A fixed dose triple combination therapy of acetylsalicylic acid, atorvastatin and Ramipril for the prevention of recurrent events in people with prior cardiovascular disease.

Application for inclusion in the WHO Model List of Essential Medicines

General Items

1. Summary statement of the proposal for inclusion

Cardiovascular disease (CVD) is the leading cause of death worldwide, yet CVD risk factor control and secondary prevention rates remain low. A fixed-dose combination of blood pressure and cholesterol lowering and antiplatelet treatments into a single pill, or polypill, has been proposed as one strategy to reduce the global burden of ASCVD given its potential for better adherence, lower costs and improved operational logistics especially in health systems in low-resource settings.

Core cardiovascular disease medications such as aspirin, statins, and blood pressure-lowering drugs including ACE inhibitors have been included in the World Health Organization (WHO) Essential Medicines List (EML) for many years. The first year of listing for aspirin was 1990, for an ACE inhibitor was 2003 and for a statin, 2007. This application seeks to add a fixed-dose combinations (FDCs) of these three types of medication—“a polypill”—to the EML for the prevention of recurrent events in individuals with prior heart disease or stroke.

There is consensus among international guidelines that patients who have had a heart attack or ischemic stroke (an atherothrombotic event) should take an antiplatelet agent, statin, and blood pressure lowering drugs long-term to reduce the risk of a recurrent non-fatal or fatal CVD event. A high proportion of CVD deaths occur in people who already had an event and can be reduced with good pharmacological therapy and lifestyle management.

WHO aims to reduce the premature mortality from non-communicable diseases (NCDs), including CVD, by 25% by 2025 and to meet the SDG targets for a 30% reduction in premature NCD deaths by 2030. Furthermore, one of the nine voluntary targets in the Global Action Plan for the Prevention and Control of NCDs is that at least 50% of people at high risk of CVD (including those who have had a prior event) receive multidrug therapy and counselling to prevent heart attacks and strokes.

One key strategy to achieve this goal will be to increase the proportion of people with established atherosclerotic CVD who receive an antiplatelet agent, statin, and blood pressure lowering drugs as recommended by WHO guidelines and all other major guidelines. More than 80% of premature deaths from cardiovascular diseases occur in low-
and middle-income countries. However, less than 20% patients with prior disease take all recommended medication classes for CVD secondary prevention and control in these regions. Current estimates suggest that up to 32 million people worldwide are without access to three-drug secondary prevention therapy and that the majority are in LMICs as shown in Figure 1. (G. Roth, GBD, Unpublished data). Unless treatment rates are increased substantially, the goals and targets will be out of reach.

Widespread use of Fixed dose combination (FDC) therapy (two or more actives which are already indicated for use in a fixed ratio of doses) is one strategy with the potential to substantially increase to the use of recommended medications in people who have had a CVD event. FDCs are available and are used in many countries. Research into the use of FDC therapy for CVD secondary prevention has been advocated by the WHO since 2001 given the potential advantages of scalability, affordability and adherence.

Evidence from 3080 patients with a prior CVD event in four randomised controlled trials conducted in a range of settings across Australasia, Europe, India and South America has demonstrated that, when compared with usual care or separate components, FDC therapy improves adherence and risk factor control, is acceptable to both patients and physicians, does not appear to have any harms beyond what would be expected for the component medications and is likely to be cost-effective, even in a high income country. Furthermore, there is a strong public health evidence base, supporting the use of FDCs in healthcare systems in low-resource settings given the operational advantages in their use for improving costs, supply logistics, patient and provider use.

This application makes the case for including in the WHO EML, a FDC for people with atherothrombotic CVD that contains:

a. Aspirin 100mg

b. Atorvastatin 20mg

c. Ramipril 2.5mg
2. **Name of the focal point in WHO submitting the application**
Dr. Oyere Onuma, Medical Officer, Cardiovascular Disease, Management of Noncommunicable Diseases Unit, WHO HQ, Geneva.

3. **Name of the organization(s) consulted and/or supporting the application**
World Heart Federation
The George Institute, Sydney, Australia
London School of Hygiene and Tropical Medicine, London, UK
Northwestern University School of Medicine, Chicago, USA
Mount Sinai School of Medicine, New York, USA

4. **International Nonproprietary Name (INN, generic name) of the medicine and Anatomical Therapeutic Chemical (ATC) code of the medicine.**
   a) Acetylsalicylic acid (non-INN. The WHO establishes that aspirin does not have INN because this name was already in wide use when the INN system began, and it was a well-established name).
   b) Atorvastatin
   c) Ramipril

5. **Formulation proposed for inclusion**
We propose the following formulation:
Aspirin 100 mg + atorvastatin 20 or 40 mg + ramipril 2.5, 5 or 10 mg as a fixed-dose combination.

6. **Whether listing is requested as an individual medicine or as an example of a therapeutic group**
We propose listing under the “square box” substitutable category. Trinomia (atorvastatin version) is an example of the class of product. Therapeutic alternatives would be limited to combinations with:
- aspirin 75-100mg +
- atorvastatin 20mg or simvastatin 40mg +
- ramipril 2.5mg or enalapril 5mg or lisinopril 10mg or other dose-equivalent ACE inhibitor ([http://www.globalrph.com/aceinh.cgi](http://www.globalrph.com/aceinh.cgi))

Minimum effective dosages for statin and ACE inhibitor have been listed but higher dosages may be required to achieve optimal LDL- and BP-lowering. Ideally additional combinations would be available with higher dosages of both of these components. Alternatively, additional (separate) statin and ACE inhibitor may be required.
Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

WHO recommends that all people who have had a CVD event should be treated with blood pressure-lowering therapy, statins and aspirin, as well being offered lifestyle advice (Appendix 1). These medications are also recommended for all people with a history of CVD in guidelines from Europe, the US and Australasian. These medications are typically to be used lifelong to prevent recurrence of CVD events.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population, likely impact of treatment on the disease)

8.1 Burden

CVD is the major cause of global mortality, morbidity worldwide. An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths and 37% of premature deaths resulting from all NCDs. Of these deaths, ischaemic heart disease was the most common and stroke the second most common cause of death in 2012 and this ranking is projected to remain the same in 2030.

More than 80% of CVD deaths in 2012 occurred in low and middle income countries (LMICs). CVD occurs earlier in life in LMICs than in high income countries, exacerbating the social and economic impact of CVD in these countries. Further, because of their lower incomes, these countries and their health care systems are less well equipped to deal with this burden than high income countries. CVD events and deaths are more common among people who have already had a prior CVD event than those who have not had such an event.

8.2 Recommended management

WHO recommends that all people who have had a CVD event should be treated with blood pressure-lowering therapy, statins and aspirin, as well being offered lifestyle advice (Appendix 1). The guidelines in Europe, the US and Australasian guidelines also make similar recommendations for all people with a history of CVD.

8.3 Treatment gaps

Despite clear international guideline recommendations that people with a history of CVD recommendations should receive aspirin, statin and blood pressure-lowering therapy, the use of these medications is low internationally, particularly in lower income countries. The Prospective Urban Rural Epidemiology (PURE) study surveyed people with a history of
coronary heart disease or stroke from 2003 to 2009 regarding their use of aspirin, statin, ACE inhibitor (or angiotensin-receptor blocker, ARB) and another blood pressure lowering drug (Figure 2). 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 (i.e. antiplatelet drugs, β blockers, ACE inhibitors or ARBs, and statins) recommended preventive medications. In low-income countries, 80% of patients with a prior CVD event reporting taking no cardiovascular preventive medications, compared with 69% in lower middle-income countries, 45.1% in upper middle-income countries and 11% in high-income countries.

Figure 2: Number of cardiovascular preventive medications taken by individuals who had had a cardiovascular event, by country economic status

For coronary heart disease, medications counted were: aspirin; beta blockers; angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; or statins. For stroke, medications counted were: aspirin; angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; other blood pressure-lowering drugs; or statins.

Source: PURE study

8.4 Addressing treatment gaps

The World Health Organization’s 2013 Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs) includes nine voluntary global targets. Because of the large treatment gaps for people with a history of CVD, one of these targets is that at least 50% of people at high risk of CVD (including those who have had a prior event) receive multidrug therapy and counselling to prevent heart attacks and strokes. Another of the nine targets is that there is an 80% availability of the affordable basic technologies and essential medicines required to treat major NCDs. FDC therapy is an intervention that has the potential to substantially enhance access to multidrug therapy by making recommended medicines more accessible.

The recently launched WHO/CDC HEARTS technical package clearly places the cardiovascular FDC /polypill as one of the key innovations for scaling up CVD management in primary healthcare (PHC) settings in LMICs. Given the need to rapidly scale-up care in many countries to address treatment gaps, the cardiovascular FDC allows for the
simplification of treatment, improved logistics for drug supply and improved prescribing and dispensing by non-physician health workers in the PHC. There are efforts underway to update the WHO clinical algorithms by 2018 to reflect the use of the polypill in high risk individuals for secondary prevention of recurrent events or high-risk primary prevention (when CVD risk is > 30%).

