combined dyslipidaemia
5.04	○	○	Cerebrovascular disease (e.g. ischaemic stroke, stroke of unknown type, transient ischaemic attack or "mini-stroke")
5.05	○	○	Peripheral vascular disease (e.g. peripheral revascularisation - angioplasty or surgery, amputation secondary to vascular disease, intermittent claudication)
5.06	○	○	Chronic obstructive pulmonary disease (chronic bronchitis or emphysema)
5.07	○	○	Gout
	→		**If yes:**
5.08			☐☐ How many episodes of gout have you had in the last 12 months?
5.09	○	○	Diabetes, other than during pregnancy
		→	**If no go to Q 5.13**
	→		**If yes:**
5.10	→		☐☐ years How old was the participant when diabetes was first diagnosed?
5.11	→		What type of diabetes does the participant have **(tick one only)**?
			○ Type 1
			○ Type 2
	Yes	No	
5.12	→ ○	○	HbA1c consistently >8%
5.13	○	○	Does the participant have renal disease/impairment/failure?
5.14	→		**If yes,** what type of renal disease/impairment/failure does the participant have **(tick one only)**?
			○ Overt diabetic nephropathy (ACR ≥ 30mg/mmol)
			○ Microalbuminuria (ACR of 2.5 to <30mg/mmol in men or 3.5 to <30mg/mmol in women)
			○ Other renal disease causing renal impairment (eGFR ≤ 60ml/min/1.73m²)
5.15	○	○	Does the participant have a family history of heart disease or ischaemic stroke in a first degree relative (a father or brother < 55 years, or mother or sister < 65 years)?

IMPACT
Improving Adherence using Combination Therapy

Form B1: Baseline Visit

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number

6. Blood test results

	Yes	No	
6.01	○	○	Blood test in last month?

If No, the participant is currently INELIGIBLE. Do not complete the rest of this form. Go to section 12 (Signature) and submit the data.

Tell the participant they need to have a recent fasting blood test in order to participate in the study. Give the participant a GP signed laboratory form requesting a fasting blood test and rebook the baseline visit. Remind the participant that the blood test must be taken prior to the baseline visit.

	Yes	No	
6.02	○	○	Was the blood test fasting?

6.03 Date of sample (day / month / year) 2 0

6.04 Laboratory

	Value	Units	
6.05	.	mmol/L	Total cholesterol
6.06	.	mmol/L	HDL cholesterol
6.07	.	mmol/L	LDL cholesterol
6.08	.	mmol/L	Triglycerides
6.09		µmol/L	Creatinine
6.10	.	mmol/L	Uric acid/urate
6.11		mmol/L	Sodium
6.12	.	mmol/L	Potassium
6.13		IU/L	ALT
6.14		IU/L	AST
6.15	.	mmol/L	Fasting Glucose
6.16	.	%	HbA1c (optional)

IMPACT
Improving Adherence using Combination Therapy

Form B1: Baseline Visit

Participant initials

Participant date of birth (day / month / year): 1 9

Registration number

7. Urine test results (optional)

7.01 Date of sample (in last month) (day / month / year): 2 0

7.02 Laboratory

	Value	Units	
7.03	.	mg/mmol	ACR (albumin creatinine ratio)

8. Clinical Assessment

8.01 / mm Hg Blood pressure 1 (systolic/diastolic)

8.02 bpm Heart rate 1

8.03 / mm Hg Blood pressure 2 (systolic/diastolic)

8.04 bpm Heart rate 2

8.05 / mm Hg Blood pressure 3 (systolic/diastolic)

8.06 bpm Heart rate 3

8.07 cm Height

8.08 . kg Weight

8.09 cm Waist circumference

9. Lifestyle Questions

9.01 minutes — What was the total time you spent doing moderate physical activities during the last 7 days?
(Moderate physical activities are when your breathing and heart rate increase. You may start to sweat, your legs might feel a little bit tired and you may feel out of breath. You may also find it hard to talk during the activity. This includes activities undertaken at work, while travelling from place to place, at home, and any activities that you did solely for recreation, sport, exercise or leisure. Examples might be brisk walking, carrying light loads, cleaning the windows, mowing the lawn or cycling at a regular pace.)

9.02 minutes — What was the total time you spent doing vigorous physical activities during the last 7 days?
(Vigorous physical activities are when your heart beats very fast, your breathing is fast and you start sweating. You may also feel exhausted and out of breath. Your legs would probably be feeling pretty heavy. It would be very hard to talk during the activity. Examples might be heavy lifting, digging, aerobics, swimming and fast cycling.)

IMPACT
Improving Adherence using Combination Therapy

Form B1: Baseline Visit

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number -

	Yes	No	
9.03	○	○	Have you ever smoked cigarettes (ready made or roll your own) regularly (ie on most days for at least a year)? **If No, go to question 9.08**
9.04			____ years **If yes,** how many years have you smoked regularly?
	Yes	No	
9.05	○	○	Are you a current cigarette smoker?
9.06			____ years **If no,** what was your age (in years) when you last smoked regularly?
9.07			____ cigarettes/day **If yes,** on average, how many cigarettes do you smoke per day?
9.08			____ units How much alcohol do you drink a week (30ml straight spirits, 330ml can of beer and 100 ml glass table wine are one unit of alcohol each)

10. Socio-economic questions

	Yes	No	
10.01	○	○	Do you hold a community services card **(if unsure, tick no)?**

10.02 What is your highest completed educational qualification **(tick one only)**?

- ○ None
- ○ Primary school
- ○ Secondary school
- ○ Undergraduate degree
- ○ Postgraduate degree or diploma
- ○ Technical/vocational qualification

	Yes	No	
10.03	○	○	Are you currently in paid employment?
10.04			____ days **If yes,** how many days off work have you had in the last 12 months due to sickness or injury

10.05 From all sources of income, what was the total gross income of your household in the last 12 months (before tax or anything was taken out of it) **(tick one only)**

- ○ Less than $15,000 ($1–$288 per week)
- ○ $15,000-$29,999 ($289–$577 per week)
- ○ $30,000-$59,999 ($578–$1154 per week)
- ○ $60,000-$99,999 ($1155–$1923 per week)
- ○ $100,000 or more ($1924+ per week)
- ○ Participant chose not to answer question

IMPACT
Improving Adherence using Combination Therapy

Form B1: Baseline Visit

Participant initials

Participant date of birth
day month 19 year

Registration number
-

11. Eligibility

	Yes	No	
11.01	○	○	Participant remains eligible for the trial
11.02		→	**If no,** please specify reason

12. Signature of Research Nurse

12.01 signature | printed name | day month 20 year

IMPACT
Improving Adherence using Combination Therapy

Form M: Medications

Participant initials

Participant date of birth
day month 19 year

Registration number -

1. Medications

Record all oral medications (plus insulin) taken by participant from Baseline visit until the end of the study.

