de Cates, AN; Farr, MR; Wright, N; Jarvis, MC; Rees, K; Ebrahim, S; Huffman, MD (2014) Fixed-dose combination therapy for the prevention of cardiovascular disease. Cochrane Database Syst Rev, 4. CD009868. ISSN 1469-493X DOI: https://doi.org/10.1002/14651858.CD009868.pub2

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Fixed-dose combination therapy for the prevention of cardiovascular disease (Review)

de Cates AN, Farr MRB, Wright N, Jarvis MC, Rees K, Ebrahim S, Huffman MD

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Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD009868.
DOI: 10.1002/14651858.CD009868.pub2.

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[Intervention Review]

Fixed-dose combination therapy for the prevention of cardiovascular disease

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Editorial group: Cochrane Heart Group.
Publication status and date: New, published in Issue 4, 2014.
Review content assessed as up-to-date: 19 July 2013.

Citation: de Cates AN, Farr MRB, Wright N, Jarvis MC, Rees K, Ebrahim S, Huffman MD. Fixed-dose combination therapy for the prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD009868. DOI: 10.1002/14651858.CD009868.pub2.

ABSTRACT

Background

Cardiovascular disease (CVD) is the leading cause of death and disability 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 CVD by up to 80% given its potential for better adherence and lower costs.

Objectives

To determine the effectiveness of fixed-dose combination therapy on reducing fatal and non-fatal CVD events and on improving blood pressure and lipid CVD risk factors for both primary and secondary prevention of CVD. We also aimed to determine discontinuation rates, adverse events, health-related quality of life, and costs of fixed-dose combination therapy.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2013, Issue 6), MEDLINE Ovid (1946 to week 2 July 2013), EMBASE Ovid (1980 to Week 28 2013), ISI Web of Science (1970 to 19 July 2013), and the Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), and Health Economics Evaluations Database (HEED) (2011, Issue 4) in *The Cochrane Library*. We used no language restrictions.

Selection criteria

We included randomised controlled trials of a fixed-dose combination therapy including at least one blood pressure lowering and one lipid lowering component versus usual care, placebo, or a single drug active component for any treatment duration in adults ≥ 18 years old with no restrictions on presence or absence of pre-existing cardiovascular disease.

Data collection and analysis

Three review authors independently selected studies for inclusion and extracted the data. We evaluated risk of bias using the Cochrane risk of bias assessment tool. We sought to include outcome data on all-cause mortality, fatal and non-fatal CVD events, adverse events, changes in systolic and diastolic blood pressure, total and low density lipoprotein (LDL) cholesterol concentrations, discontinuation rates, quality of life, and costs. We calculated risk ratios (RR) for dichotomous data and weighted mean differences (MD) for continuous data with 95% confidence intervals (CI) using fixed-effect models when heterogeneity was low (I^2 < 50%) and random-effects models when heterogeneity was high (I^2 > 50%).

Main results

We found nine randomised controlled trials with a total of 7047 participants. Seven of the nine trials evaluated the effects of fixed-dose combination therapy on primary CVD prevention, and the trial length ranged from six weeks to 15 months. We found a moderate to high risk of bias in the domains of selection, performance, detection, attrition, and other types of bias in five of the nine trials. Compared with the comparator groups, the effects of the fixed-dose combination treatment on mortality (1.2% versus 1.0%, RR 1.26, 95% CI 0.67 to 2.38, N = 3465) and cardiovascular events (4.0% versus 2.9%, RR 1.38, 95% CI 0.91 to 2.10, N = 2479) were uncertain (low quality evidence). The low event rates for these outcomes, limited availability of data as only two out of nine trials reported on these outcomes, and a high risk of bias in at least one domain suggest that these results should not be viewed with confidence. Adverse events were common in both the intervention (30%) and comparator (24%) groups, with participants randomised to fixed-dose combination therapy being 20% (95% CI 9% to 30%) more likely to report an adverse event. Notably, no serious adverse events were reported. Compared with placebo, the rate of discontinuation among participants randomised to fixed-dose combination was higher (14% versus 11%, RR 1.26 95% CI 1.02 to 1.55). The weighted mean differences in systolic and diastolic blood pressure between the intervention and control arms were -7.05 mmHg (95% CI -10.18 to -3.87) and -3.65 mmHg (95% CI -5.44 to -1.85), respectively. The weighted mean differences (95% CI) in total and LDL cholesterol between the intervention and control arms were -0.75 mmol/L (95% CI -1.05 to -0.46) and -0.81 mmol/L (95% CI -1.09 to -0.53), respectively. There was a high degree of statistical heterogeneity in comparisons of blood pressure and lipids ($I^2 \geq 70\%$ for all) that could not be explained, so these results should be viewed with caution. Fixed-dose combination therapy improved adherence to a multi-drug strategy by 33% (26% to 41%) compared with usual care, but this comparison was reported in only one study. The effects of fixed-dose combination therapy on quality of life are uncertain, though these results were reported in only one trial. No trials reported costs.

Authors' conclusions

Compared with placebo, single drug active component, or usual care, the effects of fixed-dose combination therapy on all-cause mortality or CVD events are uncertain; only few trials report these outcomes and the included trials were primarily designed to observe changes in CVD risk factor levels rather than clinical events. Reductions in blood pressure and lipid parameters are generally lower than those previously projected, though substantial heterogeneity of results exists. Fixed-dose combination therapy is associated with modest increases in adverse events compared with placebo, single drug active component, or usual care but may be associated with improved adherence to a multidrug regimen. Ongoing trials of fixed-dose combination therapy will likely inform key outcomes.

PLAIN LANGUAGE SUMMARY

Fixed-dose combination therapy for the prevention of cardiovascular disease

Cardiovascular diseases (CVD), including heart attacks and strokes, are the leading cause of death and disability worldwide. Drug therapy with blood pressure and cholesterol lowering medications, particularly statins, have been proven to reduce the likelihood that individuals will experience a fatal or non-fatal cardiovascular event. Aspirin has also been proven to prevent heart attacks, certain types of strokes, and death in people with prior cardiovascular disease. The concept of fixed-dose combination therapy is to combine mulitple medications in a single pill as this has been shown to improve adherence in patients with high blood pressure and human immunodeficiency virus (HIV). There have been recent randomised controlled clinical trials to evaluate the effect of fixed-dose combination therapy for CVD prevention. The aim of this systematic review was to determine the effects of fixed-dose combination therapy on all-cause mortality, fatal and non-fatal CVD events, adverse events, blood pressure, lipids, discontinuation rates, quality of life, and costs for CVD prevention.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE until 2013. We found nine randomised controlled trials of two-drug through to five-drug fixed-dose combination therapy with placebo, single drug active component, or usual care in 7047 patients, dating from 2009 to 2013. Trials were generally short-term, ranging from six weeks to 15 months, and included middle-age adults with and without prior CVD.

Compared with placebo, single drug active component, or usual care, the effects of fixed-dose combination therapy on all-cause mortality or CVD events were uncertain. However, the event rates for these outcomes were relatively uncommon, only two out of nine trials reported these outcomes, these trials were primarily designed to observed changes in CVD risk factor levels rather than clinical events, and the trials had a high risk of bias in at least one domain, suggesting that these results should not viewed with confidence. Of 1000 people treated with fixed-dose combination therapy during the study period, 297 (range 264 to 315) would experience a side effect compared with 242 people treated with placebo. Fixed-dose combination therapy was associated with lower systolic blood pressure (-7.05 mmHg, range -10.18 to -3.87) and total cholesterol (-0.75 mmol/L, range -1.05 to -0.46). However, there was a high degree of statistical heterogeneity in these comparisons so these results should be viewed with caution. Of 1000 patients treated with fixed-dose combination therapy during the study period, 140 (range 122 to 186) would discontinue the therapy compared with 115 patients treated with placebo. The effects on quality of life were uncertain, and no cost data were reported. Ongoing trials of fixed-dose combination therapy will likely inform these important endpoints.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Fixed-dose combination therapy for the prevention of cardiovascular disease (CVD)

Patient or population: Adults older than 18 years, with no restriction regarding presence of CVD; participants generally had elevated risk of CVD (as estimated by the presence of at least one abnormal cardiovascular risk factor) without prevalent CVD (two studies included > 10% of participants with prior CVD)
Settings: Outpatient
Intervention: Fixed-dose combination therapy of varying drug combinations ranging from two to five drugs
Comparison: Usual care, placebo, or single drug therapy from alternate drug class

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard practice or placebo	Fixed-dose combination therapy				
All-cause mortality	**Total**		RR = 1.26 [0.67, 2.38]	3465 (2 studies)	⊕⊕◯◯ **low**	Downgraded due to study limitations (risk of bias) in 1 of 2 included studies and imprecision of effect
	10 per 1000	**12 per 1000** (7 to 24)				
CVD event	**Total**		RR = 1.38 [0.91, 2.10]	2479 (2 studies)	⊕⊕◯◯ **low**	Downgraded due to study limitations (risk of bias) in 1 of 2 included studies and imprecision of effect
	29 per 1000	**40 per 1000** (26 to 61)				
Any adverse event 6 weeks to 15 months	**Total**		RR = 1.19 [1.09, 1.30]	4864 (7 studies)	⊕⊕◯◯ **low**	Downgraded due to study limitations (risk of bias) and difficulty in assessing indirectness of evidence
	242 per 1000	**297 per 1000** (264 to 315)				
Systolic blood pressure mmHg	The mean change in systolic blood pressure ranged across control groups from -17.9 mmHg to -2 mmHg	The mean change in systolic blood pressure in the intervention groups was on average a -7.05 mmHg (95% CI -10.18 to -3.87)		5787 (9 studies)	⊕⊕⊕◯ **moderate**	Downgraded due to study limitations (risk of bias) and unexplained heterogeneity

		greater reduction compared with control				
Diastolic blood pressure mmHg	The mean change in diastolic blood pressure ranged across control groups from -9.8 mmHg to -0.5 mmHg	The mean change in diastolic blood pressure in the intervention groups was on average a -3.65 mmHg (95% CI -5.44 to -1.85) greater reduction compared with control		5787 (9 studies)	⊕⊕⊕◯ **moderate**	Downgraded due to study limitations (risk of bias) and unexplained heterogeneity
Total cholesterol mmol/L	The mean change in total cholesterol ranged across control groups from -1.6 mmol/L to 0 mmol/L	The mean change in total cholesterol in the intervention groups was on average a -0.75 mmol/L (-1.05 to -0.46) greater reduction compared with control		5569 (9 studies)	⊕⊕◯◯ **low**	Downgraded due to study limitations (risk of bias) , unexplained heterogeneity, and funnel plot asymmetry
LDL cholesterol mmol/L	The mean change in LDL cholesterol ranged across control groups ranged from -1.4 mmol/L to -0.04 mmol/L.	The mean change in LDL cholesterol in the intervention groups was on average a -0.81 mmol/L (95% CI -1.09 to -0.53) greater reduction compared with control		5365 (8 studies)	⊕⊕⊕◯ **moderate**	Downgraded due to study limitations (risk of bias) and unexplained heterogeneity
Discontinuation for any reason 6 weeks to 15 months	**Total**		RR = 1.26 [1.02, 1.55]	2423 (6 studies)	⊕⊕◯◯ **low**	Downgraded due to study limitations (risk of bias) and difficulty in assessing indirectness of evidence
	120 per 1000	**140 per 1000** (122 to 186)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is the outcomes of the study control arms. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CVD** = cardiovascular disease;
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is a principal cause of death worldwide. In 2010, more than 17 million deaths globally were attributed to CVD, over 80% of which occurred in low and middle-income countries (WHO 2010 (a)). Furthermore, the situation is not expected to improve, with global CVD mortality estimated to increase by six million over the next 20 years (WHO 2010 (a)). Ischaemic heart disease and cerebrovascular diseases, the major CVDs, are also major causes of disability resulting in 130 million disability-adjusted life years (DALYs) lost in 2010 (WHO 2011). Therefore, preventing deaths and disease due to CVD is a priority for global public health.

Optimising modifiable risk factors reduces CVD mortality and morbidity (Cowie 2005). Individuals with both hypertension and dyslipidaemia have a greater risk of CVD than those with either hypertension or dyslipidaemia alone (Neaton 1992; Thomas 2002), highlighting the importance of considering overall CVD risk as opposed to individual risk factors (Perk 2012). Therefore, adopting a multi-factorial approach to CVD risk management, where multiple risk factors are modified simultaneously, is a more effective way of reducing CVD events than focusing on single risk factors in isolation (Gaede 2003).

Current national and international approaches to CVD prevention incorporate both primary and secondary prevention (Perk 2012; NICE 2010). Primary prevention aims to prevent CVD events in those who have no clinical evidence of CVD. To achieve this, guidelines recommend intervening when the 10 year risk for any CVD event when the 10 year risk exceeds recommended thresholds or when the risk of a fatal CVD event is estimated to be at 5% using validated risk scores (NICE 2008; NICE 2010; Perk 2012; Stone 2013). CVD incidence and mortality are reduced by antihypertensives (Collins 1990) and statins, which improve the lipid profile (Taylor 2013). Secondary prevention requires blood pressure control, cholesterol lowering, and use of antiplatelet drugs to prevent further CVD events, which is known to be effective (ATT-Collaboration 2002; Baigent 2005; Rashid 2003).

The same CVD risk factors operate globally (Yusuf 2004) making multi-factorial prevention strategies relevant, but conventional approaches targeting high risk individuals, conducting investigations, prescribing various medications, regular monitoring, and drug dose titration to optimise CVD risk factors are difficult to implement. Three major issues arise for global CVD prevention.

(i) Reducing risk factors in a selected high risk group does not yield as much benefit to a population as reducing risk factors in the whole population (Cooney 2009; NICE 2010).

(ii) Lipid-lowering with statins reduces CVD events at pre-treatment lipid levels that are considered normal (Colhoun 2004; HPSCG 2002; O'Keefe 2004; Sever 2003) making blood testing for lipid levels less relevant and potentially increasing the number of people who would benefit from statins.

(iii) Implementing conventional CVD prevention would be a challenge for the healthcare systems in most low and middle-income countries due to financial and time costs, human resource availability, laboratory capacity, drug acquisition, and adminstration. Therefore, alternative and complementary population-wide strategies are required.

Description of the intervention

A fixed-dose combination pill was proposed in 2001 by a World Health Organization (WHO) and Wellcome Trust expert group (WHO 2002) and was subsequently specified as a combination of four drugs (beta-blocker, angiotensin converting enzyme (ACE)-inhibitor, aspirin, and statin), which was estimated to reduce CVD events by 75% in people with clinical evidence of CVD (Yusuf 2002). This concept was followed in 2003 by a proposed Polypill® (a combination of folic acid, aspirin, three low-dose antihypertensives, and a low-dose statin), which was intended for both secondary prevention and primary prevention in all people aged 55 years and over and was estimated to reduce CVD events by about 80% (Wald 2003). Recent evidence has indicated that the effects of fixed-dose combination treatment may be less than was initially proposed, but that this strategy may improve the blood pressure and lipid profile to near expected levels (PILL-collaborative 2011; TIPS 2009). The controversial aspect of the Polypill® was that it was intended to be used at a population level without screening of blood cholesterol or blood pressure (Wald 2011) because an age threshold of 55 years and above would be used to determine eligibility for treatment (Lonn 2010; Wald 2003).