8.5 Fixed dose combination therapy

8.5.1 Origin
The use of FDC therapy in the secondary prevention of CVD appears to have been first proposed in 2001 during a WHO meeting to discuss strategies for the secondary prevention of non-communicable diseases. One of ten recommendations arising from that meeting was the development of a daily FDC containing aspirin, statin and two blood pressure lowering agents, for people who have had a prior CVD event, to address suboptimal implementation of guidelines and poor patient adherence. The idea of using FDC therapy for all CVD, along with the term ‘polypill’, was then popularised by Wald and Law in 2003 with the publication of their paper “A strategy to reduce cardiovascular disease by more than 80%” in the British Medical Journal. Wald and Law proposed providing FDC therapy to everyone above a certain age (e.g. 55 years), rather than a targeted approach as is currently proposed.

8.5.2 Development
While the idea of combining several drugs into a single pill or capsule seems simple, there are a number of important challenges to the development of FDCs. First, a decision must be made about the specific medications and dosages to be included. Factors that influence this decision include: target population, effectiveness and safety of each medication, whether any medications are currently under patent and whether all medications can be given once daily. Second, a pharmaceutical formulation of the combination medications that is bioequivalent to its constituent components with adequate stability and shelf-life must be developed. This is a particular challenge because of physicochemical interactions between drugs, a problem that increases with the number of components in the combination.

8.5.3 Regulatory requirements
In order to obtain regulatory approval for FDC therapy and depending on specific requirements by country, complex pharmacodynamics and pharmacokinetic testing is required to demonstrate bioequivalence of the combination to its constituent components, and the product must undergo testing for stability and safety. In addition, demonstration of improvement in adherence and risk factor control is required for registration of FDC therapy for use in people who have had a CVD event. Demonstration of an effect of FDC therapy on outcomes is not a requirement for regulatory approval among people who have had a CVD event because of the strength of the evidence and consistency in international guideline recommendations supporting the use of the component medications in this group of patients.
8.5.4 Availability and use
Currently four CVD FDCs are available internationally (Appendix 2). Polycap (Cadila), Ramitorva (Cadila) and Starpill (Cipla) are available in India, and Polycap is also available in Zambia. Trinomia is available in eight countries in Latin America (including Mexico, Argentina, Chile, Guatemala, Nicaragua, Honduras, Dominican Republic, Salvador) and ten countries in Europe (Spain, Germany, Italy, Belgium, Ireland, Greece, Bulgaria, Serbia, Romania and Portugal). It has additionally received regulatory approval in five more countries including France, Poland, Czech Republic, Finland and Sweden. Trinomia registration is additionally on going in more than 30 countries worldwide where commercialization is expected between 2017 and 2018. All four FDCs contain aspirin, either simvastatin or atorvastatin, and an ACE inhibitor (Ramipril) or angiotensin receptor blocker (losartan). Two of the FDCs also contain a beta blocker (atenolol).

To date, neither the Food and Drug Administration nor the European Medicines Agency has approved FDC therapy for CVD, although the FDA has recently met to consider its use in people who have had a CVD event.\(^{27}\) There is limited data on the current use of or sales of FDC therapy, however, as noted by one author “despite being approved and available in more than 20 countries, widespread penetration of the polypill has not been reported”.\(^{27}\)

8.5.5 Potential advantages and disadvantages
A number of potential advantages and disadvantages to FDC therapy are listed in Table 1 along with the evidence for these advantages or disadvantages among people with a history of CVD.

Table 1. Potential advantages and disadvantages of fixed dose combination therapy for the management of cardiovascular risk

<table>
<thead>
<tr>
<th>Potential advantages</th>
<th>Potential disadvantages(^{28})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplification in clinical management</td>
<td>Lack of choice of components and doses</td>
</tr>
<tr>
<td>Advantage in settings with limited number of experts</td>
<td>Uncertainty regarding cause of side effects</td>
</tr>
<tr>
<td>Scalability and coverage</td>
<td>Additional treatment may be needed to achieve treatment targets in people with high levels of individual risk factors</td>
</tr>
<tr>
<td>Affordability</td>
<td>Deterioration of lifestyle behaviours if perceived as a panacea</td>
</tr>
<tr>
<td>Ease of use for patients and prescribers</td>
<td></td>
</tr>
<tr>
<td>Improved adherence</td>
<td></td>
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<tr>
<td>Improved logistics for procurement, delivery and supply</td>
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<tr>
<td>Lower total cost of production, storage, transport, dispensing and other health system costs.</td>
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</tr>
</tbody>
</table>

8.5.5.1 Scalability
Traditionally CVD treatment has been based on the careful selection of suitable patients, the prescription of a single drug at a time, frequent dose titration and physician visits.\(^{29}\) This approach, while ideal in high income settings, is not feasible in many resource limited settings at the scale needed to meet WHO’s voluntary global target that at least 50% of people who have had a prior CVD event receive multidrug therapy, particularly in LMICs.\(^{19}\)
Simplified approaches to CVD management, which have demonstrated improvements in access to medications and outcomes are required to meet this target. An intervention using a bundle consisting of fixed doses of generic statins and ACEIs with simplified delivery showed reduced MI and stroke hospitalization rates among high risk patients. The simplified regimen allows for the training of non-physician healthcare workers to deliver the medication and lifestyle advice to patients who have had a CVD event, with physician referral reserved for those with side effects, new symptoms or when alternative drugs or a dose escalation to achieve adequate risk factor control is required.

This strategy, including the use of FDCs/combination ART has been used successfully in the scale-up of HIV treatment in many LMICs as part of a public health approach to deliver simplified treatment using non-physician health workers. The use of FDCs in ART scale-up research on this approach has shown reduced drug resistance and improved adherence to therapy using this strategy in ART delivery, as well as improved patient and provider preference. The potential for operational benefits with treatment simplification, increased security of supply systems and lower drug supply costs as well as reducing the risk of medication errors by prescribers, dispensers or patients themselves is also a key benefit of FDCs. Availability of fixed dose combination therapy is widely acknowledged as a key component in the successful scale up of HIV treatment globally and has also been used the first-line in TB and malaria treatments globally.

It is clear that FDCs for CVD can play a similarly central role in the delivery and scale-up of chronic non-communicable disease care for CVD as they have in the use of FDCs/combination ART in chronic communicable diseases such as HIV. The similarities lie in the chronic care model and the clear advantages of early detection and appropriate treatment. Monitoring of therapy with CVD FDCs is less complicated as there is no need for testing for CD4 counts and viral loads, weight-based dosing, and no concerns regarding viral drug resistance. In resource-limited settings, the operational arguments for a cardiovascular FDC including reduced costs, supply logistics, treatment simplification for providers and patients are stronger. The significant public health implications of the use of FDCs/polypill in scaling up care is the reason for its identification as a central recommendations in the WHO HEARTS technical package for CVD management in primary healthcare.

One analysis estimated the number of CVD deaths that would be averted using FDC therapy to scale up the use of cardiovascular preventive medications above coverage levels among people with a prior CVD event or at high risk of their first event (10-year CVD risk ≥15%) in the 23 low and middle-income countries that accounted for 80% of global chronic diseases deaths. The analysis found that over a 10-year period 17.9 million deaths from CVD would be averted (95% CI 7.4 to 25.7 million) of which 56% would be in people under 70 years of age. The estimated total cost of this programme (including medication, health service delivery, laboratory testing and running the programme) was US$47 billion (US$33 to $61 billion) over 10 years (US$55 per treated individual per year or US$1.08 per population per year).

8.5.5.2 Affordability
FDC therapy is less expensive than equivalent treatment with individual medications through the use of generic components, reduction in packaging, distribution and marketing
costs, and a reduction in physician visits and laboratory tests. Reduced cost would make FDC therapy very attractive to low-income countries, where the burden of CVD is increasing and current access to many (patented) cardiovascular medications is limited due to their cost and access to physicians is limited.

The incremental cost-effectiveness ratios (ICERs) of FDC therapy (aspirin, two blood pressure-lowering agents and statin) in six low- and middle-income World Bank regions were estimated to range from US$306 to $388 per QALY gained for people with a prior CVD event. These ICERs were well below WHO cost-effectiveness ratio thresholds (<3 times the gross national income per head) for each of the six regions assessed.