		1.01	1.02	1.03	1.04
Drug name (generic or trade name)					
Drug class name (auto-populated on website)					
Start Date (day/month/year)					
Ongoing		○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Stop Date (day/month/year)					
Complete for oral CVD drugs only	Dose				
	Units				
	Frequency				
	Reason for stopping				
How many days in the last week have you taken this medication?	Baseline				
	1 month assessment				
	6 month assessment				
	12 month assessment				
	End of trial				

IMPACT
Improving Adherence using Combination Therapy

Form M: Medications

Participant initials

Participant date of birth
day month 1 9 year

Registration number -

		1.05	1.06	1.07	1.08
Drug name (generic or trade name)					
Drug class name (auto-populated on website)					
Start Date (day/month/year)					
Ongoing		○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
Stop Date (day/month/year)					
Complete for oral CVD drugs only	Dose				
	Units				
	Frequency				
	Reason for stopping				
How many days in the last week have you taken this medication?	Baseline				
	1 month assessment				
	6 month assessment				
	12 month assessment				
	End of trial				

IMPACT
Improving Adherence using Combination Therapy

Form M: Medications

Participant initials

Participant date of birth
1 9
day month year

Registration number
-

Units		Frequency				Days
g	gram	OD	Once daily	AD	Alternate days	0
mg	milligram	BD	Twice daily	PRN	As required	1
ug	microgram	TDS	Three times a day	AC	Before meals	2
mL	millilitre	QDS	Four times a day	PC	After meals	3
puff		Q2H	Every 2 hours	Stat	At once	4
IU	International Units	Q3H	Every 3 hours	OW	Once weekly	5
topical	%	Q4H	Every 4 hours	OM	Once monthly	6
drop		Q6H	Every 6 hours			7
tablet		Q8H	Every 8 hours			NA

2. Review and Update check

This form has been reviewed and updated where necessary for:

	Yes	No	
2.01	○	○	Baseline
2.02	○	○	1 month assessment
2.03	○	○	6 month assessment
2.04	○	○	12 month assessment
2.05	○	○	End of Study

3. Signature of research nurse

3.01 _____ (signature) _____ (printed name) 2 0 (day month year)

Appendix 14 Form B2: General practitioner approval and randomisation

IMPACT
Improving Adherence using Combination Therapy

Form B2: GP Approval and Randomisation Page 1 of 1

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number -

Summary of eligibility information for GP review

The following data will be displayed on screen:

- CVD risk category
- Current medications (list of generic and trade names sorted alphabetically by generic name)
- Relevant test results summary table
- Contraindications/cautions/indications. N.B. not all relevant measures may be recorded here.
- Polypill recommendation (if applicable)

1. GP Approval and Polypill Recommendation

	Yes	No	
1.01	○	○	The GP believes that each of the Polypill components are indicated
1.02	○	○	The GP is unsure as to whether a Polypill-based strategy or usual care is better
1.03	○	○	Participant randomisation approved?
1.04			If no, specify reason

1.05 If participant randomised to the Polypill Group, which version would you prescribe? *(tick one only)*

- ○ Beta blocker version
- ○ Thiazide version

Randomisation

Randomisation result will be displayed on screen if successful.

2. Signature of GP

2.01 signature | printed name | day / month / year 2 0

Appendix 15 Medication classification

Classification	Sub-classification	Medications
Antiplatelet	Aspirin	Aspirin
	Non-aspirin antiplatelet	Dipyridamole
		Clopidogrel
		Ticagrelor
Lipid lowering	Statin	Simvastatin
		Atorvastatin
		Pravastatin
	Non-statin lipid-lowering	Bezafibrate
		Exetimibe
BP lowering	ACE inhibitor	Captopril
		Cilazapril
		Enalapril
		Lisinopril
		Quinapril
	Alpha Adrenoceptor Blocker	Doxazosin
		Tamulosin
		Terazosin
	Angiotensin II antagonist	Candesartan
		Losartan
	Beta Adrenoceptor Blocker	Atenolol
		Carvedilol
		Celiprolol
		Metoprolol
		Nadolol
	Dihydropyridine Calcium Channel Blocker	Amlodipine
		Felodipine
	Other Calcium Channel Blocker	Diltiazem
		Verapamil
	Loop Diuretic	Frusemide
		Bumetanide
	Potassium Sparing Diuretic	Amiloride
		Spironalactone
	Thiazide and related diuretic	Bendrofluazide
		Chlorthalidone
		Hydrochlorothiazide
		Indapamide

Appendix 16 Form C: Follow-up

IMPACT
Improving Adherence using Combination Therapy

Form C: Follow-up

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number

The purpose of this form is to collect information from IMPACT participants at their follow-up visits/phone calls.

Ask the participant to get all of the medicines they are currently taking (including prescription and over-the-counter medicines) before starting this form.

1. Vital status and assessment details

1.01 Follow-up assessment **(tick one only)**

- ○ 1 month
- ○ 6 month
- ○ 12 month
- ○ End of study

1.02 day / month / year 2 0 Date of assessment

1.03 Assessment type **(tick one only)**

- ○ Face-to-face with participant (home, work, clinic)
- ○ Phone call with participant
- ○ Phone call or contact with health care provider
- ○ Other

If other, please specify

	Yes	No	
1.04	○	○	Information available for this scheduled visit?

→ **If Yes**, go to section 2: Practice nurse, GP and specialist visits

1.05 **If No**, reason for missed visit

- ○ Unable to contact participant
- ○ Participant died [Complete Form X]
- ○ Refuses further participation
- ○ Other

1.06 → **If other**, please specify

→ **Go to Section 13 (Signature)**

IMPACT
Improving Adherence using Combination Therapy

Form C: Follow-up

Participant initials | Participant date of birth (day / month / year: 1 9) | Registration number

2. Practice nurse, GP and specialist visits

Since the last assessment, how many times have you seen the following health practitioners:

2.01 ☐☐ A practice nurse

2.02 ☐☐ The GP who enrolled you into this study

2.03 ☐☐ Any other GPs

2.04 ☐☐ A doctor at a private A & E (accident and medical centre)

2.05 ☐☐ A doctor in a public hospital A&E (and you were not admitted)

2.06 ☐☐ A specialist in a **public** outpatients' clinic for your heart, blood pressure, diabetes or stroke care.

2.07 ☐☐ A specialist in a **private** outpatients' clinic for your heart, blood pressure, diabetes or stroke care.