While aspirin is indicated for secondary prevention of CVD, the use of aspirin for primary prevention of CVD is generally indicated when the absolute risk of cardiovascular disease outweighs the risk of severe bleeding (Baigent 2009). Also, doubt exists regarding folic acid since recent large randomised trials have indicated no CVD benefit (Armitage 2010; Holmes 2011). On the other hand, statins and antihypertensives as single treatments are known to be relatively safe and individually beneficial in terms of reducing CVD risk and thereby cardiovascular events for both secondary prevention and primary prevention (ALLHAT-investigators 2002; Colhoun 2004; CTT 2012; HPSCG 2002; Julius 2004; Kearney 2008; LaRosa 2005; Ostergren 2008; Papademetriou 2003; Sever 2003; Taylor 2013; Turnbull 2003). Therefore, although uncertainty exists regarding possible components, the consensus is that the ideal fixed-dose combination therapy for primary and secondary CVD prevention should include at least one antihypertensive and one statin.

There is some recent evidence regarding the efficacy and safety of antihypertensives and statins when administered concomitantly (Messerli 2006; Preston 2007), and of multiple antihypertensives when administered as a single tablet (Gupta 2010; Bangalore

2007). Clinicians may be wary of combination therapy due to the potential restrictions on individualised management (Viera 2011); that is, the ability to amend standard therapy because of medical history or adverse events, such as avoiding a beta-blocker in an asthmatic or changing from an ACE-inhibitor due to cough, and because of the inability to titrate each drug prescribed according to clinical response (Lonn 2010). It is also unclear if there are unique adverse events associated with fixed-dose combination therapy beyond the individual components.

How the intervention might work

The effectiveness of the drugs comprising a fixed-dose combination are generally well understood, and the principles behind using pharmacotherapy at a population level are that the drugs themselves are inexpensive, simple to administer for easier clinical decision making, might not require a medically trained practitioner, and may provide a more effective option that the promotion of lifestyle changes for multiple risk factor control. Yet convincing evidence of the benefits of such interventions has not been achieved. (Beaglehole 2011; Ebrahim 2011; Lonn 2010). Although modifying national health policy has been successful in some high-income countries, such as in Scandinavia (Vartiainen 2010), population-level pharmacotherapy can be politically challenging in both high and low to middle-income countries (Lonn 2010; Yusuf 2011) and may not meet with patient approval. However, patient adherence to the fixed-dose combination therapy is expected to be better than with multiple tablets, but it has been argued that they will likely have a greater potential for adverse effects than behavioural or lifestyle changes and that a purely biological approach is too narrow to allow the social, economic, and behavioural complexities of CVD prevention to be appreciated and confronted (Franco 2004).

Recent global epidemiological data from the Prospective Urban Rural Epidemiology (PURE) Study investigators indicate that the overall use of secondary prevention medication was less than 30% and that levels of use are particularly poor in low and middle-income countries and in rural regions (Yusuf 2011). The likely result is inadequate prevention of further CVD events. Prescribing fixed-dose combination therapy to individuals who are above an accepted absolute risk threshold for initiation of pharmacotherapy for primary CVD prevention may help to resolve these challenges. However, fixed-dose combination therapy still has many unknowns. These include (i) the best constituents, whether two or three or four or five drugs are required; and (ii) evidence of safety, effectiveness, and cost-effectiveness, and whether increasing the number of constituents will produce a favourable risk-benefit profile and be worth the increased cost. In particular, the evidence is sparse concerning benefits and risks of fixed-dose combination therapy for primary prevention in those people with low CVD risk. Several authors have questioned whether a fixed-dose combination strategy may have unforeseen negative effects on other aspects of CVD risk reduction, for example, individuals neglecting to exercise because of a sense of CVD security with fixed-dose combination therapy (Lonn 2010). As yet there are limited long-term follow-up outcome and safety data, which is of particular importance beacuse the Polypill® concept was designed with long-term use of fixed-dose combination therapy in mind.

Why it is important to do this review

Various fixed-dose combination pills are now being manufactured, and there is evidence that physicians are aware of this option and are potentially willing to prescribe it, though perhaps not without some reservations (Viera 2011). There is an emerging literature of randomised controlled trials comparing fixed-dose combination therapy with placebo or standard practice in both the primary and secondary prevention of CVD, as well as in assessing safety and tolerability (Elley 2012). Since the publication of this review (Elley 2012), additional fixed-dose combination trial data have been published.

OBJECTIVES

To determine the effectiveness of fixed-dose combination therapy on reducing fatal and non-fatal CVD events and on improving CVD risk factors for both primary and secondary prevention of CVD. We also aimed to determine discontinuation rates, adverse events, health-related quality of life, and costs of fixed-dose combination therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT).

Types of participants

Adults 18 years and older with no restriction regarding presence of CVD.

Types of interventions

A fixed-dose combination therapy, a combination of several active components into a single pill with the aim being to optimise CVD risk and reduce CVD fatal and non-fatal events. At least one statin and one antihypertensive agent should be included. We examined

different combinations and doses in stratified analyses, where possible.
Trials were considered where the comparison group was usual care, placebo, or a single drug comparator.

Types of outcome measures

Primary outcomes

- Clinical outcomes including mortality (cardiovascular and all-cause); non-fatal CVD endpoints such as myocardial infarction, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), angina or angiographically defined ischaemic heart disease, stroke, transient ischaemic attack (TIA), carotid endarterectomy, or peripheral arterial disease (PAD).
- Adverse events including overall rates of discontinuation, proportion of participants experiencing specific symptoms or results and rates of discontinuation by specific symptoms. These included but were not limited to: myalgias, cough, elevated liver enzymes, gastric irritation or dyspepsia.

Secondary outcomes

- Systolic and diastolic blood pressure
- Total and LDL cholesterol
- Adherence
- Health-related quality of life, measured according to any well validated and adjusted scale concerning quality of life
- Costs of fixed-dose combination therapy

Search methods for identification of studies

Electronic searches

The following electronic databases were searched:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 6, 2013) on *The Cochrane Library;*
- MEDLINE (Ovid) (1946 to week 2 July 2013);
- EMBASE (Ovid) (1980 to Week 28 2013);
- ISI Web of Science (1970 to 19 July 2013);
- Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), and Health Economics Evaluations Database (HEED) in *The Cochrane Library* (2011, Issue 4).

The searches were limited to records published since 2000. The fixed-dose combination therapy was conceptualised in 2001, so relevant trials will only appear after this date. The searches were initially run in January 2012 (Appendix 1) and updated in July 2013 (Appendix 2). The latest searches utilised limits to core clinical journals in MEDLINE and priority journals in EMBASE. The Cochrane sensitive-maximising RCT filter (Lefebvre 2011) was used for MEDLINE and adaptations of it were used for EMBASE and Web of Science.

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials on 11 July 2011. This search was updated on 24 December 2011 to review existing ongoing studies that had been identified and identify any recent registrations. In addition, reference lists of reviews and retrieved articles were checked for additional studies and citation searches performed on key articles. Experts in the field were contacted for unpublished and ongoing trials. Authors were contacted where necessary for additional information.

Data collection and analysis

Selection of studies

From the searches, the title and abstract of each paper were reviewed by three authors (AdeC, MF, NW) and potentially relevant references retrieved. Following this initial screening, the full text reports of potentially relevant studies were obtained, and three authors (AdeC, MF, NW) independently selected studies to be included in the review using predetermined inclusion criteria. The rapid review search was completed by one author (MH). In all cases disagreements about any study inclusions were resolved by consensus, and a fourth author (KR) was consulted if disagreement persisted.

Data extraction and management

Data were extracted independently by two authors (AdeC, MF) using a proforma, and principal investigators were contacted to provide additional relevant information where necessary. Data extraction from the rapid review was performed by one author (MH). Details of the study design, participant characteristics, study setting, intervention and comparator, and outcome data including details of outcome assessment, adverse effects, and methodological quality (randomisation, blinding, attrition) were extracted from each of the included studies. Disagreements about extracted data were resolved by consensus, and a third author was consulted if disagreement persisted (KR).

Assessment of risk of bias in included studies

Risk of bias was assessed according to the Cochrane risk of bias assessment tool, including examining the quality of the random

sequence generation and allocation concealment, description of dropouts and withdrawals (including intention-to-treat analysis), blinding (participants, personnel, and outcome assessment), and selective outcome reporting (Higgins 2011). For cluster randomised trials, we have followed the *Cochrane Handbook for Systematic Reviews of Interventions* recommendations for assessing risk of bias, with particular attention across the domains of: recruitment; baseline imbalances; loss of clusters; incorrect analyses; and comparability with individually randomised trials (Higgins 2011). The risk of bias in the included studies was assessed independently by three authors (AdeC, MF, MH).

Measures of treatment effect

Data were processed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Dichotomous outcomes were expressed as relative risks, and 95% confidence intervals (CI) were calculated for each study. For continuous variables, net changes were compared (that is intervention group minus control group differences) and a weighted mean difference (MD) and 95% CI were calculated for each study. For TIPS 2009, we compared the effects of fixed-dose combination therapy on mean (SD) levels of blood pressure and cholesterol against the study arms without active components as reported by the study authors. Where SDs were not reported in the outcomes of interest (TIPS 2009), we used baseline SDs per Elley 2012 and Furukawa 2006.

Assessment of heterogeneity

For each outcome, tests of heterogeneity were carried out using the Chi^2 test of heterogeneity and the I^2 statistic. Where no or minimal heterogeneity was present, we performed fixed-effect model meta-analyses. Where substantial heterogeneity was detected (I^2 > 50%), we evaluated the results for possible explanations (for example participants and interventions) and performed random-effect model meta-analyses with cautious intepretation.

Subgroup analysis and investigation of heterogeneity

If there were sufficient studies, we aimed to conduct the following subgroup analyses.

- Age.
- Sex.
- Primary prevention (populations where 10% or less had pre-existing CVD) versus secondary prevention (population where > 10% had pre-existing CVD).
- Two-drug versus three-drug or more fixed-dose combination therapies.
- Comparator group as usual care versus placebo or inactive control.

The first four of these analyses were pre-specified in our protocol, and the last subgroup analysis was performed post hoc. Data were available to perform subgroup analyses on the latter three analyses.

Sensitivity analysis

Sensitivity analyses were performed by excluding studies at high risk of bias. We created funnel plots and performed tests of asymmetry (Egger 1997) according to the available outcomes of systolic blood pressure and total cholesterol to assess possible publication bias through funnel plot asymmetry.

RESULTS

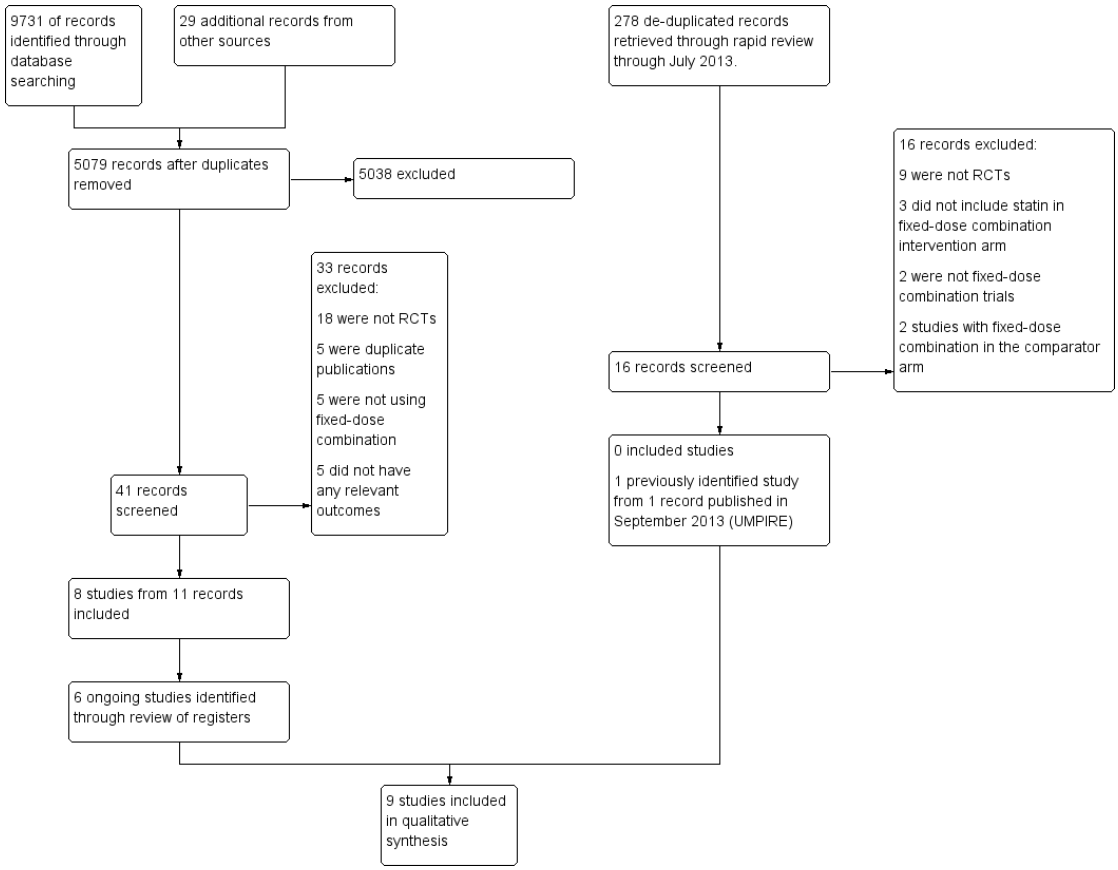
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The searches in 2012 generated 9731 hits and 5067 papers after de-duplication. Screening the titles and abstracts identified 41 papers for formal inclusion or exclusion. Of these, eight RCTs (eight papers, three abstracts) met the inclusion criteria. We identified five ongoing trials (FOCUS 2011; IMPACT 2011; Kanyini-GAP 2010; Merat 2010; PolyIran 2010). The search in 2013 generated 287 hits and 278 papers after de-duplication. Screening titles and abstracts identified 16 papers for formal inclusion or exclusion. None of these studies met the inclusion criteria. We further identified one paper published after the latest search (UMPIRE 2013) through communication with the study authors. The study flow diagram is presented in Figure 1. One study was a cluster randomised trial (CRUCIAL 2011), one study was a randomised, cross-over design clinical trial (Wald 2012), and the remaining seven were individual-level randomised trials.

Figure 1. Study flow.



Included studies

Details of the methods, participants, intervention, comparison group and outcome measures for each of the studies included in the review are shown in the Characteristics of included studies table. Nine trials were included with 7047 participants randomised. The three largest trials (CRUCIAL 2011; TIPS 2009; UMPIRE 2013) randomized 5518 (78%) of all participants. The duration of the intervention and follow-up periods was generally short-term (six weeks in one study (TOGETHER 2010), eight weeks in one study (CUSP 2009), 12 weeks in four studies (PILL 2011; Soliman 2009; TIPS 2009; Wald 2012)), but three studies had median follow-up periods of 12 to 15 months (CRUCIAL 2011; Malekzadeh 2010; UMPIRE 2013). All trials reported changes in blood pressure and cholesterol, whereas mortality was only reported in two trials (CRUCIAL 2011; UMPIRE 2013). Three trials (CRUCIAL 2011; Soliman 2009; UMPIRE 2013) compared fixed-dose combination therapy against usual care, whereas the other six trials compared combination therapy against either active control or placebo. One trial (TIPS 2009) included nine arms with different drug combinations, which led to restricting our analyses to comparisons between fixed-dose combination therapy and groups without either blood pressure or cholesterol lowering drugs (depending upon the analysis) and lowered the sample sizes in these analyses.