The price of Trinomia has been and will continue to be implemented on a per country basis. The objective of Trinomia is to be cost-effective and therefore depending on the specific country environment, different prices would be adopted. Depending on the dose of ramipril and on the country where the product is already available, Trinomia retail market prices are at present in the range of 13 – 24€ per month (USD $13.8 – $25.5 per month, or USD $0.5 to $1 per day) which represents 30-50% of the LSP of 3 generics acquired separately (€25-50/month or $32-$65/month). In the present market conditions, in Guatemala, Nicaragua, Dominican Republic, Honduras, El Salvador, the market price of the fixed-dose combination of aspirin + simvastatin + ramipril (trade name: Trinomia) is below the sum of the three corresponding generics in those markets.

8.5.5.3 Adherence
Even if cardiovascular preventive medications are prescribed and dispensed, their preventive potential is dependent on an individual’s adherence to them. 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”. A 2003 WHO report estimated that less than 50% of those prescribed long-term medications for chronic conditions take their medications regularly. Similarly low rates of adherence (less than 40%) have been reported among people taking cardiovascular preventive medications. Non-adherence to cardiovascular preventive medications has been associated with increased vascular events, mortality, hospitalisations and costs. Two of four key potentially modifiable barriers to patient adherence identified by a systematic review were cost and regimen complexity, both of which could be improved by FDC therapy. A key recommendation of a 2001 WHO meeting was that FDC therapy should be developed and evaluated to address suboptimal implementation of guidelines and poor patient adherence among people with a prior CVD event.
9. Review of benefits: Summary of comparative effectiveness in a variety of clinical settings:

9.1 Identification of clinical evidence
Two main types of randomised controlled trials (RCTs) have assessed the effectiveness of FDC therapy: (1) those that have compared FDC therapy with an inactive control, in people without indications for any of the components of FDC therapy, and (2) those that have compared FDC therapy with an active control, in people with indications for all of the components of FDC therapy. We summarize the trials using an inactive control briefly with published meta-analyses, and trials comparing with an active control are described in more detail.

9.2.1 Meta-analyses of FDC therapy vs inactive control in people without indications

9.2.1 Elley et al
A 2012 meta-analysis by Elley and colleagues included RCTs of a FDC containing at least one statin and one blood pressure-lowering agent compared with a placebo (or one active component) for at least six weeks.41 Six trials (with a combined total of 2,218 participants) were identified: The Indian Polycap Study (TIPS),42 Neutel 2009,43 Malekzadeh 2010,44 Grimm 2010,45 Programme to Improve Life and Longevity (PILL) Collaborative Group 201146 and Wald 201247.

FDC therapy was associated with a reduction in 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) compared with the control group (an inactive control).41 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.41 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).41,48

The reviewers noted that while the reductions in risk factors observed in their meta-analysis were lower than predicted by Wald and Law (who estimated that a cardiovascular ‘polypill’ would reduce blood pressure by 20/11 mm Hg and low density lipoprotein cholesterol by 1.8 mmol/L22), actual reductions in risk factors depend on baseline risk factor levels and the number and doses of medications contained within each combination.41 They compared observed risk factor reductions with their own estimates that took into account components and baseline risk factor levels (see Appendix 1). This analysis found that observed risk factor reductions were in fact similar to those expected for some trials, and where reductions were less than expected plausible explanations were identified (degree of loss to follow-up, participant adherence and use of concomitant blood pressure and lipid lowering medication).41
9.2.2: Meta-analyses of FDC therapy vs active control in people with indications

Webster et al, results from a prospective, individual patient data meta-analysis of 3140 patients in six countries (SPACE) (Appendix 3). The latest metaanalysis published 2015 included individual patient data from three trials comparing polypill-based care with usual care in individuals with CVD or high calculated cardiovascular risk contributed IPD. Primary outcomes were self-reported adherence to combination therapy (anti-platelet, statin and ≥ two blood pressure (BP) lowering agents), and difference in mean systolic BP (SBP) and LDL-cholesterol at 12 months. Analyses used random effects models. Among 3140 patients from Australia, England, India, Ireland, New Zealand and The Netherlands (75% male, mean age 62 years), median follow-up was 15 months. At baseline, 84%, 87% and 61% respectively were taking a statin, anti-platelet agent and at least two BP lowering agents. At 12 months, compared to usual care, participants in the polypill arm had higher adherence to combination therapy (80% vs. 50%, RR 1.58; 95% CI, 1.32 to 1.90; p b 0.001), lower SBP (−2.5 mmHg; 95% CI, −4.5 to −0.4; p = 0.02) and lower LDL-cholesterol (−0.1 mmol/L; 95% CI, −0.2 to 0.0; p = 0.04). Baseline treatment levels were a major effect modifier for adherence and SBP (p-homog < 0.0001 and 0.02 respectively) with greatest improvements seen among those under-treated at baseline. The meta-analysis concluded that a the use of a polypill therapy significantly improved adherence, SBP and LDL-cholesterol in high risk patients compared with usual care, especially among those who were under-treated at baseline (Figure 3).

Figure 3. Primary outcomes in SPACE Metanalysis (Webster et al): Mean difference in adherence, SBP and LDLc in polypill vs usual care.
9.3 Trials of FDC therapy vs active control in people with indications

Trials were identified by searches of clinicaltrials.gov and Medline on 25 August 2015. Five trials were identified (see Table 2), including one limited to participants with a prior CVD event (FOCUS50), one limited to participants at high risk of their first CVD event (Soliman51) and three trials that included both types of participants (UMPIRE52, Kanyini-GAP53 and IMPACT54).
Table 2. Key features of randomised controlled trials including patients at high risk of their first CVD event that have compared a cardiovascular FDC with active control

<table>
<thead>
<tr>
<th>Trial</th>
<th>Location</th>
<th>Setting</th>
<th>Main inclusion criteria</th>
<th>FDC components</th>
<th>Control</th>
<th>N</th>
<th>Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliman 2011</td>
<td>Sri Lanka</td>
<td>Secondary care</td>
<td>10-year CVD risk 20%*, no prior CVD event</td>
<td>Aspirin 75mg + Simvastatin 20mg + Lisinopril 10mg + HCTZ 12.5mg</td>
<td>Usual care</td>
<td>0</td>
<td>216</td>
</tr>
<tr>
<td>UMPIRE 2013</td>
<td>Europe, India</td>
<td>Mainly secondary care</td>
<td>Prior CVD event OR High risk of first CVD event (5-year CVD risk &gt;15%)</td>
<td>Aspirin 75mg + Simvastatin 40mg + Lisinopril 10mg + (HCTZ 12.5mg or Atenolol 50mg)</td>
<td>Usual care</td>
<td>1771 (88%)</td>
<td>233</td>
</tr>
<tr>
<td>Kanyini-GAP 2014</td>
<td>Australia</td>
<td>Primary care</td>
<td>Prior CVD event (5-year CVD risk &gt;15%)</td>
<td>Aspirin 75mg + Simvastatin 40mg + Lisinopril 10mg + (HCTZ 12.5mg or Atenolol 50mg)</td>
<td>Usual care</td>
<td>381 (61%)</td>
<td>242</td>
</tr>
<tr>
<td>IMPACT 2014</td>
<td>New Zealand</td>
<td>Primary care</td>
<td>Prior CVD event (MI)</td>
<td>Aspirin 100mg + Simvastatin 40mg + Ramipril (2.5, 5 or 10mg)</td>
<td>Separate FDC components</td>
<td>695 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>FOCUS 2014</td>
<td>Europe, South America</td>
<td>Secondary care</td>
<td>Prior CVD event (MI)</td>
<td>Aspirin 100mg + Simvastatin 40mg + Ramipril (2.5, 5 or 10mg)</td>
<td>Separate FDC components</td>
<td>695 (100%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3080 (76%)</td>
<td>971</td>
</tr>
</tbody>
</table>

CVD=cardiovascular disease; FDC=fixed dose combination; FOCUS=Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention; HCTZ=hydrochlorothiazide; IMPACT=IMProving Adherence using Combination Therapy; Kanyini GAP=Kanyini Guidelines Adherence to the Polypill; MI=myocardial infarction; 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.56

Over three quarters (76%) of participants across all five trials had a prior CVD event. The individual trials are described in Appendix 4. The findings on effectiveness are summarised below, and are restricted to the 3080 participants with a prior CVD event.