	Yes	No	
2.08	○	○	Are you currently in paid employment?
2.09	→ ☐☐☐ days		**If yes,** how many days off work have you had since the last assessment due to sickness or injury.

3. Serious Adverse Events since last assessment

	Yes	No	
3.01	○	○	Have you had a Serious Adverse Event since the last assessment? (A serious adverse event is any event (whether or not related to the Polypill or usual care medication) that results in death, is life threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, malignancy, overdose or other important medical event (e.g. transient ischaemic attack, severe hypoglycaemia, severe hyperglycaemia

Complete Form X for all Serious Adverse Events

4. Polypill participants

For participants taking the polypill only

4.01 What time of the day do you usually take the polypill? **(Tick one only)**

- ○ In the morning
- ○ At lunchtime
- ○ In the evening
- ○ No fixed time

If this is a 12 month or end of study assessment, proceed to section 5 (current lifestyle interventions). Otherwise, go to section 13 (signature).

IMPACT
Improving Adherence using Combination Therapy

Form C: Follow-up

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number

5. Current lifestyle interventions [12 month + end of study visits only]

5.01 ____ minutes — What was the total time you spent doing moderate physical activities during the last 7 days?
(Moderate physical activities are when your breathing and heart rate increase. You may start to sweat, your legs might feel a little bit tired and you may feel out of breath. You may also find it hard to talk during the activity. This includes activities undertaken at work, while travelling from place to place, at home, and any activities that you did solely for recreation, sport, exercise or leisure. Examples might be brisk walking, carrying light loads, cleaning the windows, mowing the lawn or cycling at a regular pace)

5.02 ____ minutes — What was the total time you spent doing vigorous physical activities during the last 7 days?
(Vigorous physical activities are when your heart beats very fast, your breathing is fast and you start sweating. You may also feel exhausted and out of breath. Your legs would probably be feeling pretty heavy. It would be very hard to talk during the activity. Examples might be heavy lifting, digging, aerobics, swimming and fast cycling.

6. Gout [12 month only]

	Yes	No	
6.01	○	○	Have you ever had gout?
6.02	→ ____		**If yes,** how many episodes of gout have you had in the last 12 months?

7. Socio-economic questions [12 month + end of study only]

	Yes	No	
7.01	○	○	Do you hold a community services card?

8. Lifestyle questions [12 month + end of study only]

	Yes	No	
8.01	○	○	Are you a current cigarette smoker?
	Yes	No	
8.02	○	○	**If no,** have you stopped smoking since starting this study? **If no, go to question 8.05**
8.03			____ (day / month / year 2 0) If yes, date stopped smoking
8.04			→ ____ On average, how many cigarettes do you smoke per day?
8.05			____ units — How much alcohol do you drink a week (30ml straight spirits, 330ml can of beer and 100 ml glass table wine are one unit of alcohol each)

IMPACT
Improving Adherence using Combination Therapy

Form C: Follow-up

Participant initials | Participant date of birth (day / month / year) | Registration number

9. Participant Acceptability [12 month + end of study only]

9.01 During the study, how easy did you find it to take all the medicines prescribed by your doctor? (including the polypill) **(tick one only)**

- ○ Very easy
- ○ Easy
- ○ Average
- ○ Difficult
- ○ Very difficult

10. Clinical Assessment [12 month + end of study only]

10.01	day / month / 2 0 year	Date measurements taken
10.02	___ / ___ mm Hg	Blood pressure 1 (systolic/diastolic)
10.03	___ bpm	Heart rate 1
10.04	___ / ___ mm Hg	Blood pressure 2 (systolic/diastolic)
10.05	___ bpm	Heart rate 2
10.06	___ / ___ mm Hg	Blood pressure 3 (systolic/diastolic)
10.07	___ bpm	Heart rate 3
10.08	___ . ___ kg	Weight
10.09	___ cm	Waist circumference

11. Blood test results [12 month + end of study only]

	Yes	No	
11.01	○	○	Recent blood test taken (within 1 month)

If no, tell the participant they need to have a fasting blood test. Give the participant a GP signed laboratory form. Go to section 13 (signature) and submit the data.

If yes

	Yes	No	
11.02	○	○	Was the blood test fasting?

11.03 day / month / 2 0 year — Date of sample

11.04 Laboratory

IMPACT
Improving Adherence using Combination Therapy

Form C: Follow-up

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number

	Value	Units	
11.05	.	mmol/L	Total cholesterol
11.06	.	mmol/L	HDL cholesterol
11.07	.	mmol/L	LDL cholesterol
11.08	.	mmol/L	Triglycerides
11.09		µmol/L	Creatinine
11.10	.	mmol/L	Uric acid/urate
11.11		mmol/L	Sodium
11.12	.	mmol/L	Potassium
11.13		IU/L	ALT
11.14		IU/L	AST
11.15	.	mmol/L	Fasting Glucose
11.16	.	%	HbA1c (Optional)

12. Urine test results [12 month + end of study only (optional)]

12.01 (day / month / year) 2 0 — Date of sample (within 1 month)

12.02 Laboratory

	Value	Units	
12.03	.	mg/mmol	ACR (albumin creatinine ratio)

Researcher Instructions

- Check Form Z details (address, GP, pharmacy) at each visit.
- For particpants in the polypill group ask if there are any problems with obtaining their polypill prescriptions from the pharmacy.
- Update Form M and X if applicable after submitting this form.

13. Signature of Research Nurse

13.01 signature | printed name | (day / month / year) 2 0

Appendix 17 Polypill dispensing log

IMPACT
Improving Adherence using Combination Therapy

IMPACT TRIAL TREATMENT DISPENSING RECORD

Pharmacy name:
Contact name:

Red Heart Pills
1C

Instructions for Use: Use black pen, initial and date changes, cross out with one line. Do not use twink

PHARMACY TO COMPLETE									
Date of Dispensing	Participant ID Number	Initials	DOB	Batch Number	Expiry Date	Amount (tabs)	Amount of Participant Payment	Invoice Amount to CTRU	Pharmacist Initials

DF01

IMPACT
Improving Adherence using Combination Therapy

IMPACT TRIAL TREATMENT DISPENSING RECORD

Pharmacy name:
Contact name:

Red Heart Pills
2C

Instructions for Use: Use black pen, initial and date changes, cross out with one line. Do not use twink

PHARMACY TO COMPLETE									
Date of Dispensing	Participant ID Number	Initials	DOB	Batch Number	Expiry Date	Amount (tabs)	Amount of Participant Payment	Invoice Amount to CTRU	Pharmacist Initials

DF01

IMPACT
Improving Adherence using Combination Therapy

Form X: Serious Adverse Events

Participant initials

Participant date of birth
day month year 1 9

Registration number

The purpose of this form is to collect information on all Serious Adverse Events (SAEs) occurring in participants on the IMPACT study.