The included studies frequently had complex inclusion and exclusion criteria that were generally based upon freedom from prior cardiovascular disease, an age threshold ranging from > 21 years to > 55 years in women, a composite measure of short-term (10 year) risk (five year predicted Framingham CVD risk $\geq$ 7.5% in PILL 2011), or one to three elevated cardiovascular disease risk factors. UMPIRE 2013 specifically enrolled participants with established CVD or a five year risk of CVD $\geq$ 15%, while CRUCIAL 2011 included > 18% of particpants with peripheral artery disease (PAD) and > 14% with prior transient ischaemic attack (TIA) or stroke. The participants were generally middle-aged with a mean (SD) age ranging from 52.6 (9.6) years (CUSP 2009) to 62.1 (10.4) years (UMPIRE 2013). The majority of trials enrolled predominantly

men with two trial randomising more then 80% men (PILL 2011; UMPIRE 2013) compared with one trial that enrolled only 27% men (Soliman 2009). Baseline systolic blood pressure ranged from 125 mmHg to 166 mmHg, and baseline total cholesterol ranged from 4.2 to 6.1 mmol/L.

The drugs included in the various fixed-dose combination pills varied (Table 1) with three studies including two drugs (CRUCIAL 2011; CUSP 2009; TOGETHER 2010), five studies including four drugs (PILL 2011; Soliman 2009; Malekzadeh 2010, Wald 2012; UMPIRE 2013), and one study including five drugs (TIPS 2009). Aspirin was included in five studies (Malekzadeh 2010; PILL 2011; Soliman 2009; TIPS 2009; UMPIRE 2013), and blood pressure and cholesterol lowering drugs were included, by definition, in all nine studies. The blood pressure components included either a calcium channel blocker, thiazide diuretic, beta-blocker, ACE-inhibitor, or angiotensin receptor blocker (ARB), or a combination thereof. In terms of lipid lowering drugs, simvastatin was used in five trials (PILL 2011; Soliman 2009; TIPS 2009; Wald 2012; UMPIRE 2013), and atorvastatin was used in four trials (CRUCIAL 2011; CUSP 2009; Malekzadeh 2010; TOGETHER 2010).

Excluded studies

Details and reasons for exclusion for the studies that most closely missed the inclusion criteria are presented in the Characteristics of excluded studies table. The majority of excluded studies were not RCTs.

Risk of bias in included studies

Details are provided for each of the included studies in the risk of bias tables in Characteristics of included studies and in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

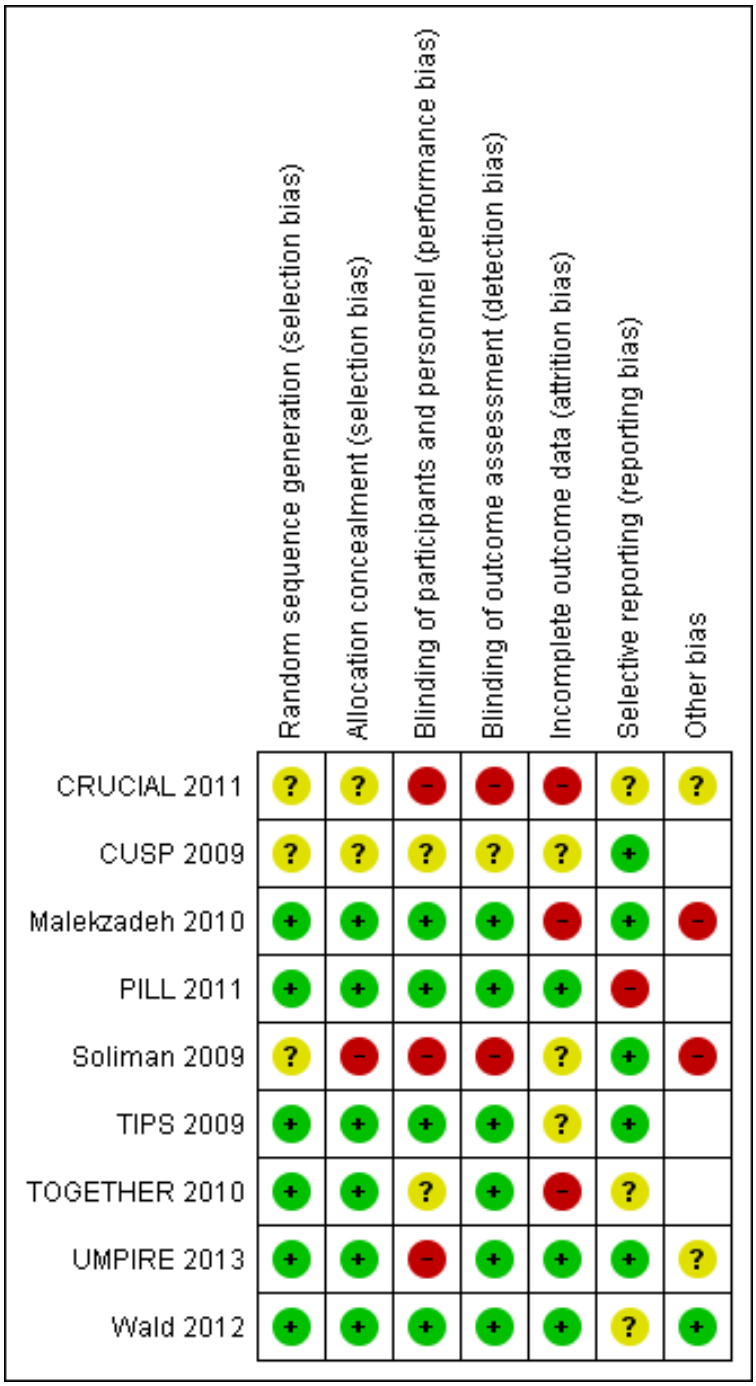
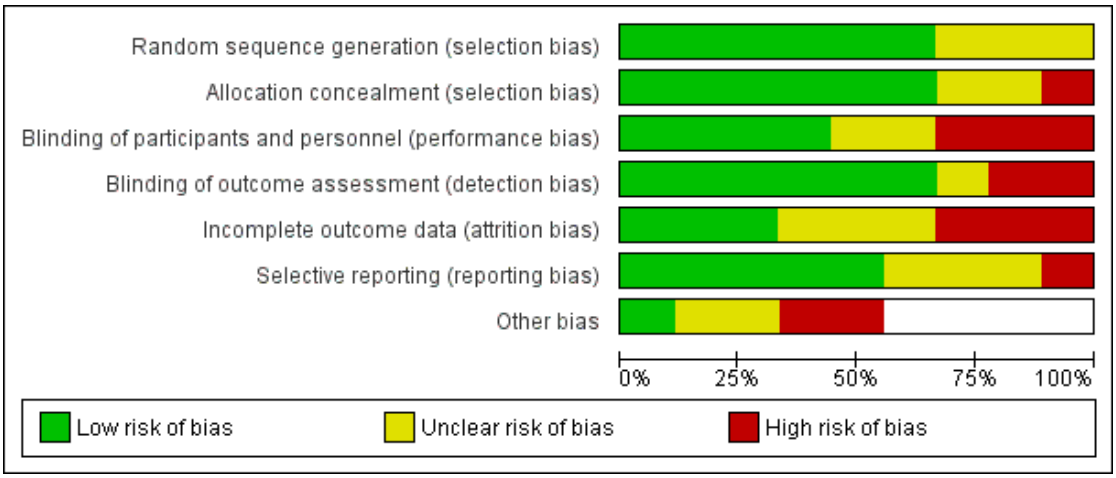


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

The methods of random sequence generation and allocation concealment were unclear in three of the included studies (CRUCIAL 2011; CUSP 2009; Soliman 2009). In the six studies where randomisation and allocation concealment were clear, the methods used were judged to have a low risk of bias (Malekzadeh 2010; PILL 2011; TIPS 2009; TOGETHER 2010; Wald 2012; UMPIRE 2013).

Blinding

Three of the nine included studies had a high risk for performance bias because the comparator group was usual care (CRUCIAL 2011; Soliman 2009; UMPIRE 2013). However, one of these studies included blinded outcome assessment (UMPIRE 2013) and had low risk of detection bias. The remaining six trials stated that they were double blinded (participants and study personnel, including outcome assessors, were blinded to treatment allocation) and were regarded as having low risk of bias in this domain.

Incomplete outcome data

Most studies reported losses to follow-up but there were differences in the proportion of losses to follow-up between the interevention and control arms. Two studies had a high risk of attrition bias (CRUCIAL 2011; TOGETHER 2010), including use of last observation carried forward for missing continuous variables. Four studies had an unclear risk of attrition bias (CUSP 2009; Malekzadeh 2010; Soliman 2009; TIPS 2009), and three studies had low risk of attrition bias (Malekzadeh 2010; Wald 2012; UMPIRE 2013).

Selective reporting

The risk of bias associated with selective reporting was low in five studies (CUSP 2009; Malekzadeh 2010; Soliman 2009; TIPS 2009; UMPIRE 2013), unclear in three studies (CRUCIAL 2011; TOGETHER 2010; Wald 2012), and high in one study (PILL 2011).

Other potential sources of bias

In CRUCIAL 2011, different doses of fixed-dose combination therapy were used among participants randomised to the intervention arm, which was associated with an uncertain risk of bias because the option for drug titration could attenuate the effect size if investigators did not titrate the dose of fixed-dose combination therapy; conversely, the differential dosing could accentuate the effect size because of higher drug doses. In Malekzadeh 2010, a run-in period was used to exclude potential participants who had adherence rates < 70%. In Soliman 2009, participants had varying degrees of background blood pressure and lipid lowering therapies

between groups. In other cases there was insufficient information to judge the risk of bias in other sources of bias not covered above, and all were categorised as unclear. In UMPIRE 2013, participants randomised to the intervention arm received fixed-dose combination therapy at no cost compared with participants randomised to usual care who were responsible for their drug costs, which may have led to increased adherence in the intervention arm.

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

All-cause mortality

Two studies (CRUCIAL 2011; UMPIRE 2013) reported death rates at the end of the study period with follow-up at 12 and 15 months, respectively. Mortality rates were low in both groups (1.2% in the intervention group compared with 1.0% in the comparator group), and participants randomised to the intervention had no evidence of increased mortality compared with the comparator group (RR 1.26, 95% CI 0.67 to 2.38) (Analysis 1.1) in the context of relatively few events. Both studies included > 10% of participants with prevalent CVD and both studies included usual care as the comparator group, so no subgroup analyses could be performed in these domains. The results were similar when restricting this analysis to UMPIRE 2013, which included a fixed-dose combination intervention with four components (compared with two in CRUCIAL 2011) (data not shown).

Major CVD events

Only two out of nine studies (Malekzadeh 2010; UMPIRE 2013) reported rates of cardiovascular events. Cardiovascular events were uncommon in both groups (4.0% rate in the intervention group compared with 2.9% in the comparator group), and participants randomised to the intervention had no evidence of increased event rates compared with the comparator group (RR 1.38, 95% CI 0.91 to 2.10) (Analysis 1.2). However, these results were imprecise, and there was only one event reported in both arms of Malekzadeh 2010. Participants in Malekzadeh 2010 did not have prevalent CVD, and the comparator group received placebo, compared with the participants in UMPIRE 2013. Both trials included four-drug fixed-dose combination therapy.

Adverse events

Seven trials including 4864 participants reporting aggregated rates of adverse events in both groups were included in the meta-analysis. The risk for adverse events was higher in participants in the intervention arm compared with participants in the control arm (30% versus 24%, RR 1.19, 95% CI 1.09 to 1.30) (Analysis 1.3). Specific side effects that were evaluated included myalgias (five studies, 12% versus 11%, RR 1.14, 95% CI 0.81 to 1.60), increased liver enzymes (three studies, 8% versus 7%, RR 1.01, 95% CI 0.72 to 1.43), cough (four studies, 6% versus 3%, RR 2.34, 95% CI 0.77 to 7.08), gastric irritation and dyspepsia (four studies, 3% versus 2%, RR 1.33, 95% CI 0.66 to 2.74), and bleeding (one study, 2% versus 0.5%, RR 4.00, 95% CI 0.45 to 35.46). Results were similar after excluding trials with >10% of participants with prevalent CVD or usual care as the comparator group (CRUCIAL 2011; UMPIRE 2013 for both) (RR 1.36, 95% CI 1.16 to 1.60) and after excluding trials with less than three drug combinations (CRUCIAL 2011; CUSP 2009; TOGETHER 2010) (RR 1.31, 95% CI 1.13 to 1.51). Rates of discontinuation were reported in both groups in the six trials with active control or placebo as the comparator and were higher in participants randomised to fixed-dose combination therapy (14% versus 11.5%, RR 1.26, 95% CI 1.02 to 1.55) (Analysis 4.1).

Secondary outcomes

Blood pressure

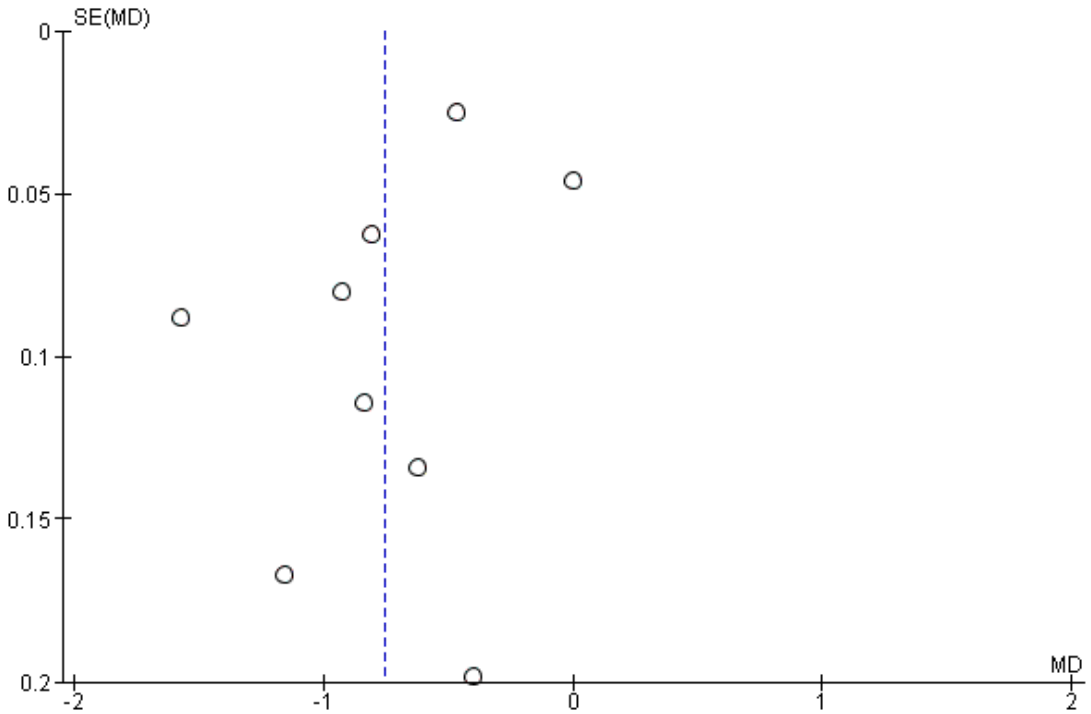
All nine trials reported changes in systolic and diastolic blood pressure in 5787 participants. There was a large degree of heterogeneity among the trials for both systolic blood pressure (I^2 = 92%) and diastolic blood pressure (I^2 = 91%). No single trial explained this heterogeneity, nor was it explained by primary versus secondary prevention trials nor two-drug versus three or more drug combinations. Using a random-effects model, the WMD in systolic blood pressure between the intervention and control arms was -7.02 mmHg (95% CI -10.18 to -3.87) (Analysis 2.1), and the WMD in diastolic blood pressure between the intervention and control arms was -3.65 mmHg (95% CI -5.44 to -1.85) (Analysis 2.2). Trials that included usual care in the comparator group (CRUCIAL 2011; CUSP 2009; UMPIRE 2013) did not have as large reductions in systolic blood pressure (MD -4.76 mmHg, 95% CI -11.24 to -1.71) compared with other trials (Analysis 2.5). These results should be interpreted with caution given the degree of heterogeneity. There was no evidence of funnel plot asymmetry for systolic blood pressure.