9.3.1 Adherence

9.3.1.1 Adherence measured by questionnaire and pill count

FOCUS defined ‘good adherence’ as a score of 20 out of 20 on the Morisky-Green questionnaire as well as a pill count of 80-110%.50 After nine months a greater proportion of FDC therapy (178/350, 51%) than control (141/345, 41%) participants were classified as having good adherence (p=0.02).50
9.3.1.2 Adherence measured by self-report
FDC therapy was associated with a statistically significant improvement in the self-reported use of recommended cardiovascular preventive medications among participants with a history of CVD at baseline in UMPIRE\textsuperscript{52}, Kanyini GAP\textsuperscript{53} and IMPACT\textsuperscript{54} (Table 3). The magnitude of the relative improvement ranged from 26% to 50% and the absolute improvement in use of recommended medications was 19% in UMPIRE\textsuperscript{52} and 27% in IMPACT\textsuperscript{54}.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of follow-up, median</th>
<th>N</th>
<th>Self-reported use of recommended(^*) medications at end of trial, n/N (%)</th>
<th>Risk ratio (95% CI)</th>
<th>Absolute improvement in adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMPIRE 2013\textsuperscript{52}</td>
<td>15 months</td>
<td>1771</td>
<td>743/850 (87%)</td>
<td>1.29 (1.22 to 1.36)</td>
<td>19%</td>
</tr>
<tr>
<td>Kanyini GAP 2014\textsuperscript{53}</td>
<td>18 months</td>
<td>381</td>
<td>Not reported</td>
<td>1.26 (1.08 to 1.48)</td>
<td>Not reported</td>
</tr>
<tr>
<td>IMPACT 2014\textsuperscript{54}</td>
<td>23 months(^\dagger)</td>
<td>233</td>
<td>94/116 (81%)</td>
<td>1.50 (1.25 to 1.82)</td>
<td>27%</td>
</tr>
</tbody>
</table>

CI=confidence interval; EOT=end of trial; FDC=fixed dose combination; IMPACT=IMProving Adherence using Combination Therapy; 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.
\(^\dagger\)Results in this table are at 12 months
Statistically significant results in bold

9.3.2 Systolic blood pressure
End of trial mean systolic blood pressure was statistically significantly lower in FDC therapy compared with usual care participants with a history of CVD in UMPIRE (Table 4). There were no statistically significant differences between FDC therapy and control groups among participants with a history of CVD in the control of systolic BP in the other three trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of follow-up, months</th>
<th>N</th>
<th>Mean systolic BP at EOT except where otherwise specified, mm Hg (SE or 95% CI)</th>
<th>Difference (95% CI or p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMPIRE 2013\textsuperscript{52}</td>
<td>15 (median)</td>
<td>1771</td>
<td>128.6 (0.6)</td>
<td>-2.7 (-4.2 to -1.1)</td>
</tr>
<tr>
<td>Kanyini GAP 2014\textsuperscript{53}</td>
<td>18 (median)</td>
<td>381</td>
<td>Not reported</td>
<td>-2.9 (-6.1 to 0.3)</td>
</tr>
<tr>
<td>IMPACT 2014\textsuperscript{54}</td>
<td>23 (median)</td>
<td>233</td>
<td>Not reported</td>
<td>-3.7 (-8.9 to 1.3)(^*)</td>
</tr>
<tr>
<td>FOCUS 2014\textsuperscript{50}</td>
<td>9 (median)</td>
<td>695</td>
<td>-0.32 (-2.02 to 1.38)(^\dagger)</td>
<td>-1.2 (-0.76 to 2.53)(^\dagger)</td>
</tr>
</tbody>
</table>

Total 3080

CI=confidence interval; EOT=end of trial; FDC=fixed dose combination; FOCUS=Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention; IMPACT=IMProving Adherence using Combination Therapy; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; SBP=systolic blood pressure; SE=standard error; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events

\(^*\)Statistically significant results
\(^\dagger\)Results in this table are at 12 months

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9.3.3 Cholesterol

End of trial mean low density lipoprotein cholesterol was statistically significantly lower in FDC therapy compared with usual care participants in UMPIRE with a history of CVD (Table 5). There were no statistically significant differences between FDC therapy and control groups in the control of cholesterol in the other three trials among participants with a history of CVD.

Table 5. FDC therapy compared with control among patients who have had a CVD event – effect on cholesterol in trials completed to date

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of follow-up, months</th>
<th>N</th>
<th>Cholesterol fraction reported</th>
<th>Mean cholesterol, mmol/L, at end of trial, except where otherwise specified, (SE)</th>
<th>Difference, mmol/L (95% CI or p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMPIRE 2013</td>
<td>15 (median)</td>
<td>1771</td>
<td>LDL</td>
<td>2.19 (0.02)</td>
<td>-0.10 (-0.17 to -0.04)</td>
</tr>
<tr>
<td>Kanyini GAP</td>
<td>18 (median)</td>
<td>381</td>
<td>Total</td>
<td>Not reported</td>
<td>0.12 (-0.05 to 0.30)</td>
</tr>
<tr>
<td>IMPACT 2014</td>
<td>23 (median)</td>
<td>233</td>
<td>LDL</td>
<td>Not reported</td>
<td>-0.03 (-0.19 to 0.12)</td>
</tr>
<tr>
<td>FOCUS 2014</td>
<td>9</td>
<td>695</td>
<td>LDL</td>
<td>0.14 (-0.01 to 0.28)†</td>
<td>0.06 (-0.02 to 0.14)‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08 (p=0.34)§</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3080</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval; EOT=end of trial; FDC=fixed dose combination; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; LDL=low density lipoprotein; SE=standard error; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events

*Difference in mean change in LDL cholesterol between baseline and 12 months
†Unpublished, obtained from study investigator
‡Mean change in LDL cholesterol between baseline and 9 months
¶Difference between groups in mean change in LDL cholesterol between baseline and 9 months
Statistically significant results in bold

9.3.4 Cardiovascular events

IMPACT, Kanyini-GAP and UMPIRE found no statistically significant difference between FDC therapy and usual care groups in the proportion of patients experiencing a cardiovascular event (fatal or nonfatal) during the trial (see Table 10). Trial results were not available according to baseline history of a CVD event and therefore these results are for all 3140 participants across all three of these trials. None of these trials was powered to assess the effect of FDC therapy compared with usual care on cardiovascular events. This outcome was not reported for FOCUS.\(^\text{50}\)
Table 6. FDC therapy compared with usual care among patients who have had a CVD event or who are at high risk of their first event – effect on in-trial cardiovascular events in trials completed to date

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of follow-up, median</th>
<th>N</th>
<th>Patients experiencing a cardiovascular event (fatal or nonfatal) during the trial, n/N (%)</th>
<th>Risk ratio (95% CI) or p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>FDC therapy</td>
<td>Usual care</td>
</tr>
<tr>
<td>UMPIRE 2013</td>
<td>15 months</td>
<td>2,004</td>
<td>50/1002 (5%)</td>
<td>35/1002 (3%)</td>
</tr>
<tr>
<td>Kanyini GAP 2014</td>
<td>18 months</td>
<td>623</td>
<td>26/311 (8%)</td>
<td>22/312 (7%)</td>
</tr>
<tr>
<td>IMPACT 2014</td>
<td>23 months†</td>
<td>513</td>
<td>16/257 (6%)</td>
<td>18/256 (7%)</td>
</tr>
</tbody>
</table>

CI = confidence interval; EOT = end of trial; FDC = fixed dose combination; IMPACT = IMProving Adherence using Comnbination Therapy; 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.
† Results in this table are at 12 months
Statistically significant results in bold

9.3.5 Acceptability
Information on FDC therapy acceptability by patients and physicians was collected by Soliman (people at high risk of their first CVD event), Kanyini-GAP and IMPACT. Participant data on FDC therapy acceptability were not reported separately according to history of CVD event for Kanyini-GAP or IMPACT (both of which were conducted in people with a history of CVD or at high risk of their first event).

A study by Laba et al assessing the influence of polypill-based treatment attributes and patient characteristics on preferences for CVD preventive treatment showed that treatment preference decreased with tablet number. The discrete choice experiment further demonstrated that patients value and are willing to pay a premium for each tablet reduction.

9.3.5.1 Patients
Approximately 90% of participants (93% of usual care and 86% of FDC therapy participants) in the Soliman trial reported that they would ‘definitely’ or ‘probably’ take a polypill for life if it were shown to be effective in reducing CVD risk.

In IMPACT, participants in both treatment arms were asked to rate their ease of taking all of their prescribed medications (including FDC therapy for those thus randomised) on a five-point Likert scale after 12 months. A response of ‘very easy’ or ‘easy’ was reported by 88% (224/256) of FDC therapy and 82% (212/257) of usual care participants. The overall p value for the comparison between treatment arms across all five categories was 0.06.

Kanyini-GAP undertook in-depth, semi-structured interviews with a purposive sample of 47 trial participants on polypill strategy acceptability, factors affecting adherence and trial implementation. Of these 47 participants,
- 22 were in the FDC therapy arm and 25 were in usual care arms,
- 21 were at high risk of their first CVD event (primary prevention) and 26 had already had a CVD event (secondary prevention), and
• 28 were nonindigenous and 19 were indigenous.