- Enter all SAEs occurring within the same episode or hospital admission in chronological order. (N.B. Each new hospital admission must be reported on a separate Form X.)

A Serious Adverse Event is any event (whether or not related to the Polypill or usual care medication) that results in death, is life threatening,[a] requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, malignancy, overdose or other important medical event.[b]

[a] Life-threatening: the participant was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe.

[b] Other important medical event: any event that is not immediately life-threatening and does not result in death or hospitalisation but which may jeopardise the participant or may require intervention to prevent one of the other outcomes listed as a SAE above e.g transient ischaemic attack, severe hypoglycaemia or severe hyperglycaemia.

IMPACT
Improving Adherence using Combination Therapy

Form X: Serious Adverse Events

Participant initials

Participant date of birth
day month 19 year

Registration number -

1. Detail of Serious Adverse Event

	Diagnosis (one per line) If diagnosis not known, enter signs and/or symptoms (one per line) Use concise medical terminology.	Onset date day month year	Event Type [1]	Maximum Severity [2]	Relationship to Polypill [3]	(Polypill group only) Unexpected ADR to Polypill [4]	Outcome Status [5]	Resolution Date (leave blank if ongoing or unknown/lost to follow up) day month year
1.01		20						20
1.02		20						20
1.03		20						20
1.04		20						20

[1]Event type
0 Death
1 Life-threatening
2 Hospitalisation or prolongation of hospitalisation
3 Persistent or significant disability
4 Congenital abnormality
5 Malignancy
6 Overdose
7 Other medically important event

[2]Maximum severity
1 Mild
2 Moderate
3 Severe

[3]Relationship to Polypill
1 Definitely
2 Probably
3 Possibly
4 Unlikely
5 Not related
6 Not in Polypill group

[4]Unexpected Adverse Drug Reaction to Polypill
An adverse reaction, the nature or severity of which is not consistent with the Investigator's Brochure.
1 Expected
2 Unexpected
3 Not applicable – i.e. relationship unlikely or not related

[5]Outcome Status
1 Resolved
2 Ongoing
3 Death
4 Unknown/lost to follow up

IMPACT
Improving Adherence using Combination Therapy

Form X: Serious Adverse Events

Participant initials

Participant date of birth (day / month / year) 1 9

Registration number -

2 Details of procedures

	Procedure (one per line) The diagnosis leading to the procedure must be recorded in section 1.	Date of procedure (day / month / year)
2.01		2 0
2.02		2 0
2.03		2 0

3 Hospitalisation

3.01 Yes ○ No ○ Was the participant admitted to hospital (i.e. completed formal admission procedures)?

→ If No, go to section 4

→ If Yes,

3.02 2 0 (day / month / year) Admission date

3.03 2 0 (day / month / year) Discharge date or date died in hospital (leave blank if still in hospital)

IMPACT
Improving Adherence using Combination Therapy

Form X: Serious Adverse Events

Participant initials

Participant date of birth
day month year 1 9

Registration number -

4. Death

	Yes	No	
4.01	○	○	Did the participant die? **If No, go to section 5** **If Yes,**
4.02			day month year 2 0 Date of death
4.03			Immediate cause of death
4.04			Underlying cause of death
4.05	○	○	Autopsy performed

IMPACT
Improving Adherence using Combination Therapy

Form X: Serious Adverse Events

Participant initials

Participant date of birth
day month year 1 9

Registration number

5. Suspected Unexpected Serious Adverse Drug Reaction (SUSAR)

5.01 Yes ○ No ○ Is a Polypill SUSAR being reported? (Serious **and** unexpected **and** definitely, probably or possibly related to the Polypill)
→ **Go to section 6.**

5.02 → List all the medications that the participant was taking at the time of the first event reported on this form

Drug name (generic or trade name)	Dose	Units	Frequency	Route

5.03 Yes ○ No ○ Has the Polypill been stopped since the last study assessment?
→ **If no go to section 6**

5.04 → Yes ○ No ○ Was the Polypill stopped due to any event reported on this form?

5.05 → day month year 2 0 Date Polypill stopped

IMPACT
Improving Adherence using Combination Therapy

Form X: Serious Adverse Events

Participant initials

Participant date of birth
1 9
day month year

Registration number
-

6. Supporting Documentation

	Yes	No	
6.01	○	○	Are any of the following being reported on this form: • A cardiovascular event or procedure • A death • An event that is Definitely , Probably or Possibly related to the Polypill

→ If no, go to section 7

→ If yes, please send copies of the relevant document(s) as soon as possible to the IMPACT Study Centre. Refer to the Manual of Procedures for guidance on documentation required for particular events. Remove patient name/address and label all pages with patient registration number and initials.
Indicate below which documents will be sent (answer each question)

	Yes	No	
6.02	○	○	Clinical notes describing the event (eg discharge summary)
6.03	○	○	ECG
6.04	○	○	Cardiac enzymes, troponins
6.05	○	○	Other laboratory reports
6.06	○	○	CT report
6.07	○	○	MRI report
6.08	○	○	Autopsy report
6.09	○	○	Death certificate (NB insufficient without additional documentation)
6.10	○	○	Other relevant documentation (eg echocardiography report, coroners report)

IMPACT
Improving Adherence using Combination Therapy

Form X: Serious Adverse Events

Participant initials

Participant date of birth
day month 1 9 year

Registration number -

7. Narrative/Comments

7.01 Provide brief narrative of the event if necessary to supplement information above/supporting documentation

8. Signature of Study Researcher

8.01 signature | printed name | day month 2 0 year

Appendix 19 Manual of procedures for Clinical Adjudication Committee

Clinical Endpoint Adjudication Committee (CEAC)

Manual of Procedures

Version 1.1
3 May 2011

Version history

Version Number	Date
Version 1	28 May 2010
Version 1.1	3 May 2011

1. Clinical Endpoint Adjudication Committee

A Clinical Endpoint Adjudication Committee (CEAC) consisting of independent specialist physicians has been formed to provide final verification of clinical endpoints that occur during the conduct of the IMPACT study.

The verification process, termed Adjudication, will involve the Endpoint Adjudicators performing a formal review of potential endpoints by assessment according to criteria defined in this manual (see Appendix 4). Endpoint Adjudicators will be blinded to the patient's treatment group.

Endpoints that will undergo Adjudication include cardiovascular events, renal events, major bleeds and all deaths occurring after registration and within 30 days following termination of follow-up.