Lipids

All nine trials reported changes in total cholesterol in 5569 participants, and eight trials reported changes in LDL cholesterol in 5365

participants. There was a large degree of heterogeneity among the trials for both total cholesterol (I^2 = 97%) and LDL cholesterol (I^2 = 97%). No single trial explained this heterogeneity, nor was it explained by primary versus secondary prevention trials, nor two-drug versus three or more drug combinations. Using a random effects model, the weighted mean difference (WMD) in total cholesterol between the intervention and control arm was -0.75 mmol/L (95% CI -1.05 to -0.46) (Analysis 3.1). Using a random-effects model, WMD in LDL cholesterol between the intervention and control arms was -0.81 mmol/L (95% CI -1.09 to -0.53) (Analysis 3.2). Trials that included usual care in the comparator group (CRUCIAL 2011; CUSP 2009; UMPIRE 2013) did not have as large reductions in total cholesterol (MD -0.28 mmol/L, 95% CI -0.66 to 0.10) compared with other trials (Analysis 3.5). These results should be interpreted with caution given the degree of heterogeneity. There was evidence of funnel plot asymmetry for total cholesterol (Figure 4).

Figure 4. Funnel plot of comparison: 3 Cholesterol, outcome: 3.1 Total cholesterol.



Adherence

In trials with usual care comparisons, assessing adherence or discontinuation was problematic. In fact, only one (UMPIRE 2013) out of three trials that included a usual care arm reported adherence, which was defined as taking aspirin, statin, and two or more blood pressure lowering drugs at least 4 days per week. In UMPIRE, adherence at 15 months was 86% in the intervention group compared with 65% in the comparator group (RR = 1.33 [95% CI: 1.26, 1.41]). However, the discontinuation rate among individuals randomized to fixed-dose combination was 22%.

Health-related quality of life

One trial (UMPIRE 2013) reported health-related quality of life measures at the end of the study period using the EQ-5D instrument. Mean (SD) summary index scores were similar between the intervention and comparator groups (0.82 (0.01) versus 0.81 (0.1), P = 0.43).

Costs

No studies have reported costs or cost-effectiveness associated with fixed-dose combination therapy to date.

DISCUSSION

Summary of main results

The trials included in this systematic review demonstrated no differences in mortality and cardiovascular events between participants randomised to the fixed-dose combination group compared with comparator groups. However, the event rates for these outcomes were low so they were relatively uncommon, only two out of nine trials reported these outcomes, and these trials included at least one domain that had a high risk of bias, suggesting that these results should not viewed with confidence. Adverse events were common in both the intervention (30%) and comparator (24%) groups, with participants randomised to fixed-dose combination therapy being 20% (95% CI 9% to 30%) more likely to report an adverse event. Notably, no serious adverse events were reported. The trials reported weighted mean reductions in systolic (-7.02 mmHg, 95% CI -10.18 to -3.87) and diastolic blood pressure (-3.65 mmHg, 95% CI -5.44 to -1.85) and total (-0.75 mmol/L, 95% CI -1.05 to -0.46) and LDL cholesterol (-0.81 mmol/L, 95% CI -1.09 to -0.53). However, there was substantial heterogeneity in these estimates, which should be interpreted with caution. The trials demonstrated a 26% (95% CI 2% to 55%) increased risk of discontinuing the study medication (discontinuation rate range 10% to 23%) compared with either usual care, placebo, or a single drug (aspirin, statin, or thiazide in the case of TIPS 2009). We were unable to explain the heterogeneity of effects on blood pressure or lipids in terms of primary versus secondary prevention trials, the number of drugs in the fixed-dose combination pills, or the comparator group being active control, placebo or usual care. It is possible that the heterogeneity is due to the characteristics of the patients studied, differences in the potency of the antihypertensives and statins used, and the differences in treatments used in the comparison groups.

Overall completeness and applicability of evidence

The included trials used five different polypills: three of the studies (CRUCIAL 2011; CUSP 2009; TOGETHER 2010) included polypills with only two drugs (one blood pressure lowering drug (amlodipine) and one statin (atorvastatin)); three studies (PILL 2011; Soliman 2009; UMPIRE 2013) used the Dr Reddy's Lab Red Heart Pill that includes four drugs (aspirin, lisinopril, simvastatin, and hydrochlorothiazide), and the remaining studies included different four-drug (Malekzadeh 2010; Wald 2012) or five-drug combinations (TIPS 2009). The decision to combine the estimates of these different drug combinations and different comparators was made and meta-analysis for this review was performed to evaluate the estimated effect size of fixed-dose combination therapy. A rationale for fixed-dose combination therapy is that it is more likely to be taken than multiple dose regimens. However, we found a higher likelihood of discontinuation for fixed-dose treatment than for placebo. Comparisons of adherence across trials are hampered by differing definitions, which should be standardised in future reporting of these trials. Trials using 'usual care' comparison groups have reported reasonably high levels of adherence and low levels of discontinuation, but these may be misleading as there is no relevant comparison.

There are six ongoing trials (FOCUS 2011; IMPACT 2011; Kanyini-GAP 2010; Merat 2010; PolyIran 2010; TIPS-3 2012), including three that are part of the Single Pill Against Cardiovascular Events (SPACE) collaboration. These results are likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Quality of the evidence

Our review was limited by the presence of a moderate to high risk of bias in the domains of selection, performance, detection, attrition, and other types of bias in five of the nine trials that were included, which limits the confidence with which we have in these results. Using other GRADE domains, the quality of evidence was also limited by the imprecision of results for the effects on all-cause and CVD mortality, the heterogeneity of effects on blood pressure and cholesterol, and funnel plot asymmetry suggestive of publication bias (total cholesterol only). Indirectness of evidence was further limited in evaluating the effects of fixed-dose combination on adverse events and discontinuation rates, particularly because these comparisons excluded participants receiving 'usual care' (because these groups cannot 'discontinue' usual care). However, these comparisons are likely very relevant in assessing the overall effect of fixed-dose combination therapy.

Potential biases in the review process

For the TIPS 2009 and Wald 2012 studies, we relied upon the point estimates and standard deviations extracted by Elley 2012, since these data points were not specifically provided in the text of the manuscripts or by the study authors. Elley and colleagues estimated the outcome standard deviations using baseline standard deviations as reported by Furukawa and colleagues (Furukawa 2006).

Agreements and disagreements with other studies or reviews

Our results demonstrated modestly lower reductions in systolic (-7.02 mmHg versus -9.20 mmHg) and diastolic blood pressure (-3.65 mmHg versus -5.00 mmHg) and lower total (-0.75 mmol/L versus -1.22 mmol/L) and LDL cholesterol (-0.81 mmol/L versus -1.02 mmol/L) compared with an earlier systematic review (Elley 2012). The absolute and relative adverse event rates were similar to those reported by Elley 2012, but the absolute and relative discontinuation rates were lower in our review. These differences are accounted for by our inclusion of three additional studies (CRUCIAL 2011; Soliman 2009; UMPIRE 2013).

The changes in blood pressure were lower than those predicted by Wald and Law (diastolic blood pressure: -3.65 mmHg versus -11 mmHg), which may be due to the use of one blood pressure lowering drug in three of the studies (CRUCIAL 2011; CUSP 2009; TOGETHER 2010), all of which used a calcium channel blocker (amlodipine) rather than a combination of thiazide, ACE-inhibitor, or beta-blocker as previously proposed (Wald 2003). In addition, the baseline blood pressure from which Wald and Law were operating was 150/90 mmHg (Wald 2003, Lonn 2010), compared with a range of blood pressures of 125 to 165 mmHg/78 to 91 mmHg, with seven of nine studies having a baseline systolic blood pressure less than 150 mmHg. The changes in LDL cholesterol were also lower than those predicted by Wald and Law (-0.75 mmol/L versus 1.8 mmol/L), likely due to differences in the dose and type of statin used in these trials (Wald 2003). The baseline LDL cholesterol proposed by Wald and Law was 4.8 mmol/L (Lonn 2010), compared with a range of LDL cholesterol from 2.3 to 3.7 mmol/L with all nine studies having a mean baseline LDL cholesterol less than 4.8 mmol/L. Three trials used simvastatin 20 mg (Soliman 2009; PILL 2011; TIPS 2009) compared with simvastatin 40 mg proposed by Wald and Law (Wald 2003).

Bangalore and colleagues have previously performed a systematic review and meta-analysis of the effect of fixed-dose combination therapy on adherence for chronic conditions including hypertension, diabetes, and HIV (Bangalore 2007) and reported a 24% (95% CI 19% to 29%) lower rate of discontinuation compared with control. These results were similar to those reported by Gupta and colleagues, who reported an increased odds of adherence with fixed-dose combination therapy for blood pressure compared with usual care (OR 1.21, 95% CI 1.03 to 1.43) (Gupta 2010). Gupta and colleagues demonstrated trends toward improved blood pressure control and side effects (Gupta 2010). The differences in discontinuation rates and adherence between these studies and our study may be due to the fact that patients in the Bangalore and Gupta meta-analyses received active drug in either arm compared with our meta-analysis where comparator group participants received either usual care (and possibly no drugs), placebo, or alternative drugs with potentially lower rates of side effects (TIPS 2009).

Virdee and colleagues interviewed 11 primary care physicians and five practice nurses in nine Birmingham, UK practices about their knowledge and attitudes toward fixed-dose combination therapy (Virdee 2013). The majority of respondents were uncertain about how they would incorporate fixed-dose combination therapy in their practice and whether it was designed for primary or secondary CVD prevention. Most felt reluctant about using a specific age cut-off to initiate therapy, despite acknowledging potential advantages to this approach. Most respondents felt unease at the concept of minimial or no monitoring of patients taking a fixed-dose combination therapy, despite the proposal by Wald and Law (Wald 2003). In March 2010, Viera and colleagues surveyed US physicians about their willingness to prescribe fixed-dose combination therapy. Nearly two out of every three physicians reported that they would prescribe fixed-dose combination therapy for patients at moderate risk for CVD and more than four out of every five physicians reported that they would prescribe fixed-dose combination therapy for patients at high risk for CVD. These disparate data using different methods of data collection suggest varying potential for uptake among physicians.

AUTHORS' CONCLUSIONS

Implications for practice

Compared with usual care, active control, or placebo for CVD prevention, the effects of fixed-dose combination therapy on all-cause mortality or CVD events are uncertain due to low event rates, imprecision, and risk of bias. Participants randomised to fixed-dose combination therapy had moderately higher rates of adverse events (RR 1.18, 95% CI 1.09 to 1.30) and discontinuation (RR 1.26, 95% CI 1.02 to 1.55). Fixed-dose combination therapy is associated with a -7.05 mmHg (95% CI -10.18 to -3.87) and -3.65 mmHg (95% CI -5.44 to -1.85) greater reduction in systolic and diastolic blood pressure and a -0.75 mmol/L (95% CI -1.05 to -0.46) and -0.81 mmol/L (95% CI -1.09 to -0.53) greater reduction in total and LDL cholesterol, but there is substantial heterogeneity in these results. The heterogeneity may reflect differences in primary compared with secondary prevention studies, the composition of fixed-dose combinations, comparator groups, or all of the above. Fixed-dose combination therapy improved adherence to a multi-drug strategy by 33% (26% to 41%) compared with usual care, but this comparison was reported in only one study. Fixed-dose combination therapy may be an alternative therapy for risk factor control in patients for CVD prevention but future studies will likely have an important effect on these estimates.

Implications for research

High-quality randomised controlled trials are needed to evaluate if the effect of fixed-dose combination therapies on risk factor levels translates into improvements in fatal and non-fatal events in both primary and secondary CVD prevention settings. Studies evaluating the effects of fixed-dose combination therapy compared with

usual multiple variable dose therapies should also be performed to compare adherence rates more directly, since discontinuation rates are generally lower among participants receiving placebos. Larger studies are also needed to evaluate the risk of serious adverse events.

ACKNOWLEDGEMENTS

We are grateful for the assistance from Dr Curt Furberg who provided additional information on data reported in Soliman 2009, for the assistance from Dr Tom Marshall and colleagues for extra data for Malekzadeh 2010, for the assistance of Henry Lishi Li for translation of one excluded manuscript, and for the assistance of Ms Amy Rogers for her editorial assistance.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CRUCIAL 2011

Methods	Open label cluster randomised trial
Participants	136 clusters; 1461 total participants (779 intervention; 682 control participants), men and women aged 35-79 years with hypertension and total cholesterol <250 mg/dl plus three or more risk factors (current smoker, peripheral artery disease, type 2 diabetes, family history of early CHD before aged 55 years in first dgree relative; left ventricular hypertrophy on electrocardiogram [ECG]; history of transient ischemic attack or stroke three or more months prior to screening; ECG abnormalities; age >55 years [men] or >65 years [women], total cholesterol >250mg/dl, or HDL <40mg/dl)
Interventions	Intervention: Single pill amlodipine/atorvastatin (5mg/10mg to 10mg/10mg; site investigators could request dosages of 5/20 mg and 10/20 mg) in addition to other hypertensive / lipid lowering therapy as required, as well as therapeutic lifestyle counselling change Control: Usual care, including therapeutic lifestyle counselling change
Outcomes	SBP, DBP, LDL-C, total cholesterol; all-cause mortality reported
Notes	Control: inactive/usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Investigators - randomly assigned", "randomisation was stratified", "investigator as unit of randomisation"
Allocation concealment (selection bias)	Unclear risk	Due to cluster randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	High risk	93/779 (11.9%) discontinued intervention; 44/682 (6.5%) discontinued in usual care arm
Selective reporting (reporting bias)	Unclear risk	Not all outcomes available for meta-analysis

Other bias	Unclear risk	Significant differences between two arms in terms of baseline blood pressure and ECG abnormalities/PVD; underpowered according to authors' own calculations; different doses of intervention were available upon request to investigators

CUSP 2009

Methods	Individual-level randomised controlled trial
Participants	130 participants (66 intervention; 64 control) with coexisting, untreated hypertension (SBP=140-169 mmHg or DBP=90-105 mmHg) and dyslipidemia (LDL-C=110-160 mg/dl) but without a history of cardiovascular disease; age >21 years
Interventions	Intervention: Single pill amlodipine/atorvastatin (5mg/20mg) + therapeutic lifestyle changes Control: Therapeutic lifestyle changes
Outcomes	Target for BP <140/90 mm Hg and LDL-C <100 mg/dL [2.59 mmol L] at week 4 and week 8: the percentage of patients in whom the single LDL-C goal was reached at weeks 4 and 8; mean changes from baseline in SBP and DBP at weeks 4 and 8; mean changes from baseline in LDL-C at weeks 4 and 8; 10-year Framingham risk of CHD at weeks 4 and 8
Notes	Control: inactive/usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specifically stated: "Patients were randomised in a double-blind manner"
Allocation concealment (selection bias)	Unclear risk	Not specifically stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specifically stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specifically stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how data from particpants lost to follow-up were handled

Selective reporting (reporting bias)	Low risk	Primary outcomes reported (week 4 blood pressure and LDL targets)