FDC therapy was found to be generally acceptable to patients.\(^5\)\(^7\) FDC therapy participants commented frequently on cost-savings, ease, and convenience of a daily-dosing pill.\(^5\)\(^7\) Indigenous patients considered FDC therapy to be acceptable and beneficial for indigenous patients given their high disease burden.\(^5\)\(^7\)

9.3.5.2 Physicians and other health care providers

A total of 86 physicians participating in the Soliman trial, along with the Council of General Practitioners in Sri Lanka, were asked whether they would prescribe FDC therapy for their patients if cardiovascular benefit was ‘documented in a large clinical trial’.\(^5\)\(^1\) 58 physicians (69%) responded, of whom 23 were internists, 22 were general practitioners and 2 were classified as ‘other’.\(^5\)\(^1\) For people with a prior CVD event (secondary prevention), 93% (54/58) agreed (responses ‘Yes, definitely’ or ‘Yes, maybe’), and for people without a prior CVD event (primary prevention), 86% (50/58) agreed.\(^5\)\(^1\) Investigators reported that responses ‘did not vary by speciality’.\(^5\)\(^1\)

IMPACT invited the general practitioner of each of the 256 participants randomised to FDC therapy to complete a post-trial survey on the acceptability of FDC therapy.\(^5\)\(^4\) General practitioners with more than one participant randomised to FDC therapy complete a separate survey for each participant.\(^5\)\(^4\) Overall, 89% (227/256) of participants’ general practitioners responded. Most participants’ general practitioners considered that FDC therapy was very satisfactory or satisfactory for: starting treatment (206/227, 91%), blood pressure control (180/220, 82%), cholesterol control (170/218, 78%), tolerability (181/223, 81%) and prescribing according to local guidelines (185/219, 84%). FDC therapy participants’ general practitioners were asked to identify the most important advantages and disadvantages of FDC therapy. Fifty-seven percent (127/221) of participants’ general practitioners reported improved treatment adherence to be the most important advantage of FDC therapy, whereas for 37% (82/221) of participants’ general practitioners, lack of flexibility was cited as the most important disadvantage.\(^5\)\(^4\) Ninety percent (203/225) of participants’ general practitioners reported that if they had another patient like this they would start them on FDC therapy if it were available.\(^5\)\(^4\)

Kanyini-GAP undertook in-depth, semi-structured interviews with a purposive sample of 47 health providers (25 general practitioners, 13 pharmacists, 6 indigenous health workers and 3 chronic care nurses) participating in the trial on polypill strategy acceptability, factors affecting adherence and trial implementation.\(^5\)\(^7\) FDC therapy was found to be generally acceptable to providers.\(^5\)\(^7\) Most providers considered that FDC therapy would facilitate improved patient medication use.\(^5\)\(^7\) Providers noted the inflexibility of the FDC therapy regimen, with dosages sometimes inappropriate for patients with complex management considerations.\(^5\)\(^7\) Many providers suggested that FDC therapy, in the formulation used within the Kanyini-GAP trial, might be more suited to high risk primary prevention patients.\(^5\)\(^7\) Many providers considered that the formulation used in the trial was inappropriate for some secondary prevention patients because of the low and inflexible
dosing. Indigenous Health Service providers considered FDC therapy to be acceptable and beneficial for indigenous patients given their high disease burden.57

9.4 Summary of effectiveness findings

1. When compared with inactive control, FDC therapy is associated with reductions in systolic blood pressure and low density lipoprotein cholesterol similar to that expected with individual components.
2. FDC therapy was consistently associated with improved adherence compared with active control across trials in patients with a prior CVD event.
3. FDC therapy was associated with improved control of systolic blood pressure and cholesterol when compared with usual care in UMPIRE, the largest trial. No differences were observed between FDC therapy and active treatment arms in the other trials.
4. No trials conducted to date have been powered to assess differences between FDC therapy and active comparators in CVD events among patients with a prior CVD event.
5. FDC therapy was generally acceptable to patients across a range of settings and including patients with and without a prior CVD event.
6. FDC therapy was generally acceptable to physicians (both general practitioners and specialists) and other health care providers across a range of settings and among patients both with and without a prior CVD event.

10. Summary of comparative evidence on safety:

10.1 Identification of clinical evidence
As with effectiveness, two main types RCTs have assessed the safety of FDC therapy: (1) those that have compared FDC therapy with an inactive control, in people without indications for any of the components of FDC therapy, and (2) those that have compared FDC therapy with an active control, in people with indications for all of the components of FDC therapy. For this reason, trials comparing FDC therapy with an inactive control have been summarised briefly using the findings of meta-analyses, and trials comparing FDC therapy with an active control are described in more detail.

10.2 Meta-analyses of FDC therapy vs inactive control in people without indications

10.2.1 Elley et al
As described above, the 2012 meta-analysis by Elley and colleagues included RCTs of a FDC containing at least one statin and one blood pressure-lowering agent compared with a placebo (or one active component) for at least six weeks.41 Six trials (with a combined total of 2,218 participants) were identified. Trial treatment discontinuation was more frequent in the FDC therapy than the control group (20% vs 14%, OR 1.5, 95% CI 1.2 to 1.9).41 There was no statistically significant difference between FDC therapy and control groups in the proportion of participants reporting adverse effects (36% FDC therapy vs 28% control, OR 1.5, 95% CI 0.7 to 2.5).41

10.2.2 de Cates et al
A 2013 Cochrane meta-analysis by de Cates and colleagues included RCTs of FDCs containing at least one statin and one blood pressure lowering agent compared with usual care, placebo or a single drug comparator.\textsuperscript{59} 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 FDC therapy with usual care: Soliman 2011,\textsuperscript{51} Cluster Randomized Usual care vs. Caduet Investigation Assessing Long-term-risk (CRUCIAL) 2011,\textsuperscript{60} and Use of a Multi-drug Pill In Reducing cardiovascular Events (UMPIRE) 2013.\textsuperscript{52}

Most of the analyses for the meta-analysis are not reported here because they combined trials with active and inactive comparators. Three of the analyses (for treatment discontinuation, liver chemistries and bleeding) are not reported because they did not include trials with an active control.\textsuperscript{59}

FDC therapy 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)\textsuperscript{59} as in the meta-analysis of Elley et al (20% vs 14%, OR 1.5, 95% CI 1.2 to 1.9).\textsuperscript{41} This was primarily because of differences between meta-analyses in how the numbers of participants that discontinued trial treatment from the Malekzadeh 2010 trial\textsuperscript{44} were derived.

de Cates found no difference between FDC therapy and control groups in elevated liver chemistries (RR 1.01, 95% CI 0.72 to 1.43).\textsuperscript{59}

Bleeding was more common in the FDC therapy 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).\textsuperscript{59}

### 10.3 Trials of FDC therapy vs active control in people with indications

Safety findings are presented in this section from the five trials that have compared FDC therapy with an active comparator: FOCUS\textsuperscript{50} (limited to participants with a prior CVD event); Soliman\textsuperscript{51} (limited to participants at high risk of their first CVD event); and UMPIRE,\textsuperscript{52} Kanyini-GAP\textsuperscript{53} and IMPACT\textsuperscript{54} (that included participants with a prior CVD event and at high risk of their first CVD event). Findings have not been separated according to history of a CVD event at baseline as the SPACE trials reported safety findings for all participants combined. Over three quarters (76%) of participants across all five trials had a prior CVD event.

#### 10.3.1 Serious adverse events

No statistically significant difference in the proportion of participants experiencing a serious adverse event was reported by UMPIRE, Kanyini-GAP, IMPACT or FOCUS (Table 7). Across trials there was considerable variation in the proportion of control participants experiencing a serious adverse event – from 7% in FOCUS to 41% in Kanyini GAP. The lowest rates were observed in FOCUS (7%) and UMPIRE (10%) which were largely conducted in secondary care settings. In contrast, Kanyini-GAP (41%) and IMPACT (36%) were conducted in primary care and of longer duration than the other two trials.
Table 7. FDC therapy compared with usual care – serious adverse events in trials completed to date that have reported this outcome

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of follow-up, months</th>
<th>N</th>
<th>Participants with at least one serious adverse event, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prior CVD</td>
<td>High risk of first event*</td>
<td>Total</td>
</tr>
<tr>
<td>UMPIRE 2013</td>
<td>15 (median)</td>
<td>1771</td>
<td>233</td>
<td>2,004</td>
</tr>
<tr>
<td>Kanyini GAP 2014</td>
<td>18 (median)</td>
<td>381</td>
<td>242</td>
<td>623</td>
</tr>
<tr>
<td>IMPACT 2014</td>
<td>23 (median)</td>
<td>233</td>
<td>280</td>
<td>513</td>
</tr>
<tr>
<td>FOCUS 2014</td>
<td>9 (median)</td>
<td>695</td>
<td>0</td>
<td>695</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td>3080</td>
</tr>
</tbody>
</table>

FDC=fixed dose combination; FOCUS=Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events

*5-year CVD risk >15%

10.3.2 Side effects

Data on side effects was collected by Soliman and FOCUS. The SPACE trials only collected information on serious adverse events. Some information on side effects to FDC therapy is available from the SPACE trials from the reported reasons for discontinuation, as described below.