2. Personnel

- Endpoint Adjudication Committee (see Appendix 1)
- IMPACT office (see Appendix 2)

3. Events for Adjudication

The CEAC is to make an assessment of the following events when reported by the investigator to the IMPACT office:

- All Deaths
- Cardiovascular Disease
    - Cerebrovascular Disease Events
        - Non-fatal Stroke
        - Transient Ischemic Attack
        - Sub-arachnoid haemorrhage
    - Coronary Heart Disease Events
        - Non-fatal Myocardial Infarction
        - Coronary Artery Bypass Graft
        - Percutaneous Coronary Intervention
        - Hospitalisation for Unstable Angina
        - All Heart Failure events leading to death or requiring hospital admission
    - Peripheral Arterial Disease Events
        - New symptomatic claudication
        - Amputation due to ischaemia
        - Peripheral arterial revascularisation procedure
- Renal Disease
    - New onset of Microalbuminuria
    - Progression to Macroalbuminuria
    - 50% loss of estimated Glomerular Filtration Rate
    - Commencement of renal replacement therapy for end-stage renal disease
- Major Bleeding Events

4. Pre-adjudication

a. Information collected from the investigators

Investigators will be asked to report any serious adverse events (SAEs) including all deaths, cardiovascular events and procedures occurring after registration and within 30 days following termination of follow-up. SAEs are coded by the CTRU Medical Coder using MedDRA (Medical Dictionary for Regulatory Activities), which will allow the identification of events for adjudication. Copies of relevant documents will be obtained and submitted for adjudication. Original data such as actual electrocardiograms or CT / MRI films will not be required. It is anticipated that documentation required will include copies of the following:

- Discharge/Admission Summary
- Clinical Notes
- Imaging/Procedural/Analysis Reports
- Laboratory reports
- ECG reports / descriptions of ECG findings
- Autopsy Report
- Death Certificate
- Physician Narrative
- File Note

b. Preparation of documents

The Project Manager will review the source documentation and check that the following requirements have been met:

- All documentation has been identified with the relevant site number, participant's registration number, and participant's initials
- Participant identifiers have been masked
- Information regarding the participant's treatment allocation (Red Heart Pill or usual care) has been masked
- Documentation dates correlate with the date of the event
- Documentation is of satisfactory clarity
- Documentation received is complete

For each event to be adjudicated, the Project Manager will prepare the following:

- Cover Sheet
- Adjudication Package

5. Adjudication (see Appendix 4)

a. Flow of information

The Project Manager will email the relevant CEAC member (see Appendix 1) when an event requires adjudication. Relevant documentation will be available to the adjudicator on a secure study webfolder. The adjudicator will be able to adjudicate the event via the study website. To gain access to the websites, an authorised user name and a password will be provided to each member.

b. Adjudication

When an event is received the CEAC member will determine whether the:

- Event meets the specified diagnostic criteria (see Appendix 3)
- Reported date of event/death is correct
- Reported proximate /underlying cause of death is correct

If the adjudicator disagrees with the investigator they will need to specify the correct death/event date or diagnosis/cause of death (or explain why they are unable to specify these). The decision of the adjudicator will supersede that of the investigator.

Where the adjudicator disagrees with the event diagnosis, they are also requested to document if the event meets the definition of another study endpoint (and if so, to specify which) or if the event doesn't meet the definition of any study endpoint.

The results of adjudication will be recorded electronically using the study website and completed within one month of receipt.

c. Insufficient information to adjudicate

If the assigned CEAC member has insufficient information to enable them to complete the adjudication, they should indicate their request for additional information via the study website. The Study Manager will facilitate provision of this information from the investigator.

d. Assigned adjudicator uncertainties

If the member is unable to adjudicate the event because they are uncertain how the event should be adjudicated, they should discuss the event with other expert colleagues in their local institution in the first instance. See below for residual uncertainties.

e. Residual assigned adjudicator uncertainties

Any residual assigned adjudicator uncertainties should be discussed by the entire committee at the next CEAC meeting and the event adjudicated according to CEAC consensus. If the CEAC cannot reach a consensus, the final diagnosis will be assigned by the Chair of the committee.

f. CEAC meetings

The CEAC will meet as required by teleconference. In addition to the CEAC members, the Project Manager(s), Research Fellow and the Principal Investigator may also attend as observers.

6. Publication

Membership of the CEAC will be acknowledged in all publications that include adjudicated outcomes.

APPENDIX 1 – CEAC members

Name	Events to adjudicate
Dr Neil Anderson (Neurologist)	• Death where proximate or underlying cause is cerebrovascular disease • Non fatal stroke • Transient ischaemic attack • Subarachnoid haemorrhage
Dr Ruvin Gabriel (Cardiologist)	• Death where proximate or underlying cause is coronary heart disease or peripheral arterial disease • Non fatal myocardial infarction • Non fatal unstable angina hospitalisation • Heart failure hospitalisation or death • Coronary artery bypass graft • Percutaneous coronary intervention • New symptomatic claudication • Amputation due to ischaemia • Peripheral arterial revascularisation procedures
Dr Kate Scott (Chair and Geriatrician)	• New onset of microalbuminuria • Progression to macroalbuminuria • 50% loss of estimated glomerular filtration rate • Commencement of renal replacement therapy for end-stage renal disease • Major bleeding event • All other deaths

APPENDIX 2 – IMPACT office

Name	Title
Raina Elley	Principal Investigator
Angela Wadham	Senior Project Manager
Elizabeth Glen	Project Manager
Vanessa Selak	Research Fellow
Terry Holloway	Medical Coder

APPENDIX 3 - Endpoint definitions

Death

The assigned CEAC member will review all the documentation provided for each death. The final determination of the cause of death will be made by the CEAC member. The CEAC member is to assign a single proximate and, where appropriate, a single underlying cause of death. Where multiple underlying causes of death are identified, the main underlying cardiovascular cause of death (where present) should be assigned. Where multiple underlying causes of death are identified and there is no underlying cardiovascular cause of death, the most clinically relevant underlying cause of death should be assigned. For example, a patient who died from pneumonia thought to be secondary to aspiration because of prior ischaemic stroke, the proximate cause would be "pneumonia" and the underlying cause would be "cerebral infarction". Note: "cardiac arrest", "collapse", "respiratory failure" and "syncope" are modes of dying, not causes of death. Further guidance on assigning cause(s) of death should be sought from A Guide to Certifying Causes of Death (New Zealand Health Information Service, 2001).

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records, including lab reports or imaging reports
2. Autopsy report (if performed)
3. Death Certificate

Non-fatal Stroke

A non-fatal stroke event is a stroke which does not result in death within 28 days from onset. Any recurrence or exacerbation of the condition in the same vascular territory within 28 days is considered part of the original episode, except when in a different vascular territory, whereas beyond that time period it is considered a separate event.