Malekzadeh 2010

Methods	Block randomisation
Participants	475 participants (241 polypill; 234 control) without cardiovascular disease, hypertension, or hyperlipidaemia aged 50 to 79 years (men) and 55 to 79 years (women)
Interventions	Intervention: Polypill (aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg and hydrochlorothiazide 12.5 mg) Control: placebo
Outcomes	Hospital admissions / major cardiovascular events / seated and standing BP, LDL-C, total cholesterol, triglycerides, HDL-C and fasting glucose
Notes	Control: inactive/placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation
Allocation concealment (selection bias)	Low risk	Computer generation allocation to numbered list of blister packs manufactured by Alborz Darou
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical blister packs used for participant blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors (clinicians) blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of loss to follow-up at 12 months (experimental 32%; control 22%)
Selective reporting (reporting bias)	Low risk	Primary outcome reported (changes in blood pressure and LDL cholesterol)
Other bias	High risk	Run-in period excluded participants with low (<70%) adherence; large differences in baseline characteristics between intervention and control groups

PILL 2011

Methods	Individual-level randomised controlled trial
Participants	378 participants (189 intervention; 189 control) with 5-year Framingham coronary heart disease risk ≥7.5% or if Framingham risk was between 5% and 7.5%, two or more additional untreated risk factors were needed (body mass index >30kg/m2, waist circumference >102cm in men or >88cm in women; heart rate > 80 bpm; fasting glucose 5.6-7 mmol/L, triglycerides >1.7 mmol/L; family history of first degree relative with premature ischemic heart disease or stroke (men < 55 years; women: <65 years), or glomerular filtration rate <60ml/min
Interventions	Intervention: Red heart pill (aspirin 75 mg, lisinopril 10mg, hydrochlorothiazide 12. 5mg and simvastatin 20mg) Control: placebo
Outcomes	Change in SBP; change in LDL-C; tolerability; secondary outcomes included adherence, DBP, total cholesterol, HDL-C, total cholesterol:HDL cholesterol ratio, non-HDL cholesterol, triglycerides, frequency of switching/adding open-label treatment, estimated effects on CVD risk
Notes	Control: inactive/placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer based randomisation
Allocation concealment (selection bias)	Low risk	Central computer based randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Specifically reported and use of placebo control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors and study staff all blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of loss to follow-up (experimental 2%; control 1%)
Selective reporting (reporting bias)	High risk	Last observation carried forward for missing data at week 12

Soliman 2009

Methods	Open label, parallel group randomised clinical trial
Participants	216 (105 Polypill; 111 control); ≥40 years for men and ≥50 years for women; estimated 10 year World Health Organization total cardiovascular risk score ≥20% without established cardiovascular disease
Interventions	Intervention: Red Heart pill 2b (75 mg aspirin, 20 mg simvastatin, 10 mg lisinopril and 12.5 mg hydrochlorothiazide) Control: Standard practice defined by the study investigators
Outcomes	SBP, total cholesterol, 10-year cardiovascular disease risk, adherence, fasting glucose, creatinine, potassium, and liver enzymes
Notes	Control: inactive/usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No method of randomisation stated
Allocation concealment (selection bias)	High risk	Open label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how missing data were handled
Selective reporting (reporting bias)	Low risk	Primary outcomes (blood pressure, cholesterol, ten year CVD risk) all reported
Other bias	High risk	Use of non-study antihypertensives and statins very different between centres

TIPS 2009

Methods	Individual-level randomised controlled trial
Participants	2053 participants (205 aspirin; 205 thiazide; 209 thiazide + ramipril; 207 thiazide + atenolol; 205 ramipril + atenolol; 204 thiaizde + ramipril + atenolol; 204 thiaizide + ramipril + atenolol + aspirin; 202 simvastatin; 412 Polycap [thiazide + ramipril + atenolol + simvastatin + aspirin); 45 to 80 years old without prior cardiovascular disease but with

TIPS 2009 (*Continued*)

	at least one risk factor: type 2 diabetes; blood pressure >140/90 mmHg but <160/100 mmHg; smoker within the past five years; waist-to-hip ratio >0.85 for women and 0.90 for men; LDL cholesterol >3.1 mmol/L but less 4.5 mmol/L or HDL cholesterol <1.04 mmol/L
Interventions	Intervention: Polycap (thiazide 12·5 mg, atenolol 50 mg, ramipril 5 mg, simvastatin 20 mg, aspirin 100 mg) Control: 8 other drug/drug combination groups listed above
Outcomes	LDL for the effect of lipid-lowering drugs, BP for antihypertensive drugs, heart rate for the effects of atenolol, urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin, rates of discontinuation of drugs for safety
Notes	Control: active

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer randomisation
Allocation concealment (selection bias)	Low risk	Central computer randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo control using identical capsule
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinding reported; probably occurred given research team's prior studies
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how missing SBP and LDL-C data at week 12 follow-up were handled
Selective reporting (reporting bias)	Low risk	Primary outcomes reported

TOGETHER 2010

Methods	Individual-level randomised, double dummy controlled trial
Participants	244 participants (122 intervention; 122 control) with history of hypertension but no history of CVD or diabetes with ≥2 risk factors: age ≥45 years for men; ≥55 years for women; current smoker; family history of premature coronary heart disease in first degree relative; HDL cholesterol <40 mg/dl; waist circumference >102 cm in men and >88 cm in women

TOGETHER 2010 (*Continued*)

Interventions	Intervention: single pill amlodipine (5/10mg) plus atorvastatin 20mg + therapeutic lifestyle changes Control: amlodipine (5/10mg) + therapeutic lifestyle changes
Outcomes	Proportion achieving a BP goal <140/90 mmHg and LDL-C<100 mg/dl at week 6; BP and LDL-C goal at week 4; BP goal at weeks 4 and 6; change in SBP, DBP, LDL-C, total cholesterol, HDL-C, triglycerides at weeks 4 and 6; predicted 10 year Framingham coronary heart disease risk score, adverse events
Notes	Control: active

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central, computer based telerandomisation
Allocation concealment (selection bias)	Low risk	Central, computer based telerandomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind labeled bottles but unclear if pills were identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reportedly double blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Last observation carried forward used for non-completers for final analysis
Selective reporting (reporting bias)	Unclear risk	Primary outcomes reported

UMPIRE 2013

Methods	Randomised, open label, blinded endpoint clinical trial of an FDC-based treatment strategy compared with usual care
Participants	≥18 years old and established CVD or an estimated 5 year CVD risk of 15% or greater in India and 3 European countries (England, Ireland, and the Netherlands)
Interventions	Intervention: one of two versions of the fixed-dose combination ((1) aspirin 75mg, simvastatin 40mg, lisinopril 10mg, atenolol 50mg or (2) aspirin 75mg, simvastatin 40mg, lisinopril 10mg, hydrochlorothiazide 12.5mg) Control: usual care

Outcomes	Primary: adherence to indicated medications (self-reported current use of antiplatelet, statin, and ≥2 BP-lowering therapies, defined as taking the medication for at least 4 days during the week preceding the visit) at baseline and at the end of the trial and changes in SBP and LDL-C from baseline to the end of the trial Secondary: adherence at 12 months, reasons for stopping cardiovascular medications, quality of life, serious adverse events, and changes in total cholesterol, HDL-C, triglycerides, and creatinine from baseline to 12 months and end of study and cardiovascular events (including coronary heart disease, heart failure leading to death or hospital admission, and cerebrovascular or peripheral arterial disease events)
Notes	Control: inactive/usual care Trial is part of "Single Pill Against Cardiovascular Events (SPACE)" collaboration, which encompasses the "Improving Adherence using Combination Therapy (IMPACT)" and "Kaniyini Guidelines Adherence with the Polypill (Kanyini-GAP)" trials

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation occurred through web-based clinical data management system
Allocation concealment (selection bias)	Low risk	Randomisation occurred through web-based clinical data management system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	At the end of the study, data on self-reported adherence, systolic BP, and LDL-C were available for 1921 (96%), 1849 (92%) , and 1807 (90%) randomized participants, respectively
Selective reporting (reporting bias)	Low risk	All primary outcomes reported; quality of life outcomes were not reported in this initial report
Other bias	Unclear risk	Participants randomized to the intervention arm received fixed-dose combination therapy at no cost compared with participants randomized to usual care who were responsible for their drug costs

Wald 2012

Methods	Individual-level randomised double-blind placebo-controlled cross-over trial
Participants	86 individuals (43 Polypill then placebo; 43 placebo then Polypill) aged 50 years or over without history of cardiovascular disease who were previously taking simvastatin and blood pressure lowering drugs; limited to participants living in London or could travel easily to London
Interventions	Intervention: fixed-dose combination (amlodipine 2.5mg, losartan 25mg, hydrochlorothiazide 12.5mg, simvastatin 40mg) daily for 12 weeks Control: placebo
Outcomes	SBP, DBP, total cholesterol, LDL-C, HDL-C, triglycerides, apoB, adherence
Notes	Control: inactive/placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation
Allocation concealment (selection bias)	Low risk	Computer generated block randomisation with sequential identical blister packs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors reported as being blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcomes reported
Selective reporting (reporting bias)	Unclear risk	Adverse event data not clearly described; only proportion of individuals with "symptom", which was assumed to be an adverse event
Other bias	Low risk	No need for intention-to-treat analysis as cross-over design. Any losses to follow-up clear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Avenell 2012	Not related to cardiovascular outcomes
Bakris 2012	Did not include statin fixed-dose combination intervention
Blank 2005	Intervention fixed-dose combination therapy but not RCT
Boger-Megiddo 2010	Case-control study, not RCT
CAPABLE 2009a	Intervention fixed-dose combination therapy but not RCT
CAPABLE 2009b	Intervention fixed-dose combination therapy but not RCT
Chapman 2010	Intervention polypill but not RCT
Chyrsant 2011	Review article, not RCT
Derosa 2013	Did not include statin fixed-dose combination intervention
Gemini-AALA 2009	Intervention fixed-dose combination therapy but not RCT
JEWEL 2006	Intervention fixed-dose combination therapy but not RCT
JEWEL 2006a	See above
Li 2011	Non-randomized, non-comparator study
Liew 2009	Intervention fixed-dose combination therapy but not RCT (cost-effectiveness analysis)
Neldam 2012	Not RCT
Neutel 2012	Not RCT
Nitsch 2013	NSAID coprescription, not RCT
Patel 2010	Intervention fixed-dose combination therapy but not RCT
Sun 2012	Comparator: fixed-dose combination
TIPS-2 2012	Comparator group includes fixed-dose combination therapy
Wald review 2012	Review article, not RCT
Weber 2012	Retrospective analysis, not RCT
Weber 2013	Secondary analysis of ACCOMPLISH trial

(*Continued*)

Zhu 2012	Did not include statin fixed-dose combination intervention

Characteristics of ongoing studies *[ordered by study ID]*

FOCUS 2011

Trial name or title	FOCUS
Methods	Randomised controlled trial
Participants	1340 post-MI patients followed up for 9 months
Interventions	Fixed-dose combination (aspirin 100mg, ramipril 2.5mg/5mg/10mg, simvastatin 40mg) or three drugs separately
Outcomes	Primary outcomes: adherence to treatment Secondary outcomes: changes in SBP/DBP/LDL-C, adverse events, economic data
Starting date	Protocol published November 2011
Contact information	
Notes	

IMPACT 2011

Trial name or title	IMProving Adherence using Combination Therapy (IMPACT)
Methods	Open-label randomised controlled trial
Participants	600 participants who have had CVD events or are at high risk of CVD followed up for 12 months
Interventions	Fixed-dose combination (aspirin 75mg, simvastatin 40mg, lisinopril 10mg, hydrochlorothiazide 12.5mg/atenolol 50mg) or current medications
Outcomes	Primary outcomes: adherence to prescribed medication, changes in SBP/LDL-C Secondary outcomes: other serum lipids, medication dispensing, barriers to adherence, CVD events, other serious adverse events, quality of life, prescriber acceptability
Starting date	Protocol published July 2011
Contact information	
Notes	Linked to Kanyini-GAP and UMPIRE

Kanyini-GAP 2010

Trial name or title	Kanyini-Guidelines Adherence with the Polypill (Kanyini-GAP)
Methods	Open randomised controlled trial
Participants	1000 participants at high risk of cardiovascular events recruited from mainstream GP practices and Aboriginal health services followed up for an average of 18 months
Interventions	One of two versions of fixed-dose combination (chosen by treating clinician: (1) aspirin 75mg, simvastatin 40mg, lisinopril 10mg, atenolol 50mg or (2) aspirin 75mg, simvastatin 40mg, lisinopril 10mg, hydrochlorothiazide 12.5mg) or to usual care
Outcomes	Primary outcomes: change in cholesterol / SBP, self-reported use of aspirin / simvastatin / at least two antihypertensives Secondary outcomes: cardiovascular events, renal outcomes, self-reported barriers to indicated therapy, prescription of indicated therapy, serious adverse events, changes in quality of life
Starting date	Protocol published August 2010
Contact information	
Notes	Linked closely to IMPACT and UMPIRE

Merat 2010

Trial name or title	Polypill and Nonalcoholic Steatohepatitis (PolyIran-L)
Methods	Unclear in trial registration
Participants	Unclear in trial registration, followed up for 5 years
Interventions	Fixed-dose combination (unspecified)
Outcomes	Cardiovascular events (also non-alcoholic steatohepatitis-specific outcomes)
Starting date	Registered 19/11/2010 (NCT01245608)
Contact information	
Notes	No publication of protocol, design or any data as yet

PolyIran 2010

Trial name or title	PolyIran
Methods	Three-armed open randomised controlled trial
Participants	30000 participants over 50 years in Iran followed up between 2 and 5 years

PolyIran 2010 (*Continued*)

Interventions	Fixed-combination therapy (aspirin, statin, antihypertensives - not detailed) + minimal care; minimal care alone; usual care alone
Outcomes	Cardiovascular events, cardiovascular-specific mortality
Starting date	Registered 14/12/2010 (NCT01271985)
Contact information	
Notes	No publication of protocol, design or any data as yet

TIPS-3 2012

Trial name or title	The International Polycap Study-3
Methods	2 x 2 x 2 randomised controlled trial, factorial design (3 arms: Polycap D, aspirin, vitamin D)
Participants	5500 participants (women 60 years or older and men 55 years or older) without known heart disease or prior stroke and without a clear indication or contraindication to any of the study medications and INTERHEART risk score of 10 or greater
Interventions	Polycap DS vs. placebo; embedded in trial comparing enteric coated aspirin vs. placebo and vitamin D vs. placebo
Outcomes	Composite of major CVD (CV death, non-fatal stroke, non-fatal MI), plus heart failure, resuscitated cardiac arrest, or revascularisation with evidence of ischemia in participants taking Polycap versus placebo
Starting date	Protocl updated on clinicaltrials.gov on October 2012 (ClinicalTrials.gov Identifier:NCT01646437)
Contact information	Dr. Salim Yusuf, Population Health Research Institute
Notes	

DATA AND ANALYSES

Comparison 1. Mortality, cardiovascular events, and adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	3465	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.67, 2.38]
2 Cardiovascular events	2	2479	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.91, 2.10]
3 Any adverse event	7	4864	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.09, 1.30]

Comparison 2. Blood pressure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic blood pressure	9	5787	Mean Difference (IV, Random, 95% CI)	-7.02 [-10.18, -3.87]
2 Diastolic blood pressure	9	5787	Mean Difference (IV, Random, 95% CI)	-3.65 [-5.44, -1.85]
3 Systolic blood pressure: primary prevention trials	7	2366	Mean Difference (IV, Random, 95% CI)	-7.45 [-11.05, -3.84]
4 Systolic blood pressure: 3+ drugs only	6	4014	Mean Difference (IV, Random, 95% CI)	-7.00 [-11.40, -2.60]
5 Systolic blood pressure: comparator as usual care	3	3624	Mean Difference (IV, Random, 95% CI)	-4.76 [-11.24, 1.71]