Soliman (215 participants at high risk of their first CVD event) found no statistically significant difference between FDC therapy and usual care groups in the proportion of patients experiencing:

- epigastric pain (16% vs 19%, P=0.482),
- musculoskeletal pain (27% vs 28%, P=0.864),
- cough (26% vs 17%, P=0.144), or
- other (unspecified) side effects (16% vs 12%, P=0.415).

FOCUS (695 participants with a history of myocardial infarction) found no statistically significant difference between FDC therapy and the control groups (which received the FDC therapy components separately) in the proportion of participants experiencing:

- any adverse event (35% vs 33%),
- musculoskeletal adverse event (5% vs 10%),
- cough (1% vs 2%),
- dizziness (1% vs 1%), or
- hypotension (0% vs 0%).


10.3.3 Treatment discontinuation

Findings on treatment discontinuation are presented in this section from the four trials that have compared FDC therapy with an active comparator: FOCUS\textsuperscript{50} (limited to participants with a prior CVD event) and UMPIRE\textsuperscript{52}, Kanyini-GAP\textsuperscript{53} and IMPACT\textsuperscript{54} (that included participants with a prior CVD event and at high risk of their first CVD event). Findings have not been separated according to history of a CVD event at baseline as the SPACE trials reported discontinuation rates for all participants combined. Eighty percent of participants across all four trials had a prior CVD event.

Only the FOCUS trial was able to validly compared treatment discontinuation rates between FDC therapy and a control group because, unlike the other trials that compared FDC therapy with usual care, the comparator for the FOCUS trial was the separate components of the FDC therapy being used.\textsuperscript{50} FOCUS reported that treatment was discontinued (due to side effects in all cases) in 14 FDC therapy patients (14/345, 4%) and 13 control participants (13/350, 4%).

The FDC therapy discontinuation rate was reported in UMPIRE, Kanyini-GAP, IMPACT and FOCUS (Table 8). This outcome was not reported by Soliman. Across trials there was considerable variation in the FDC therapy discontinuation rate – from 4% in FOCUS to 37% in IMPACT. SPACE trial FDC therapy discontinuation rates were similar when annualised to take into account the differences between trials in duration (18 to 19%). FOCUS FDC therapy discontinuation rates remained much lower even after being annualised (5%). The differences between SPACE trial and FOCUS FDC therapy discontinuation rates may reflect differences in trial reporting practices.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration, months</th>
<th>Discontinuation, %</th>
<th>Stated reason for discontinuation (%*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During trial (n/N)</td>
<td>Per year</td>
</tr>
<tr>
<td>UMPIRE 2013\textsuperscript{52}</td>
<td>15 (median)</td>
<td>22% (219/1002)</td>
<td>18% Patient choice (6%), Cough (5%), Medical practitioner decision NFS (3%), Dizziness (2%), Serious adverse event (2%), Other adverse event (3%), Other reasons (e.g. increased creatinine level, 2%)</td>
</tr>
<tr>
<td>Kanyini GAP 2014\textsuperscript{53}</td>
<td>18 (median)</td>
<td>29% (90/311)</td>
<td>19% Medical practitioner decision NFS (42%), Patient choice (17%), Cessation by a specialist or during hospitalisation (15%), Cough (15%), Dizziness / hypotension (6%)</td>
</tr>
<tr>
<td>IMPACT 2014\textsuperscript{54}</td>
<td>23 (median)</td>
<td>37% (94/257)</td>
<td>19% Medical practitioner decision NFS (6%), Dizziness or hypotension (5%), Cough (4%), Patient choice (4%), Deterioration in renal function (2%), Fatigue (2%), Inadequate risk factor control (2%), Unknown reason (2%), Bleed (1%), Gastritis / dyspepsia / ulcer (1%), Other side effect (5%), Other reason (3%)</td>
</tr>
<tr>
<td>FOCUS 2014</td>
<td>9</td>
<td>4% (14/350)</td>
<td>5% Not reported</td>
</tr>
</tbody>
</table>

FDC=fixed dose combination; FOCUS=Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention; Kanyini GAP=Kanyini Guidelines Adherence with the Polypill; NFS=not further specified; UMPIRE=Use of a Multi-drug Pill in Reducing Cardiovascular Events

*% of total patients in UMPIRE and IMPACT, % of patients discontinuing in KANYINI-GAP
The reasons for FDC therapy discontinuation were provided by UMPIRE, Kanyini-GAP and IMPACT (Table 8). Three major classes of reasons are evident: (1) patient choice, (2) medical practitioner decision and (3) side effects. The side effects that were most commonly reported as a reason for FDC therapy discontinuation were: cough (approximately 4%, 70/1570, of all FDC therapy participants across the three trials) and dizziness / hypotension (approximately 2%, 38/1570).

10.3.4 Lifestyle behaviour
Data on lifestyle behaviour was collected by the three SPACE trials. All three trials assessed body weight, waist circumference, body mass index and duration of physical activity and found no statistically significant difference between FDC therapy and usual care groups in these measures. UMPIRE and Kanyini GAP also assessed participation in exercise, diet and smoking cessation programmes and found no difference in participation between FDC therapy and usual care groups.

10.4 Summary of safety findings
1. No major safety concerns have emerged regarding the use of FDC therapy when compared with an inactive control.
2. No statistically significant differences in serious adverse events were observed between FDC therapy and active control groups.
3. No statistically significant differences in side effects were observed between FDC therapy and active control groups.
4. When FDC therapy was compared with the same components administered separately there was no difference in the rate of treatment discontinuation.
5. When FDC therapy was compared with usual care, the annual rate of treatment discontinuation was approximately 18-19%.
6. The main reasons for FDC therapy discontinuation were patient choice, medical practitioner decision and side effects.
7. The most commonly reported side effects causing FDC therapy discontinuation were cough and dizziness/hypotension.
8. No statistically significant differences in lifestyle behaviours were observed between FDC therapy and usual care groups.

11. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

11.1 Cost analysis
A within-trial cost analysis of FDC therapy compared with usual care has been published using data from Kanyini-GAP (that included patients at high risk of their first and patients with a history of a CVD event) and linked health service and medication administrative claims data. This FDC cost analysis of a trial comparing FDC therapy with an active control has been published. The analysis found no significant difference between FDC therapy and usual care groups in health service expenditure, and a statistically significantly lower mean pharmaceutical expenditure of AUD$989 (95% CI $648 to $1331) per patient per year in the FDC therapy compared with the usual care group. The pharmaceutical expenditure analysis did not include the cost of FDC therapy, therefore the overall potential health
system savings are dependent on the reimbursement price of the polypill. Investigators note that under Australian guidelines government reimbursement would be no greater than the sum of the costs of the generic components, which was AUD$1.70 per day (AUD$620.5 per year) at the time the trial was conducted. Assuming reimbursement at this maximum price, the annual savings to the health system would be $368.5 per patient.

11.2 Cost-effectiveness

Becerra 2015 undertook a cost-effectiveness analysis using a Markov model to evaluate the public health and economic benefits of adherence to FDC therapy for the secondary prevention of CVD among patients who had a myocardial infarction in the United Kingdom. The analysis used data from UMPIRE on the effect of FDC therapy compared with usual care on adherence. To the author’s best knowledge, this is the only FDC therapy cost-effectiveness analysis published to date that has used at least some data from a trial comparing FDC therapy with an active control. The analysis estimated that for each 10% increase in adherence, an additional 6.7% of CVD events (fatal and non-fatal) could be prevented.

The investigators’ base case estimate was that 10 years of FDC therapy (containing aspirin 100mg + atorvastatin 20mg + ramipril [2.5, 5 or 10mg]) compared with usual care would:
- improve adherence by approximately 20%,
- prevent 47/323 (15%) CVD events (fatal and nonfatal) per 1000 patients,
- with incremental cost-effectiveness ratio of GBP8205 per QALY gained (ranging from cost saving to GBD 21,430 per QALY gained in scenario analyses that varied structural assumptions).

Probabilistic sensitivity analyses for the base-case assumptions showed an 82% chance of FDC therapy being cost-effective at a willingness-to-pay threshold of GBP 20,000 per QALY gained compared with usual care.

Investigators estimated that 3260 nonfatal and 5290 fatal CVD events could be prevented in the United Kingdom over a decade, assuming:
- 450,000 adults are at risk of a first or subsequent myocardial infarction,
- uptake of FDC therapy is 10% among patients who experience a first or subsequent myocardial infarction, and that
- FDC therapy improves adherence by 20%.

Investigators concluded that FDC therapy appears to be a cost-effective strategy to prevent CVD events in the United Kingdom.