Criteria

A non-fatal stroke is defined as an event that satisfies all of the following clinical criteria:

1. Sudden onset
2. Focal neurological impairment or deficit
3. Lasting more than 24 hour, or, if less than 24 hours with evidence of acute infarction on CT or MRI consistent with the neurological deficit
4. Of presumed vascular origin

Type

Non-fatal strokes should be classified according to the following types:

1. Haemorrhagic
    a. Documentation of intracranial blood (intraparenchymal, intraventricular or subdural) (NB: there is a separate category for sub-arachnoid haemorrhage)
2. Non-haemorrhagic
    a. No evidence of intracranial blood on neuro-imaging
3. Unknown

a. Type of stroke cannot be determined due to lack of imaging or other diagnostic information

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records.
2. Imaging Report (e.g. CT report, MRI report, MRA report)
3. Autopsy report (if death occurs after 28 days from onset of symptoms)

Transient Ischemic Attack

Criteria

Defined as an event that satisfies all of the following criteria:

1. Documented clinical history of acute loss of focal neurological function or monocular (amaurosis fugax) function
2. Symptoms lasting less than 24 hours with no evidence of acute infarction on imaging studies (if any such study performed)
3. Presumed to be due to a result of vascular disease of an arterial, embolic or thrombotic kind

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. Imaging Report (e.g. CT report, MRI report, MRA report)
3. Autopsy report (if death occurs after 28 days from onset of symptoms)

Sub-arachnoid haemorrhage

Criteria

Defined as an event that satisfies all of the following:

1. Documented history of typical symptoms and/or signs (e.g. sudden onset of headache, neck stiffness, loss of consciousness)
2. Evidence of blood in the subarachnoid space (e.g. on CT or MRI imaging, analysis of the CSF on lumbar tap, cerebral angiography, or autopsy report)

Source of Information

Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records.

1. Any of the following:
   a. CT or MRI report
   b. Lumbar Puncture & Cerebrospinal Fluid Analysis Report
   c. Cerebral Angiography Report
2. Autopsy report (if death occurs after 28 days from onset of symptoms)

Non-fatal Myocardial Infarction

A non-fatal myocardial infarction event is a myocardial infarction that does not result in death within 28 days from onset. Any recurrence or exacerbation of the condition within that period is considered part of the original episode, whereas beyond that time it is considered a separate event.

Silent myocardial infarction *(defined as incidental findings of electrocardiographic evidence of previous myocardial infarction with no history ischaemic symptoms) is not included as a primary outcome.*

Criteria

Defined as an event that satisfies any one of the following:

1. The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following three criteria meets the diagnosis of myocardial:
    a. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
        i. Symptoms of ischaemia
        ii. ECG changes indicative of new ischaemia (new ST-T changes or new left branch bundle block [LBB])
        iii. Development of pathological Q waves in the ECG
        iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    b. For percutaneous coronary interventions (PCI) in patients with normal baseline biomarker values, increases of biomarkers greater than 3 x 99th percentile URL will be defined as PCI-related myocardial infarction
    c. For coronary artery bypass grafting (CABG) in patients with normal baseline biomarker values, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium will be defined as CABG-related myocardial infarction

OR

2. Post-mortem diagnosis where death occurred more than 28 days from symptom onset: autopsy findings of acute myocardial infarction.

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records.
2. ECG Report
3. Cardiac Marker Lab Reports (eg. CK, CKMB, or troponins)
4. Autopsy reports (if death occurred after 28 days from incidence)

Coronary Artery Bypass Graft

Criteria

1. Evidence of a surgical procedure, in either an emergency or elective setting, during which a graft vessel is used to shunt an occluded segment of the coronary artery

Source of Information

1. Clinical Notes, Procedural Report, Discharge Summary

Percutaneous Coronary Intervention

Criteria

1. Evidence of a procedure (non-surgical) during which a narrowed coronary artery is mechanically widened percutaneously.

Source of Information

1. Clinical Notes, Procedural Report, Discharge Summary

Hospitalisation for Unstable Angina

Criteria

Defined as an event that satisfies all of the following criteria:

1. Hospitalisation (including attendance at an accident and emergency department for > 24 hours) for unstable angina
2. History of typical ischaemic symptoms
3. Ischaemic symptoms with at least one of the following three features:
   a. Occurs at rest (or with minimal exertion) and lasts >10 minutes
   b. Severe and new onset (within the last 4-6 weeks)
   c. Occurs with a crescendo pattern (i.e. distinctly more severe, prolonged, or frequent than previously)
4. Does not fulfil criteria for diagnosis of myocardial infarction

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. ECG Report
3. Cardiac Marker Lab Reports (eg. CK, CKMB, or troponins)
4. Autopsy reports (if death occurred after 28 days from incidence)

All Heart Failure events leading to death or requiring hospital admission

Criteria

Defined as an event that satisfies 1, 2, and either 3 or 4 of the items below:

1. Administration of intravenous diuretic, escalation of diuretic doses and/or inotropes for heart failure

   AND

2. Heart failure on chest x-ray

   AND

3. Hospitalisation (including attendance at an accident and emergency department for > 24 hours) for heart failure

   OR

4. Death (as a result of heart failure)

If criteria for heart failure hospitalisation are met, heart failure should be classified into one of the following types:

1. New onset
2. Exacerbation

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. Chest x-ray report
3. Death Certificate (if applicable)
4. Autopsy Report (if performed and applicable)

New Symptomatic Claudication

Criteria

Defined as an event satisfying all the following criteria:

1. Typical symptoms and signs
   a. Calf, thigh or buttock pain on exertion which is relieved by rest, or
   b. Rest pain, or
   c. Loss of lower limb pulses
2. ≥ 1 test abnormality (ankle brachial pressure index [ABPI] <0.9 in either leg, ultrasound or angiographic evidence of stenosis)

Absence of other cause for symptoms

Asymptomatic peripheral arterial disease is not included as an endpoint.

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records

Amputation due to Ischaemia

Criteria

Defined as surgical amputation of at least one toe due to arterial insufficiency.

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records

Peripheral Arterial Revascularisation

Criteria

Evidence of a procedure where arterial revascularisation (carotid endarterectomy or stenting, open repair or endoluminal stenting of thoracic, thoracoabdominal or abdominal aortic aneurysm or dissection, limb revascularisation procedure) is undertaken.