Comparison 3. Cholesterol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cholesterol	9	5569	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.05, -0.46]
2 LDL cholesterol	8	5365	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.09, -0.53]
3 Total cholesterol: primary prevention trials	7	2147	Mean Difference (IV, Random, 95% CI)	-0.92 [-1.18, -0.65]
4 Total cholesterol: 3+ drugs only	6	3796	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.10, -0.21]
5 Total cholesterol: comparator as usual care	3	3624	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.66, 0.10]

Comparison 4. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation of study drug	6	2423	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.02, 1.55]
2 Myalgias	5	3014	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.81, 1.60]
3 Increased liver chemistries	3	1427	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.72, 1.43]
4 Cough	4	2093	Risk Ratio (M-H, Random, 95% CI)	2.34 [0.77, 7.08]
5 Dyspepsia/gastrointestinal irritation	4	3417	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.64, 2.74]
6 Bleeding	1	378	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.45, 35.46]

Analysis 1.1. Comparison 1 Mortality, cardiovascular events, and adverse events, Outcome 1 All-cause mortality.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 1 Mortality, cardiovascular events, and adverse events

Outcome: 1 All-cause mortality

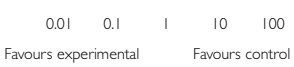
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CRUCIAL 2011	5/779	2/682		12.4 %	2.19 [0.43, 11.24]
UMPIRE 2013	17/1002	15/1002		87.6 %	1.13 [0.57, 2.26]
Total (95% CI)	**1781**	**1684**		**100.0 %**	**1.26 [0.67, 2.38]**

Total events: 22 (Experimental), 17 (Control)

Heterogeneity: Chi^2 = 0.53, df = 1 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 0.73 (P = 0.47)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Mortality, cardiovascular events, and adverse events, Outcome 2 Cardiovascular events.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 1 Mortality, cardiovascular events, and adverse events

Outcome: 2 Cardiovascular events

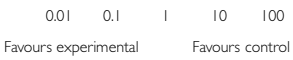
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Malekzadeh 2010	0/241	1/234		4.2 %	0.32 [0.01, 7.91]
UMPIRE 2013	50/1002	35/1002		95.8 %	1.43 [0.94, 2.18]
Total (95% CI)	**1243**	**1236**		**100.0 %**	**1.38 [0.91, 2.10]**

Total events: 50 (Experimental), 36 (Control)

Heterogeneity: $Chi^2 = 0.82$, df = 1 (P = 0.37); $I^2 = 0.0\%$

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Mortality, cardiovascular events, and adverse events, Outcome 3 Any adverse event.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 1 Mortality, cardiovascular events, and adverse events

Outcome: 3 Any adverse event

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CRUCIAL 2011	380/779	300/682		53.6 %	1.11 [0.99, 1.24]
CUSP 2009	21/66	22/64		3.7 %	0.93 [0.57, 1.51]
Malekzadeh 2010	97/241	71/234		12.1 %	1.33 [1.04, 1.70]
PILL 2011	81/189	59/189		9.9 %	1.37 [1.05, 1.80]
TOGETHER 2010	18/122	11/122		1.8 %	1.64 [0.81, 3.32]
UMPIRE 2013	118/1002	102/1002		17.1 %	1.16 [0.90, 1.49]
Wald 2012	24/86	11/86		1.8 %	2.18 [1.14, 4.17]
Total (95% CI)	**2485**	**2379**		**100.0 %**	**1.19 [1.09, 1.30]**

Total events: 739 (Experimental), 576 (Control)

Heterogeneity: Chi^2 = 8.60, df = 6 (P = 0.20); I^2 =30%

Test for overall effect: Z = 3.94 (P = 0.000080)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Blood pressure, Outcome 1 Systolic blood pressure.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 2 Blood pressure

Outcome: 1 Systolic blood pressure

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CRUCIAL 2011	760	-19.8 (17.1)	657	-10 (16.4)		12.6 %	-9.80 [-11.55, -8.05]
CUSP 2009	63	-13.4 (12.6)	60	-5.1 (15.5)		9.8 %	-8.30 [-13.31, -3.29]
Malekzadeh 2010	241	-3.7 (23.9)	234	-1.3 (25.1)		10.4 %	-2.40 [-6.81, 2.01]
PILL 2011	189	-16.7 (16.2)	189	-6.8 (16.5)		11.4 %	-9.90 [-13.20, -6.60]
Soliman 2009	99	-28.8 (24.9)	104	-26.9 (25.7)		8.0 %	-1.90 [-8.86, 5.06]
TIPS 2009	392	-12.4 (12.3)	390	-5 (12.3)		12.6 %	-7.40 [-9.12, -5.68]
TOGETHER 2010	118	-4 (11)	115	-1 (12.5)		11.7 %	-3.00 [-6.03, 0.03]
UMPIRE 2013	1002	-7.8 (17.7)	1002	-6 (16.1)		12.7 %	-1.80 [-3.28, -0.32]
Wald 2012	86	-17.9 (10.4)	86	0 (16)		10.8 %	-17.90 [-21.93, -13.87]
Total (95% CI)	**2950**		**2837**			**100.0 %**	**-7.02 [-10.18, -3.87]**

Heterogeneity: Tau^2 = 19.82; Chi^2 = 98.50, df = 8 (P<0.00001); I^2 =92%

Test for overall effect: Z = 4.36 (P = 0.000013)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Blood pressure, Outcome 2 Diastolic blood pressure.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 2 Blood pressure

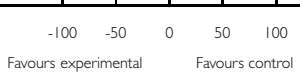
Outcome: 2 Diastolic blood pressure

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CRUCIAL 2011	760	-10.5 (10.2)	657	-5.3 (9.5)		12.8 %	-5.20 [-6.23, -4.17]
CUSP 2009	63	-9.1 (8.5)	60	-5.8 (10.9)		8.9 %	-3.30 [-6.77, 0.17]
Malekzadeh 2010	241	-0.8 (14.8)	234	-0.1 (14.4)		10.4 %	-0.70 [-3.33, 1.93]
PILL 2011	189	-8.1 (10.2)	189	-2.9 (10.3)		11.3 %	-5.20 [-7.27, -3.13]
Soliman 2009	99	-11.3 (12.3)	104	-10.8 (12)		9.1 %	-0.50 [-3.85, 2.85]
TIPS 2009	392	-8.1 (8.1)	390	-2.5 (8.1)		12.7 %	-5.60 [-6.74, -4.46]
TOGETHER 2010	118	-1.7 (8.2)	115	-1.1 (7)		11.5 %	-0.60 [-2.56, 1.36]
UMPIRE 2013	1002	-4.6 (9.14)	1002	-3.1 (9.13)		13.0 %	-1.50 [-2.30, -0.70]
Wald 2012	86	-9.8 (8)	86	0 (10)		10.2 %	-9.80 [-12.51, -7.09]
Total (95% CI)	**2950**		**2837**			**100.0 %**	**-3.65 [-5.44, -1.85]**

Heterogeneity: $Tau^2 = 6.30$; $Chi^2 = 87.01$, df = 8 (P<0.00001); $I^2 = 91\%$

Test for overall effect: Z = 3.98 (P = 0.000070)

Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2 Blood pressure, Outcome 3 Systolic blood pressure: primary prevention trials.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 2 Blood pressure

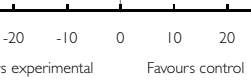
Outcome: 3 Systolic blood pressure: primary prevention trials

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CUSP 2009	63	-13.4 (12.6)	60	-5.1 (15.5)		13.1 %	-8.30 [-13.31, -3.29]
Malekzadeh 2010	241	-3.7 (23.9)	234	-1.3 (25.1)		13.9 %	-2.40 [-6.81, 2.01]
PILL 2011	189	-16.7 (16.2)	189	-6.8 (16.5)		15.3 %	-9.90 [-13.20, -6.60]
Soliman 2009	99	-28.8 (24.9)	104	-26.9 (25.7)		10.6 %	-1.90 [-8.86, 5.06]
TIPS 2009	392	-12.4 (12.3)	390	-5 (12.3)		16.9 %	-7.40 [-9.12, -5.68]
TOGETHER 2010	118	-4 (11)	115	-1 (12.5)		15.7 %	-3.00 [-6.03, 0.03]
Wald 2012	86	-17.9 (10.4)	86	0 (16)		14.4 %	-17.90 [-21.93, -13.87]
Total (95% CI)	**1188**		**1178**			**100.0 %**	**-7.45 [-11.05, -3.84]**

Heterogeneity: $Tau^2 = 19.25$; $Chi^2 = 43.81$, df = 6 ($P<0.00001$); $I^2 = 86\%$

Test for overall effect: Z = 4.05 (P = 0.000052)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Blood pressure, Outcome 4 Systolic blood pressure: 3+ drugs only.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 2 Blood pressure

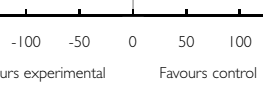
Outcome: 4 Systolic blood pressure: 3+ drugs only

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Malekzadeh 2010	241	-3.7 (23.9)	234	-1.3 (25.1)		16.0 %	-2.40 [-6.81, 2.01]
PILL 2011	189	-16.7 (16.2)	189	-6.8 (16.5)		17.3 %	-9.90 [-13.20, -6.60]
Soliman 2009	99	-28.8 (24.9)	104	-26.9 (25.7)		12.9 %	-1.90 [-8.86, 5.06]
TIPS 2009	392	-12.4 (12.3)	390	-5 (12.3)		18.6 %	-7.40 [-9.12, -5.68]
UMPIRE 2013	1002	-7.8 (17.7)	1002	-6 (16.1)		18.7 %	-1.80 [-3.28, -0.32]
Wald 2012	86	-17.9 (10.4)	86	0 (16)		16.5 %	-17.90 [-21.93, -13.87]
Total (95% CI)	**2009**		**2005**			**100.0 %**	**-7.00 [-11.40, -2.60]**

Heterogeneity: Tau^2 = 26.38; Chi^2 = 74.66, df = 5 (P<0.00001); I^2 =93%

Test for overall effect: Z = 3.12 (P = 0.0018)

Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2 Blood pressure, Outcome 5 Systolic blood pressure: comparator as usual care.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 2 Blood pressure

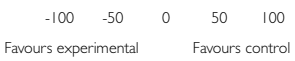
Outcome: 5 Systolic blood pressure: comparator as usual care

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CRUCIAL 2011	760	-19.8 (17.1)	657	-10 (16.4)		36.7 %	-9.80 [-11.55, -8.05]
Soliman 2009	99	-28.8 (24.9)	104	-26.9 (25.7)		26.3 %	-1.90 [-8.86, 5.06]
UMPIRE 2013	1002	-7.8 (17.7)	1002	-6 (16.1)		37.0 %	-1.80 [-3.28, -0.32]
Total (95% CI)	**1861**		**1763**			**100.0 %**	**-4.76 [-11.24, 1.71]**

Heterogeneity: $Tau^2 = 28.89$; $Chi^2 = 47.68$, df = 2 (P<0.00001); $I^2 = 96\%$

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 Cholesterol, Outcome 1 Total cholesterol.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 3 Cholesterol

Outcome: 1 Total cholesterol

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CRUCIAL 2011	760	-0.45 (0.48)	657	0.02 (0.47)		11.8 %	-0.47 [-0.52, -0.42]
CUSP 2009	63	-0.72 (0.32)	60	0.09 (0.37)		11.6 %	-0.81 [-0.93, -0.69]
Malekzadeh 2010	241	-0.89 (1.53)	234	-0.27 (1.39)		10.8 %	-0.62 [-0.88, -0.36]
PILL 2011	189	-0.99 (1.24)	189	-0.15 (0.96)		11.1 %	-0.84 [-1.06, -0.62]
Soliman 2009	99	-1.4 (1.2)	104	-1 (1.6)		9.8 %	-0.40 [-0.79, -0.01]
TIPS 2009	375	-0.75 (0.9)	189	0.18 (0.9)		11.5 %	-0.93 [-1.09, -0.77]
TOGETHER 2010	118	-1.47 (0.71)	115	0.1 (0.63)		11.4 %	-1.57 [-1.74, -1.40]
UMPIRE 2013	1002	-0.1 (1.03)	1002	-0.1 (1.03)		11.7 %	0.0 [-0.09, 0.09]
Wald 2012	86	-1.16 (1.18)	86	0 (1)		10.3 %	-1.16 [-1.49, -0.83]
Total (95% CI)	**2933**		**2636**			**100.0 %**	**-0.75 [-1.05, -0.46]**

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 345.48$, df = 8 ($P<0.00001$); $I^2 = 98\%$

Test for overall effect: $Z = 5.01$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Cholesterol, Outcome 2 LDL cholesterol.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 3 Cholesterol

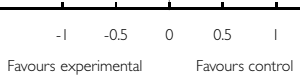
Outcome: 2 LDL cholesterol

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CRUCIAL 2011	760	-0.66 (0.71)	657	0.07 (0.81)		13.0 %	-0.73 [-0.81, -0.65]
CUSP 2009	63	-1.03 (0.44)	59	0.13 (0.69)		12.3 %	-1.16 [-1.37, -0.95]
Malekzadeh 2010	241	-0.6 (0.56)	234	-0.15 (0.96)		12.7 %	-0.45 [-0.59, -0.31]
PILL 2011	189	-0.93 (0.96)	189	-0.18 (0.96)		12.4 %	-0.75 [-0.94, -0.56]
TIPS 2009	375	-0.7 (0.79)	189	0.02 (0.8)		12.7 %	-0.72 [-0.86, -0.58]
TOGETHER 2010	118	-1.27 (0.6)	115	0.01 (0.65)		12.6 %	-1.28 [-1.44, -1.12]
UMPIRE 2013	1002	-0.15 (1.49)	1002	-0.11 (1.48)		12.8 %	-0.04 [-0.17, 0.09]
Wald 2012	86	-1.4 (0.95)	86	0 (0.9)		11.6 %	-1.40 [-1.68, -1.12]
Total (95% CI)	**2834**		**2531**			**100.0 %**	**-0.81 [-1.09, -0.53]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 205.35$, df = 7 ($P<0.00001$); $I^2 = 97\%$

Test for overall effect: $Z = 5.66$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Cholesterol, Outcome 3 Total cholesterol: primary prevention trials.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 3 Cholesterol

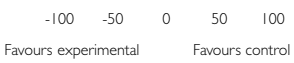
Outcome: 3 Total cholesterol: primary prevention trials

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CUSP 2009	63	-0.72 (0.32)	59	0.09 (0.37)		15.7 %	-0.81 [-0.93, -0.69]
Malekzadeh 2010	241	-0.89 (1.53)	234	-0.27 (1.39)		14.0 %	-0.62 [-0.88, -0.36]
PILL 2011	189	-0.99 (1.24)	189	-0.15 (0.96)		14.6 %	-0.84 [-1.06, -0.62]
Soliman 2009	99	-1.4 (1.2)	104	-1 (1.6)		12.1 %	-0.40 [-0.79, -0.01]
TIPS 2009	375	-0.75 (0.9)	189	0.18 (0.9)		15.4 %	-0.93 [-1.09, -0.77]
TOGETHER 2010	118	-1.47 (0.71)	115	0.1 (0.63)		15.2 %	-1.57 [-1.74, -1.40]
Wald 2012	86	-1.16 (1.18)	86	0 (1)		13.0 %	-1.16 [-1.49, -0.83]
Total (95% CI)	**1171**		**976**			**100.0 %**	**-0.92 [-1.18, -0.65]**