More recently, Barrios et al used an adapted version of the Markov model from Becerra 2015 to compare the cost-effectiveness of the polypill (aspirin 100mg + atorvastatin 20mg + ramipril [2.5, 5 or 10mg]) compared with its mono-components) over a 10-year time horizon, with some data from the SPACE meta-analysis study. The cardiovascular polypill instead of its mono-components simultaneously would avoid 46 nonfatal and 11 fatal cardiovascular events per 1000 patients treated. The polypill would also be a more effective and cheaper strategy from the Spanish Public Health System perspective. The number of patients needed to treat (NNT) with the cardiovascular polypill was 22.2 to avoid a nonfatal
cardiovascular event and 45.4 to avoid a fatal cardiovascular event. Probabilistic analysis of the base case found a 90.9% probability that the polypill would be a cost-effective strategy compared with multiple monotherapy at a willingness-to-pay of 30,000 euros per quality-adjusted life year.

Finally, early data from Kaskens et al adapted the Markov model from Becerra 2015 over a 20 years horizon, with a 5% discount rate, considering costs from institutional Mexican sources, clinical and adherence data from the FOCUS study, and the Mexican Healthcare System perspective. A polypill (ASA 100mg, simvastatin 40mg and ramipril 5-10mg) for secondary prevention of cardiovascular events with or without a recent history of MI gained 5.76175 life years and 4.78911 QALY’s, in comparison the life years gained with its mono-components (5.74624 and 4.77445 QALY’s).

The polypill is a cost-effective option compared with its mono-components with an ICER of €8,187.95 in terms of life years gained and €8,662.68 in terms of QALY’s. In conclusion, polypill is a cost-effective option compared with its mono-components from the Mexican Healthcare System perspective.

Summary of cost and cost-effectiveness findings
1. Only one within-trial cost analysis of FDC therapy compared with usual care was identified (Kanyini-GAP). This analysis found the following:
   - No significant difference between FDC therapy and usual care groups in health service expenditure.
   - A statistically significantly lower mean pharmaceutical expenditure of AUD$989 (95% CI $648 to $1331) per patient per year in the FDC therapy compared with the usual care group.
   - Potential savings to the health system would depend on government reimbursement for FDC therapy, the costs of which were not included in the analysis.
2. Several cost-effectiveness analysis using at least some data from a trial comparing FDC therapy with an active control were identified (Becerra 2015, Barrios 2016, Keskens 2016). This analysis estimated an incremental cost-effectiveness ratio of GBP8205 per QALY gained under the following assumptions:
   - Use restricted to 450,000 UK adults with or at risk of myocardial infarction
   - Uptake of FDC therapy 10%
   - FDC therapy improves adherence by 20%
   - Polypill effective and cheaper strategy for Spanish Public Health System
   - Polypill cost-effective compared to components in Mexican Healthcare system

Integration of evidence
The current status of FDC therapy for patients with a prior CVD event is summarised according to currently available evidence, against potential advantages and disadvantages (Table 9). Current evidence-based advantages and disadvantages of FDC therapy for people with a prior CVD event are summarised in Table 10.
Table 9. Potential advantages and disadvantages of FDC therapy and relevant evidence for people who have had a CVD event he management of CVD risk

<table>
<thead>
<tr>
<th>Evidence for people who had a CVD event</th>
<th>Gaps in evidence / other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential advantages</strong></td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>Consistent RCT evidence that adherence improved</td>
</tr>
<tr>
<td>Acceptability (based on scientific evidence, simple and user friendly)</td>
<td>Reduction in BP and cholesterol when compared with usual care in UMPIRE</td>
</tr>
<tr>
<td></td>
<td>Consistent evidence from patients and physicians that acceptable</td>
</tr>
<tr>
<td></td>
<td>No statistically significant differences between FDC therapy and active control groups in serious adverse effects or side effects</td>
</tr>
<tr>
<td></td>
<td>No difference in discontinuation rate when compared with same components administered separately. Annual discontinuation rate approximately 18-19% in trials that compared FDC therapy with usual care</td>
</tr>
<tr>
<td><strong>Applicability (flexible and can be applied in a range of less well-resourced settings)</strong></td>
<td>Adherence and acceptability demonstrated in RCTs in a range of settings</td>
</tr>
<tr>
<td>Affordability</td>
<td>Medication costs likely to be lower according to data from RCT in Australia Likely to be cost-effective in UK model using data from UMPIRE RCT Highly cost-effective in low- and middle-income countries</td>
</tr>
<tr>
<td>Accessibility (infrastructure of most less well-resourced settings will be able to implement the guidelines)</td>
<td>No – RCTs conducted in relatively well resourced settings</td>
</tr>
</tbody>
</table>
Lack of ability to titrate

This concern was not voiced by physicians who had used FDC therapy in the Kanyini GAP trial (during in-depth semi-structured interviews) or in the IMPACT trial (in a post-trial questionnaire which specifically asked about disadvantages of FDC therapy). Providers noted that the lack of choice of components and doses limited the usefulness of FDC therapy.

Lack of choice of components and doses

No – but this is a real disadvantage of the currently available FDCs. There is a need for a greater range of components and doses.

Uncertainty regarding cause of side effects

No

Failure to achieve treatment targets in people with high levels of individual risk factors

SPACE meta-analysis: increase in the proportion of patients that achieved all three European guideline BP, LDL-cholesterol and antiplatelet agent treatment targets in patients with history of CVD, when compared with usual care.

No

Deterioration of lifestyle behaviours if perceived as a panacea

No evidence from three RCTs that any deterioration in lifestyle behaviours

No but needs to be implemented in conjunction with a comprehensive CVD management strategy that includes locally-appropriate and affordable strategies to address lifestyle behaviours at the population and individual level.

<table>
<thead>
<tr>
<th>Table 10. Current evidence-based advantages and disadvantages of fixed dose combination therapy for the management of cardiovascular risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>• Improves adherence</td>
</tr>
<tr>
<td>• Expected reductions in risk factors (blood pressure and cholesterol) when compared with inactive control</td>
</tr>
<tr>
<td>• More likely to achieve guideline targets for blood pressure, cholesterol and antiplatelet treatment compared with usual care</td>
</tr>
<tr>
<td>• Acceptable to both patients and physicians across a range of settings</td>
</tr>
<tr>
<td>• Highly likely to be highly cost-effective for people with CVD in low- and middle-income countries</td>
</tr>
</tbody>
</table>
Regulatory Information

12. Summary of regulatory status of the medicine

The proposed formulation is currently available as “Trinomia”. “Trinomia” is manufactured by Ferrer Internacional, S.A. of Spain. Trinomia (atorvastatin version – there is also a version containing simvastatin) has been approved in the following countries: Austria, Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden. Trinomia (atorvastatin version) is currently marketed and available in Spain.

15. Availability of pharmacopoeial standards
Each of the drug substances has a monograph in both the European and United States Pharmacopeias.
References
## Appendix 1

WHO CVD preventive medication and lifestyle advice recommendations for people who have had a CVD event

### BP-lowering therapy

“BP reduction should be considered in all patients with established CHD, particularly with BP >140/90 mm Hg. Lifestyle factors (particularly high alcohol intake) should be addressed first and if BP is still above 140/90 mm Hg, drug treatment indicated. When beta-blockers and ACE inhibitors cannot be given, or in cases where BP remains high, treatment with a thiazide diuretic is likely to reduce risk of recurrent vascular events. A target BP of 130/80-85 mm Hg is appropriate”

“ACE inhibitors are recommended in all patients following myocardial infarction”

“Treatment with beta-blockers is recommended in all patients with a history of myocardial infarction and those with CHD who have developed major left ventricular dysfunction leading to heart failure”

“BP reduction should be considered in all patients with previous TIA or stroke to a target of <130/<80-85 mm Hg”

### Statins

“Treatment with statins is recommended for all patients with established CHD. Treatment should be continued in the long term, probably lifelong. Patients at high baseline risk are particularly likely to benefit.”

“Treatment with a statin should be considered for all patients with established CeVD, especially if they also have evidence of established CHD.”

### Aspirin

“All patients with established CHD should be treated with regular aspirin in the absence of clear contraindications. Treatment should be initiated early and continued lifelong”

“All patients with a history of TIA or stroke presumed due to cerebral ischaemia or infarction should be treated with long-term (probably lifelong) aspirin in the absence of clear contraindications”

### Tobacco smoking

- Strong encouragement and support to stop smoking by a health professional
- Advise to stop other forms of tobacco use
- Offer nicotine replacement therapy to those who smoke >10 cigarettes/day
- Advise non-smokers to avoid exposure to second-hand tobacco smoke as much as possible

### Unhealthy diet

- Reduce total fat intake to <30% and saturated fat to <10% of calories
- Eliminate / reduce intake of transfatty acids as much as possible
- Most dietary fat should be polyunsaturated (up to 10% of calories) or monounsaturated (10-15% of calories)
- Reduce daily salt intake by at least one-third, and if possible, to <5g or <90 mmol /day
- Encouragement to eat at least 400g a day of a range of fruits and vegetables, as well as whole grains and pulses

### Physical inactivity

- Regular light-to-moderate intensity physical activity
- Offer supervised exercise programmes where feasible

### Overweight / obesity

- Advise weight loss through the combination of a reduced energy diet and increased physical activity

### >3 units of alcohol/ day

- Advise to reduce alcohol consumption

ACE=angiotensin converting enzyme, BP=blood pressure, CeVD=cerebrovascular disease, CHD=coronary heart disease, CVD=cardiovascular disease, LDL=low density lipoprotein, PVD=peripheral vascular disease, TIA=transient ischaemic attack

CVD event defined as angina, myocardial infarction, stroke, transient ischaemic attack, peripheral vascular disease, coronary revascularization or carotid endarterectomy. Source: World Health Organization
## Appendix 2
Cardiovascular fixed dose combinations and countries in which regulatory approval has been obtained

<table>
<thead>
<tr>
<th>FDC name</th>
<th>Manufacturer</th>
<th>Components</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aspirin</td>
<td>Statin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycap</td>
<td>Cadila</td>
<td>Aspirin 100mg</td>
<td>Simvastatin 20mg</td>
</tr>
<tr>
<td>Ramitorva / Lifepill</td>
<td>Cadila / Zydus (Cardiva)</td>
<td>Aspirin 75mg</td>
<td>Atorvastatin 10mg</td>
</tr>
<tr>
<td>Starpill</td>
<td>Cipla</td>
<td>Aspirin 75mg</td>
<td>Atorvastatin 10mg</td>
</tr>
<tr>
<td>Trinomia</td>
<td>Ferrer</td>
<td>Aspirin 100mg</td>
<td>Simvastatin 40mg or atorvastatin 20mg</td>
</tr>
</tbody>
</table>

ACE=angiotensin converting enzyme, ARB=angiotensin receptor blocker, BP=blood pressure, FDC=fixed dose combination, HCTZ=hydrochlorothiazide

*Currently marketed and available
Adapted from Huffman 2015 and Huffman 2014
Appendix 3
Actual vs expected reductions in systolic blood pressure and low density lipoprotein cholesterol in trials comparing a fixed dose combination (at least one statin and one blood pressure lowering agent) with inactive control

<table>
<thead>
<tr>
<th>Trial</th>
<th>Actual vs Expected Reductions in Systolic Blood Pressure (SBP)</th>
<th>Actual vs Expected Reductions in LDL-Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antihypertensive</td>
<td>Standard dose equivalent [50%]</td>
</tr>
<tr>
<td>Malekzadeh, 2010</td>
<td>Enalapril 2.5 mg</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide 12.5 mg</td>
<td>0.5</td>
</tr>
<tr>
<td>Neutel, 2009</td>
<td>Amlodipine 5 mg</td>
<td>1</td>
</tr>
<tr>
<td>PILL collaboration, 2011</td>
<td>Lisinopril 10 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide 12.5 mg</td>
<td>0.5</td>
</tr>
<tr>
<td>Wald, 2012</td>
<td>Hydrochlorothiazide 12.5 mg</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Losartan 25 mg</td>
<td>0.5</td>
</tr>
<tr>
<td>The Indian Polycap Study, 2009</td>
<td>Hydrochlorothiazide 12.5 mg</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Atenolol 50 mg</td>
<td>1</td>
</tr>
<tr>
<td>Grimm, 2010</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*rounded to nearest 10 mm Hg;
**based on mean baseline SBP & standard dose equivalence (from Law 2009) [4];
mean baseline LDL = percentage reduction in LDL cholesterol for the statin at that dose (from Law 2003) [5];
*estimate: two drugs at half dose therefore an overestimate of likely effect;
**estimate: two drugs at half dose therefore an underestimate of likely effect; 12.7 mmHg for two drugs at standard dose;
estimate: three drugs at standard dose; 15.2 mmHg for three drugs at half standard dose.
Source: Elley 2012[^41]
Appendix 4
Description of trials that have compared FDC with an active control

Soliman 2011
The trial by Soliman and colleagues was a feasibility study that sought to assess the efficacy, safety and acceptability of FDC therapy among patients at high risk of a first cardiovascular event. Participants were recruited from three tertiary hospital sites in Sri Lanka and received a FDC (containing aspirin 75mg, simvastatin 20mg, lisinopril 10mg and hydrochlorothiazide 12.5mg) or usual care for three months.

FOCUS 2014
The Fixed Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) trial compared a FDC (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. 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%.

SPACE Collaboration
Three trials have been completed to date in which FDC therapy was compared with an active comparator (usual care) among patients with a prior CVD event or at high risk of their first CVD event: UMPIRE, Kanyini-GAP and IMPACT. All three trials 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. The three trials used very similar inclusion criteria and primary outcomes, and the same FDCs. The main inclusion criteria were prior CVD event or 5-year cardiovascular risk ≥15%. 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. FDC therapy (called the Red Heart Pill) contained aspirin 75mg, simvastatin 40mg, lisinopril 10mg and either atenolol 50mg or hydrochlorothiazide 12.5mg. Additional information on each trial is provided below.

UMPIRE 2013
The UMPIRE trial randomised a total of 2004 participants from India (n=1000) and Europe (England, Ireland and the Netherlands) (n=1004) to FDC therapy or usual care for a median of 15 months. Participants from India were recruited from hospital specialist clinics and participants from Europe were recruited from research databases, hospital clinics and general practice registries. The FDC was dispensed six-monthly from the trial centre free of charge. Participants in the usual care group continued to receive their medication according to local dispensing schedules (usually three-monthly) and payments. Most participants (85%) had a prior CVD event, and 62% reported using combination medication (antiplatelet, statin and two or more blood pressure lowering agents) at baseline.

Kanyini-GAP 2014
The Kanyini-GAP trial randomised 623 participants from Australian general practice to FDC therapy or usual care for a median of 18 months. Half of the participants (51%) were of indigenous ethnicity. The prescribing, dispensing and payment for FDC therapy were the
same as if FDC therapy were to be marketed in Australia and subsidised through their Pharmaceutical Benefits Scheme. At baseline, 61% of participants had a prior CVD event and 50% of participants reported use of combination medication (antiplatelet, statin and two or more blood pressure lowering agents).

**IMPACT 2014**
The IMPACT trial randomised 513 participants from New Zealand general practice to FDC therapy or usual care for a median of 23 months. Half of the participants (50%) were of indigenous ethnicity. The prescribing, dispensing and payment for FDC therapy were the same as if FDC therapy were to be marketed in New Zealand and subsidised through their Pharmaceutical Management Agency. At baseline, 45% of participants had a prior CVD event and 43% of participants reported using combination medication (antiplatelet, statin and two or more blood pressure lowering agents).
Appendix 5

Key features of trials comparing FDC with an active control that are currently underway.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion criteria</th>
<th>FDC</th>
<th>Control</th>
<th>N</th>
<th>Follow-up</th>
<th>Primary outcome</th>
<th>Results due</th>
</tr>
</thead>
<tbody>
<tr>
<td>PolyIran</td>
<td>50-79 years, +/- CVD history</td>
<td>Aspirin 81mg + enalapril 5mg (or valsartan 40mg) + atorvastatin 20mg + HCTZ 12.5mg (+ ‘minimal care’) delivered by local auxiliary health workers</td>
<td>‘Minimal care’ (direct education and pamphlet on CVD risk reduction, biannual follow-ups and BP measurements)</td>
<td>7000</td>
<td>5 years</td>
<td>CVD</td>
<td>2018 (follow-up phase)</td>
</tr>
<tr>
<td>HOPE-4</td>
<td>≥50 years and high BP or diabetes</td>
<td>Access to FDC therapy (contents not specified) as part of intensive CVD risk detection, counselling and follow-up programme delivered by NPHWs</td>
<td>Usual care (information on lifestyle modification and advice to see usual physician as appropriate)</td>
<td>9500</td>
<td>1 year</td>
<td>Mean difference in change CVD risk</td>
<td>2020 (recruiting now)</td>
</tr>
</tbody>
</table>

BP=blood pressure, CVD=cardiovascular disease; FDC=fixed dose combination; HCTZ=hydrochlorothiazide; NPHW=non-physician health workers; TIPS= The International Polycap Study

Note: compiled from articles reviews and a search of clinicaltrials.gov (using the search terms “polypill” and “fixed dose combination” and restricted to “vascular diseases”) on 25 August 2015

PolyIran

The Prevention of CVD in Middle-aged and Elderly Iranians Using a Single PolyPill (PolyIran) trial will assess the effect of FDC therapy compared with ‘minimal’ usual care on cardiovascular outcomes among 7,000 participants, with or without a prior CVD event, and aged 50 to 79 years (results due 2018) (see Table 21).

HOPE-4

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 FDC among 9500 participants and assess cardiovascular outcomes.