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. Operation or procedural reports

New onset of Microalbuminuria

Criteria

Defined by the presence of both:

1. Absence of microalbuminuria at baseline (i.e. ACR < 3mg/mmol)
2. Microalbuminuria during trial (3mg/mmol ≤ ACR ≤ 33.9 mg/mmol

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. Laboratory test reports

Progression to Macroalbuminuria

Criteria

Defined by the presence of both:

1. Absence of macroalbuminuria at baseline (i.e. ACR $\leq$ 33.9 mg/mmol)
2. Development of macroalbuminuria during the trial (ACR > 33.9 mg/mmol)

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. Laboratory test reports

50% loss of estimated Glomerular Filtration Rate

Criteria

Both:

1. Reduction of eGFR of >50% from baseline
2. eGFR < 60mLs/min/1.73m2

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. Laboratory test reports
3. Calculation of eGFR using Modification of Diet in Renal Disease (MDRD) formula

Commencement of Renal Replacement Therapy for End-Stage Renal Disease

Criteria

The requirement for renal replacement therapy (dialysis or transplantation) due to end-stage kidney disease (transient dialysis support for acute renal failure does not constitute renal replacement therapy for ESKD)

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records

Major Bleeding Events

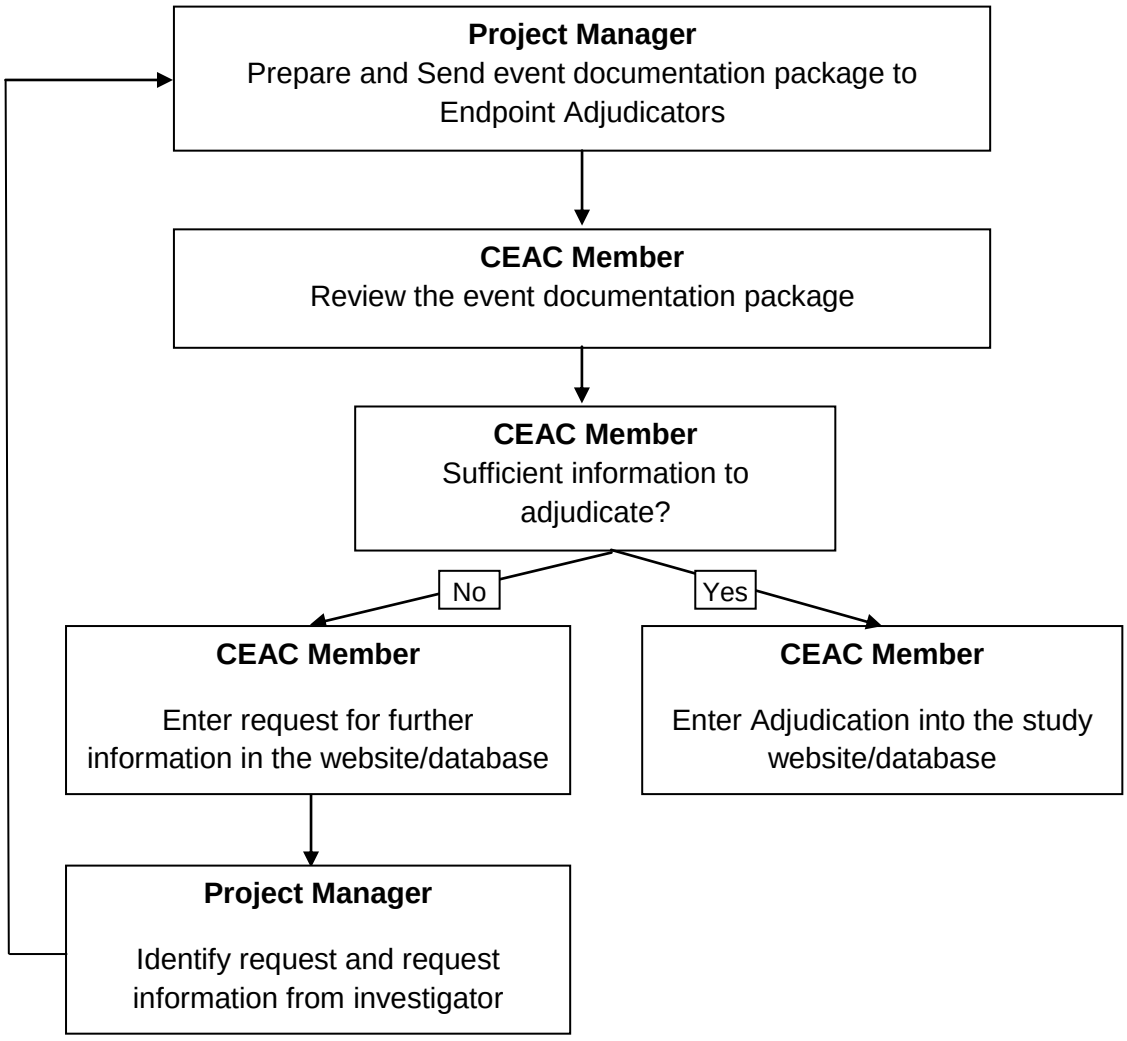
Criteria

Active bleeding that results in a reduction of haemoglobin of at least 20g/l, or requires transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ.

Source of Information

1. Hospital Admission Summary, Hospital Discharge Summary, Clinical Notes, or any other relevant medical records
2. Laboratory report(s)

APPENDIX 4 – Clinical Endpoint Procedures Chart



APPENDIX 5 – Serious Adverse Event Form (Form X)

APPENDIX 6 – IMPACT Protocol

APPENDIX 4 – IMPACT Endpoint Tracking and Adjudication Website User Guide for Adjudicators

Appendix 20 General practitioner survey

IMPACT
Improving Adherence using Combination Therapy

Polypill Acceptability Questionnaire

Participant name	NHI	Trial ID	GP Name

Please answer each question for **this** participant. Tick **one** answer only per question.

		Very Satisfactory	Satisfactory	OK	Unsatisfactory	Not applicable	If not applicable, specify reason
2.02	In terms of starting this participant on the polypill, I found it:	○	○	○	○	○	
2.03	In terms of blood pressure control for this participant, I found polypill-based care:	○	○	○	○	○	
2.04	In terms of cholesterol control for this participant, I found polypill-based care:	○	○	○	○	○	
2.05	How well tolerated was the polypill by this participant?	○	○	○	○	○	
2.06	In terms of prescribing according to the NZ cardiovascular risk management guidelines for this participant, I found polypill-based care:	○	○	○	○	○	

		Lack of flexibility	Increased cost	Increased length of consultation	More adverse effects	No important disadvantage	Other disadvantage	If other disadvantage, please specify
2.07	What was the **most** important disadvantage with the polypill for this participant? *(Tick one only)*	○	○	○	○	○	○	

		Improved medication adherence	Reduced cost	Reduced length of consultation	Fewer adverse effects	No important advantage	Other advantage	If other advantage, please specify
2.09	What was the **most** important advantage with the polypill for this participant? *(Tick one only)*	○	○	○	○	○	○	

2.11	If you had another patient like this, would you start them on the polypill if it was available?	**Yes:** ○	**No:** ○	**If no, specify reason:**		

Completed by: **GP:** ○ **RN visit:** ○ **RN phone call:** ○

Name of person completing form:		Signature of person completing form:		Date:	__ __ / __ __ / 2 0 __

day month year

If you have any questions about this form please contact the IMPACT project manager on 09 9232337 or impact@ctru.auckland.ac.nz

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Appendix 21 End of study participant survey

IMPACT
Improving Adherence using Combination Therapy

ID number

End of Study Participant Survey

You have now completed all the visits for the IMPACT study and we would value your feedback about your experience on the study.

		Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
1.	You felt well informed about the trial before you signed the consent form.	○	○	○	○	○
2.	The "personal manner" of the research nurse was courteous, friendly, helpful, etc.	○	○	○	○	○
3.	The nurse was knowledgeable about the trial and cardiovascular risk management.	○	○	○	○	○
4.	Overall you had a good study experience.	○	○	○	○	○

		Yes	No
5.	Did you know who to contact if you had any concerns about the trial?	○	○
6.	Was the $ amount of vouchers offered adequate for the time involved in the study?	○	○
7.	Have you participated in other medical research studies?	○	○
8.	Would you participate in another medical research study?	○	○

		Phone	Mobile call	Mobile text	Internet	Letter
9.	How would you prefer to be contacted during a study?	○	○	○	○	○

		Personal health benefit	Helping other people and medical research	Wanted to take polypill	Receive extra care from research nurse and GP	Other reason
10.	Why did you decide to take part in the study?	○	○	○	○	○

If you selected "Other reason," please list those reasons below

11.	Were there any things you did or didn't like about being involved in the study? If yes, please specify.

DF01

12.	What could we do in the future to help keep participants involved for the length of the study?

13.	Is there anything else you would like to tell us?

For those on the **polypill** group please answer the following questions.

		Yes	No
14.	Were there any advantages with taking the polypill?	○	○

Tick all that apply	Less pills to take	Cheaper prescription costs	Less side effects to medication	Fewer visits to the GP required	Other advantage
If yes, what were the advantages?	○	○	○	○	○

If you selected "Other advantage," please list below

		Yes	No
15.	Were there any disadvantages with taking the polypill?	○	○

Tick all that apply	More pills to take	More expensive prescription costs	More side effects to medication	Extra visits to GP required	Other disadvantage
If yes, what were the disadvantages?	○	○	○	○	○

If you selected "Other disadvantage," please list below

		Yes	No
16.	Did you have any problems getting the polypill from a pharmacy?	○	○

If yes, what was the problem?

Thank you for taking the time to fill in our survey. Your feed-back is important to us.

Appendix 22 Serious adverse drug reaction report

IMPACT Serious Adverse Drug Reaction (SADR) Report for DRL

☐ Initial report of the event OR ☐ Follow up of a previously reported event

Date form completed:

Co-investigator Name: Site Number:

GP Practice Name:

1. Participant Details

Registration number: Patient Initials:

Patient DOB: Age: Sex: ☐ Male ☐ Female

Height: Weight:

Date of Registration: Date of Randomisation:

2. Serious Adverse Event

2.1 Reported at trial visit:

☐ RAND ☐ 1M ☐ 6M ☐ 12M ☐ End of Study ☐ Other-specify time

2.2 Event diagnosis:

2.3 Onset date of event (approximate date if actual is not known):

2.4 Narrative (if relevant)

2.5 Type of Serious Adverse Event

☐ Death
☐ Hospitalization or prolongation of hospitalisation
☐ Congenital abnormality
☐ Overdose
☐ Life Threatening
☐ Persistent or significant disability
☐ Malignancy
☐ Other Medically Important event

2.6 Severity of Serious Adverse Event

☐ Mild ☐ Moderate ☐ Severe

2.7 Red Heart Pill Information

RHP version allocated at randomisation: ☐ 1c ☐ 2c

RHP start date: or ☐ not started

If applicable:

RHP version changed to: ☐ 1c ☐ 2c Date Changed:

☐ Temporarily discontinued RHP Date stopped:

☐ Permanently discontinued RHP Date stopped:

Dechallenge (withdraw of RHP after a possible ADR) and/or Rechallenge (reintroduction of the same RHP which had been withdrawn due to ADR following +ve dechallenge) information if applicable:

3. Medications

(List all medications that the participant was taking just prior to and during the event including the Red Heart Pill)

3A: Medication used to treat SAE

Name (trade or generic)	Route	Strength / units	Frequency	Start date/ Stop date	Indication

3B: Concomitant medication

Name (trade or generic)	Route	Strength / units	Frequency	Start date/ Stop date	Indication

4. Hospitalisation (Complete if applicable)

Date of Admission: Date of Discharge:

List of Events while hospitalised / Date of Events:

List of Procedures while hospitalised / Date of Procedures:

5. Outcome of Serious Adverse Event

☐ Ongoing

☐ Resolved
Resolved date:

☐ Resolved with sequelae
Resolved date:
Sequelae:

☐ Death
Date of Death:

6. Death (Complete if applicable)

Immediate Cause of Death:

Underlying Cause of Death:

Autopsy performed: ☐ Yes ☐ No Date of Autopsy:

7. Participant history / Concurrent diseases

8. Details of laboratory results / investigations conducted and results

9. Follow-up information (complete when available)

10. List supporting documents attached e.g. autopsy report

11. IMPACT Principal Investigator / Research Fellow

11.1 Relationship to Red Heart Pill (As reported by co-investigator)

☐ Not related ☐ Unlikely
☐ Possibly Related* ☐ Probably Related*
☐ Definitely Related* ☐ Not Applicable
*If possibly, probably or definitely related please justify relationship of SAE to the Red Heart Pill

11.2 Expectedness of Serious Adverse Drug Reaction to Red Heart Pill (As reported by co-investigator)

☐ Expected ☐ Unexpected ☐ Not applicable

11.3 Cardiovascular Clinical Endpoint

Is this event a Cardiovascular Clinical Endpoint ☐ Yes ☐ No

11.4 Principal Investigator /Research Fellow

PI/RF thinks this event is a:
☐ SAE only (adverse event is not related to the study drug).
☐ SADR (adverse event is at least possibly related to the RHP)
☐ SUSAR (serious adverse event is at least possibly related and is unexpected i.e. not listed in the Investigator Brochure)

Other comments:

Principal Investigator /Research Fellow Name:

Principal Investigator /Research Fellow Signature: Date:

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