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 71.00$, df = 6 ($P<0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 6.76$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3 Cholesterol, Outcome 4 Total cholesterol: 3+ drugs only.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 3 Cholesterol

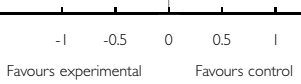
Outcome: 4 Total cholesterol: 3+ drugs only

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Malekzadeh 2010	241	-0.89 (1.53)	234	-0.27 (1.39)		16.6 %	-0.62 [-0.88, -0.36]
PILL 2011	189	-0.99 (1.24)	189	-0.15 (0.96)		16.9 %	-0.84 [-1.06, -0.62]
Soliman 2009	99	-1.4 (1.2)	104	-1 (1.6)		15.6 %	-0.40 [-0.79, -0.01]
TIPS 2009	375	-0.75 (0.9)	189	0.18 (0.9)		17.3 %	-0.93 [-1.09, -0.77]
UMPIRE 2013	1002	-0.1 (1.03)	1002	-0.1 (1.03)		17.5 %	0.0 [-0.09, 0.09]
Wald 2012	86	-1.16 (1.18)	86	0 (1)		16.1 %	-1.16 [-1.49, -0.83]
Total (95% CI)	**1992**		**1804**			**100.0 %**	**-0.65 [-1.10, -0.21]**

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 156.12$, df = 5 ($P<0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 2.86 (P = 0.0043)

Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3 Cholesterol, Outcome 5 Total cholesterol: comparator as usual care.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 3 Cholesterol

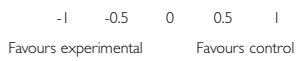
Outcome: 5 Total cholesterol: comparator as usual care

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CRUCIAL 2011	760	-0.45 (0.48)	657	0.02 (0.47)		36.9 %	-0.47 [-0.52, -0.42]
Soliman 2009	99	-1.4 (1.2)	104	-1 (1.6)		26.8 %	-0.40 [-0.79, -0.01]
UMPIRE 2013	1002	-0.1 (1.03)	1002	-0.1 (1.03)		36.3 %	0.0 [-0.09, 0.09]
Total (95% CI)	**1861**		**1763**			**100.0 %**	**-0.28 [-0.66, 0.10]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 80.16$, df = 2 (P<0.00001); $I^2 = 98\%$

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Not applicable

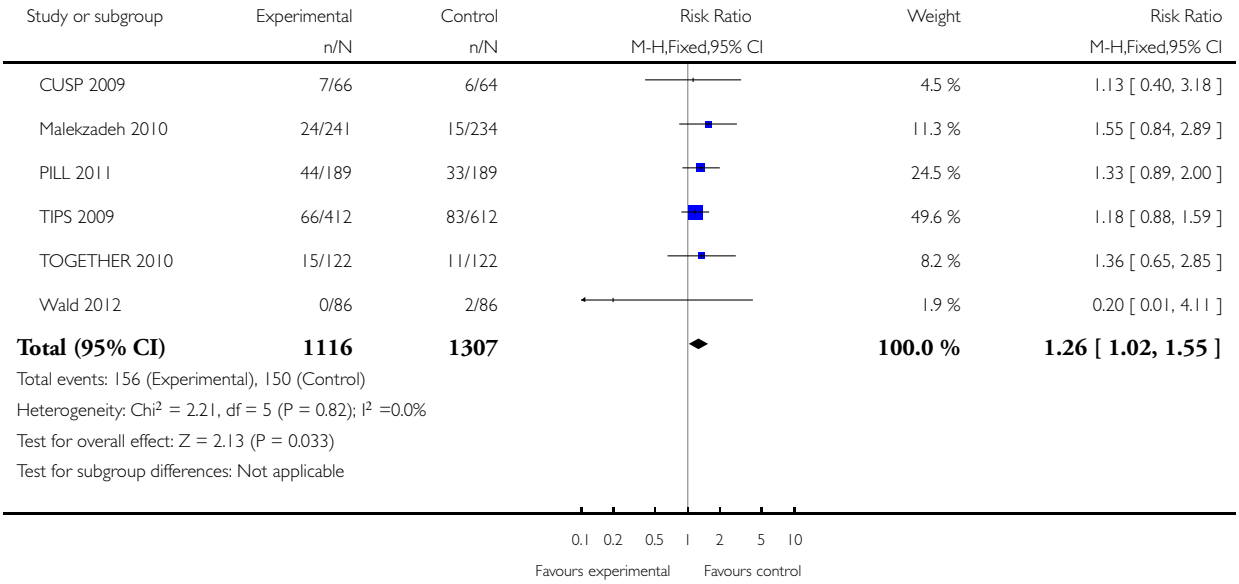


Analysis 4.1. Comparison 4 Adverse events, Outcome 1 Discontinuation of study drug.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 4 Adverse events

Outcome: 1 Discontinuation of study drug



Analysis 4.2. Comparison 4 Adverse events, Outcome 2 Myalgias.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 4 Adverse events

Outcome: 2 Myalgias

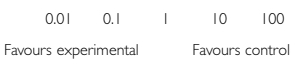
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
PILL 2011	13/189	14/189		26.3 %	0.93 [0.45, 1.92]
Soliman 2009	29/105	26/111		47.4 %	1.18 [0.75, 1.86]
TOGETHER 2010	6/122	7/122		13.1 %	0.86 [0.30, 2.48]
UMPIRE 2013	3/1002	6/1002		11.3 %	0.50 [0.13, 1.99]
Wald 2012	9/86	1/86		1.9 %	9.00 [1.17, 69.51]
Total (95% CI)	**1504**	**1510**		**100.0 %**	**1.14 [0.81, 1.60]**

Total events: 60 (Experimental), 54 (Control)

Heterogeneity: $Chi^2 = 5.90$, df = 4 (P = 0.21); $I^2 = 32\%$

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable



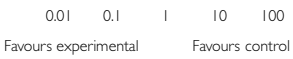
Analysis 4.3. Comparison 4 Adverse events, Outcome 3 Increased liver chemistries.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 4 Adverse events

Outcome: 3 Increased liver chemistries

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CUSP 2009	1/66	0/64		0.9 %	2.91 [0.12, 70.15]
Malekzadeh 2010	43/241	38/234		70.0 %	1.10 [0.74, 1.64]
TIPS 2009	12/412	16/410		29.1 %	0.75 [0.36, 1.56]
Total (95% CI)	**719**	**708**		**100.0 %**	**1.01 [0.72, 1.43]**
Total events: 56 (Experimental), 54 (Control)					
Heterogeneity: Chi^2 = 1.24, df = 2 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.07 (P = 0.94)					
Test for subgroup differences: Not applicable					

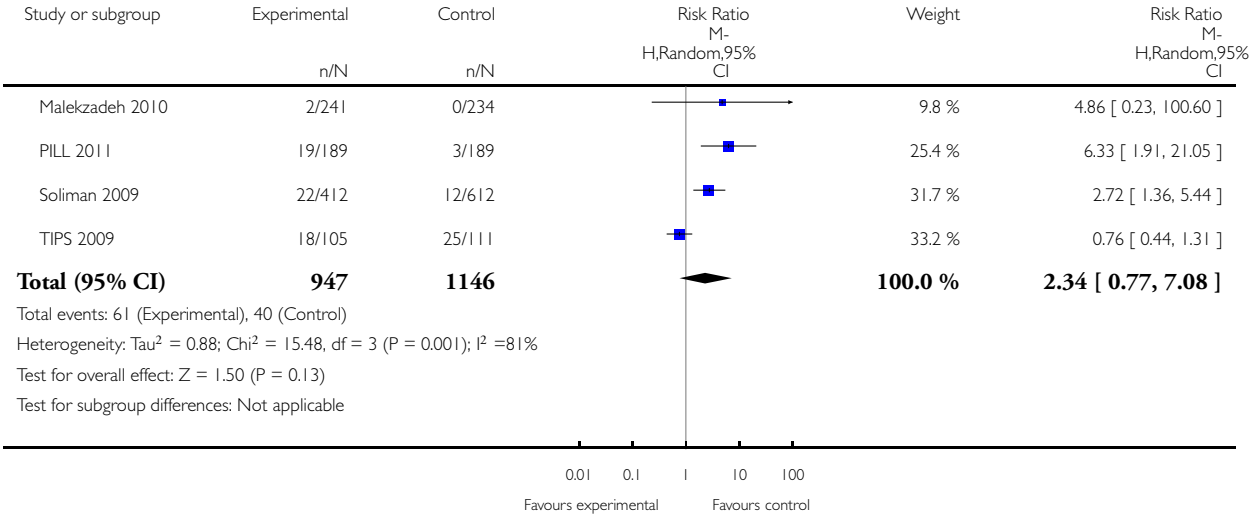


Analysis 4.4. Comparison 4 Adverse events, Outcome 4 Cough.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 4 Adverse events

Outcome: 4 Cough

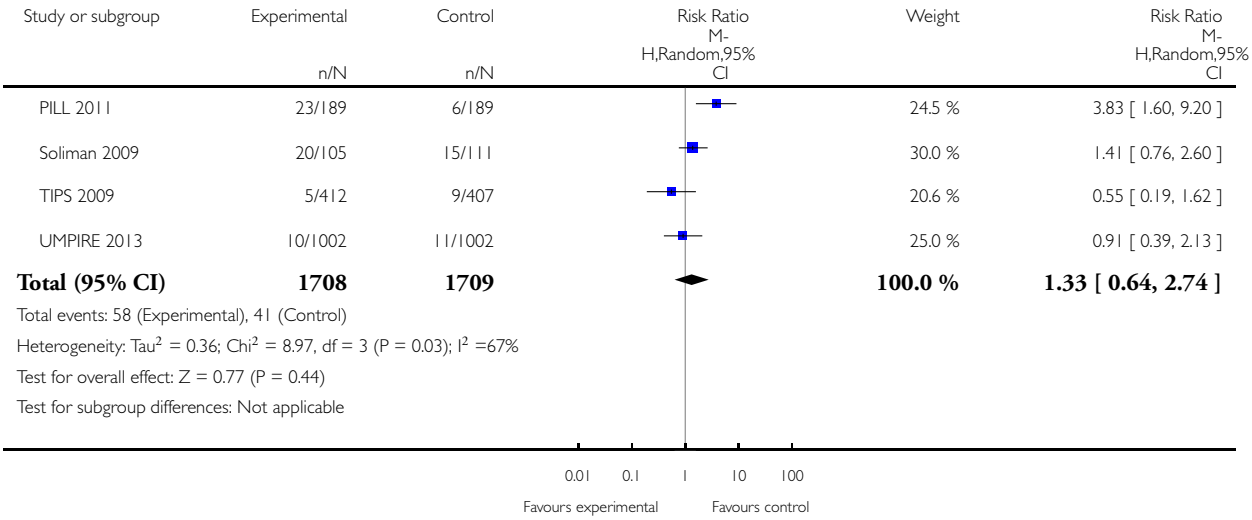


Analysis 4.5. Comparison 4 Adverse events, Outcome 5 Dyspepsia/gastrointestinal irritation.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 4 Adverse events

Outcome: 5 Dyspepsia/gastrointestinal irritation

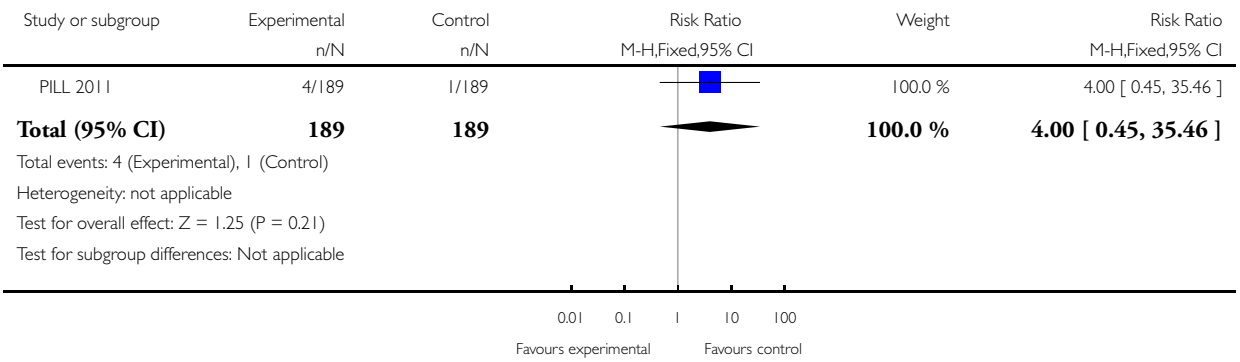


Analysis 4.6. Comparison 4 Adverse events, Outcome 6 Bleeding.

Review: Fixed-dose combination therapy for the prevention of cardiovascular disease

Comparison: 4 Adverse events

Outcome: 6 Bleeding



ADDITIONAL TABLES

Table 1. Polypill content by trial

Study	Polypill contents (dose)	Comparator
CRUCIAL 2011	Amlodipine 5 to 10 mg Atorvastatin 10mg[1]	Usual care
CUSP 2009	Amlodipine 5 mg Atorvastatin 20 mg	Placebo
Malekzadeh 2010	Aspirin 81 mg Atorvastatin 20 mg Enalapril 2.5 mg Hydrochlorothiazide 12.5 mg	Placebo
PILL 2011	Aspirin 75 mg Hydrochlorothiazide 12.5 mg Lisinopril 10 mg Simvastatin 20 mg	Placebo
Soliman 2009	Aspirin 75 mg Hydrochlorothiazide 12.5 mg Lisinopril 10 mg Simvastatin 20 mg	Usual care
TIPS 2009	Aspirin 100 mg Atenolol 50 mg Hydrochlorothiazide 12.5 mg Ramipril 5 mg Simvastatin 20 mg	8 other drug/drug combination groups: 1) Aspirin 100mg 2) Aspirin 100mg, hydrochlorothiazide 12.5mg, atenolol 50mg, ramipril 5mg 3) Hydrochlorothiazide 12.5mg 4) Hydrochlorothiazide 12.5mg, atenolol 50mg 5) Hydrochlorothiazide 12.5mg, ramipril 5mg 6) Hydrochlorothiazide 12.5mg, atenolol 50mg, ramipril 5mg 7) Ramipril 5mg, atenolol 50mg 8) Simvastatin 20mg
TOGETHER 2010	Amlodipine 5 to 10 mg Atorvastatin 10mg	Amlodipine 5 to 10 mg
UMPIRE 2013	Aspirin 75mg Atenolol 50mg Lisinopril 40mg Simvastatin 40mg	Usual care

Table 1. Polypill content by trial (*Continued*)

	or Aspirin 75mg Hydrochlorothiazide 12.5mg Lisinopril 40mg Simvastatin 40mg	
Wald 2012	Amlodipine 2.5 mg Hydrochlorothiazide 12.5 mg Losartan 25 mg Simvastatin 40mg	Placebo

[1] Site investigators could request dosages of amlodipine and atorvastatin 5/20 mg and 10/20 mg

APPENDICES

Appendix 1. Search strategies 2012

The Cochrane Library

#1 MeSH descriptor Cardiovascular Diseases explode all trees
#2 cardio*
#3 cardia*
#4 heart*
#5 coronary*
#6 angina*
#7 ventric*
#8 myocard*
#9 pericard*
#10 isch?em*
#11 emboli*
#12 arrhythmi*
#13 thrombo*
#14 atrial fibrillat*
#15 tachycardi*
#16 endocardi*
#17 (sick next sinus)
#18 MeSH descriptor Stroke explode all trees
#19 (stroke or stokes)
#20 cerebrovasc*
#21 cerebral vascular
#22 apoplexy
#23 (brain near/2 accident)
#24 ((brain* or cerebral or lacunar) near/2 infarct*)
#25 MeSH descriptor Hypertension explode all trees

#26 hypertensi*
#27 peripheral next arter* next disease*
#28 ((high or increased or elevated) near/2 (blood next pressure))
#29 MeSH descriptor Hyperlipidemias explode all trees
#30 hyperlipid*
#31 hyperlip?emia*
#32 hypercholesterol*
#33 hypercholester?emia*
#34 hyperlipoprotein?emia*
#35 hypertriglycerid?emia*
#36 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
#37 MeSH descriptor Drug Combinations, this term only
#38 polypill*
#39 (drug near/2 combin*)
#40 ((multi* or several) near/2 (ingredient* or component))
#41 policap
#42 quintapill
#43 (single near/2 pill* near/2 comb*)
#44 single-pill
#45 Red Heart pill*
#46 (#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45)
#47 36 and 46, from 2000 to 2012

MEDLINE Ovid

1 exp Cardiovascular Diseases/
2 cardio*.tw.
3 cardia*.tw.
4 heart*.tw.
5 coronary*.tw.
6 angina*.tw.
7 ventric*.tw.
8 myocard*.tw.
9 pericard*.tw.
10 isch?em*.tw.
11 emboli*.tw.
12 arrhythmi*.tw.
13 thrombo*.tw.
14 atrial fibrillat*.tw.
15 tachycardi*.tw.
16 endocardi*.tw.
17 (sick adj sinus).tw.
18 exp Stroke/
19 (stroke or stokes).tw.
20 cerebrovasc*.tw.
21 cerebral vascular.tw.
22 apoplexy.tw.
23 (brain adj2 accident*).tw.
24 ((brain* or cerebral or lacunar) adj2 infarct*).tw.
25 exp Hypertension/
26 hypertensi*.tw.

27 peripheral arter* disease*.tw.
28 ((high or increased or elevated) adj2 blood pressure).tw.
29 exp Hyperlipidemias/
30 hyperlipid*.tw.
31 hyperlip?emia*.tw.
32 hypercholesterol*.tw.
33 hypercholester?emia*.tw.
34 hyperlipoprotein?emia*.tw.
35 hypertriglycerid?emia*.tw.
36 or/1-35
37 Drug Combinations/
38 polypill*.tw.
39 (drug adj2 combin*).tw.
40 ((multi* or several) adj2 (ingredient* or component*)).tw.
41 policap.tw.
42 quintapill.tw.
43 (single adj2 pill* adj2 comb*).tw.
44 single-pill.tw.
45 Red Heart pill*.tw.
46 or/37-45
47 randomised controlled trial.pt.
48 controlled clinical trial.pt.
49 randomised.ab.
50 placebo.ab.
51 drug therapy.fs.
52 randomly.ab.
53 trial.ab.
54 groups.ab.
55 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56 exp animals/ not humans.sh.
57 55 not 56
58 36 and 46
59 58 and 57
60 limit 59 to yr="2000 -Current"

EMBASE Ovid

1 exp Cardiovascular Diseases/
2 cardio*.tw.
3 cardia*.tw.
4 heart*.tw.
5 coronary*.tw.
6 angina*.tw.
7 ventric*.tw.
8 myocard*.tw.
9 pericard*.tw.
10 isch?em*.tw.
11 emboli*.tw.
12 arrhythmi*.tw.
13 thrombo*.tw.
14 atrial fibrillat*.tw.
15 tachycardi*.tw.
16 endocardi*.tw.

17 (sick adj sinus).tw.
18 exp cerebrovascular disease/
19 (stroke or stokes).tw.
20 cerebrovasc*.tw.
21 cerebral vascular.tw.
22 apoplexy.tw.
23 (brain adj2 accident*).tw.
24 ((brain* or cerebral or lacunar) adj2 infarct*).tw.
25 exp Hypertension/
26 hypertensi*.tw.
27 peripheral arter* disease*.tw.
28 ((high or increased or elevated) adj2 blood pressure).tw.
29 exp Hyperlipidemias/
30 hyperlipid*.tw.
31 hyperlip?emia*.tw.
32 hypercholesterol*.tw.
33 hypercholester?emia*.tw.
34 hyperlipoprotein?emia*.tw.
35 hypertriglycerid?emia*.tw.
36 or/1-35
37 Drug Combinations/
38 polypill*.tw.
39 (drug adj2 combin*).tw.
40 ((multi* or several) adj2 (ingredient* or component*)).tw.
41 policap.tw.
42 quintapill.tw.
43 (single adj2 pill* adj2 comb*).tw.
44 single-pill.tw.
45 Red Heart pill*.tw.
46 or/37-45
47 36 and 46
48 random$.tw.
49 factorial$.tw.
50 crossover$.tw.
51 cross over$.tw.
52 cross-over$.tw.
53 placebo$.tw.
54 (doubl$ adj blind$).tw.
55 (singl$ adj blind$).tw.
56 assign$.tw.
57 allocat$.tw.
58 volunteer$.tw.
59 crossover procedure/
60 double blind procedure/
61 randomised controlled trial/
62 single blind procedure/
63 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62
64 (animal/ or nonhuman/) not human/
65 63 not 64
66 47 and 65
67 limit 66 to yr="2000 -Current"

ISI Web of Science

25 #24 AND #23
24 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
23 #22 AND #14
22 #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15
21 TS=(single-pill or "red heart pill")
20 TS=(single near/2 pill* near/2 comb*)
19 TS=(policap or quintapill)
18 TS=(several near/2 ingredient* or several near/2 component)
17 TS=(multi* near/2 ingredient* or multi* near/2 component)
16 TS=(drug near/2 combin*)
15 TS=polypill*
14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
13 TS=(hyperlipid* or hyperlip?emia* or hyperchlosterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*)
12 TS=(high near/2 "blood pressure" or increased near/2 "blood pressure" or elevated near/2 "blood pressure")
11 TS=(hypertensi* or "peripheral arter* disease*")
10 TS=(brain* near/2 infarct* OR cerebral near/2 infarct* OR lacunar near/2 infarct*)
9 TS=(brain near/2 accident)
8 TS=apoplexy
7 TS=(stroke or strokes or cerebrovasc* or "cerebral vascular")
6 TS=("sick sinus")
5 TS=(tachycardi* or endocardi*)
4 TS="atrial fibrillat*"
3 TS=(pericard* or isch?em* or emboli* or arrhythmi* or thromo*)
2 TS=(cardia* or heart* or coronary* or angina* or ventric* or myocard*)
1 TS=(cardio)

Appendix 2. Search strategies 2013

The Cochrane Library

#1 MeSH descriptor Cardiovascular Diseases explode all trees
#2 cardio*
#3 cardia*
#4 heart*
#5 coronary*
#6 angina*
#7 ventric*
#8 myocard*
#9 pericard*
#10 isch?em*
#11 emboli*
#12 arrhythmi*
#13 thrombo*
#14 atrial fibrillat*
#15 tachycardi*
#16 endocardi*
#17 (sick next sinus)
#18 MeSH descriptor Stroke explode all trees
#19 (stroke or stokes)

#20 cerebrovasc*
#21 cerebral vascular
#22 apoplexy
#23 (brain near/2 accident)
#24 ((brain* or cerebral or lacunar) near/2 infarct*)
#25 MeSH descriptor Hypertension explode all trees
#26 hypertensi*
#27 peripheral next arter* next disease*
#28 ((high or increased or elevated) near/2 (blood next pressure))
#29 MeSH descriptor Hyperlipidemias explode all trees
#30 hyperlipid*
#31 hyperlip?emia*
#32 hypercholesterol*
#33 hypercholester?emia*
#34 hyperlipoprotein?emia*
#35 hypertriglycerid?emia*
#36 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
#37 MeSH descriptor Drug Combinations, this term only
#38 polypill*
#39 (drug near/2 combin*)
#40 ((multi* or several) near/2 (ingredient* or component))
#41 policap
#42 quintapill
#43 (single near/2 pill* near/2 comb*)
#44 single-pill
#45 Red Heart pill*
#46 (#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45)
#47 36 and 46, from 2000 to 2013

MEDLINE Ovid

1 exp Cardiovascular Diseases/
2 cardio*.tw.
3 cardia*.tw.
4 heart*.tw.
5 coronary*.tw.
6 angina*.tw.
7 ventric*.tw.
8 myocard*.tw.
9 pericard*.tw.
10 isch?em*.tw.
11 emboli*.tw.
12 arrhythmi*.tw.
13 thrombo*.tw.
14 atrial fibrillat*.tw.
15 tachycardi*.tw.
16 endocardi*.tw.
17 (sick adj sinus).tw.
18 exp Stroke/
19 (stroke or stokes).tw.
20 cerebrovasc*.tw.

21 cerebral vascular.tw.
22 apoplexy.tw.
23 (brain adj2 accident*).tw.
24 ((brain* or cerebral or lacunar) adj2 infarct*).tw.
25 exp Hypertension/
26 hypertensi*.tw.
27 peripheral arter* disease*.tw.
28 ((high or increased or elevated) adj2 blood pressure).tw.
29 exp Hyperlipidemias/
30 hyperlipid*.tw.
31 hyperlip?emia*.tw.
32 hypercholesterol*.tw.
33 hypercholester?emia*.tw.
34 hyperlipoprotein?emia*.tw.
35 hypertriglycerid?emia*.tw.
36 or/1-35
37 Drug Combinations/
38 polypill*.tw.
39 (drug adj2 combin*).tw.
40 ((multi* or several) adj2 (ingredient* or component*)).tw.
41 policap.tw.
42 quintapill.tw.
43 (single adj2 pill* adj2 comb*).tw.
44 single-pill.tw.
45 Red Heart pill*.tw.
46 or/37-45
47 randomized controlled trial.pt.
48 controlled clinical trial.pt.
49 randomized.ab.
50 placebo.ab.
51 drug therapy.fs.
52 randomly.ab.
53 trial.ab.
54 groups.ab.
55 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56 exp animals/ not humans.sh.
57 55 not 56
58 36 and 46
59 58 and 57
60 limit 59 to yr="2000 -Current"
61 (2012* or 2013*).ed.
62 60 and 61
63 limit 62 to "core clinical journals (aim)"

EMBASE Ovid

1 exp Cardiovascular Diseases/
2 cardio*.tw.
3 cardia*.tw.
4 heart*.tw.
5 coronary*.tw.
6 angina*.tw.
7 ventric*.tw.

8 myocard*.tw.
9 pericard*.tw.
10 isch?em*.tw.
11 emboli*.tw.
12 arrhythmi*.tw.
13 thrombo*.tw.
14 atrial fibrillat*.tw.
15 tachycardi*.tw.
16 endocardi*.tw.
17 (sick adj sinus).tw.
18 exp cerebrovascular disease/
19 (stroke or stokes).tw.
20 cerebrovasc*.tw.
21 cerebral vascular.tw.
22 apoplexy.tw.
23 (brain adj2 accident*).tw.
24 ((brain* or cerebral or lacunar) adj2 infarct*).tw.
25 exp Hypertension/
26 hypertensi*.tw.
27 peripheral arter* disease*.tw.
28 ((high or increased or elevated) adj2 blood pressure).tw.
29 exp Hyperlipidemias/
30 hyperlipid*.tw.
31 hyperlip?emia*.tw.
32 hypercholesterol*.tw.
33 hypercholester?emia*.tw.
34 hyperlipoprotein?emia*.tw.
35 hypertriglycerid?emia*.tw.
36 or/1-35
37 Drug Combinations/
38 polypill*.tw.
39 (drug adj2 combin*).tw.
40 ((multi* or several) adj2 (ingredient* or component*)).tw.
41 policap.tw.
42 quintapill.tw.
43 (single adj2 pill* adj2 comb*).tw.
44 single-pill.tw.
45 Red Heart pill*.tw.
46 or/37-45
47 36 and 46
48 random$.tw.
49 factorial$.tw.
50 crossover$.tw.
51 cross over$.tw.
52 cross-over$.tw.
53 placebo$.tw.
54 (doubl$ adj blind$).tw.
55 (singl$ adj blind$).tw.
56 assign$.tw.
57 allocat$.tw.
58 volunteer$.tw.
59 crossover procedure/
60 double blind procedure/

61 randomized controlled trial/
62 single blind procedure/
63 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62
64 (animal/ or nonhuman/) not human/
65 63 not 64
66 47 and 65
67 limit 66 to yr="2000 -Current"
68 (2012* or 2013*).em.
69 67 and 68
70 limit 69 to priority journals

ISI Web of Science

25 #24 AND #23
24 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
23 #22 AND #14
22 #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15
21 TS=(single-pill or "red heart pill")
20 TS=(single near/2 pill* near/2 comb*)
19 TS=(policap or quintapill)
18 TS=(several near/2 ingredient* or several near/2 component)
17 TS=(multi* near/2 ingredient* or multi* near/2 component)
16 TS=(drug near/2 combin*)
15 TS=polypill*
14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
13 TS=(hyperlipid* or hyperlip?emia* or hyperchlosterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*)
12 TS=(high near/2 "blood pressure" or increased near/2 "blood pressure" or elevated near/2 "blood pressure")
11 TS=(hypertensi* or "peripheral arter* disease*")
10 TS=(brain* near/2 infarct* OR cerebral near/2 infarct* OR lacunar near/2 infarct*)
9 TS=(brain near/2 accident)
8 TS=apoplexy
7 TS=(stroke or strokes or cerebrovasc* or "cerebral vascular")
6 TS=("sick sinus")
5 TS=(tachycardi* or endocardi*)
4 TS="atrial fibrillat*"
3 TS=(pericard* or isch?em* or emboli* or arrhythmi* or thromo*)
2 TS=(cardia* or heart* or coronary* or angina* or ventric* or myocard*)
1 TS=(cardio)

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of the protocol. Angharad de Cates screened titles and abstracts, assessed studies for inclusion and exclusion, extracted data, contacted authors, and drafted the review. Matthew Farr screened titles and abstracts, assessed studies for inclusion and exclusion, and extracted data. Nicola Wright screened titles and abstracts and assessed studies for inclusion and exclusion. Karen Rees supervised the first three authors and contributed to writing the review. Mark Huffman contacted authors, screened titles and abstracts for the rapid review, extracted data, contributed to the analyses, and contributed to writing the review. Shah Ebrahim interpreted findings and contributed to writing the review. Mark Huffman and Shah Ebrahim performed the analyses.

DECLARATIONS OF INTEREST

Mark Huffman has received grant support (modest) from Scientific Therapeutic Initiative (subsidiary of Astra Zeneca) for a project unrelated to this paper. He has also received travel support from the World Heart Federation through a grant (significant) from Astra Zeneca on research training in implementation science, health system strengthening, and health policy.

SOURCES OF SUPPORT

Internal sources

- Warwick Medical School, University of Warwick, UK.
- Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, UK.

External sources

- NIHR Cochrane Programme Grant, UK.
- Karen Rees is also funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care West Midlands at University Hospitals Birmingham NHS Foundation Trust, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The background section has been shortened. Previous inclusion of HDL cholesterol and triglycerides as outcomes were excluded, and subgroup analysis evaluating the comparator group as usual care versus placebo or inactive control added.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticholesteremic Agents [*administration & dosage]; Antihypertensive Agents [*administration & dosage]; Aspirin [*administration & dosage]; Cardiovascular Diseases [mortality; *prevention & control]; Drug Combinations; Placebo Effect; Platelet Aggregation Inhibitors [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans