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

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[Intervention Review]

Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases

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ABSTRACT

Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability worldwide, yet ASCVD risk factor control and secondary prevention rates remain low. A fixed-dose combination of blood pressure- and cholesterol-lowering and antiplatelet treatments into a single pill, or polypill, has been proposed as one strategy to reduce the global burden of ASCVD.

Objectives

To determine the effect of fixed-dose combination therapy on all-cause mortality, fatal and non-fatal ASCVD events, and adverse events. We also sought to determine the effect of fixed-dose combination therapy on blood pressure, lipids, adherence, discontinuation rates, health-related quality of life, and costs.

Search methods

We updated our previous searches in September 2016 of CENTRAL, MEDLINE, Embase, ISI Web of Science, and DARE, HTA, and HEED. We also searched two clinical trials registers in September 2016. 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 an active drug comparator for any treatment duration in adults 18 years old or older, with no restrictions on presence or absence of pre-existing ASCVD.

Data collection and analysis

Three review authors independently selected studies for inclusion and extracted the data for this update. We evaluated risk of bias using the Cochrane 'Risk of bias' assessment tool. We calculated risk ratios (RR) for dichotomous data and 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 ($I^2 \geq 50\%$). We used the GRADE approach to evaluate the quality of evidence.

Main results

In the initial review, we identified nine randomised controlled trials with a total of 7047 participants and four additional trials (n = 2012 participants; mean age range 62 to 63 years; 30% to 37% women) were included in this update. Eight of the 13 trials evaluated the effects of fixed-dose combination (FDC) therapy in populations without prevalent ASCVD, and the median follow-up ranged from six weeks to 23 months. More recent trials were generally larger with longer follow-up and lower risk of bias. The main risk of bias was related to lack of blinding of participants and personnel, which was inherent to the intervention. Compared with the comparator groups (placebo, usual care, or active drug comparator), the effects of the fixed-dose combination treatment on mortality (FDC = 1.0% versus control = 1.0%, RR 1.10, 95% CI 0.64 to 1.89, I^2 = 0%, 5 studies, N = 5300) and fatal and non-fatal ASCVD events (FDC = 4.7% versus control = 3.7%, RR 1.26, 95% CI 0.95 to 1.66, I^2 = 0%, 6 studies, N = 4517) were uncertain (low-quality evidence). The low event rates for these outcomes and indirectness of evidence for comparing fixed-dose combination to usual care versus individual drugs suggest that these results should be viewed with caution. Adverse events were common in both the intervention (32%) and comparator (27%) groups, with participants randomised to fixed-dose combination therapy being 16% (RR 1.16, 95% CI 1.09 to 1.25, 11 studies, 6906 participants, moderate-quality evidence) more likely to report an adverse event . The mean differences in systolic blood pressure between the intervention and control arms was -6.34 mmHg (95% CI -9.03 to -3.64, 13 trials, 7638 participants, moderate-quality evidence). The mean differences (95% CI) in total and LDL cholesterol between the intervention and control arms were -0.61 mmol/L (95% CI -0.88 to -0.35, 11 trials, 6565 participants, low-quality evidence) and -0.70 mmol/L (95% CI -0.98 to -0.41, 12 trials, 7153 participants, moderate-quality evidence), respectively. There was a high degree of statistical heterogeneity in comparisons of blood pressure and lipids ($I^2 \geq 80\%$ for all) that could not be explained, so these results should be viewed with caution. Fixed-dose combination therapy improved adherence to a multidrug strategy by 44% (26% to 65%) compared with usual care (4 trials, 3835 participants, moderate-quality evidence).

Authors' conclusions

The effects of fixed-dose combination therapy on all-cause mortality or ASCVD events are uncertain. A limited number of trials reported these outcomes, and the included trials were primarily designed to observe changes in ASCVD risk factor levels rather than clinical events, which may partially explain the observed differences in risk factors that were not translated into differences in clinical outcomes among the included trials. Fixed-dose combination therapy is associated with modest increases in adverse events compared with placebo, active comparator, or usual care but may be associated with improved adherence to a multidrug regimen. Ongoing, longer-term trials of fixed-dose combination therapy will help demonstrate whether short-term changes in risk factors might be maintained and lead to expected differences in clinical events based on these changes.

PLAIN LANGUAGE SUMMARY

Fixed-dose combination drug therapy for the prevention of heart disease and stroke

Review question: We reviewed the evidence about the effect of fixed-dose combination drug therapy on the prevention of heart attacks and strokes. We found 13 studies including 9059 participants.

Background: We wanted to discover whether using fixed-dose combination therapy was better or worse than other alternatives, such as usual care, placebo, or giving drugs separately, for the prevention of heart attacks and strokes. This report represents an update from a previous review published in 2014.

Study characteristics: The evidence is current to September 2016. Four studies included individuals with a prior heart attack or stroke or with a high predicted risk for having an initial heart attack and five studies had long-term (12 months or more) follow-up. The main risk of bias was related to lack of blinding of participants and personnel, which was inherent to the intervention. Most study participants were middle-aged men with moderate elevations in blood pressure or cholesterol. Two studies specifically included ethnic Aboriginal or Maori minorities in half of the study participants. The fixed-dose combinations ranged from two to five drugs; all studies included at least one blood pressure-lowering and one cholesterol-lowering drug.

Key results: The effects of fixed-dose combination drug therapy on all-cause mortality and fatal and non-fatal heart attacks and strokes are uncertain, primarily due to the low number of participants experiencing these events in these studies (fewer than 5% for both) and comparisons with usual care (low-quality evidence). Fixed-dose combination drug therapy leads to more adverse events than control (32% versus 27%), including placebo (moderate-quality evidence). This information is not surprising since aspirin, blood pressure-lowering drugs and cholesterol drugs are known to increase the risk for side effects compared with placebo. Fixed-dose combination therapy may modestly lower blood pressure (˜6 mmHg) and cholesterol (-0.6 mmol/L in LDL cholesterol), but these effects were not consistent (moderate-quality evidence for blood pressure and LDL cholesterol but low-quality evidence of total cholesterol). Fixed-dose combination therapy appears to improve adherence to medications to prevent ASCVD (moderate-quality evidence).

Quality of the evidence: The quality of evidence from these studies generally ranged from moderate to low. Ongoing trials of fixed-dose combination drug therapy will likely inform clinical endpoints to guide decision-making.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases (ASCVD)

Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases (ASCVD)

Patient or population: adults older than 18 years, with no restriction regarding presence of ASCVD; participants generally had elevated risk of ASCVD (as estimated by the presence of at least one abnormal cardiovascular risk factor) without prevalent CVD (two studies included ≥ 10% of participants with prior ASCVD)

Settings: outpatient

Intervention: fixed-dose combination therapy of varying drug combinations ranging from two to five drugs

Comparison: usual care, placebo, or active drug therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk based on event rates or mean changes from baseline in the comparator group	Corresponding risk				
	Comparator group, including placebo, usual care, or active drug comparator	Fixed-dose combination therapy				
All-cause mortality Median follow-up range: 9 to 23 months	**Total**		RR = 1.10 (0.64 to 1.89)	5300 (5 studies)	⊕⊕⊖⊖ **Low**[a,b]	Low event rates among trials that were not designed nor powered to detect differences in clinical outcomes. Four of the five trials included had high-quality usual care as the comparator group
	10 per 1000	**11 per 1000** (6 to 19)				
ASCVD event, such as fatal or non-fatal myocardial infarction or stroke. Median follow-up range: 8 weeks to 23 months	**Total**		RR = 1.26 (0.95 to 1.66)	4517 (6 studies)	⊕⊕⊖⊖ **Low**[a,b]	Low event rates among trials that were not designed nor powered to detect differences in clinical outcomes. Four of the five trials included had high-quality usual care as the comparator group
	37 per 1000	**46 per 1000** (35 to 61)				

Any investigator-defined adverse event Median follow-up range: 6 weeks to 23 months	**271 per 1000**	**314 per 1000** (295 to 339)	RR = 1.16 (1.09 to 1.25)	6906 (11 studies	⊕⊕⊕⊖ **Moderate**[c]	We would expect the rate of adverse events to be higher with fixed-dose combination compared with placebo, and the difference between fixed-dose combination and usual care depends on what care is provided
Systolic blood pressure, **mmHg** Median follow-up range: 6 weeks to 12 months	The mean change in systolic blood pressure ranged across control groups from -17.9 mmHg to 0.9 mmHg	The mean difference in change in systolic blood pressure between the intervention and comparator groups was -6.34 mmHg (95% CI -9.03 to -3.64)		7638 (13 studies)	⊕⊕⊕⊖ **Moderate**[d]	
Total cholesterol, **mmol/L** Median follow-up range: 6 weeks to 23 months	The mean change in total cholesterol ranged across control groups from -1.6 mmol/L to 0.2 mmol/L.	The mean difference in change in total cholesterol between the intervention and comparator groups was -0.61 mmol/L (-0.88 to -0.35)		6565 (11 studies)	⊕⊕⊖⊖ **Low**[d,e]	
LDL cholesterol, **mmol/L** Median follow-up range: 6 weeks to 23 months	The mean change in LDL cholesterol ranged across control groups from -1.4 mmol/L to 0.1 mmol/L	The mean difference in change in LDL cholesterol between the intervention and comparator groups was -0.70 mmol/L (95% CI -0.98 to -0.41)		7153 (12 studies)	⊕⊕⊕⊖ **Moderate**[d]	
Adherence, **variable definitions** Median follow-up range: 9 to 23 months	**534 per 1000**	**769 per 1000** (673 to 882)	RR = 1.44 (1.26 to 1.65)	3835 (4 studies)	⊕⊕⊕⊖ **Moderate**[b]	All four trials included had high-quality comparator care as the comparator group either as usual care or provision of individual drug components

*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).
ASCVD = atherosclerotic 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.

[a]Downgraded by one level due to imprecision due to low event rates.
[b]Downgraded one level due to indirectness of evidence, including high quality 'usual care' as comparator group in four of five trials study limitations, which may not be comparable to settings where fixed-dose combination therapy might be deployed, including low- and middle-income country settings with low treatment rates.
[c]Downgraded one level due to indirectness of evidence, including different comparators that could be usual care, placebo, or active comparator.
[d]Downgraded one level due to heterogeneity likely due to different participants, fixed-dose combinations, and comparator groups.
[e]Downgraded one level due to reporting bias demonstrated through funnel plot asymmetry.

BACKGROUND

Description of the condition

Atherosclerotic cardiovascular disease (ASCVD) is a principal cause of death worldwide. In 2013, more than 17 million deaths globally were attributed to ASCVD, over 80% of which occurred in low- and middle-income countries (Roth 2015). Furthermore, the situation is not expected to improve, with global ASCVD mortality estimated to increase, largely because of population growth and aging (Roth 2015). These trends are largely driven by atherosclerotic cardiovascular diseases, principally ischaemic heart disease and cerebrovascular disease. Therefore, preventing deaths and disease due to ASCVD is a priority for global public health (WHO 2013).

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

Current national and international approaches to ASCVD prevention incorporate both primary and secondary prevention (Perk 2012; NICE 2010). Primary prevention aims to prevent ASCVD events in those who have no clinical evidence of ASCVD who are considered to be at elevated risk for an ASCVD event. To achieve this, guidelines recommend intervening usually when five- or 10-year predicted risk levels exceed thresholds where benefits outweigh risks (NICE 2008; NICE 2010; Perk 2012; Stone 2013). ASCVD 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 ASCVD events, which is known to be effective (ATT-Collaboration 2002; Baigent 2005; Karmali 2016; Rashid 2003).

The same ASCVD risk factors operate globally (O'Donnell 2010; Yusuf 2004) making multifactorial prevention strategies relevant, but conventional approaches targeting high risk individuals, conducting investigations, prescribing various medications, regular monitoring, and drug dose titration to optimise ASCVD risk factors are difficult to implement. In fact, access, availability, and adherence to medications for the prevention and control of ASCVD are generally low (Yusuf 2011). In response to this treatment gap, the World Health Organization has set an 80% availability target for essential medicines in public and private pharmacies for the prevention and control of ASCVD and other noncommunicable diseases and a 50% treatment target for eligible individuals to reduce the risk of premature mortality from noncommunicable disease by 25% by 2025 (WHO 2013). In collaboration with the Centers for Disease Control and Prevention, World Heart Federation, and other organisations, the World Health Organization's Global Hearts technical package has also recommended fixed-dose combination therapy for improving adherence to multidrug therapy (WHO 2016).

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 2001) 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 ASCVD events by 75% in people with clinical evidence of ASCVD (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 ASCVD events by about 80% (Wald 2003). More contemporary 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 ASCVD (Baigent 2009), the use of aspirin for primary prevention of ASCVD is generally indicated when the absolute risk of cardiovascular disease outweighs the risk of severe bleeding (Karmali 2016). Also, doubt exists regarding folic acid since recent large randomised trials have indicated no ASCVD 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 ASCVD 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 minimal fixed-dose combination for primary and secondary ASCVD prevention should include at least one antihypertensive and one statin.

There is widespread 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 (Bangalore 2007; Gupta 2010). 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 a person with asthma 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 is 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 than 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 ASCVD prevention to be appreciated and confronted (Franco 2004).

However, fixed-dose combination therapy still has several unknowns. These include (i) the best constituents, whether two or three or four or five drugs are required; (ii) evidence of safety, effectiveness, and cost-effectiveness; and (iii) whether increasing the number of constituents will produce a favourable risk-benefit profile. In particular, the evidence is limited concerning benefits and risks of fixed-dose combination therapy for primary prevention in those people with low or intermediate ASCVD risk (event rates at or below 1% per year).

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 ASCVD, as well as in assessing safety and tolerability (de Cates 2014; Elley 2012). Since the publication of these reviews (de Cates 2014; Elley 2012), additional fixed-dose combination trial data have been published, which provide the rationale for this update. Also, in 2016, the Sixth Joint Task Force of the European Society of Cardiology and Other Societies identified fixed-dose combination therapy as a IIb, level of evidence B recommendation for improving adherence in the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (ESC 2016), and the World Health Organization has identified fixed-dose combination therapy as a strategy to improve adherence (WHO 2016).

OBJECTIVES

To determine the effect of fixed-dose combination therapy on all-cause mortality, fatal and non-fatal ASCVD events, and adverse events. We also sought to determine the effect of fixed-dose combination therapy on blood pressure, lipids, adherence, discontinuation rates, health-related quality of life, and costs.

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 ASCVD.

Types of interventions

A fixed-dose combination therapy, a combination of several active components into a single pill with the aim being to optimise ASCVD risk and reduce ASCVD 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 an active drug comparator.

Types of outcome measures

Primary outcomes

- Clinical outcomes including mortality (cardiovascular and all-cause); non-fatal ASCVD 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). The previous version of the review included the broader outcome of CVD, but we have narrowed this definition for this update to include only ASCVD.
- Investigator-defined adverse events including the proportion of participants experiencing specific symptoms including: myalgias, cough, elevated liver enzymes, gastric irritation or dyspepsia.

Secondary outcomes

- Systolic and diastolic blood pressure
- Total and LDL cholesterol
- Adherence
- Discontinuation rates
- 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

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 8, 2016) in the Cochrane Library;
- MEDLINE (Ovid) (1946 to 19 September 2016);
- Embase (Ovid) (1980 to Week 38, September 2016);
- ISI Web of Science (1970 to 19 September 2016);
- Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), and Health Economics Evaluations Database (HEED) in the Cochrane Library (2016, Issue 8).

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), January 2015, February 2016, and September 2016 (Appendix 3). We used the Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) 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) (apps.who.int/trialsearch/) for ongoing trials on 24 December 2011 and the latter two registers on 27 September 2016 for this update to review existing ongoing studies that had been identified and to find any recent registrations. In addition, we checked reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles. We contacted experts in the field for unpublished and ongoing trials and study authors where necessary for additional information.

Data collection and analysis

Selection of studies

From the searches, three review authors (EB, MP, MH) reviewed the title and abstract of each paper for this update and retrieved potentially relevant references. Following this initial screening, we obtained the full-text reports of potentially relevant studies, and three authors (EB, MP, MH) independently selected studies to be included in the review using predetermined inclusion criteria. In all cases we resolved disagreements about any study inclusions by consensus.

Data extraction and management

Two review authors (EB, MH) independently extracted data using a proforma, and contacted principal investigators to provide additional relevant information where necessary. EB and MH extracted 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) from each of the included studies. We resolved disagreements about extracted data by consensus.

Assessment of risk of bias in included studies

We assessed risk of bias 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 2011a). 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 2011b). Two review authors (EB, MH) independently assessed the risk of bias in the included studies.

One author (MDH) evaluated the quality of evidence using the GRADE approach for this update using the checklist outlined by Meader 2014. We have reported the rationale for downgrading the quality of evidence for each of our included outcomes: imprecision due to low event rates; indirectness of evidence; including high quality 'usual care' as comparator group, which may not be comparable to settings where fixed-dose combination therapy might be deployed (including low- and middle-income country settings with low treatment rates), as well as different comparators that could be usual care, placebo or active comparator. Additional reasons for downgrading the overall quality of evidence include heterogeneity likely due to different participants, fixed-dose combinations, and comparator groups and reporting bias. We have reported the absolute and relative effects, quality of evidence, and specific reason(s) applied for downgrading the overall quality of evidence for each listed outcome in our Summary of findings for the main comparison.

Measures of treatment effect

We processed data in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We expressed dichotomous outcomes as risk ratios (RR), and calculated 95% confidence intervals (CI) for each study. For continuous variables, we compared net changes (that is intervention group minus control group differences) and calculated mean difference (MD) and 95% CI for each study. For TIPS 2009, we compared the effects of fixed-dose combination therapy on mean (standard deviation (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.

Unit of analysis issues

One trial was a cross-over trial (Wald 2012), and the fixed-dose combination was unlikely to have a cross-over effect on the measured risk factors. Thus, we analysed the treatment effect as a parallel-group trial (Deeks 2011). No trials were cluster-randomised trials.

Dealing with missing data

We sought missing data from investigators to obtain key information or missing numerical outcome data where possible. We obtained updated data from two trials (Malekzadeh 2010; Soliman 2009) in the initial version of this review and none for this update. We investigated attrition rates, losses to follow-up, withdrawals, and critically appraised methods for handling missing data and imputation methods. If SDs for outcomes were not reported and were not provided by study authors, then we imputed these values from data within the trial using methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 16.1.3 (Higgins 2011b).

Assessment of heterogeneity

For each outcome, we carried out tests of heterogeneity using the Chi^2 test of heterogeneity and the I^2 statistic (Higgins 2003). Where no or minimal heterogeneity was present, we performed fixed-effect model meta-analyses. Where substantial heterogeneity was detected ($I^2 \geq 50\%$), we evaluated the results for possible explanations (for example participants and interventions) and performed random-effects model meta-analyses with cautious interpretation.

Assessment of reporting biases

We evaluated reporting bias by creating funnel plots for outcomes with at least 10 trials to evaluate for asymmetry which could represent true heterogeneity, poor methodological design leading to small study bias, publication bias or a combination thereof.

Data synthesis

We synthesised our results through fixed-effect or random-effects meta-analyses based on heterogeneity identified for each outcome. We have reported RRs or MDs with corresponding 95% CIs. To evaluate the quality of evidence for each outcome, we used the GRADE approach (GRADE 2013) and the 'Checklist to aid consistency and reproducibility of GRADE assessments' (Meader 2014) for these assessments, which we included in the 'Summary of findings' table.

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 ASCVD) versus secondary prevention (population where > 10% had pre-existing ASCVD)
- Two-drug versus three-drug or more fixed-dose combination therapies
- Comparator group as usual care versus placebo or inactive control

Data were available to perform subgroup analyses on the latter three analyses.

Sensitivity analysis

We performed sensitivity analyses 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; Characteristics of studies awaiting classification.

Results of the search

We have presented the PRISMA flowchart in Figure 1 (Moher 2009). The 2014 review included 14 reports of nine trials (CRUCIAL 2011; CUSP 2009; Malekzadeh 2010; PILL 2011; Soliman 2009; TIPS 2009; TOGETHER 2010; UMPIRE 2013; Wald 2012). Our updated search identified 5629 reports, and we identified five reports through handsearching and 16 trials through trials register searches. After de-duplication, we screened 4376 records and excluded 4236 records based on review of the title or abstract. After full-text review of the remaining 140 reports, we excluded 96 records and included 22 reports of eight trials. This included eight additional reports of four trials included in the 2014 systematic review and 14 reports of four new trials.

Figure 1. Flow diagram

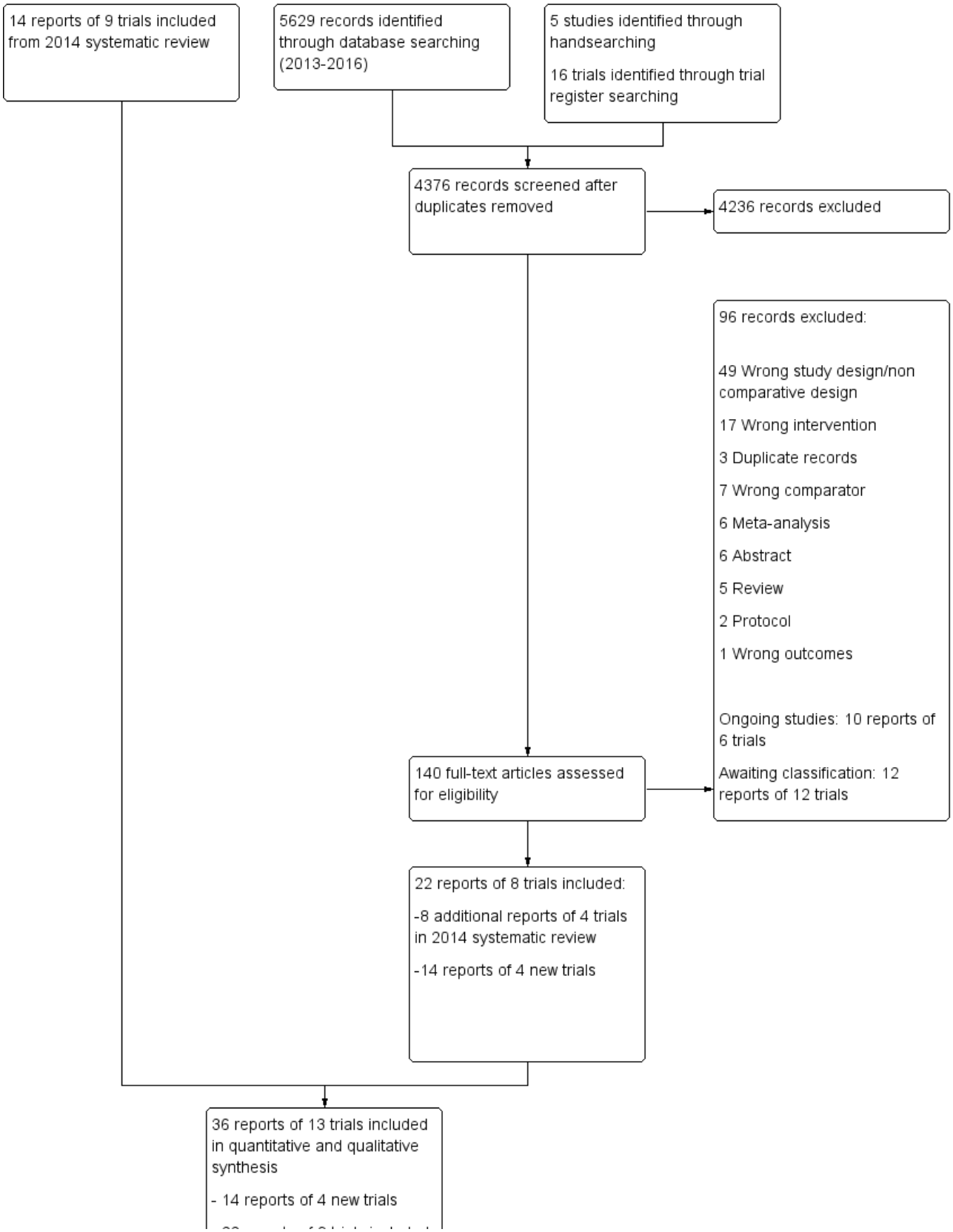
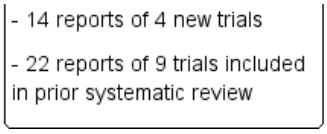


Figure 1. (Continued)



Overall, we have included 36 reports of 13 trials in this update (CRUCIAL 2011; CUSP 2009; FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; Malekzadeh 2010; OLSTA 2016; PILL 2011; Soliman 2009; TIPS 2009; TOGETHER 2010; UMPIRE 2013; Wald 2012), as well as 10 reports of six ongoing trials (NCT01826019; INTEGRATE; PolyIran; NCT02278471; NCT02596126; NCT01646437) and 12 reports of 12 trials awaiting classification (Fommei 2015; NCT00530946; NCT01004705; NCT01005290; NCT01362218; NCT01406431; NCT01764178; NCT02075619; NCT02569814; NCT02662894; NCT02791958; NCT02842359).

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. We included nine trials with 7047 participants randomised in the initial review, with four additional trials (FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; OLSTA 2016; n = 2012 participants) in this update. The six largest trials (CRUCIAL 2011; FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; TIPS 2009; UMPIRE 2013) randomized 7349 (81%) 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 two studies (CUSP 2009, OLSTA 2016), 12 weeks in four studies (PILL 2011; Soliman 2009; TIPS 2009; Wald 2012)) or medium-term (nine months in one study (FOCUS 2014)); however, five studies had a median follow-up period of 12 months or more (CRUCIAL 2011; IMPACT 2014; Kanyini GAP 2014; Malekzadeh 2010; UMPIRE 2013). All trials reported changes in blood pressure and cholesterol, whereas mortality was only reported in five trials (CRUCIAL 2011; FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; UMPIRE 2013). Five trials (CRUCIAL 2011; IMPACT 2014; Kanyini GAP 2014; Soliman 2009; UMPIRE 2013) compared fixed-dose combination therapy against usual care, whereas the other 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 older than 21 years to older than 55 years in women, a composite measure of short-term (10-year) risk (5-year predicted Framingham ASCVD risk ≥ 7.5% in PILL 2011), or one to three elevated cardiovascular disease risk factors. FOCUS 2014, IMPACT 2014, Kanyini GAP 2014 and UMPIRE 2013 specifically enrolled participants with established ASCVD or an elevated risk of ASCVD (≥ 15% predicted risk over five years), while CRUCIAL 2011 included more than 18% of participants with peripheral artery disease (PAD) and more than 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 63.7 (12.7) years (Kanyini GAP 2014). The majority of trials enrolled predominantly men, with two trials randomising more than 80% men (PILL 2011; UMPIRE 2013) compared with one trial that enrolled only 27% men (Soliman 2009). Two trials enrolled 50% ethnic Aboriginal/Torres Strait Islander (Kanyini GAP 2014) or Maori (IMPACT 2014) individuals by design. Baseline systolic blood pressure ranged from 125 mmHg to 166 mmHg, and baseline total cholesterol ranged from 4.2 mmol/L to 6.1 mmol/L.

The drugs included in the various fixed-dose combination pills varied (Table 1), with four studies including two drugs (CRUCIAL 2011; CUSP 2009; OLSTA 2016; TOGETHER 2010), one study including three drugs (FOCUS 2014), seven studies including four drugs (IMPACT 2014; Kanyini GAP 2014; Malekzadeh 2010; PILL 2011; Soliman 2009; UMPIRE 2013; Wald 2012), and one study including five drugs (TIPS 2009). Eight studies included aspirin (FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; Malekzadeh 2010; PILL 2011; Soliman 2009; TIPS 2009; UMPIRE 2013), and blood pressure- and cholesterol-lowering drugs were included, by definition, in all 13 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 eight trials (FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; PILL 2011; Soliman 2009; TIPS 2009; UMPIRE 2013; Wald 2012), atorvastatin was used in four trials (CRUCIAL 2011; CUSP 2009; Malekzadeh 2010; TOGETHER 2010), and rosuvastatin was used in one trial (OLSTA 2016).

Excluded studies

Details and reasons for exclusion for the studies that underwent full-text review 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

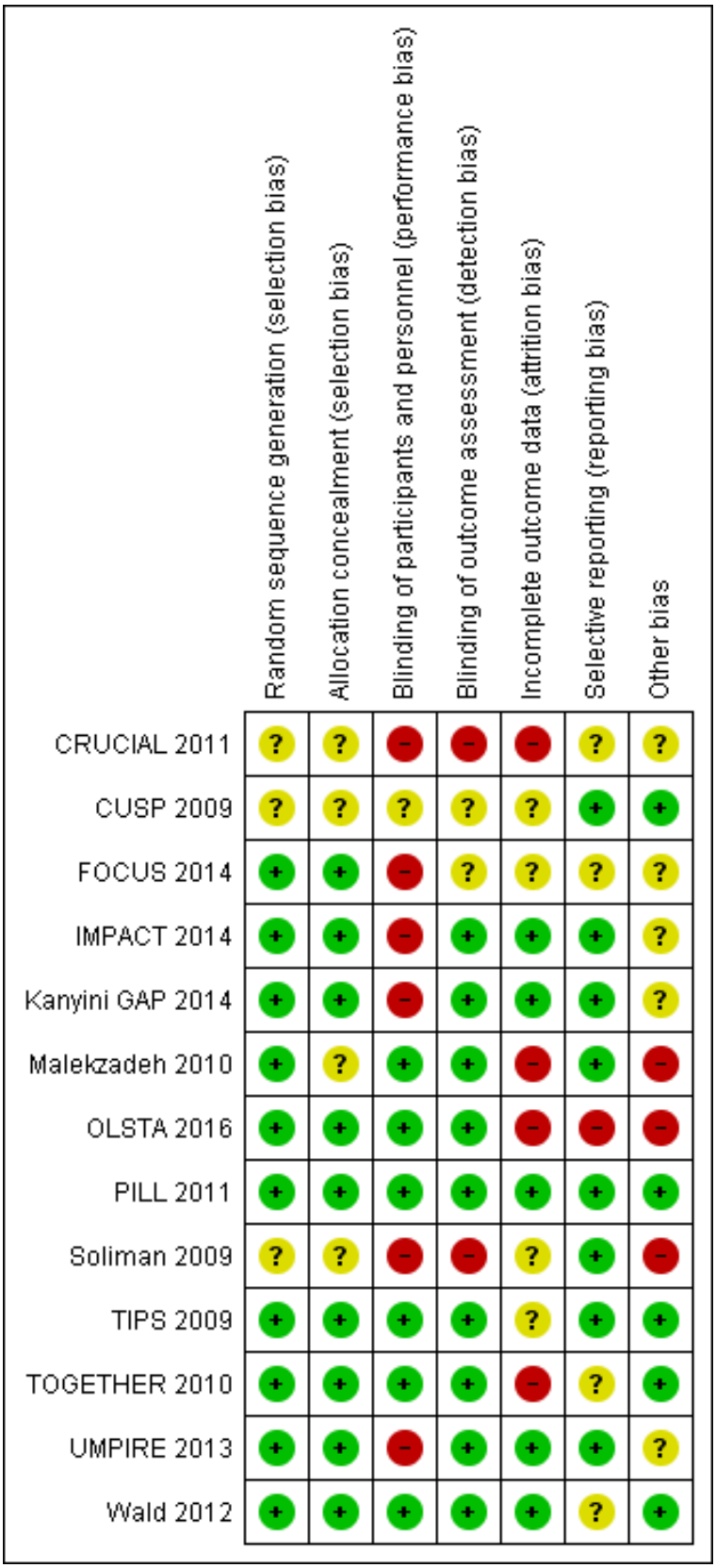
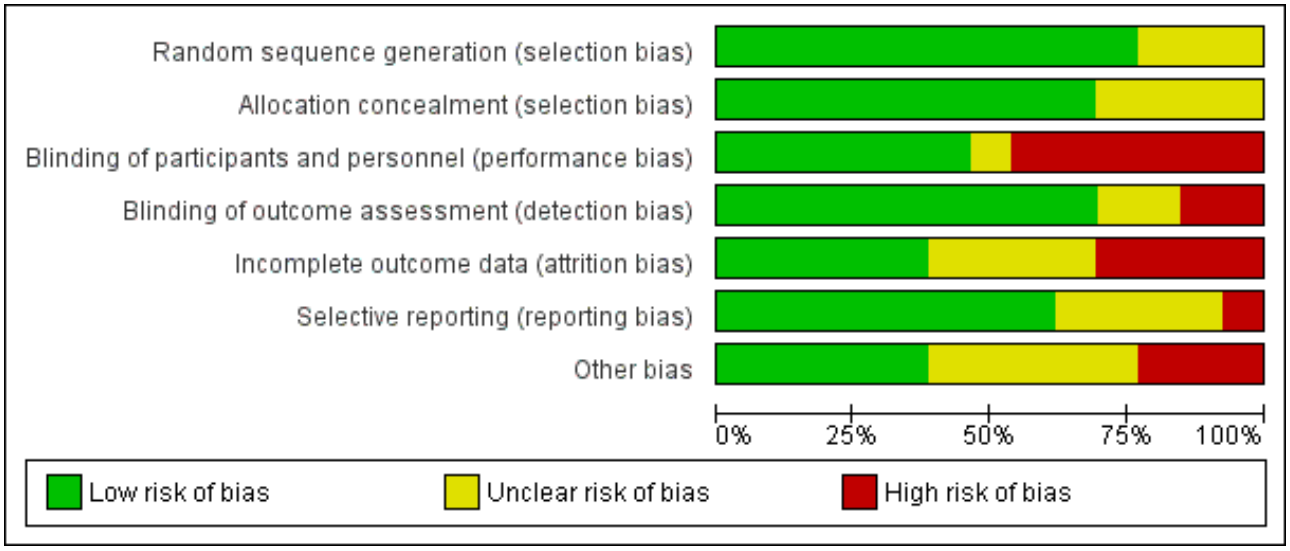


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

The methods of random sequence generation or allocation concealment were unclear in four of the included studies (CRUCIAL 2011; CUSP 2009; Malekzadeh 2010; Soliman 2009). In the nine studies where randomisation and allocation concealment were clear, we judged the methods used to have a low risk of bias (FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; OLSTA 2016; PILL 2011; TIPS 2009; TOGETHER 2010; UMPIRE 2013; Wald 2012).

Blinding

Five of the 13 included studies had a high risk for performance bias because the comparator group was usual care (CRUCIAL 2011; IMPACT 2014; Kanyini GAP 2014; Soliman 2009; UMPIRE 2013). However, three of these studies included blinded outcome assessment (IMPACT 2014; Kanyini GAP 2014; UMPIRE 2013) and had low risk of detection bias except for self-reported outcomes (e.g. self-reported adherence). One trial did not report whether or not the outcome assessment committee was blinded for adjudicating clinical events (FOCUS 2014), but the participants and personnel were not blinded to group allocation. The remaining seven 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 generally minimal differences in the proportion of losses to follow-up between the intervention and control arms. Four studies had a high risk of attrition bias (CRUCIAL 2011; Malekzadeh 2010; OLSTA 2016; TOGETHER 2010), including use of last observation carried forward for missing continuous variables. Four studies had an unclear risk of attrition bias (CUSP 2009; FOCUS 2014; Soliman 2009; TIPS 2009), and five studies had low risk of attrition bias (IMPACT 2014; Kanyini GAP 2014; PILL 2011; UMPIRE 2013; Wald 2012).

Selective reporting

The risk of bias associated with selective reporting was low in eight studies (CUSP 2009; IMPACT 2014; Kanyini GAP 2014; Malekzadeh 2010; PILL 2011; Soliman 2009; TIPS 2009; UMPIRE 2013), unclear in four studies (CRUCIAL 2011; FOCUS 2014; TOGETHER 2010; Wald 2012), and high in one study (OLSTA 2016).

Other potential sources of bias

Malekzadeh 2010 used a run-in period to exclude potential participants who had adherence rates less than 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 we categorised them all 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. In FOCUS 2014, the threshold of adherence using the Morisky-Green Questionnaire was changed from 16 or more to 20 during the study, which has uncertain effects on this outcome. OLSTA 2016 was funded, executed, and monitored by the manufacturing company of the fixed-dose combination that was studied.

Effects of interventions

See: **Summary of findings for the main comparison** Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases (ASCVD)

Primary outcomes

All-cause mortality

Five secondary prevention trials, including 5300 participants, reported all-cause mortality rates at the end of the study period with median follow-up ranging from 9 to 23 months (CRUCIAL 2011; FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; UMPIRE 2013). Mortality rates were low in both groups (1% in the intervention

group compared with 1% in the comparator group; only 53 total deaths), and participants randomised to the intervention had no evidence of increased mortality compared with the comparator group (RR 1.10, 95% CI 0.64 to 1.89, I^2 = 0%, Analysis 1.1) in the context of relatively few events. There were no differences among subgroups related to type of comparator (Analysis 1.2; Analysis 1.3) or number of drugs in the intervention (Analysis 1.4; Analysis 1.5).

Major ASCVD events

Only six out of 13 studies, including 4517 participants, reported rates of ASCVD events (FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; Malekzadeh 2010; OLSTA 2016; UMPIRE 2013). ASCVD events were uncommon in both groups (4.7% rate in the intervention group compared with 3.7% in the comparator group; only 188 total ASCVD events), resulting in uncertainty of the effect of fixed-dose combination therapy on this outcome (RR 1.26, 95% CI 0.95 to 1.66, I^2 = 0%, Analysis 1.6). This uncertainty remained when evaluating subgroups of primary or secondary prevention trials (Analysis 1.7; Analysis 1.8), type of comparator (Analysis 1.9; Analysis 1.10), or number of drugs in the intervention (Analysis 1.11; Analysis 1.12).

Adverse events

We included 11 trials including 6906 participants reporting aggregated rates of adverse events in both groups in the meta-analysis. The risk for adverse events was higher in participants in the intervention arm compared with participants in the control arm (32% versus 27%, RR 1.16, 95% CI 1.09 to 1.25, I^2 = 0%, Analysis 2.1). There was a trend toward higher rate of adverse events in primary prevention trials (RR 1.37, 95% CI 1.17 to 1.60, Analysis 2.2) compared with secondary prevention trials (RR 1.11, 95% CI 1.03 to 1.20, Analysis 2.3) but there were no differences among other subgroups. Specific side effects that were evaluated included myalgias (8 studies, 4% versus 3%, RR 1.11, 95% CI 0.84 to 1.48, Analysis 2.8), increased liver enzymes (4 studies, 7% versus 6%, RR 1.04, 95% CI 0.74 to 1.47, I^2 = 0%, Analysis 2.9), cough (5 studies, 5% versus 3%, RR 1.86, 95% CI 0.75 to 4.59, I^2 = 76%, Analysis 2.10), gastric irritation and dyspepsia (4 studies, 3% versus 2%, RR 1.33, 95% CI 0.64 to 2.74, I^2 = 67%, Analysis 2.11), and bleeding (2 studies, 2% versus 0.2%, RR 5.68, 95% CI 1.01 to 32.03, I^2 = 0%, Analysis 2.12).

Secondary outcomes

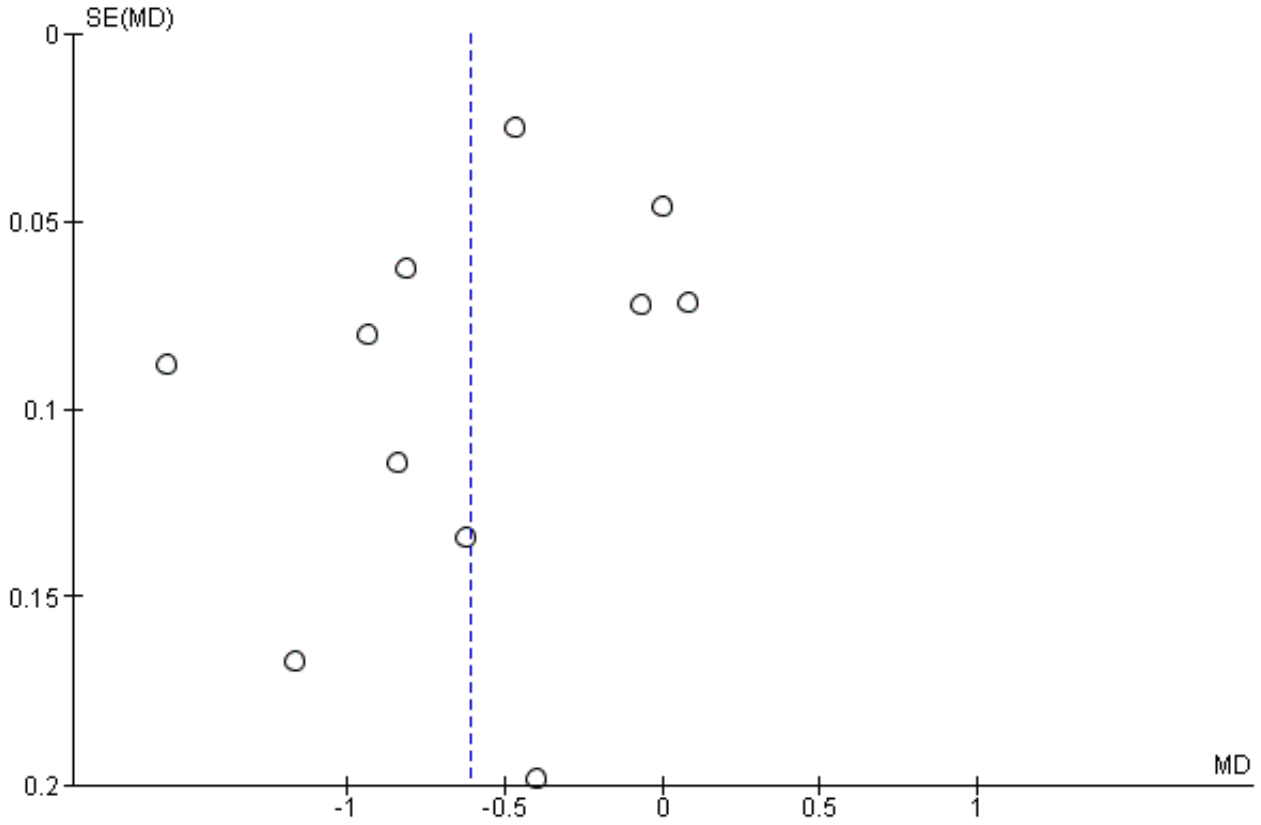
Blood pressure

All 13 trials reported changes in systolic and diastolic blood pressure in 7638 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 MD in systolic blood pressure between the intervention and control arms was -6.34 mmHg (95% CI -9.03 to -3.64, Analysis 3.1), and the MD in diastolic blood pressure between the intervention and control arms was -3.33 mmHg (95% CI -4.86 to -1.79, Analysis 3.2). Trials that included usual care in the comparator group (CRUCIAL 2011; CUSP 2009; IMPACT 2014; Kanyini GAP 2014; UMPIRE 2013) did not have as large reductions in systolic blood pressure (MD -3.44 mmHg, 95% CI -7.61 to 0.74) compared with other trials (Analysis 3.5), but the direction of effect was similar. These results should be interpreted with caution given the degree of heterogeneity. There was no evidence of funnel plot asymmetry for systolic blood pressure. There were no differences in subgroup analyses evaluating the effect on systolic blood pressure by primary or secondary prevention trials (Analysis 3.3; Analysis 3.4). The effects were lower in trials that included usual care as the comparator (MD -3.44 mmHg, 95% CI -7.61 to 0.74, Analysis 3.5) compared with trials that used a placebo as the comparator (MD -10.77 mmHg, 95% CI -12.72 to -8.81, Analysis 3.6). There were no differences between trials with 3+ drugs or 2 drugs (Analysis 3.7; Analysis 3.8).

Lipids

Eleven trials reported changes in total cholesterol in 6565 participants, and 12 trials reported changes in LDL cholesterol in 7153 participants. There was a large degree of heterogeneity among the trials for both total cholesterol (I^2 = 98%) and LDL cholesterol (I^2 = 98%). No single trial explained this heterogeneity. Using a random-effects model, the MD in total cholesterol between the intervention and control arm was -0.61 mmol/L (95% CI -0.88 to -0.35, Analysis 4.1). Using a random-effects model, MD in LDL cholesterol between the intervention and control arms was -0.70 mmol/L (95% CI -0.98 to -0.41, Analysis 4.2). Trials that included usual care in the comparator group (CRUCIAL 2011; CUSP 2009; IMPACT 2014; Kanyini GAP 2014; UMPIRE 2013) did not have as large reductions in total cholesterol (MD -0.16 mmol/L, 95% CI -0.44 to 0.12) compared with other trials (Analysis 4.5), but the direction of effect was similar. These results should be interpreted with caution given the degree of heterogeneity. There was evidence of funnel plot asymmetry for total cholesterol (Figure 4). The effects of fixed-dose combination therapy on total cholesterol were greater in the seven primary prevention trials (MD -0.92 mmol/L, 95% CI -1.18 to 0.65, Analysis 4.3) compared with the four secondary prevention trials (MD -0.16 mmol/L, 95% CI -0.49 to 0.17, Analysis 4.4), which may have been due to the higher use of placebo control in primary prevention trials. The effects were lower in trials that included usual care as the comparator (MD -0.16 mmol/L, 95% CI -0.44 to 0.12, Analysis 4.5) compared with trials that used a placebo as the comparator (MD -0.83 mmol/L, 95% CI -0.99 to -0.67, Analysis 4.6). There were no differences in the effect among trials that included 3+ drugs (MD -0.48 mmol/L, 95% CI -0.80 to -0.16, Analysis 4.7) compared with 2 drugs (MD -0.94 mmol/L, 95% CI -1.50 to -0.38, Analysis 4.8), which is expected because of the use of statin therapy in all fixed-dose combinations.

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



Adherence

Four trials reported adherence in 3835 participants (FOCUS 2014, IMPACT 2014, Kanyini GAP 2014, UMPIRE 2013; all secondary prevention trials and all combinations included 3+ drugs), and in three of these trials (IMPACT 2014, Kanyini GAP 2014, UMPIRE 2013) adherence was defined as taking aspirin, statin, and two or more blood pressure-lowering drugs. Adherence was assessed through self-report (FOCUS 2014, IMPACT 2014, Kanyini GAP 2014, UMPIRE 2013), pill count (FOCUS 2014), and linkage to pharmacy data (IMPACT 2014). Adherence was higher in the intervention group compared with the control groups (74% versus 53%, RR 1.44, 95% CI 1.26 to 1.65, I^2 = 80%, moderate-quality evidence, Analysis 5.1). The heterogeneity of effect was largely explained by IMPACT 2014, but the magnitude and direction of effect was similar after excluding this trial (post-hoc analysis: RR 1.35 95% CI 1.25 to 1.46, I^2 = 34%). The effect of fixed-dose combination therapy was similar in the three trials that used usual care as the comparator (Analysis 5.2) compared with the one trial with the comparator of providing individual drugs (Analysis 5.3).

Discontinuation

Rates of discontinuation were reported in both groups in seven trials including 3118 participants with active control or placebo as the comparator (CUSP 2009; FOCUS 2014; Malekzadeh 2010; PILL 2011; TIPS 2009; TOGETHER 2010; Wald 2012). Discontinuation rates were higher in individuals randomized to fixed-dose combination therapy (12% versus 10%, RR 1.24, 95% CI 1.01 to 1.51, I^2 = 0%, Analysis 6.1).

Health-related quality of life

Three trials including 3009 participants (IMPACT 2014, Kanyini GAP 2014, 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 demonstrated no effect of fixed-dose combination on EQ-5D scores compared with usual care (MD 0.22, 95% CI -1.02 to 1.46, I^2 = 0%, Analysis 7.1).

Costs

One study (Kanyini GAP 2014) reported direct Medicare benefit costs (n = 551 participants) and pharmacy benefit costs (n = 458 participants) among a sub-sample of individuals randomised to fixed-dose combination therapy or usual care who agreed to have their records linked to Medicare benefits. As part of the trial design, individuals randomised to the fixed-dose combination therapy arm incurred out-of-pocket costs typical for the Pharmaceutical Benefits Scheme, ranging from AUS 0 to AUS 35 per month. Unadjusted Medicare costs were similar (MD AUS 12, 95% CI -259 to 235) but unadjusted pharmacy costs appeared lowered in participants randomised to fixed-dose combination therapy (MD AUS 995, 95% CI -1366 to -624).

DISCUSSION

Summary of main results

This systematic review demonstrates that the effects of fixed-dose combination therapy on all-cause mortality or ASCVD events are uncertain. However, the event rates for these outcomes were very

low, only five (all-cause mortality) and six (ASCVD) events out of 13 trials reported these outcomes, respectively, and these trials used usual care as their comparator. The uncertainty from this update suggests that future research will likely change this estimate. The trend toward greater number of ASCVD events in the group randomised to fixed-dose combination may be due to chance, performance bias due to lack blinding of the study personnel and participants, or the effects of switching or initiating the fixed-dose combination, but merits further investigation. Adverse events were common in both the intervention (30%) and comparator (24%) groups, with participants randomised to fixed-dose combination therapy being 20% more likely to report an adverse event. Notably, no serious adverse events were reported. The trials reported reductions in systolic and diastolic blood pressure and total and LDL cholesterol. These risk factor changes would have been expected to result in a reduction in ASCVD events if sustained, but the trials reporting changes in risk factors were generally too short to detect a potential difference by their design. There was also substantial heterogeneity in these estimates, so these effects on risk factors 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 an active 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 participants studied, differences in the potency of the antihypertensives and statins used, and the differences in treatments used in the comparison groups. The apparent paradox of the intervention leading to higher discontinuation rates and higher adherence is largely dependent on the comparator group. For example, in trials that included usual care as the comparator, the trials were not able to measure and thus report discontinuation rates.

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). These trials were performed in 32 countries, including 19 low- and middle-income countries, where the burden of ASCVD is greater than in high-income countries (Roth 2015). However, the provision of usual care in trials led to far higher adherence rates than have been reported in community-based studies evaluating multidrug adherence in low- and middle-income countries (Yusuf 2011).

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 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 (NCT01826019; INTEGRATE; PolyIran; NCT02278471; NCT02596126; NCT01646437), and 12 trials that await classification (Fommei 2015; NCT00530946; NCT01004705; NCT01005290; NCT01362218; NCT01406431; NCT01764178; NCT02075619; NCT02569814; NCT02662894; NCT02791958; NCT02842359). The results of these trials are likely to have an important impact on our confidence in the estimates of effect and may change the estimates given the number of trials, number of participants, length of follow-up, and estimated number of events relative to the current evidence base. These trials evaluate the effects of combinations in various settings, including among older individuals (NCT02596126) and within complex health system interventions that incorporate clinician decision support (INTEGRATE) and non-physician health workers (NCT01826019).

Quality of the evidence

The main risk of bias was related to lack of blinding of participants and personnel, which was inherent to the intervention. Using other GRADE domains, we judged the quality of evidence of fixed-dose combination therapy for all-cause mortality and ASCVD events to be low, which was driven by imprecision (low event rates) and indirectness of evidence. The comparator of usual care was of a higher standard than might be expected outside of the research setting and particularly higher than has been reported in low- and middle-income countries based on previous research (Yusuf 2011). This observation is further supported by the SPACE collaboration demonstrating a differential effect of the intervention on adherence among individuals with low baseline treatment, suggesting that individuals who have low treatment rates at baseline are more likely to benefit (Webster 2016a). We judged the quality of evidence for fixed-dose combination therapy on adverse events to be moderate, due to indirectness of evidence, because the comparator group included individuals receiving usual care, which included drug prescription rates that were higher than those seen in non-research settings, as well as placebo, which would not be an expected comparator for fixed-dose combinations in clinical settings. We judged the quality of evidence for the effect of fixed-dose combination therapy on systolic blood pressure and LDL cholesterol to be moderate, due to unexplained heterogeneity that was likely driven by differences in populations, fixed-dose combinations, and comparator groups. We judged the quality of evidence for fixed-dose combination on total cholesterol as low because of unexplained heterogeneity as outlined for systolic blood pressure and LDL cholesterol; we further downgraded the quality of evidence for total cholesterol for reporting bias due to funnel plot asymmetry. We judged the quality of evidence for fixed-dose combination therapy on adherence to be moderate due to indirectness of evidence based on the high quality care provided in the comparator of usual care (IMPACT 2014; Kanyini GAP 2014; UMPIRE 2013) or active drug comparator provided to these participants (FOCUS 2014).

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. 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 (-6.34 mmHg versus -9.20 mmHg) and diastolic blood pressure (-3.33 mmHg versus -5.00 mmHg) and lower total (-0.61 mmol/L versus -1.22 mmol/L) and LDL cholesterol (-0.70 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 seven additional studies (CRUCIAL 2011; FOCUS 2014; IMPACT 2014; Kanyini GAP 2014; OLSTA 2016; Soliman 2009; UMPIRE 2013).

The changes in blood pressure were lower than those predicted by Wald and Law (diastolic blood pressure: -3.33 mmHg versus -11 mmHg, Wald 2003), which may be due to the number of blood pressure-lowering drugs, baseline blood pressures, or comparison to usual care groups that received very high-quality care demonstrated by adherence rates in the comparator groups, which would not be typical in most communities (Yusuf 2011). The changes in LDL cholesterol were also lower than those predicted by Wald and Law (-0.70 mmol/L versus 1.8 mmol/L) for similar reasons to those outlined above.

We have reported a similar direction and magnitude of effects that were reported in the individual participant data meta-analysis performed by the Single Pill to Avert Cardiovascular Events (SPACE) collaboration (Webster 2016a), which included data from IMPACT 2014; Kanyini GAP 2014; UMPIRE 2013. In the SPACE collaboration meta-analysis, the relative effect on adherence was larger (80% versus 50%, RR 1.58, 95% CI 1.32 to 1.90) but the effect on systolic blood pressure (SBP) (−2.5 mmHg; 95% CI −4.5 to −0.4) and LDL cholesterol (−0.1 mmol/L; 95% CI −0.2 to 0.0) were lower but with greater precision. These investigators evaluated the interaction between baseline treatment and adherence and SBP and demonstrated a greater effect of fixed-dose combination therapy on adherence and SBP among individuals with low baseline treatment compared with individuals with high baseline treatment.

Bangalore 2007 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 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 2010, 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 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 participants 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 2013 interviewed 11 primary care physicians and five practice nurses in nine Birmingham, UK practices about their knowledge and attitudes toward fixed-dose combination therapy. 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 ASCVD 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 minimal 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 people at moderate risk for ASCVD and more than four out of every five physicians reported that they would prescribe fixed-dose combination therapy for people at high risk for ASCVD. These disparate data using different methods of data collection suggest varying potential for uptake among physicians.

AUTHORS' CONCLUSIONS

Implications for practice

The effects of fixed-dose combination therapy on all-cause mortality or atherosclerotic cardiovascular disease (ASCVD) events are uncertain. A limited number of trials reported these outcomes, and the included trials were primarily designed to observe changes in ASCVD risk factor levels rather than clinical events, which may partially explain the observed differences in risk factors that were not translated into differences in clinical outcomes among the included trials. Fixed-dose combination therapy is associated with modest increases in adverse events compared with placebo, active comparators, or usual care which may result from improved adherence to a multidrug regimen. Ongoing, longer-term trials of fixed-dose combination therapy will help demonstrate whether short-term changes in risk factors might be maintained and lead to expected differences in clinical events based on these changes.

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 ASCVD-prevention settings. Ongoing trials will be informative; studies awaiting classification may be as well. The certainty of effect following the inclusion of these trials relies, at least in part, on their conduct and event rates. Some of these trials will also help demonstrate the effectiveness of fixed-dose combination therapy in conjunction with other health system interventions. Larger studies are also needed to evaluate the risk of serious adverse events in varied populations.

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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 comparator participants) from 19 countries (Costa Rica, Croatia, Czech Republic, Dominican Republic, Indonesia, Jordan, Kuwait, Lebanon, Malaysia, Mexico, Panama, Philippines, South Korea, Russia, Taiwan, Thailand, Turkey, United Arab Emirates, Venezuela) Men and women aged 35-79 years with hypertension and total cholesterol < 250 mg/dL plus 3 or more risk factors (current smoker, peripheral artery disease, type 2 diabetes, family history of early CHD before aged 55 years in first-degree relative; left ventricular hypertrophy on ECG; history of transient ischaemic 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 (5 mg/10 mg-10 mg/10 mg; 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 Comparator: usual care, including therapeutic lifestyle counselling change
Outcomes	SBP, DBP, LDL-C, total cholesterol; all-cause mortality reported
Notes	Comparator: 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	Differences between two arms in terms of baseline blood pressure, ECG abnormalities, PVD

CUSP 2009

Methods	Individual-level RCT

CUSP 2009 *(Continued)*

Participants	130 participants (66 intervention; 64 comparator) from the USA with coexisting, untreated hypertension (SBP = 140 mmHg-169 mmHg or DBP = 90 mmHg-105 mmHg) and dyslipidaemia (LDL-C = 110 mg/dL-160 mg/dL) but without a history of cardiovascular disease; age > 21 years
Interventions	Intervention: single pill amlodipine/atorvastatin (5 mg/20 mg) + therapeutic lifestyle changes Comparator: 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 participants 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	Comparator: 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 participants lost to follow-up were handled
Selective reporting (reporting bias)	Low risk	Primary outcomes reported (week 4 blood pressure and LDL targets)
Other bias	Low risk	No other sources of bias are identifiable

FOCUS 2014

Methods	"randomized, open-label, active-controlled, piggyback, 2-group parallel trial"
Participants	695 participants (350 polypill; 345 comparator) across 63 sites in 4 countries (Argentina, Italy, Paraguay, Spain) Details about Phase 2 participants (age, sex) not provided in the primary manuscript. Inclusion criteria: “The study population included men and women age > 40 years with a history of acute MI within the last 2 years...Due to slow recruitment, after the initial 591 participants had been included, an amendment to the initial protocol was approved to allow for the inclusion of patients with any past history of an acute MI, regardless of duration from enrollment.”

FOCUS 2014 *(Continued)*

	Exclusion criteria: "secondary dyslipidemia, contraindication to any of the components of the polypill, participation in another trial, previous percutaneous transluminal coronary angioplasty with a drug-eluting stent within the previous year, severe congestive heart failure (New York Heart Association functional class III to IV), serum creatinine > 2 mg/dL, any condition limiting life expectancy < 2 years, and pregnancy or pre-menopause."
Interventions	Intervention: "aspirin (100 mg), simvastatin (40 mg), and ramipril at 3 different doses (2.5 mg, 5 mg, or 10 mg, which allowed for up-titration at the discretion of the physician)" in hard-shell gelatin capsule Comparator: aspirin, simvastatin, and ramipril provided separately Drugs were provided free of cost for both arms
Outcomes	Primary • Medication adherence assessed by attendance at the final 9-month visit and the MAQ and pill count methods, simultaneously. "Participants lost for follow-up and those discontinuing medication due to adverse effects were also considered to be nonadherent for this analysis". Definition: "Pill count was calculated as: (no. of pills dispensed – no. of pills returned)/number of pills prescribed X 100. A pill count between 80% and 110% was considered good adherence." • Blood pressure • LDL cholesterol Secondary • Incidence of adverse events including death, reinfarction, and rehospitalisation for any CV cause • Rate of treatment withdrawal • Tolerability • Quality of life • "Economic endpoints" Outcomes measured at 1, 4, and 9 months Follow-up: 9 months
Notes	Comparator: individual drugs (aspirin, simvastatin, ramipril) provided separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a central electronic randomization service assigned participants to 1 of 2 arms"
Allocation concealment (selection bias)	Low risk	"a central electronic randomization service assigned participants to 1 of 2 arms"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open label trial; no evidence of blinded outcome assessment committee
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Similar loss to follow-up between groups (intervention 12.3%; comparator 10.1%, Table 2) but could influence primary outcome

FOCUS 2014 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Primary outcome was reported, but the threshold for defining adherence was changed from 16-20 during the trial. The effects of this change are uncertain. Data on 4-month outcomes not reported but not likely different than longer term trends
Other bias	Unclear risk	Relatively small study to detect any differences in clinical outcomes; could be considered low risk of small study bias for adherence

IMPACT 2014

Methods	"Open label randomised control trial"
Participants	513 participants (from 91 General Practitioners); target = 600 participants in New Zealand 256 polypill; 257 comparator Mean (SD) age: 62 (8) years for both arms Maori ethnicity: 50% for both arms Women: 39% intervention; 34% comparator CAD: 35% intervention; 38% comparator DM: 44% intervention; 41% comparator Employed: 46% intervention; 44% comparator “Given the available funding resources, the recruitment target was revised down to 500, which provided 89-93% power to detect the same differences between risk factors and 92% power to detect a 30% relative improvement in adherence.” Inclusion criteria: "Adults aged 18-79 years at high risk of cardiovascular disease (based on either established disease (coronary, cerebrovascular, or peripheral vascular) or ≥15% five year risk of a cardiovascular event); patient’s general practitioner considered all the drugs in at least one of the two versions of the fixed-dose combination treatment available were recommended and was uncertain if treatment was best provided as fixed-dose combination based treatment or as usual care" Exclusion criteria: "contraindications to any of the components of the fixed dose combination, congestive heart failure, haemorrhagic stroke, active stomach or duodenal ulcer, receipt of an oral anticoagulant, concerns by the general practitioner about the risk to a patient of changing his or her cardiovascular disease drugs, impending alteration of a drug regimen for an important length of time (for example, planned coronary bypass graft operation), or the participant was unlikely to complete the trial or trial procedures"
Interventions	Intervention: • Aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg or • Aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg, hydrochlorothiazide 12.5 mg Comparator: "The control is usual management. Physicians in both groups are encouraged to prescribe in line with New Zealand CVD risk assessment and management guidelines.” "both trial drugs and usual drugs were dispensed through community pharmacies." "Participants were required to pay what they would normally pay to receive a single government subsidised drug" "Standard patient co-payments of NZ$5 (£2.6; €3.1; $4.3) for each item every three months"

IMPACT 2014 *(Continued)*

Outcomes	Primary: • Adherence (self-reported current use of antiplatelet, statin, and at least two blood pressure-lowering drugs) at 12 months • Change in blood pressure between baseline and 12 months • Change in LDL-C between baseline and 12 months Secondary: • Serious adverse events • Cardiovascular events • Health-related quality of life (EuroQol EQ-5D) Outcomes measured: baseline, 1, 6, 12 months, end of trial Follow-up: median of 23 months in both arms
Notes	Comparator: usual care

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A central randomisation service randomly assigned (1:1) participants to fixed dose combination based treatment or usual care."
Allocation concealment (selection bias)	Low risk	"A central randomisation service randomly assigned (1:1) participants to fixed dose combination based treatment or usual care."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adherence: self-report but corroborated by pharmacy claims data but definition favours intervention (requiring second BP lowering drug, though sensitivity analyses showed similar direction of effect) LDL/SBP objectively measured and not likely too susceptible to bias SAE/CV events self-reported but objective and reviewed by endpoints committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up rates low and balanced
Selective reporting (reporting bias)	Low risk	Outcome reporting largely matches protocol; 6-month data may not have been reported but not likely different than longer term outcome trends
Other bias	Unclear risk	Small study bias to evaluate differences in clinical outcomes

Kanyini GAP 2014

Methods	"randomized, open-label trial"

Kanyini GAP 2014 *(Continued)*

Participants	623 participants (311 polypill, 312 comparator) from 33 centres (12 Aboriginal Medical Services); target = 1000 participants in Australia Mean (SD) age: 63.4 (12.5) years intervention; 63.7 (12.7) years comparator Women: 37% intervention; 37% comparator Indigenous: 51% overall (not reported by group) CVD: 59% intervention; 63% comparator CHD: 52% intervention; 54% comparator CM: 60% intervention; 55% comparator Inclusion criteria: "18 years or over and able to give informed consent, have a history of coronary heart disease (myocardial infarction, stable or unstable angina pectoris, or coronary revascularization procedure), and/ or ischaemic cerebrovascular disease, and/or peripheral vascular disease; or a calculated 5-year CVD risk of 15% or greater*...Each participant had to have, in their doctor's view, indications for all and no contraindications to any component of at least one of two polypills" *including a 5% increment for Aboriginal or Torres Strait Islander identification Exclusion criteria: "Participants were excluded if it was felt clinically inappropriate to alter medications."
Interventions	Intervention • Aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg • Aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg Comparator: "usual care" "Out-of-pocket expenses for the polypill were incurred identically to those for any other drug listed in the Pharmaceutical Benefits Scheme, which is the government subsidy programme through which most drugs are obtained in Australia."
Outcomes	Primary • Self-reported use of all medications was assessed at each visit, recorded as the number of days on which medication was taken in the immediately preceding week… antiplatelet, statin and ≥2 BP lowering therapies for ≥4 of the previous seven days)" • Blood pressure (SBP, DBP) • Lipids (total cholesterol, LDL cholesterol) Secondary • Barriers to adherence • Health-related quality of life (EQ-5D questionnaire) • Cardiovascular, renal and other serious adverse events • Reasons for stopping cardiovascular medications Time points measured: baseline, 1 month, and q6 month through 24 months Follow-up: intervention: median 20.7 months, comparator: median 18.1 months
Notes	Comparator: usual care

Risk of bias

Bias	Authors' judgement	Support for judgement

Kanyini GAP 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Central, computer-based randomization to polypill-based strategy or usual care was stratified by primary healthcare centre, type of indication (established CVD versus high risk), Indigenous identification and level of preventive treatment at baseline."
Allocation concealment (selection bias)	Low risk	"Central, computer-based randomization to polypill-based strategy or usual care was stratified by primary healthcare centre, type of indication (established CVD versus high risk), Indigenous identification and level of preventive treatment at baseline."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adherence: high risk of bias because it was self reported SBP/TC/events: low risk of bias because these are objective measures, and the latter was adjudicated by a blinded outcome assessment committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of losses to follow-up and missingness, with rates balanced between the groups
Selective reporting (reporting bias)	Low risk	No differences between primary reports and protocol
Other bias	Unclear risk	Small study bias for events but low risk of bias for adherence and change in risk factors

Malekzadeh 2010

Methods	Individual-level, blocked RCT
Participants	475 participants (241 polypill; 234 control) from Golestan, Iran without CVD, hypertension, or hyperlipidaemia aged 50-79 years (men) and 55-79 years (women)
Interventions	Intervention: polypill (aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg and hydrochlorothiazide 12.5 mg) Comparator: placebo
Outcomes	Hospital admissions/major cardiovascular events/seated and standing BP, LDL-C, total cholesterol, triglycerides, HDL-C and fasting glucose
Notes	Comparator: 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)	Unclear risk	Computer generation allocation to numbered list of blister packs manufactured by Alborz Darou, but differences between intervention and compara-

Malekzadeh 2010 *(Continued)*

		tor groups for baseline gender (38% versus 28%), systolic (125 mmHg vs 130 mmHg) and diastolic blood pressure (78 mmHg vs 81 mmHg) were seen
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

OLSTA 2016

Methods	Individual-level RCT, 2:1:1:1 design with triple dummy
Participants	181 “Korean patients with mild to moderate hypertension and dyslipidemia” defined by JNC VII and ATP III. Participants underwent 4 week run-in period and were recruited from 25 centres in Korea Exclusion criteria: • Secondary hypertension • HbA1c > 9% • CVD event within 6 months; NYHA FC III or IV heart failure • TSH, serum creatinine, liver chemistries > 1.5 times upper limit of normal • Any condition that might influence the study results FDC: 71 participants, mean (SD) age 61.9 (8.1) years; 44% women; 44% diabetes; 0% CHD Olmesartan: 38 participants, mean (SD) age 59.5 (6.9) years; 33% women; 39% diabetes; 0% CHD Rosuvastatin: 38 participants, mean (SD) age 61.8 (8.0) years; 31% women; 22% diabetes; 0% CHD Placebo: 34 participants, mean (SD) age 62.5 (8.2) years; 28% women; 31% DM; 0% CHD
Interventions	Intervention: fixed-dose combination of olmesartan medoxomil 40 mg + rosuvastatin 20 mg Comparator 1: Olmesartan medoxomil 40 mg Comparator 2: Rosuvastatin 20 mg Comparator 3: Placebo
Outcomes	Primary • Percentage change from baseline in the LDL-C at week 8 • Percentage change from baseline in DBP at week 8 Secondary

OLSTA 2016 *(Continued)*

- Percentage change from baseline in total cholesterol, triglycerides, and HDL-C at week 4 and week 8
- Percentage change from baseline in SBP at week 4 and week 8
- Percentage of participants who achieved treatment goals
- Adverse events

Notes	Reported differences in baseline characteristics, which may or may not be due to chance: 3.3 mm SBP difference between rosuvastatin and placebo arms (but only those who completed follow-up had baseline data reported); 3.3-year difference in age between olmesartan and placebo group; 16% difference in women between FDC and placebo; 22% difference in DM between FDC and rosuvastatin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized, computer generator random sequence
Allocation concealment (selection bias)	Low risk	Centralized, computer generator random sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, triple dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded study staff
Incomplete outcome data (attrition bias) All outcomes	High risk	High loss to follow-up rate in intervention group with complete case analysis only (no imputation) FDC: 10/71 (14%) Olmesartan: 2/38 (5%) Rosuvastatin: 2/38 (5%) Placebo: 5/34 (15%)
Selective reporting (reporting bias)	High risk	Protocol (NCT01764295) published in January 2013, after trial initiation
Other bias	High risk	Small study bias with short follow-up; sponsored by Daewoong Pharmaceutical, which also performed trial execution and monitoring

PILL 2011

Methods	Individual-level RCT
Participants	378 participants (189 intervention; 189 comparator) from 7 countries (Australia, Brazil, India, Netherlands, New Zealand, UK, USA) 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 ≥ 30 kg/m^2, waist circumference > 102 cm in men or > 88 cm in women; heart rate > 80 bpm; fasting glucose 5.6 mmol/L-7 mmol/L, triglycerides > 1.7 mmol/L; family history of first degree relative

PILL 2011 *(Continued)*

	with premature ischaemic 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 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) Comparator: placebo
Outcomes	Change in SBP; change in LDL-C; tolerability; secondary outcomes included discontinuation, 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	Comparator: 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%); however, last observation carried forward method used for missing continuous data at week 12
Selective reporting (reporting bias)	Low risk	Outcomes outlined in methods paper were reported in the primary manuscript
Other bias	Low risk	No other sources of bias are identifiable

Soliman 2009

Methods	Open label, parallel-group RCT
Participants	216 participants (105 polypill; 111 comparator); ≥ 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) Comparator: standard practice defined by the study investigators

Soliman 2009 *(Continued)*

Outcomes	SBP, total cholesterol, 10-year cardiovascular disease risk, adherence, fasting glucose, creatinine, potassium, and liver enzymes
Notes	Comparator: 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)	Unclear risk	No method of randomisation stated
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 RCT
Participants	2053 participants (205 aspirin; 205 thiazide; 209 thiazide + ramipril; 207 thiazide + atenolol; 205 ramipril + atenolol; 204 thiazde + ramipril + atenolol; 204 thiazide + ramipril + atenolol + aspirin; 202 simvastatin; 412 Polycap [thiazide + ramipril + atenolol + simvastatin + aspirin); 45-80 years old without prior cardiovascular disease but with 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) Comparator: 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	Comparator: active

TIPS 2009 *(Continued)*

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
Other bias	Low risk	No other sources of bias are identifiable

TOGETHER 2010

Methods	Individual-level randomised, double dummy controlled trial
Participants	244 participants (122 intervention; 122 control) from the USA 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
Interventions	Intervention: single pill amlodipine (5/10 mg) plus atorvastatin 20 mg + therapeutic lifestyle changes Comparator: amlodipine (5/10 mg) + 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	Comparator: active

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central, computer-based telerandomisation

TOGETHER 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central, computer-based telerandomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind labelled bottles and double dummy
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
Other bias	Low risk	No other sources of bias are identifiable

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 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg or (2) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg) Comparator: 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	Comparator: inactive/usual care

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

UMPIRE 2013 *(Continued)*

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 and secondary outcomes reported
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 Comparator: placebo
Outcomes	SBP, DBP, total cholesterol, LDL-C, HDL-C, triglycerides, apoB, adherence (pill counts of fixed-dose combination compared with placebo), adverse events
Notes	Comparator: 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

Wald 2012 *(Continued)*

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

apoB: apolipoprotein B
CHD: coronary heart disease
CVD: cardiovascular disease
DBP: diastolic blood pressure
ECG: electrocardiogram
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
PVD: peripheral vascular disease
RCT: randomised controlled trial
SBP: systolic blood pressure

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

Study	Reason for exclusion
Abdellatif 2012	Wrong intervention
Agabiti Rosei 2014	Wrong intervention
Agarwal 2013	Wrong intervention
Anonymous 2010	Wrong study design
Anonymous 2011	Wrong study design
Anonymous 2012a	Wrong study design
Anonymous 2012b	Wrong intervention
Anonymous 2013a	Review
Anonymous 2013b	Wrong intervention
Athyros 2013	Wrong study design
Athyros 2014	Wrong study design
Bashir 2011	Wrong study design
Becerra 2015	Wrong study design

Study	Reason for exclusion
Bittencourt 2013	Wrong study design
Bittencourt 2014	Wrong study design
Blank 2007	Review
Briasoulis 2013	Wrong intervention
Bryant 2013	Wrong study design
Carey 2012	Review
Cass 2013	Duplicate
Castellano 2014a	Wrong study design
Castellano 2014b	Wrong study design
Castellano 2015	Wrong study design
Chae 2015	Wrong comparator
ChineseExpert 2013	Wrong study design
Chrysant 2014	Wrong study design
Crunkhorn 2012	Wrong intervention
Dabhadkar 2013	Wrong study design
deCates 2014	Meta-analysis
Delgado Montero 2012	Wrong study design
Dimitrov 2012	Wrong intervention
Dresser 2012	Wrong intervention
Dresser 2013	Wrong comparator
Elley 2012	Meta-analysis
Fedacko 2013	noncomparative design
Feldman 2012	Wrong study design
Feldman 2014	Wrong study design
Feng 2012	Wrong intervention
Galindo Ocana 2012	Wrong study design
Gaziano 2013	Wrong study design
Holzgreve 2014	Review

Study	Reason for exclusion
Huang 2016	Wrong study design
Huffman 2012	Wrong study design
Huffman 2014	Wrong study design
Ito 2012	Wrong study design
Ivanovic 2013	Wrong study design
Jadhav 2014	Wrong intervention
Jang 2015	Wrong intervention
Jaques 2011	Wrong study design
Kawashiri 2015	Wrong intervention
Kereiakes 2012	Wrong intervention
Khaled 2015	Wrong study design
Laba 2014a	Wrong intervention
Laba 2014b	Abstract
Lafeber 2011	Wrong study design
Lafeber 2012	Wrong study design
Lafeber 2013a	Wrong study design
Lafeber 2013b	Wrong study design
Lafeber 2014a	Wrong study design
Lafeber 2014b	Abstract
Lafeber 2014c	Wrong outcomes
Lafeber 2014d	Wrong comparator
Lafeber 2015	Wrong comparator
Lafeber 2016	Wrong study design
Law 2006	Wrong study design
Liu 2014	Abstract
Liu 2015	Duplicate
Marazzi 2016	Wrong intervention
Mishchenko 2014	Abstract

Study	Reason for exclusion
Mossello 2015	Wrong study design
Neutel 2009	Duplicate
Nguyen 2013	Wrong study design
OliverasVila 2014	Wrong study design
Reiner 2013	Review
Selak 2013	Wrong comparator
Selak 2016	Meta-analysis
Sepanlou 2012	Wrong intervention
Sigamani 2012	Wrong comparator
Simonyi 2016	Wrong study design
Son 2013	Wrong comparator
Tanaka 2014	Noncomparative design
Truelove 2014	Abstract
Wald 2016	Wrong study design
Wang 2012	Abstract
Webster 2013	Protocol
Webster 2014	Wrong study design
Webster 2015a	Wrong study design
Webster 2015b	Meta-analysis
Webster 2016a	Meta-analysis
Webster 2016b	Wrong study design
Wei 2013	Protocol
Wijns 2014	Wrong study design
Wiley 2014	Wrong study design
Xing 2013	Meta-analysis
Zeng 2016	Wrong study design
Zomer 2013	Wrong study design

Characteristics of studies awaiting assessment *[ordered by study ID]*

Fommei 2015

Methods	Randomised cross-over trial
Participants	Well-controlled non-complicated hypertensive outpatients under multiple therapy with at least one hypertensive drug and/or a statin and/or aspirin
Interventions	Single once-a-day administration (mono-administration) with at least one hypertensive drug and/or a statin and/or aspirin Comparator: usual care (multiple administration with at least one hypertensive drug and/or a statin and/or aspirin
Outcomes	Adherence to treatment, adverse events, ambulatory blood pressure monitoring and lipid profile
Notes	

NCT00530946

Methods	Randomised open-label, parallel trial
Participants	The outpatient with concurrent hypertension and hyper-LDL-cholesterolemia is a male or female >= 20 to < 80 years of age at Visit 1.The SBP at Visit 4 (Week -1) and Visit 5 (Week 0) is continuously SBP >= 140 mmHg and < 180 mmHg, LDL-C >= 140 mg/dL and < 250 mg/dL at Visit 3 (Week -2) and 4 (Week -1)
Interventions	Drug: amlodipine 2.5 mg/atorvastatin 5 mg (single pill combination, dosed once daily for 8 weeks) Drug: amlodipine 2.5mg/atorvastatin 10mg (single pill combination, dosed once daily for 8 weeks) Drug: amlodipine 5 mg/atorvastatin 5 mg (single pill combination, dosed once daily for 8 weeks) Drug: amlodipine 5 mg/atorvastatin 10 mg (single pill combination, dosed once daily for 8 weeks) Comparator: active comparator: CI-1038 2.5 mg/5 mg (intervention: drug: amlodipine 2.5 mg/atorvastatin 5 mg) active comparator: CI-1038 2.5 mg/10 mg (intervention: drug: amlodipine 2.5 mg/atorvastatin 10 mg) active comparator: CI-1038 5 mg/5 mg (intervention: drug: amlodipine 5 mg/atorvastatin 5 mg) active comparator: CI-1038 5 mg/10 mg (intervention: drug: amlodipine 5 mg/atorvastatin 10 mg)
Outcomes	**Primary outcomes:** • Change in SBP, Percent Change in LDL **Secondary outcomes:** • Change in SBP from baseline to each observation point (4 weeks and 8weeks) • Change in DBP from baseline to each observation point (4 weeks, 8 weeks) • Percent change in LDL, total cholesterol, HDL, triglycerides, from baseline to each observation point • Change in LDL/HDL ratio (timeframe 2 weeks, 4 weeks, 8 weeks), change in total cholesterol/HDL (timeframe 2 weeks, 4 weeks, 8 weeks)

NCT00530946 *(Continued)*

	• -Change in apolipoprotein B From baseline to each observation point ((timeframe 2 weeks, 4 weeks, 8 weeks)
Notes	

NCT01004705

Methods	Randomised open-label cross-over trial
Participants	Male or female participants ≥18 years of age Previously untreated LDL cholesterol ≥ 100 mg/dL and ≤ 180 mg/dL
Interventions	Once-daily oral dose of combination of acetylsalicylic acid, simvastatin, and ramipril (containing 100 mg acetylsalicylic acid, 40 mg simvastatin, and 5 or 10 mg ramipril) Comparator: once-daily oral dose of Simvastatin 40 mg
Outcomes	**Primary outcomes** • The difference in LDL cholesterol levels between the basal and the final visit of each treatment period • Change from baseline in LDL cholesterol level following each treatment period was defined as the difference between the measurements from the baseline visit **Secondary outcomes** • The difference in mean total cholesterol between the basal and the final visit of each treatment period • Change from baseline in mean total cholesterol level following each treatment period was defined as the difference between the measurements from the baseline visit
Notes	

NCT01005290

Methods	Randomised open-label, cross-over trial
Participants	Participants will be ≥ 18 years old. Previously untreated systolic pressure result of ≥ 120 < 160 mmHg and diastolic pressure result of ≥ 80 < 100 mmHg
Interventions	A once-daily oral dose of the cardiovascular fixed-dose combination pill (containing 100 mg acetylsalicylic acid, 40 mg simvastatin, and 5 mg ramipril) for 1 week followed by a once-daily oral dose of the cardiovascular fixed-dose combination pill (containing 100 mg acetylsalicylic acid, 40 mg simvastatin, and 10 mg ramipril) for 4 weeks Comparator: a once-daily oral dose of 5 mg ramipril for 1 week followed by a once-daily oral dose of 10 mg ramipril for 4 weeks
Outcomes	**Primary outcomes** • Difference in the adjusted mean 24-h systolic pressure results (using ABPM (ambulatory blood pressure monitoring)) between the basal and the final visit of each treatment period. (Time frame: days 7 and 36 of period 1 and days 49 and 85 of period 2.) (Designated as safety issue: no) • Difference in the adjusted mean 24-h systolic pressure results using ABPM in the PP population

NCT01005290 *(Continued)*

	Secondary outcomes • Difference in the adjusted mean 24-h diastolic pressure results between the basal and the final visit of each treatment period. (Time frame: days 7 and 36 of period 1 and days 49 and 85 of period 2.) (Designated as safety issue: no) • Difference in the adjusted mean 24-h diastolic pressure results (using ABPM) between the basal and the final visit of each treatment period
Notes	

NCT01362218

Methods	Randomised open-label, parallel assignment
Participants	Male or female participants aged ≥ 18 and < 75 years Previously untreated or not treated with fibrates during the last 6 weeks or with any other lipid-lowering drug for the last 4 weeks LDL-cholesterol ≥ 130 and ≤ 220 mg/dL Systolic blood pressure ≥ 120 and < 160 mmHg and diastolic blood pressure ≥ 70 and < 100 mmHg
Interventions	Drug: cardiovascular fixed-dose combination pill (acetylsalicylic acid, simvastatin and ramipril) Comparator: simvastatin given together with the reference drugs ramipril and acetylsalicylic acid
Outcomes	**Primary outcomes** • Difference in LDL-cholesterol levels between the basal and the final visit of treatment period **Secondary outcomes** • Difference in VLDL-cholesterol levels between the basal and the final visit of treatment period • Difference in HDL-cholesterol levels between the basal and the final visit of treatment period • Difference in total cholesterol levels between the basal and the final visit of treatment period • Difference in triglyceride levels between the basal and the final visit of treatment period
Notes	

NCT01406431

Methods	Randomised, open-label, cross-over assignment
Participants	Healthy male volunteers Age 20-55 years at the time of screening BMI 19-26 kg/m2 at the time of screening
Interventions	Pitavastatin 4 mg (2 tablets), valsartan 160 mg (1 tablet). Other name: Livalo, Diovan Comparator drug: pitavastatin, valsartan
Outcomes	**Primary Outcomes:**

NCT01406431 *(Continued)*

	-Cmax of study drugs after single oral administration -AUClast of study drugs after single oral administration **Secondary Outcomes** -AUCinf, Tmax and t1/2β of study drugs after single oral administration
Notes	

NCT01764178

Methods	Randomised, open-label, cross-over trial
Participants	Healthy male volunteers Age 20-55 years at the time of screening BMI 19-26 kg/m2 at the time of screening
Interventions	Livalo fixed combination drug (pitavastatin + valsartan) Comparator: pitavastatin, valsartan
Outcomes	**Primary outcomes:** • Cmax and AUC of study drugs after single oral administration **Secondary outcomes:** • AUCinf of study drugs after single oral administration • t1/2β of study drugs after single oral administration • Tmax of study drugs after single oral administration
Notes	

NCT02075619

Methods	Open-label, single-centre, randomised, single-dose, three-way cross-over, six-sequence study
Participants	• Male or female 21-65 years of age inclusive, at the time of signing the informed consent • Alanine transaminase, alkaline phosphatase and total bilirubin <= 1.5 x upper limit of normal (ULN) (isolated bilirubin > 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) • Normal electrocardiogram (ECG) morphology and measurements. Single corrected QT interval (QTc) < 450 ms. In particular QTc < 450 msec or QT < 480 ms in subjects with Bundle Branch Block based on an average from three ECGs obtained over a brief recording period • Female participants eligible if of non-childbearing potential. Female participants must agree to use contraception until 14 days after last dose of amlodipine/rosuvastatin, i.e. after single dose of treatment period 3 • Male participants with female partners of child-bearing potential must agree to use one of the contraceptive methods and not to donate sperm. • Chinese or white self-reported by the participants for both parents and all 4 grandparents. The ethnic group is as defined by National Registration Identity Cards provided additional confirmation of ethnicity

NCT02075619 *(Continued)*

Interventions	**Experimental: Sequence 1** Four participants (2 Chinese and 2 white) will receive 1 amlodipine 10 mg tablet and 1 rosuvastatin 20 mg tablet in Period 1; 1 GSK3074477 fixed-dose combination (FDC) formulation-1 tablet in Period 2 and 1 GSK3074477 FDC formulation-2 tablet in Period 3; all treatments will be administered orally in fasted state. The 3 treatment periods will be separated by a washout period of between 12-17 days **Experimental: Sequence 2** Four participants (2 Chinese and 2 white) will receive 1 amlodipine 10 mg tablet and 1 rosuvastatin 20 mg tablet in Period 1; 1 GSK3074477 FDC formulation-2 tablet in Period 2 and 1 GSK3074477 FDC formulation-1 tablet in Period 3; all treatments will be administered orally in fasted state. The 3 treatment periods will be separated by a washout period of between 12-17 days **Experimental: Sequence 3** Four participants (2 Chinese and 2 white) will receive 1 GSK3074477 FDC formulation-1 tablet in Period 1, 1 amlodipine 10 mg tablet and 1 rosuvastatin 20 mg tablet in Period 2; and 1 GSK3074477 FDC formulation-2 tablet in Period 3; all treatments will be administered orally in fasted state. The 3 treatment periods will be separated by a washout period of between 12-17 days **Experimental: Sequence 4** Four participants (2 Chinese and 2 white) will receive 1 GSK3074477 FDC formulation-1 tablet in Period 1; 1 GSK3074477 FDC formulation-2 tablet in Period 2; and 1 amlodipine 10 mg tablet and 1 rosuvastatin 20 mg tablet in Period 3; all treatments will be administered orally in fasted state. The 3 treatment periods will be separated by a washout period of between 12-17 days **Experimental: Sequence 5** Four participants (2 Chinese and 2 white) will receive 1 GSK3074477 FDC formulation-2 tablet in Period 1; 1 amlodipine 10 mg tablet and 1 rosuvastatin 20 mg tablet in Period 2; and 1 GSK3074477 FDC formulation-1 tablet in Period 3; all treatments will be administered orally in fasted state. The 3 treatment periods will be separated by a washout period of between 12-17 days **Experimental: Sequence 6** Four participants (2 Chinese and 2 white) will receive 1 GSK3074477 FDC formulation-2 tablet in Period 1; 1 GSK3074477 FDC formulation-1 tablet in Period 2; and 1 amlodipine 10 mg tablet and 1 rosuvastatin 20 mg tablet in Period 3; all treatments will be administered orally in fasted state. The 3 treatment periods will be separated by a washout period of between 12-17 days
Outcomes	**Primary outcomes:** • Plasma pharmacokinetics (PK) parameters of amlodipine and rosuvastatin following single dose administration **Secondary outcomes:** • Safety as assessed by adverse events • Safety as assessed by vital signs • Safety as assessed by clinical laboratory safety data • Safety as assessed by Electrocardiogram (ECG) parameters
Notes	

NCT02569814

Methods	Randomised, open-label, cross-over assignment trial
Participants	Healthy men, aged 19-50 years
Interventions	Group1 Fimasartan/amlodipine combination tablet and rosuvastatin individual tablets at 1st day as period I. And then, after wash out for 2 weeks, as period II, Group 1 participants take a fimasartan/amlodipine/rosuvastatin combination tablet at 15th day Group 2 A fimasartan/amlodipine/rosuvastatin combination tablet at 1st day as period I. And then, after wash out for 2 weeks, as period II, Group 2 participants take fimasartan/amlodipine combination tablet and rosuvastatin individual tablets at 15th day
Outcomes	**Primary outcome** -Cmax of fimasartan, amlodipine and rosuvastatin **Secondary outcome** -AUCt (Area Under the Curve) of fimasartan, amlodipine and rosuvastatin
Notes	

NCT02662894

Methods	Randomised parallel-assignment, open-label trial
Participants	Participants of both sexes aged 18-65 years Participants diagnosed with uncontrolled hypertension Participants with intermediate and high risk dyslipidaemia, according to the V Brazilian Guidelines on Dyslipidemia and Prevention of Atherosclerosis Ability to understand and consent to participate in this clinical study, manifested by signing the Informed Consent
Interventions	Valsartan + rosuvastatin FDC Fixed-dose combination of valsartan (160 mg or 320 mg) + rosuvastatin (20 mg), once daily for 4 weeks Comparator: separate tablets of valsartan (160 mg or 320 mg) + rosuvastatin (20 mg), once daily for 4 weeks
Outcomes	**Primary outcomes:** • Reduction of systemic blood pressure measured between the first visit and last visit. • Percentage of participants who reach the goal of LDL-C according to intermediate risk rating (LDLc < 100 mg/dL) and high risk (LDLc < 70 mg/dL) **Secondary outcomes:** • Incidence and severity of adverse events recorded after the signing of the Informed Consent and until the end of the study

NCT02662894 *(Continued)*

Notes	

NCT02791958

Methods	Randomised, open-label, parallel-assignment trial
Participants	Men or women aged ≥ 18 and < 75 years People with Stage 1 (SBP/DBP: 140-159/90-99 mmHg) or Stage 2 (SBP/DBP: ≥ 160/≥ 100 mmHg) hypertension, either untreated or after a wash out period LDL cholesterol level of ≥ 100 mg/dL and, either untreated or after the wash out period Untreated with BP-lowering and/or lipid-lowering medication Treated with BP-lowering and/or lipid-lowering medication can be included if the medication can be safely withdrawn as per physician's judgment
Interventions	A once-daily oral dose of the Cardiovascular Fixed Dose Combination Pill AAR (acetylsalicylic acid 100 mg, atorvastatin 40 mg and ramipril 10 mg) for 4 weeks **Comparator** • Atorvastatin 40 mg: a once-daily oral dose of atorvastatin 40 mg (Lipitor®) for 4 weeks • A once-daily oral dose of ramipril 10 mg (Altace®) for 4 weeks
Outcomes	**Primary outcomes** • Difference in the adjusted mean 24-h systolic blood pressure results using ABPM between the baseline (week 0) and the final visit (week 8) • Difference in LDL cholesterol levels between the baseline (week 4) and the final visit (week 8) **Secondary outcome measures** • Difference in the adjusted mean 24-h diastolic blood pressure results (using ABPM) between the basal and the final visits • Difference in the adjusted mean 24-h mean arterial pressure results (using ABPM) between the basal and the final visits • Difference in the adjusted mean 24-h heart rate results (using ABPM) between the basal and the final visits • Difference in very low-density lipoprotein (VLDL) cholesterol levels between the basal and the final visits • Difference in HDL cholesterol levels between the basal and the final visits • Difference in total cholesterol levels between the basal and the final visits • Difference in triglyceride levels between the basal and the final visits • Incidence of treatment-emergent adverse events (safety and tolerability)
Notes	

NCT02842359

Methods	Randomised, open-label, parallel-assignment trial
Participants	Aged ≥ 19 years to < 75 years

NCT02842359 *(Continued)*

	No medication history of hyperlipidaemia and hypertension within 3 months following registration, among people with type 2 diabetes diagnosed with hyperlipidaemia and stage I hypertension (systolic blood pressure: ≥ 140 mmHg, ≤ 159 mmHg or diastolic blood pressure: ≥ 90 mmHg, ≤ 99 mmHg), with adequately controlled haemoglobin levels Diagnosis of diabetes: haemoglobin A1c ≥ 6.5% or; fasting plasma glucose level above 8 hour ≥ 126 mg/dL or plasma glucose ≥ 200 mg/dL (11.1 mmol/l) 2 h after a 75 g glucose load or symptoms (such as polyuria, polydipsia, unexplained weight loss) and a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)
Interventions	Irbesartan/atorvastatin fixed-dose combination: pharmaceutical form: tablet; route of administration: oral; other name: Rovelito **Comparators** Irbesartan SR47436: pharmaceutical form: tablet; route of administration: oral; other name: Aprovel Atorvastatin: pharmaceutical form: tablet; route of administration: oral; other name: Newvast
Outcomes	**Primary outcomes: (time frame: 4 weeks-maximum 5 weeks)** • Change from baseline in flow mediated dilatation **Secondary outcomes: (Time frame: 4 weeks up to maximum 5 weeks)** • Rate of change from baseline in nytrotyrosine marker • Rate of change from baseline in Intercellular Adhesion Molecule-1 • Rate of change from baseline in interleukin-6 • Rate of change from baseline in C-reactive protein • Change from baseline in blood pressure (irbesartan/atorvastatin fixed-dose combination group and irbesartan group) • Change from baseline in low density lipoprotein-C (irbesartan/atorvastatin fixed-dose combination group and atorvastatin group) • Change from baseline in total cholesterol (irbesartan/atorvastatin fixed-dose combination group and atorvastatin group) • Change from baseline in high density lipoprotein-C (irbesartan/atorvastatin fixed-dose combination group and atorvastatin group) • Change from baseline in triglycerides (irbesartan/atorvastatin fixed-dose combination group and atorvastatin group) • Change from baseline in apolipoprotein-A1 (irbesartan/atorvastatin fixed-dose combination group and atorvastatin group) • Change from baseline in apolipoprotein-B (irbesartan/atorvastatin fixed-dose combination group and atorvastatin group) -Percentage of participants with decreased level of blood pressure (irbesartan/atorvastatin fixed-dose combination group and irbesartan group)] • Rate of change from baseline in immunosenescence T cell fractionation • Rate of change from baseline in T-cell induced inflammatory factors
Notes	

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

INTEGRATE

Trial name or title	INTEGRATE Study: A pragmatic cluster randomised controlled trial of an integrated general practice and pharmacy-based intervention to promote the prescription and use of appropriate preventive medications among individuals at high cardiovascular risk

INTEGRATE *(Continued)*

Methods	Cluster-randomized control, open-label, parallel-assignment
Participants	All adult patients (18 years) attending the GP will be potentially be eligible to receive the HealthTracker intervention. All adult patients who are recommended for the component medications according to current guidelines are eligible to be prescribed the polypill therapy. All adult patients attending the paired pharmacy with a new prescription for a CVD prevention medication will be eligible to receive the pharmacy intervention
Interventions	The integrated intervention comprises the following three elements: (1) HealthTracker, (2) availability of the Polypills and (3) Pharmacy Adherence Support Service (PASS) ** Eight CVD polypills will be available and they are: • Name: PolyPill Hydroirb; components: hydrochlorothiazide (12.5 mg) + irbesartan (150 mg) + atorvastatin (40 mg) • Name: PolyPill Hydroirb Asp; components: hydrochlorothiazide (12.5 mg) + irbesartan (150 mg) + atorvastatin (40 mg) + 100 mg aspirin • Name: PolyPill Amloirb; components: amlodipine (5 mg) + irbesartan (150 mg) + atorvastatin (40 mg) • Name: PolyPill Amloirb Asp; components: amlodipine (5 mg) + irbesartan (150 mg) + atorvastatin (40 mg) + aspirin (100 mg) • Name: PolyPill Perindap; components: perindopril (4 mg) + indapamide (1.25 mg) + atorvastatin (40 mg) • Name: PolyPill Perindap Asp; components: perindopril (4 mg) + indapamide (1.25 mg) + atorvastatin (40 mg) + aspirin (100 mg) • Name: PolyPill Peramlo; components: perindopril (4 mg) + amlodipine (5 mg) + atorvastatin (40 mg) • Name: PolyPill Peramlo Asp; components: perindopril (4 mg) + amlodipine (5 mg) + atorvastatin (40 mg) + aspirin (100 mg)
Outcomes	**Primary Outcomes** • Proportion of high-risk participants who were not on full treatment at baseline achieving recommended target (i) BP and (ii) LDL-C target levels, at the end of the study. This is a composite primary outcome. These levels will be extracted from the general practice software systems using a general practice data auditing tool known as Clinical Audit Tool (CAT). Data is de-identified prior to extraction **Secondary Outcomes** • Proportion of high-risk participants who were not on full treatment at baseline achieving recommended target BP levels at study end • Proportion of under-treated high-risk participants achieving recommended BP or LDL-C targets. Note: not composite. Data will be extracted from the general practice software systems using CAT. Under-treated includes participants at high risk of a CV event, not on full treatment at baseline. Full treatment: at least 1 BP-lowering drug and a statin for participants without established CVD; for those with CVD, full treatment will additionally require at least 1 antiplatelet drug • Proportion of all high-risk participants achieving BP and LDL-C targets. Data will be extracted from the general practice software systems using CAT. • Proportion of participants achieving BP and LDL-C targets and prescribed antiplatelet (if relevant). Data will be extracted from the general practice software systems using CAT • Risk factor measurement and mean levels. Data will be extracted from the general practice software systems using CAT. Risk factor measurement is calculated by HealthTracker • Treatment intensity in high-risk participants. Proportion of high-risk participants who receive a dose escalation or addition to their prescribed medication during the intervention period. De-identified data will be extracted from the general practice software systems using CAT • Polypill prescriptions - will be assessed from the number of consent forms signed for the polypill and the supply of polypills

INTEGRATE *(Continued)*

	• Participation in pharmacy adherence support programmes. Will be assessed from the number of consent forms for the PASS • Proportion of non-high risk participants receiving either BP lowering or statin and or anti-platelet therapy (looking at all the therapies individually and combined)
Starting date	1 March 2016
Contact information	Prof Anushka Patel, apatel@georgeinstitute.org
Notes	

NCT01646437

Trial name or title	The International Polycap Study-3
Methods	2 x 2 x 2 randomised controlled trial, factorial design (3 arms: Polycap, aspirin, vitamin D)
Participants	5000 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 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 ischaemia in participants taking Polycap versus placebo
Starting date	June 2012; protocol updated on clinicaltrials.gov on May 2015 (ClinicalTrials.gov Identifier: NCT01646437)
Contact information	Dr. Salim Yusuf, Population Health Research Institute
Notes	

NCT01826019

Trial name or title	Heart Outcomes Prevention and Evaluation 4 (HOPE-4)
Methods	Open-label, parallel, cluster-randomised controlled trial design
Participants	HT Phase: at least 50 urban and rural communities in Canada, Colombia and Malaysia will be randomised to participate in an intensive CV risk detection and control program by NPHW or to care as usual for 12 months CVD Phase: continuation and expansion of HT Phase to include at least 190 urban and rural communities in countries within Asia, South America, Sub-Saharan Africa, and Canada that will be allocated to participate in an intensive CV risk detection and control programme supported by NPHWs or to care as usual for up to 6 years Inclusion criteria Individuals (≥ 50 years) with at least ONE of the following criteria: • SBP ≥ 160 mmHg in one visit

NCT01826019 *(Continued)*

	• SBP 140-159 mmHg in one visit AND participant-reported medical diagnosis of hypertension • SBP 140-159 mmHg in one visit AND participant taking anti-HT medication • SBP ≥ 130 mmHg in one visit AND participant-reported medical diagnosis of diabetes • SBP ≥ 130 mmHg in one visit AND participant taking medication for diabetes • Participants that do not meet criteria 1-5 AND SBP 140-159 mmHg in one visit AND SBP ≥ 140 mmHg in a second visit ≥ 24 h apart
Interventions	Intensive CV risk detection, counselling and follow-up programme by NPHW; recommended CV medications will include combinations of anti-hypertensive medications (both low and high doses) and a lipid-lowering agent (e.g. statin) in accordance with treatment algorithm (precise formulations used may differ in each country); use of treatment supporters to reinforce adherence. Comparator: usual care. Participants in control communities will be referred to usual care
Outcomes	**Primary outcomes** • Change in systolic BP (SBP) between the intervention and control communities at 6 and 12 months (time frame: baseline to 6 months and 12 months (HT phase)) • Proportion of participants with well-controlled blood pressure at 6 and 12 months (SBP < 140 mmHg in non-diabetics and SBP < 130 mmHg in diabetics (time frame: baseline to 6 months and 12 months (HT phase)) • Change in HDL, LDL, total cholesterol, triglycerides, and glucose levels at 12 months (time frame: baseline to 1 year (HT phase)) • Change in smoking status at 6 and 12 months(time frame: baseline to 6 months and 12 months (HT phase)) • Change in IHRS at 6 and 12 months and ChRS at 12 months (time frame: baseline to 6 months and 12 months (HT phase)) • Number of participants receiving prescriptions for (or taking) anti-hypertensive medications (as an indication of physician adherence to treatment guidelines) at 6 and 12 months (time frame: baseline to 6 months and 12 months (HT phase)) • Medication adherence measures at 6 and 12 months (time frame: baseline to 6 months and 12 months (HT phase)) • Clinical events (e.g. death, CVD development, hospitalisations) at 6 and 12 months (time frame: baseline to 6 months and 12 months (HT phase)) • Country-specific process outcomes at 6 and 12 months (time frame: baseline to 6 months and 12 months (HT phase)) • Change in individual components of the primary outcomes in the HT phase (time frame: baseline to 6 years (CVD phase)) • Secondary outcomes from the HT phase (time frame: baseline to 6 years (CVD phase)) **Secondary outcomes** • A descriptive analysis of the processes involved in the intervention (time frame: baseline to 6 years) • Qualitative feedback from participants, NPHWs, and supervising physicians (time frame: baseline to 6 years) • Health economic and quality-of-life evaluations (as available and appropriate). (Time frame: baseline to 6 years) • We will collect data that will allow us to determine the costs of the suggested programmes (i.e. intervention package) and the costs of what is being provided currently for CVD assessment and management in the communities studied (i.e. control)
Starting date	August 2014
Contact information	Contact: Patricio Lopez-Jaramillo, MD jplopezj@gmail.com

NCT01826019 *(Continued)*

Notes	

NCT02278471

Trial name or title	The SCCS Polypill Pilot Trial
Methods	Randomised, parallel-assignment, open-label trial
Participants	Enrolled at the SCCS site in Mobile, Alabama, obtain care at Franklin Primary Health Center, or live in the surrounding area Aged 45-75 years Baseline systolic blood pressure ≥ 120 mm Hg
Interventions	The study medication will be a fixed-dose combination pill (polypill) containing: atorvastatin 10 mg, amlodipine 2.5 mg, losartan 25 mg, and hydrochlorothiazide 12.5 mg. Once daily medication. Comparator: usual care: they will remain on the same care that they are used to receiving
Outcomes	**Primary outcomes** • Systolic blood pressure (time frame: 12 months) polypill versus usual care • Medication adherence (time frame: 12 months) polypill arm-evaluation via pill counts • LDL cholesterol (time frame: 12 months) **Secondary outcome measures** • Systolic blood pressure (time frame: 2 months) • Medication adherence (time frame: 2 months) • Medication adherence (time Frame: 12 months) • LC/MS/MS-based drug metabolite profile assay screen in the polypill arm • LDL cholesterol (time frame: 2 months)
Starting date	December 2015
Contact information	Judy P. Mitchell 251-436-7631 judy.mitchell@franklinprimary.org
Notes	

NCT02596126

Trial name or title	Secondary Prevention of Cardiovascular Disease in the Elderly Trial (SECURE)
Methods	Randomised, open-label, parallel-assignment
Participants	A total number of 3206 participants will be randomized (1:1) to treatment arms. Participants will be recruited across seven countries in Europe (Spain, Italy, Germany, France, Hungary, Poland, and Czech Republic) • Participants will be ≥ 65 years old and diagnosed with a type 1 myocardial infarction within 8 weeks prior to study enrolment Inclusion criteria

NCT02596126 *(Continued)*

	• Participants diagnosed with a type 1 myocardial infarction within the previous 8 weeks. • Participants must be ≥ 65 years old, presenting with at least one of the following additional conditions: Documented diabetes mellitus or previous treatment with oral hypoglycemic drugs or insulin. Mild to moderate renal dysfunction: creatinine clearance 60-30 mL/min/1.73 m2. Prior myocardial infarction: defined as an AMI occurring before the index event documented in a medical report. Prior coronary revascularization: coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Prior stroke: history of a documented stroke, defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue, not resulting in death. Age ≥ 75 years.
Interventions	(A) aspirin 100 mg, atorvastatin 40 mg, and ramipril (2.5 mg, or 5 mg, or 10mg) or (B) aspirin 100 mg, atorvastatin 20 mg, and ramipril (2.5 mg, or 5 mg, or 10mg) Other name: Polypill Comparator: participants allocated to the usual care arm will receive standard of care therapies for secondary prevention according to the ESC guidelines. Drugs and doses will be left at the discretion of the treating physicians

Outcomes	**Primary outcome measures**
	
	• Major adverse cardiovascular events
	• Cardiovascular death
	• Any nonfatal type 1 myocardial infarction
	• Any nonfatal ischaemic stroke
	• Any urgent coronary revascularisation not resulting in death
	
	Secondary Outcomes
	
	• Evaluate the efficacy of treatment: incidence of the first occurrence of any component of the following composite endpoint:
	  * CV death
	  * MI
	  * stroke
	• Evaluate the first occurrence of the individual components of the primary endpoint:
	  * CV death
	  * Nonfatal type 1 myocardial infarction
	  * Nonfatal ischaemic stroke
	  * Urgent coronary revascularisation
	• Change in treatment adherence: the Morisky-Medication Adherence Scale (8 item) Questionnaire will be administered
	• Change in Patient Satisfaction: the Treatment Satisfaction Questionnaire for Medication (TSQM) will be administered
	• Change in systolic and diastolic blood pressure (SBP and DBP): systolic and diastolic blood pressure will be collected and summarised at each time point
	• Change in LDL cholesterol level: non-fasting blood analysis will be collected and LDL cholesterol level evaluated at each time point
	• Regional differences in performance of the polypill in the previous endpoints

NCT02596126 *(Continued)*

	• Health economic evaluation comparing intervention and usual care arm • Cost differences and Incremental Cost-Effectiveness Ratio (ICER) will be assessed at each time point • Change in quality of life: the European Quality of Life- 5 Dimensions (EQ-5D) Questionnaire will be administered at each time point to evaluate change in quality of life. • Incidence of treatment-emergent adverse events (safety and tolerability) (time frame: 24 months) • All-cause mortality and adverse events (bleeding, renal dysfunction, drug, allergies, and refractory cough leading to drug discontinuation)
Starting date	January 2016
Contact information	Jose Maria Castellano Vazquez, MD, PhD, josemaria.castellano@cnic.es
Notes	

PolyIran

Trial name or title	PolyIran
Methods	Zelen design, randomised controlled trial nested within the Golestan cohort study (110:90 ratio)
Participants	7000 (2400 in related PolyIran Liver trial) cohort participants over 50 years in Iran followed for 5 years
Interventions	Fixed-combination therapy (aspirin 80 mg, hydrochlorthiazide 12.5 mg, valsartan 40 mg, and atorvastatin 20 mg (PolyPill 4–2, Alborz-Darou, Ghazvin, Iran),) + usual care versus usual care alone
Outcomes	**Primary outcome** • major cardiovascular events (non-fatal myocardial infarction and unstable angina) • fatal myocardial infarction • sudden death • new-onset heart failure • coronary artery revascularization procedures • stroke (fatal or non-fatal) • **Secondary outcomes** • all-cause mortality • individual components of the primary outcome • liver-related secondary outcomes: changes in liver stiffness, liver enzyme levels, Visceral Adipose Tissue thickness (VAT), Subcutaneous Adipose Tissue thickness (SAT) and carotid Intima-media thickness (IMT). • Additional secondary outcomes include the proportion of patients with pNASH and pNAFLD. Compliance and adverse events will also be assessed Measured at 2.5 years and 5 years
Starting date	October 2011
Contact information	Reza Malekzadeh MD, Digestive Disease Research Institute, Tehran University of Medical Sciences, Shariati Hospital, 1411713135, Tehran, Iran. Tel: +98 (21) 8241-5000, Fax: +98 (21) 8241-5400, E-mail: malek@tums.ac.ir

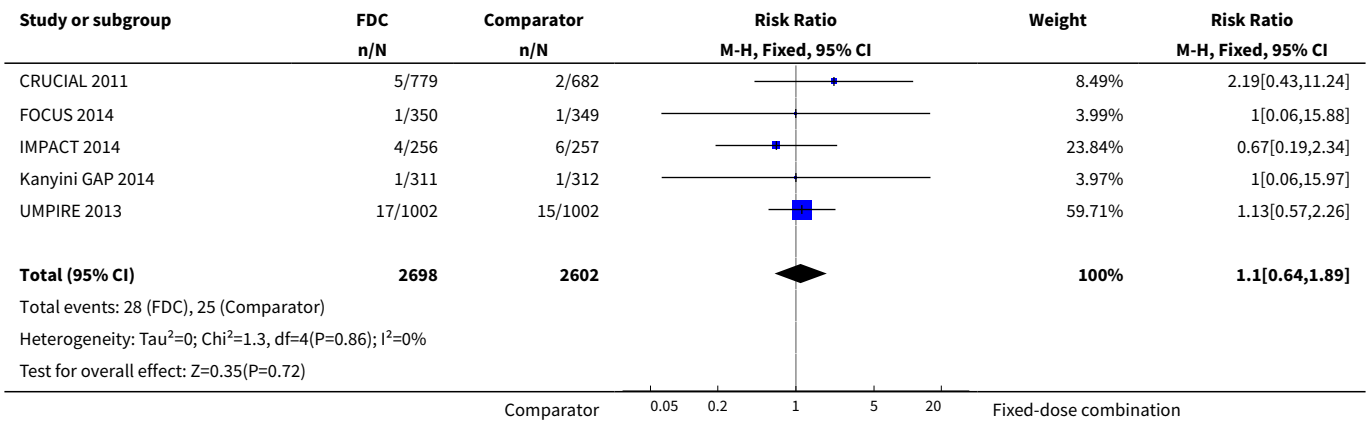
PolyIran *(Continued)*	Tom Marshall MD, School of Health and Population Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Tel: 44 (0)121 414 7832, Fax: 44 (0)121 414 7878, E-mail: T.P.Marshall@b-ham.ac.uk.
Notes	PolyIran protocol: Eur J Prev Cardiol. 2015; 22(12) 1609–1617. PolyIran Liver protocol: Arch Iran Med. 2015; 18(8): 515 – 523. Registriations: NCT00603590, NCT01245608, NCT01271985

DATA AND ANALYSES

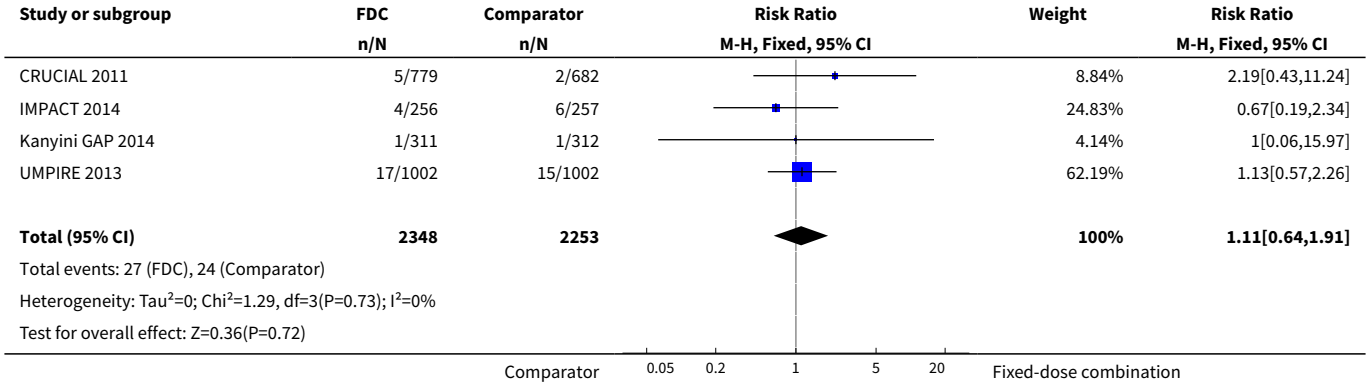
Comparison 1. Mortality and cardiovascular events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	5300	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.64, 1.89]
2 All-cause mortality: comparator as usual care	4	4601	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.64, 1.91]
3 All-cause mortality: comparator provision of individual drugs	1	699	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.88]
4 All-cause mortality: 3+ drugs	4	3839	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.56, 1.78]
5 All-cause mortality: 2+ drugs	1	1461	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [0.43, 11.24]
6 Fatal or non-fatal ASCVD events	6	4517	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.95, 1.66]
7 Fatal and non-fatal ASCVD events: primary prevention trials	2	686	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.04, 3.23]
8 Fatal and non-fatal ASCVD events: secondary prevention trials	4	3831	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.97, 1.72]
9 Fatal and non-fatal ASCVD events: comparator provision of individual drugs	2	906	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.66, 3.98]
10 Fatal and non-fatal ASCVD events: comparator as usual care	4	3611	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.91, 1.64]
11 Fatal and non-fatal ASCVD events: 3+ drugs	5	4306	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.96, 1.69]
12 Fatal and non-fatal ASCVD events: 2 drugs	1	211	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 8.05]

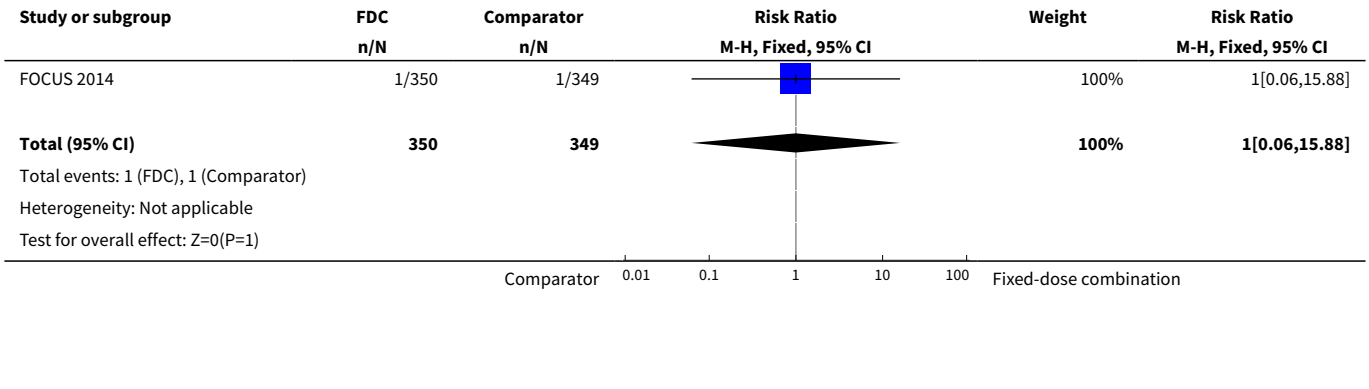
Analysis 1.1. Comparison 1 Mortality and cardiovascular events, Outcome 1 All-cause mortality.



Analysis 1.2. Comparison 1 Mortality and cardiovascular events, Outcome 2 All-cause mortality: comparator as usual care.

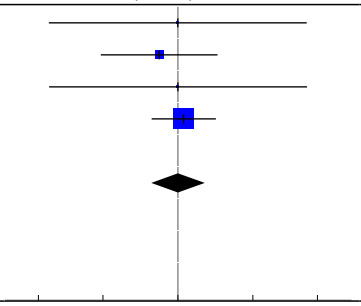


Analysis 1.3. Comparison 1 Mortality and cardiovascular events, Outcome 3 All-cause mortality: comparator provision of individual drugs.



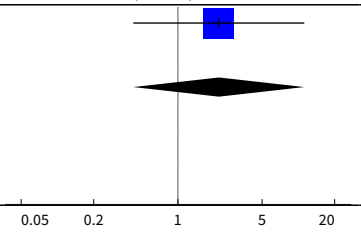
Analysis 1.4. Comparison 1 Mortality and cardiovascular events, Outcome 4 All-cause mortality: 3+ drugs.

Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
FOCUS 2014	1/350	1/349		4.36%	1[0.06,15.88]
IMPACT 2014	4/256	6/257		26.05%	0.67[0.19,2.34]
Kanyini GAP 2014	1/311	1/312		4.34%	1[0.06,15.97]
UMPIRE 2013	17/1002	15/1002		65.25%	1.13[0.57,2.26]
Total (95% CI)	**1919**	**1920**		**100%**	**1[0.56,1.78]**
Total events: 23 (FDC), 23 (Comparator)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=3(P=0.91); I^2=0%					
Test for overall effect: Z=0(P=1)					



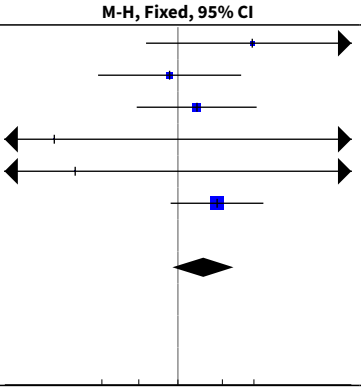
Analysis 1.5. Comparison 1 Mortality and cardiovascular events, Outcome 5 All-cause mortality: 2+ drugs.

Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CRUCIAL 2011	5/779	2/682		100%	2.19[0.43,11.24]
Total (95% CI)	**779**	**682**		**100%**	**2.19[0.43,11.24]**
Total events: 5 (FDC), 2 (Comparator)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					

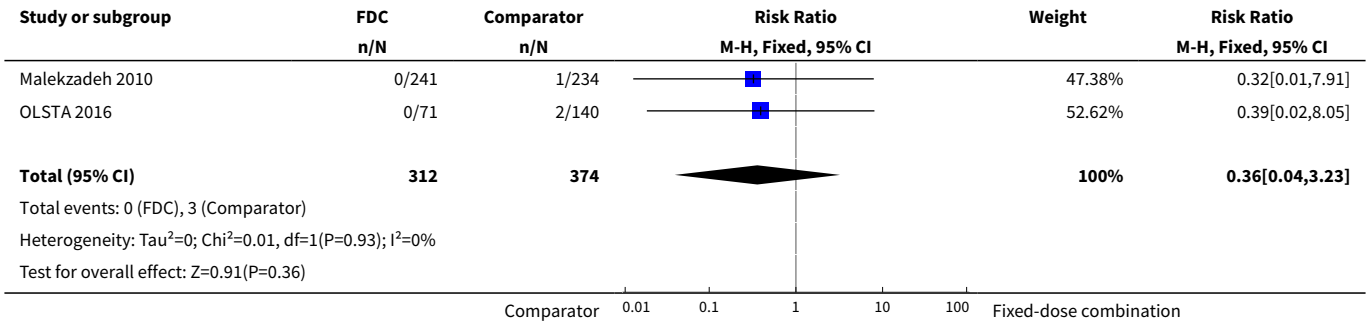


Analysis 1.6. Comparison 1 Mortality and cardiovascular events, Outcome 6 Fatal or non-fatal ASCVD events.

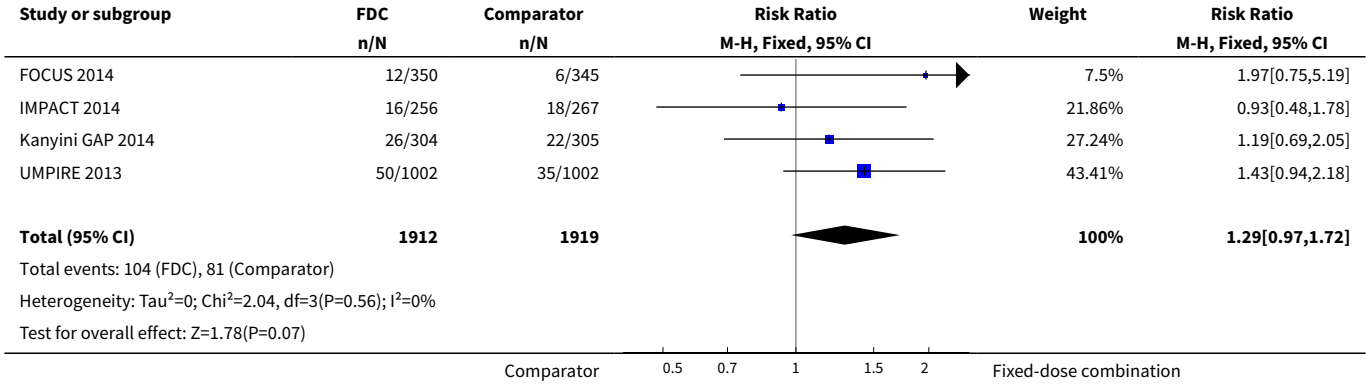
Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
FOCUS 2014	12/350	6/345		7.21%	1.97[0.75,5.19]
IMPACT 2014	16/256	18/267		21.02%	0.93[0.48,1.78]
Kanyini GAP 2014	26/304	22/305		26.2%	1.19[0.69,2.05]
Malekzadeh 2010	0/241	1/234		1.82%	0.32[0.01,7.91]
OLSTA 2016	0/71	2/140		2.02%	0.39[0.02,8.05]
UMPIRE 2013	50/1002	35/1002		41.75%	1.43[0.94,2.18]
Total (95% CI)	**2224**	**2293**		**100%**	**1.26[0.95,1.66]**
Total events: 104 (FDC), 84 (Comparator)					
Heterogeneity: Tau^2=0; Chi^2=3.33, df=5(P=0.65); I^2=0%					
Test for overall effect: Z=1.61(P=0.11)					



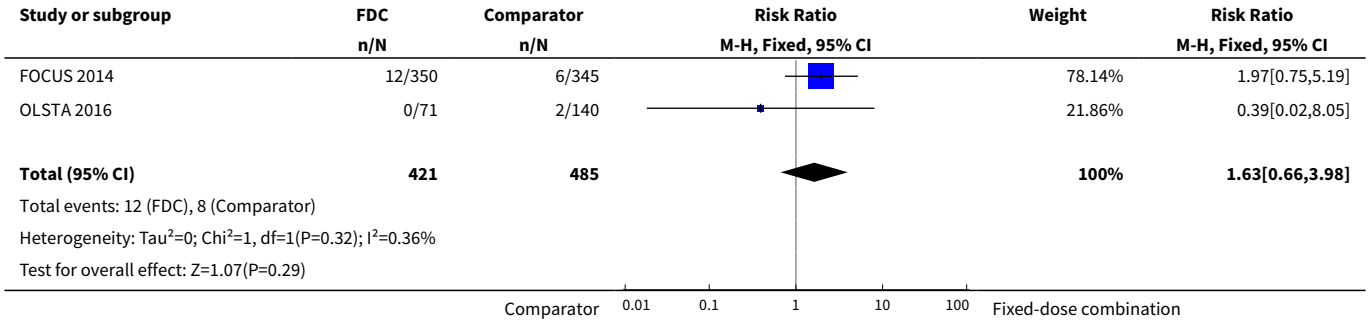
Analysis 1.7. Comparison 1 Mortality and cardiovascular events, Outcome 7 Fatal and non-fatal ASCVD events: primary prevention trials.



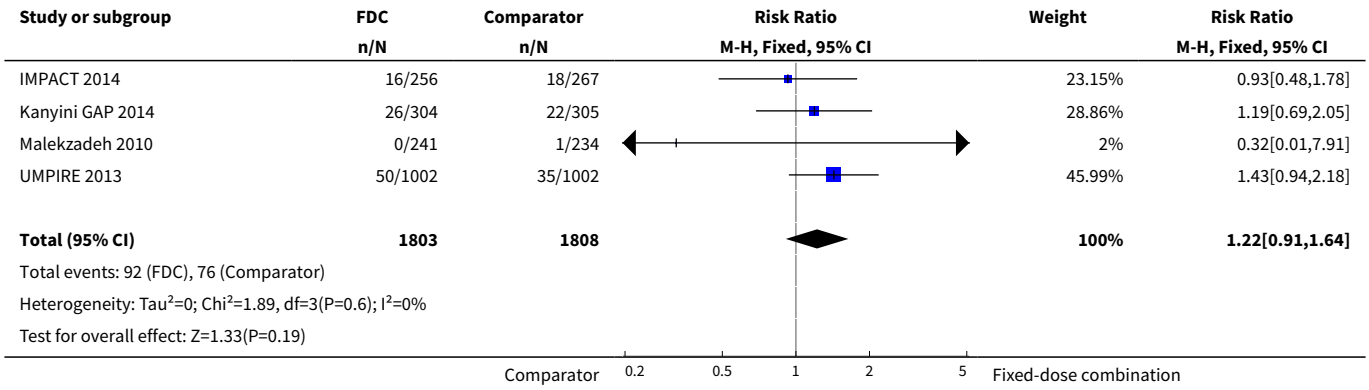
Analysis 1.8. Comparison 1 Mortality and cardiovascular events, Outcome 8 Fatal and non-fatal ASCVD events: secondary prevention trials.



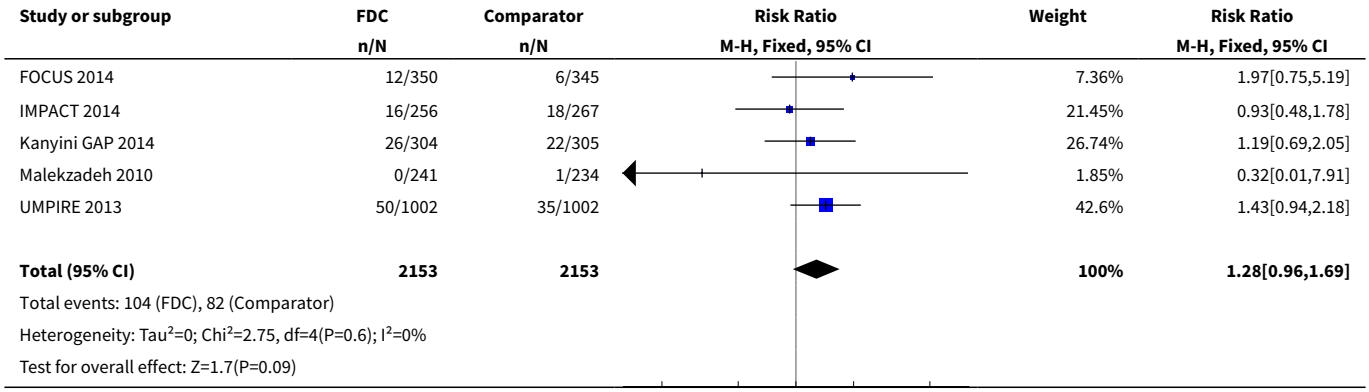
Analysis 1.9. Comparison 1 Mortality and cardiovascular events, Outcome 9 Fatal and non-fatal ASCVD events: comparator provision of individual drugs.



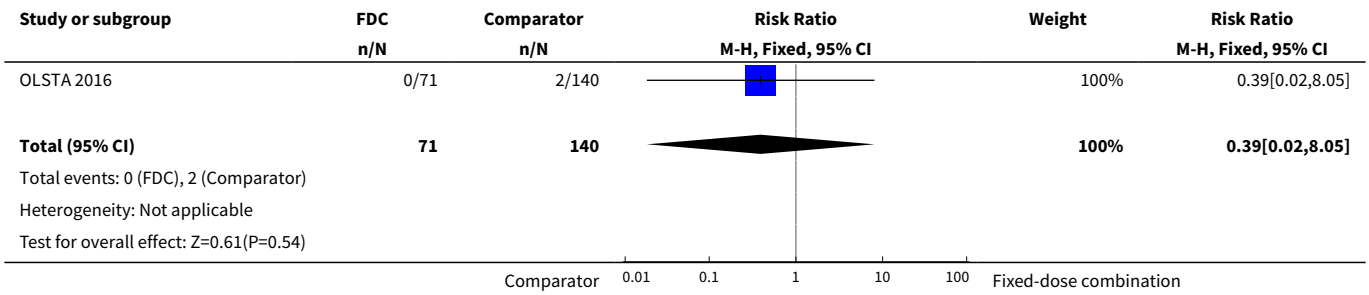
Analysis 1.10. Comparison 1 Mortality and cardiovascular events, Outcome 10 Fatal and non-fatal ASCVD events: comparator as usual care.



Analysis 1.11. Comparison 1 Mortality and cardiovascular events, Outcome 11 Fatal and non-fatal ASCVD events: 3+ drugs.



Analysis 1.12. Comparison 1 Mortality and cardiovascular events, Outcome 12 Fatal and non-fatal ASCVD events: 2 drugs.

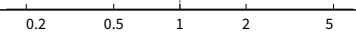


Comparison 2. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event	11	6906	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.09, 1.25]
2 Any adverse event: primary prevention trials	6	1610	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.17, 1.60]
3 Any adverse event: secondary prevention trial	5	5296	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.03, 1.20]
4 Any adverse event: comparator as usual care	4	4601	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.03, 1.21]
5 Adverse event: comparator as placebo or inactive control	7	2305	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.12, 1.43]
6 Adverse event: 3+ drugs only	7	4860	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.08, 1.30]
7 Adverse events: 2 drugs	4	2046	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.01, 1.25]
8 Myalgias	8	4745	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.84, 1.48]
9 Increased liver enzymes	4	1638	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.74, 1.47]
10 Cough	5	2788	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.75, 4.59]
11 Dyspepsia/gastrointestinal irritation	4	3417	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.64, 2.74]
12 Bleeding	2	891	Risk Ratio (M-H, Fixed, 95% CI)	5.68 [1.01, 32.03]

Analysis 2.1. Comparison 2 Adverse events, Outcome 1 Any adverse event.

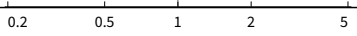
Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CRUCIAL 2011	380/779	300/682		33.82%	1.11[0.99,1.24]
CUSP 2009	21/66	22/64		2.36%	0.93[0.57,1.51]
FOCUS 2014	124/350	112/345		11.93%	1.09[0.89,1.34]
IMPACT 2014	99/256	93/257		9.81%	1.07[0.85,1.34]
Kanyini GAP 2014	144/311	127/312		13.41%	1.14[0.95,1.36]
Malekzadeh 2010	97/241	71/234		7.62%	1.33[1.04,1.7]
OLSTA 2016	17/71	24/140		1.71%	1.4[0.8,2.43]
PILL 2011	81/189	59/189		6.24%	1.37[1.05,1.8]
TOGETHER 2010	18/122	11/122		1.16%	1.64[0.81,3.32]
UMPIRE 2013	118/1002	102/1002		10.78%	1.16[0.9,1.49]
Wald 2012	24/86	11/86		1.16%	2.18[1.14,4.17]
Total (95% CI)	**3473**	**3433**		**100%**	**1.16[1.09,1.25]**
Total events: 1123 (FDC), 932 (Comparator)					



Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=10.02, df=10(P=0.44); I²=0.16%					
Test for overall effect: Z=4.3(P<0.0001)					

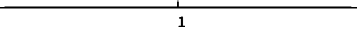
Analysis 2.2. Comparison 2 Adverse events, Outcome 2 Any adverse event: primary prevention trials.

Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CUSP 2009	21/66	22/64		11.66%	0.93[0.57,1.51]
Malekzadeh 2010	97/241	71/234		37.61%	1.33[1.04,1.7]
OLSTA 2016	17/71	24/140		8.43%	1.4[0.8,2.43]
PILL 2011	81/189	59/189		30.8%	1.37[1.05,1.8]
TOGETHER 2010	18/122	11/122		5.74%	1.64[0.81,3.32]
Wald 2012	24/86	11/86		5.74%	2.18[1.14,4.17]
Total (95% CI)	**775**	**835**		**100%**	**1.37[1.17,1.6]**
Total events: 258 (FDC), 198 (Comparator)					
Heterogeneity: Tau²=0; Chi²=4.75, df=5(P=0.45); I²=0%					
Test for overall effect: Z=3.96(P<0.0001)					



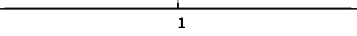
Analysis 2.3. Comparison 2 Adverse events, Outcome 3 Any adverse event: secondary prevention trial.

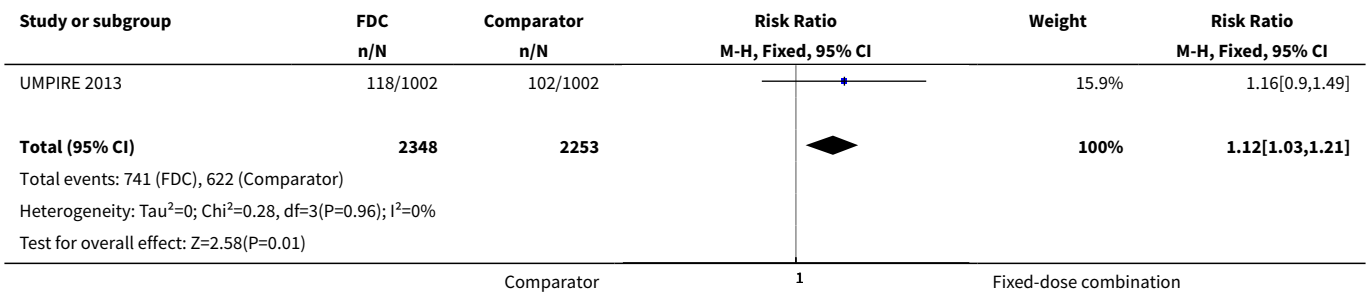
Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CRUCIAL 2011	380/779	300/682		42.41%	1.11[0.99,1.24]
FOCUS 2014	124/350	112/345		14.95%	1.09[0.89,1.34]
IMPACT 2014	99/256	93/257		12.3%	1.07[0.85,1.34]
Kanyini GAP 2014	144/311	127/312		16.81%	1.14[0.95,1.36]
UMPIRE 2013	118/1002	102/1002		13.52%	1.16[0.9,1.49]
Total (95% CI)	**2698**	**2598**		**100%**	**1.11[1.03,1.2]**
Total events: 865 (FDC), 734 (Comparator)					
Heterogeneity: Tau²=0; Chi²=0.31, df=4(P=0.99); I²=0%					
Test for overall effect: Z=2.7(P=0.01)					



Analysis 2.4. Comparison 2 Adverse events, Outcome 4 Any adverse event: comparator as usual care.

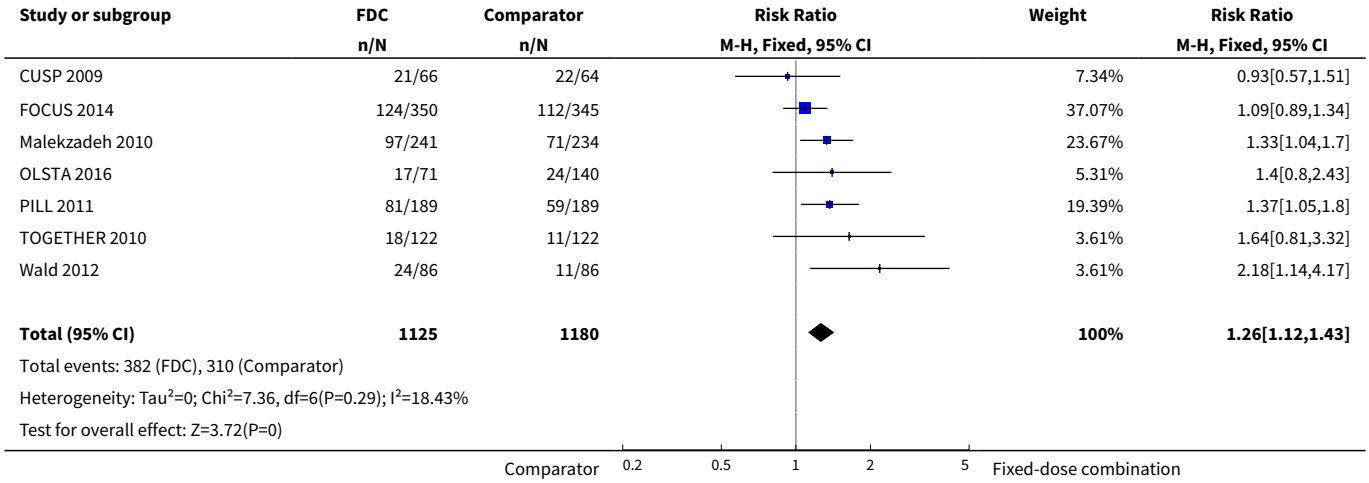
Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CRUCIAL 2011	380/779	300/682		49.87%	1.11[0.99,1.24]
IMPACT 2014	99/256	93/257		14.47%	1.07[0.85,1.34]
Kanyini GAP 2014	144/311	127/312		19.76%	1.14[0.95,1.36]





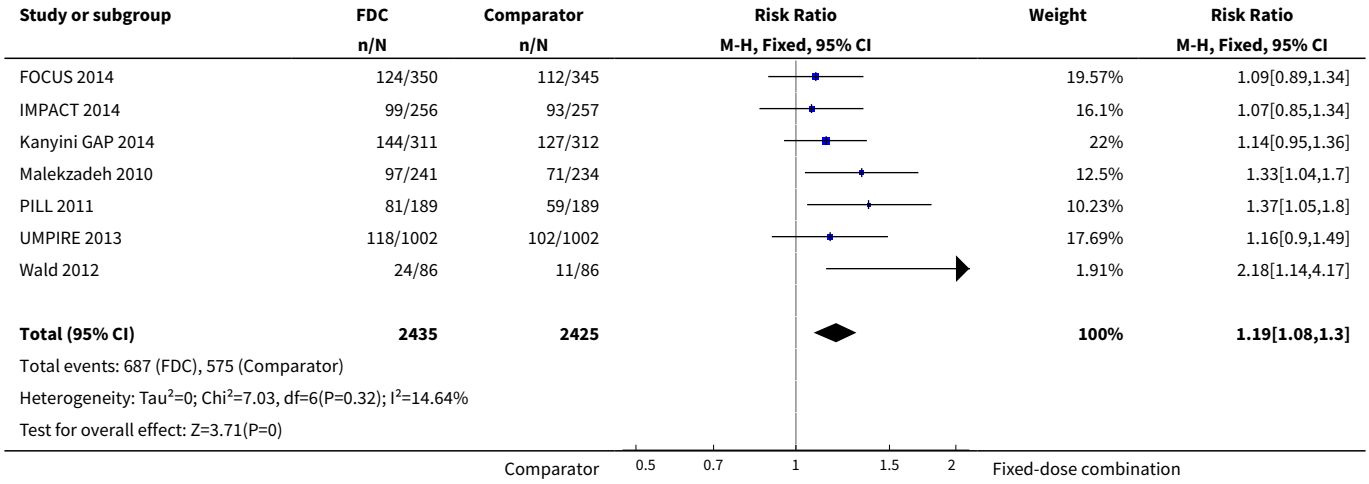
Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
UMPIRE 2013	118/1002	102/1002		15.9%	1.16[0.9,1.49]
Total (95% CI)	**2348**	**2253**		**100%**	**1.12[1.03,1.21]**
Total events: 741 (FDC), 622 (Comparator)					
Heterogeneity: Tau²=0; Chi²=0.28, df=3(P=0.96); I²=0%					
Test for overall effect: Z=2.58(P=0.01)					

Analysis 2.5. Comparison 2 Adverse events, Outcome 5 Adverse event: comparator as placebo or inactive control.



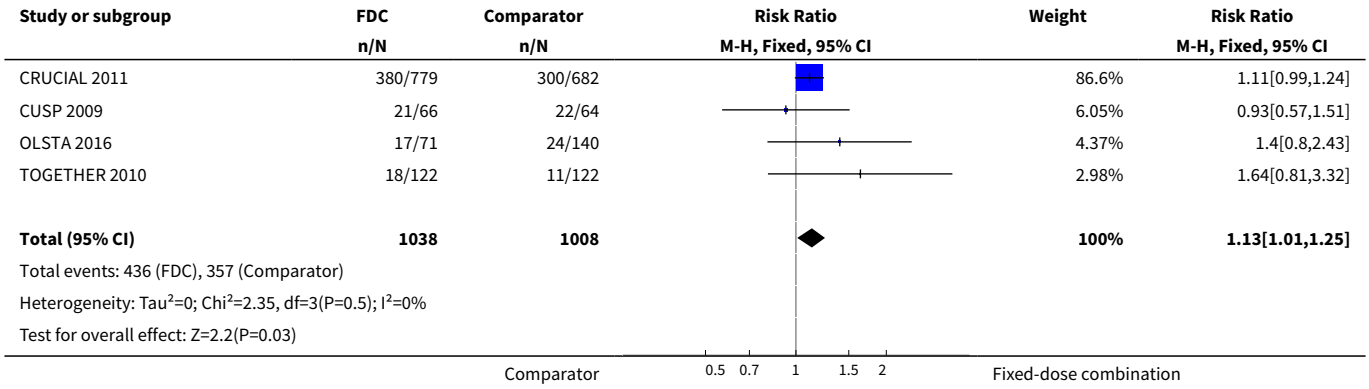
Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CUSP 2009	21/66	22/64		7.34%	0.93[0.57,1.51]
FOCUS 2014	124/350	112/345		37.07%	1.09[0.89,1.34]
Malekzadeh 2010	97/241	71/234		23.67%	1.33[1.04,1.7]
OLSTA 2016	17/71	24/140		5.31%	1.4[0.8,2.43]
PILL 2011	81/189	59/189		19.39%	1.37[1.05,1.8]
TOGETHER 2010	18/122	11/122		3.61%	1.64[0.81,3.32]
Wald 2012	24/86	11/86		3.61%	2.18[1.14,4.17]
Total (95% CI)	**1125**	**1180**		**100%**	**1.26[1.12,1.43]**
Total events: 382 (FDC), 310 (Comparator)					
Heterogeneity: Tau²=0; Chi²=7.36, df=6(P=0.29); I²=18.43%					
Test for overall effect: Z=3.72(P=0)					

Analysis 2.6. Comparison 2 Adverse events, Outcome 6 Adverse event: 3+ drugs only.

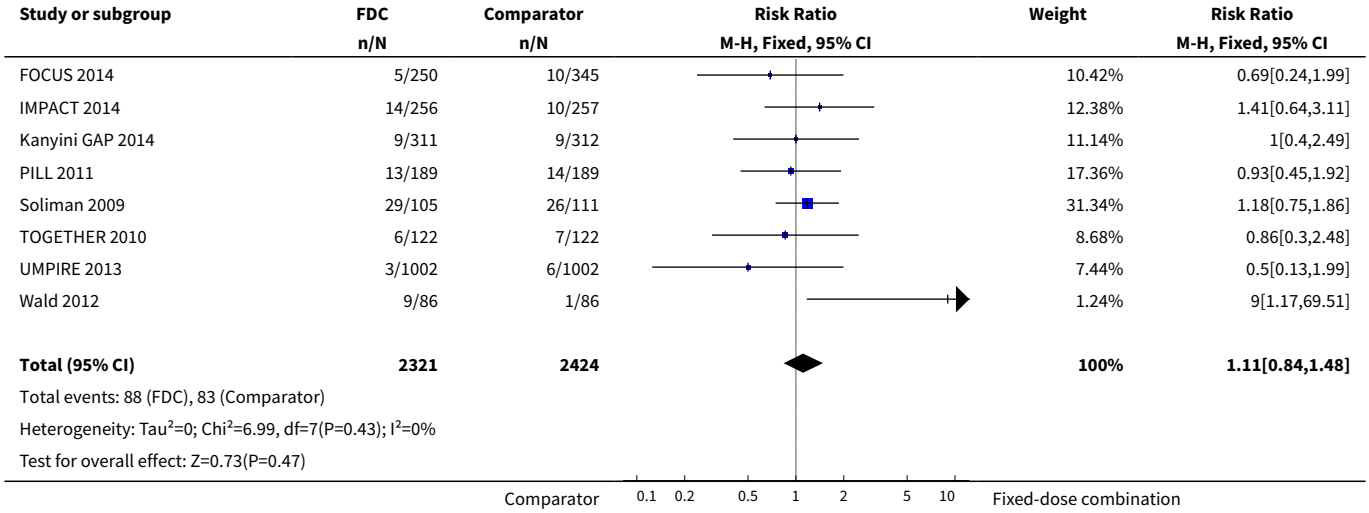


Study or subgroup	FDC n/N	Comparator n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
FOCUS 2014	124/350	112/345		19.57%	1.09[0.89,1.34]
IMPACT 2014	99/256	93/257		16.1%	1.07[0.85,1.34]
Kanyini GAP 2014	144/311	127/312		22%	1.14[0.95,1.36]
Malekzadeh 2010	97/241	71/234		12.5%	1.33[1.04,1.7]
PILL 2011	81/189	59/189		10.23%	1.37[1.05,1.8]
UMPIRE 2013	118/1002	102/1002		17.69%	1.16[0.9,1.49]
Wald 2012	24/86	11/86		1.91%	2.18[1.14,4.17]
Total (95% CI)	**2435**	**2425**		**100%**	**1.19[1.08,1.3]**
Total events: 687 (FDC), 575 (Comparator)					
Heterogeneity: Tau²=0; Chi²=7.03, df=6(P=0.32); I²=14.64%					
Test for overall effect: Z=3.71(P=0)					

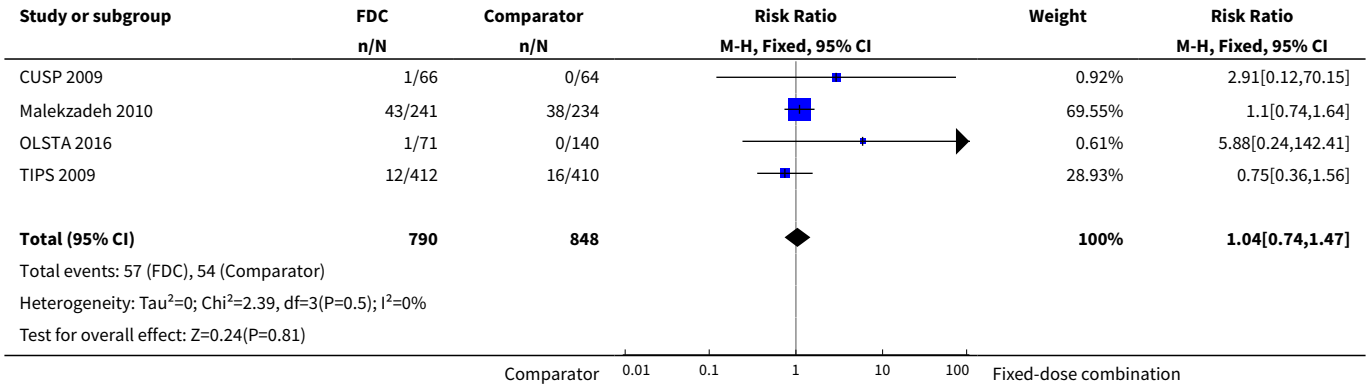
Analysis 2.7. Comparison 2 Adverse events, Outcome 7 Adverse events: 2 drugs.



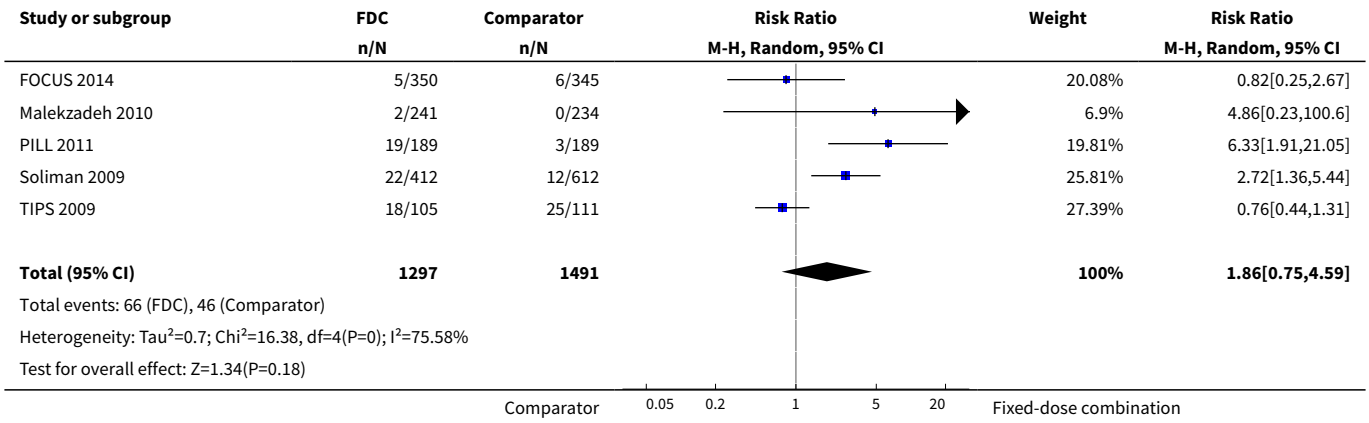
Analysis 2.8. Comparison 2 Adverse events, Outcome 8 Myalgias.



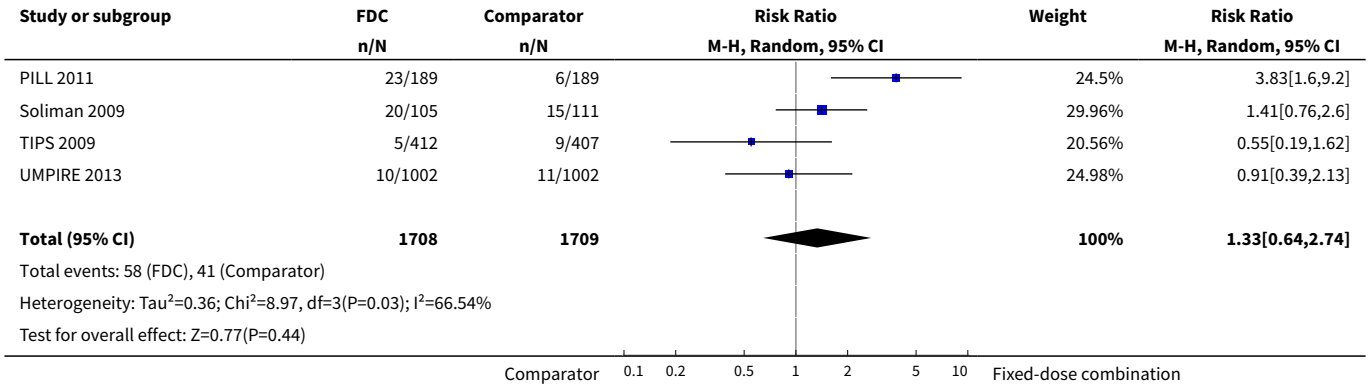
Analysis 2.9. Comparison 2 Adverse events, Outcome 9 Increased liver enzymes.



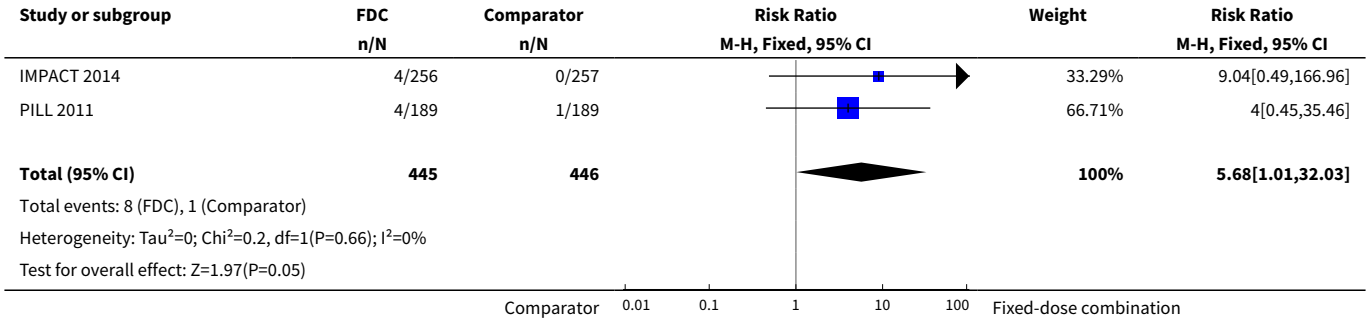
Analysis 2.10. Comparison 2 Adverse events, Outcome 10 Cough.



Analysis 2.11. Comparison 2 Adverse events, Outcome 11 Dyspepsia/gastrointestinal irritation.



Analysis 2.12. Comparison 2 Adverse events, Outcome 12 Bleeding.



Comparison 3. Blood pressure

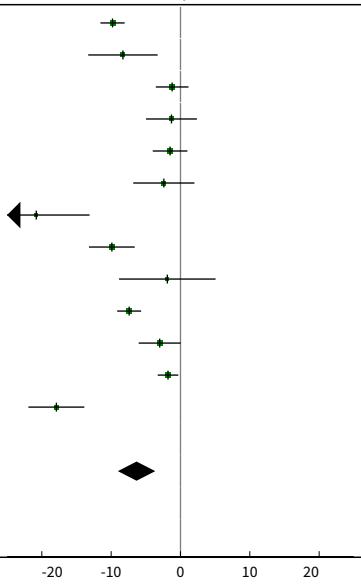
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic blood pressure	13	7638	Mean Difference (IV, Random, 95% CI)	-6.34 [-9.03, -3.64]
2 Diastolic blood pressure	13	7628	Mean Difference (IV, Random, 95% CI)	-3.33 [-4.86, -1.79]
3 Systolic blood pressure: primary prevention trials	8	2463	Mean Difference (IV, Random, 95% CI)	-8.67 [-12.41, -4.94]
4 Systolic blood pressure: secondary prevention trial	5	5175	Mean Difference (IV, Random, 95% CI)	-3.20 [-6.98, 0.59]
5 Systolic blood pressure: comparator as usual care	5	4673	Mean Difference (IV, Random, 95% CI)	-3.44 [-7.61, 0.74]
6 Systolic blood pressure: placebo or inactive control	5	1245	Mean Difference (IV, Fixed, 95% CI)	-10.77 [-12.72, -8.81]
7 Systolic blood pressure: 3+ drugs only	9	5758	Mean Difference (IV, Random, 95% CI)	-5.03 [-8.13, -1.93]
8 Systolic blood pressure: 2 drugs	4	1870	Mean Difference (IV, Random, 95% CI)	-9.56 [-14.75, -4.38]

Analysis 3.1. Comparison 3 Blood pressure, Outcome 1 Systolic blood pressure.

Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-19.8 (17.1)	657	-10 (16.4)		8.76%	-9.8[-11.55,-8.05]
CUSP 2009	63	-13.4 (12.6)	60	-5.1 (15.5)		6.93%	-8.3[-13.31,-3.29]
FOCUS 2014	350	-0.3 (16.2)	345	0.9 (15.5)		8.51%	-1.2[-3.56,1.16]
IMPACT 2014	242	-5.9 (20.6)	249	-4.6 (20.9)		7.79%	-1.3[-4.97,2.37]
Kanyini GAP 2014	283	139 (15.2)	285	140.5 (15.2)		8.44%	-1.5[-4,1]
Malekzadeh 2010	241	-3.7 (23.9)	234	-1.3 (25.1)		7.32%	-2.4[-6.81,2.01]
OLSTA 2016	61	132.6 (17.9)	36	153.4 (19.1)		5.23%	-20.8[-28.49,-13.11]
PILL 2011	189	-16.7 (16.2)	189	-6.8 (16.5)		8.01%	-9.9[-13.2,-6.6]
Soliman 2009	99	-28.8 (24.9)	104	-26.9 (25.7)		5.67%	-1.9[-8.86,5.06]
TIPS 2009	392	-12.4 (12.3)	390	-5 (12.3)		8.77%	-7.4[-9.12,-5.68]
TOGETHER 2010	118	-4 (11)	115	-1 (12.5)		8.16%	-3[-6.03,0.03]
UMPIRE 2013	1002	-7.8 (17.7)	1002	-6 (16.1)		8.85%	-1.8[-3.28,-0.32]
Wald 2012	86	-17.9 (10.4)	86	0 (16)		7.56%	-17.9[-21.93,-13.87]
Total * **	**3886**		**3752**			**100%**	**-6.34[-9.03,-3.64]**

Heterogeneity: Tau²=20.83; Chi²=144.46, df=12(P<0.0001); I²=91.69%

Test for overall effect: Z=4.6(P<0.0001)

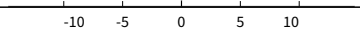


Analysis 3.2. Comparison 3 Blood pressure, Outcome 2 Diastolic blood pressure.

Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-10.5 (10.2)	657	-5.3 (9.5)		8.82%	-5.2[-6.23,-4.17]
CUSP 2009	63	-9.1 (8.5)	60	-5.8 (10.9)		6.26%	-3.3[-6.77,0.17]
FOCUS 2014	350	-0.1 (9.7)	345	0.4 (10.1)		8.47%	-0.49[-1.96,0.98]
IMPACT 2014	242	-2.5 (11.9)	239	-1.9 (12.2)		7.78%	-0.6[-2.75,1.55]
Kanyini GAP 2014	283	79 (8.5)	285	79.9 (8.5)		8.53%	-0.9[-2.3,0.5]
Malekzadeh 2010	241	-0.8 (14.8)	234	-0.1 (14.4)		7.24%	-0.7[-3.33,1.93]
OLSTA 2016	61	82.1 (9.8)	36	93 (9.2)		5.79%	-10.9[-14.78,-7.02]
PILL 2011	189	-8.1 (10.2)	189	-2.9 (10.3)		7.87%	-5.2[-7.27,-3.13]
Soliman 2009	99	-11.3 (12.3)	104	-10.8 (12)		6.4%	-0.5[-3.85,2.85]
TIPS 2009	392	-8.1 (8.1)	390	-2.5 (8.1)		8.74%	-5.6[-6.74,-4.46]
TOGETHER 2010	118	-1.7 (8.2)	115	-1.1 (7)		7.99%	-0.6[-2.56,1.36]
UMPIRE 2013	1002	-4.6 (9.1)	1002	-3.1 (9.1)		8.96%	-1.5[-2.3,-0.7]
Wald 2012	86	-9.8 (8)	86	0 (10)		7.15%	-9.8[-12.51,-7.09]
Total ***	**3886**		**3742**			**100%**	**-3.33[-4.86,-1.79]**

Heterogeneity: Tau^2=6.68; Chi^2=131.28, df=12(P<0.0001); I^2=90.86%

Test for overall effect: Z=4.24(P<0.0001)

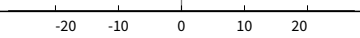


Analysis 3.3. Comparison 3 Blood pressure, Outcome 3 Systolic blood pressure: primary prevention trials.

Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CUSP 2009	63	-13.4 (12.6)	60	-5.1 (15.5)		12.09%	-8.3[-13.31,-3.29]
Malekzadeh 2010	241	-3.7 (23.9)	234	-1.3 (25.1)		12.7%	-2.4[-6.81,2.01]
OLSTA 2016	61	132.6 (17.9)	36	153.4 (19.1)		9.33%	-20.8[-28.49,-13.11]
PILL 2011	189	-16.7 (16.2)	189	-6.8 (16.5)		13.78%	-9.9[-13.2,-6.6]
Soliman 2009	99	-28.8 (24.9)	104	-26.9 (25.7)		10.05%	-1.9[-8.86,5.06]
TIPS 2009	392	-12.4 (12.3)	390	-5 (12.3)		14.95%	-7.4[-9.12,-5.68]
TOGETHER 2010	118	-4 (11)	115	-1 (12.5)		14.02%	-3[-6.03,0.03]
Wald 2012	86	-17.9 (10.4)	86	0 (16)		13.08%	-17.9[-21.93,-13.87]
Total ***	**1249**		**1214**			**100%**	**-8.67[-12.41,-4.94]**

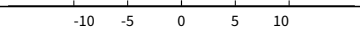
Heterogeneity: Tau^2=23.5; Chi^2=55.06, df=7(P<0.0001); I^2=87.29%

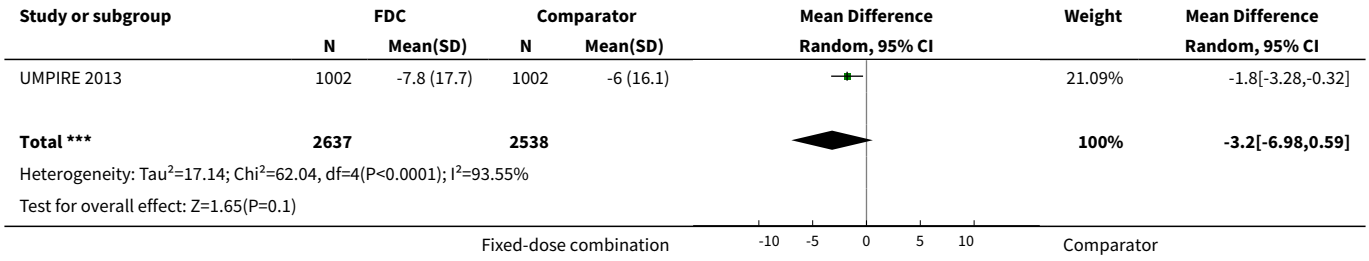
Test for overall effect: Z=4.55(P<0.0001)



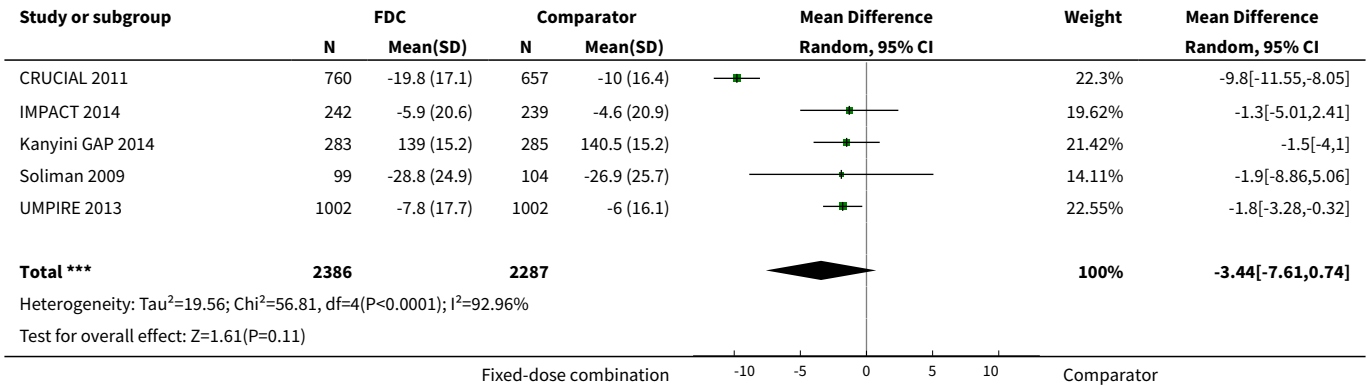
Analysis 3.4. Comparison 3 Blood pressure, Outcome 4 Systolic blood pressure: secondary prevention trial.

Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-19.8 (17.1)	657	-10 (16.4)		20.83%	-9.8[-11.55,-8.05]
FOCUS 2014	350	-0.3 (16.2)	345	0.9 (15.5)		20.1%	-1.2[-3.56,1.16]
IMPACT 2014	242	-5.9 (20.6)	249	-4.6 (20.9)		18.09%	-1.3[-4.97,2.37]
Kanyini GAP 2014	283	139 (15.2)	285	140.5 (15.2)		19.9%	-1.5[-4,1]

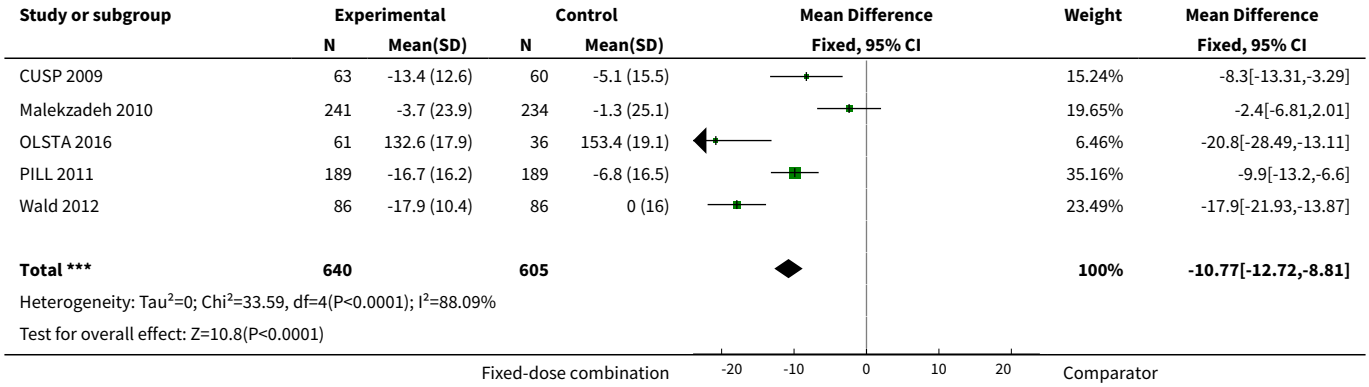




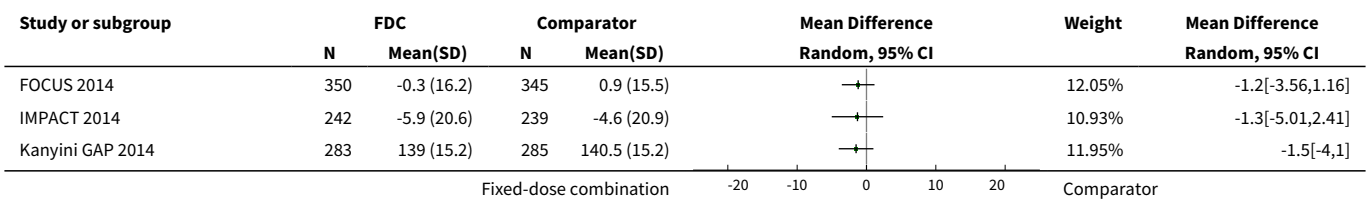
Analysis 3.5. Comparison 3 Blood pressure, Outcome 5 Systolic blood pressure: comparator as usual care.

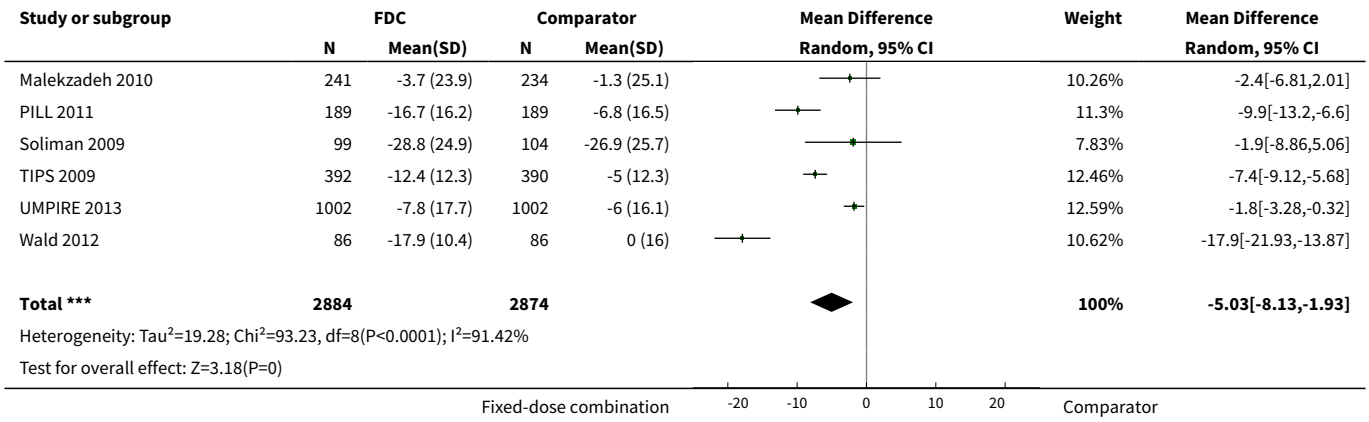


Analysis 3.6. Comparison 3 Blood pressure, Outcome 6 Systolic blood pressure: placebo or inactive control.



Analysis 3.7. Comparison 3 Blood pressure, Outcome 7 Systolic blood pressure: 3+ drugs only.



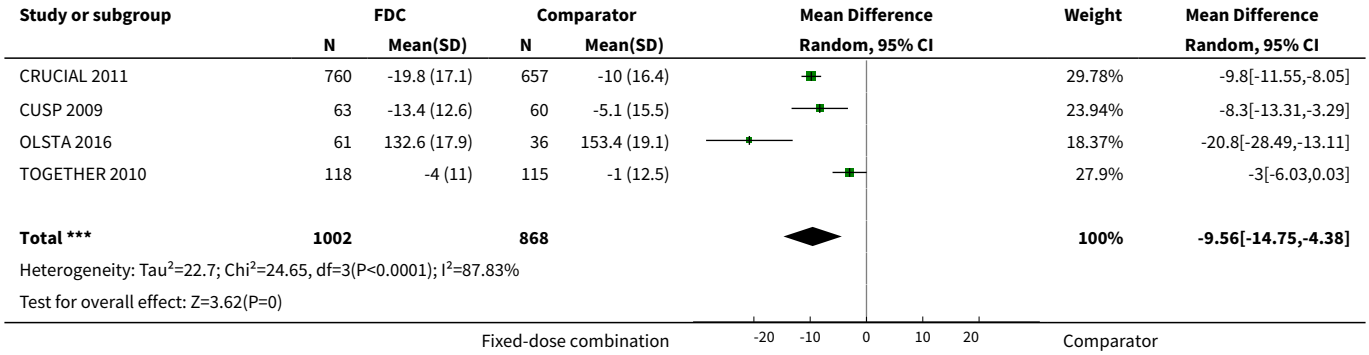


Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Malekzadeh 2010	241	-3.7 (23.9)	234	-1.3 (25.1)		10.26%	-2.4[-6.81,2.01]
PILL 2011	189	-16.7 (16.2)	189	-6.8 (16.5)		11.3%	-9.9[-13.2,-6.6]
Soliman 2009	99	-28.8 (24.9)	104	-26.9 (25.7)		7.83%	-1.9[-8.86,5.06]
TIPS 2009	392	-12.4 (12.3)	390	-5 (12.3)		12.46%	-7.4[-9.12,-5.68]
UMPIRE 2013	1002	-7.8 (17.7)	1002	-6 (16.1)		12.59%	-1.8[-3.28,-0.32]
Wald 2012	86	-17.9 (10.4)	86	0 (16)		10.62%	-17.9[-21.93,-13.87]
Total ***	**2884**		**2874**			**100%**	**-5.03[-8.13,-1.93]**

Heterogeneity: Tau²=19.28; Chi²=93.23, df=8(P<0.0001); I²=91.42%

Test for overall effect: Z=3.18(P=0)

Analysis 3.8. Comparison 3 Blood pressure, Outcome 8 Systolic blood pressure: 2 drugs.



Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-19.8 (17.1)	657	-10 (16.4)		29.78%	-9.8[-11.55,-8.05]
CUSP 2009	63	-13.4 (12.6)	60	-5.1 (15.5)		23.94%	-8.3[-13.31,-3.29]
OLSTA 2016	61	132.6 (17.9)	36	153.4 (19.1)		18.37%	-20.8[-28.49,-13.11]
TOGETHER 2010	118	-4 (11)	115	-1 (12.5)		27.9%	-3[-6.03,0.03]
Total ***	**1002**		**868**			**100%**	**-9.56[-14.75,-4.38]**

Heterogeneity: Tau²=22.7; Chi²=24.65, df=3(P<0.0001); I²=87.83%

Test for overall effect: Z=3.62(P=0)

Comparison 4. Lipids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cholesterol	11	6565	Mean Difference (IV, Random, 95% CI)	-0.61 [-0.88, -0.35]
2 LDL cholesterol	12	7153	Mean Difference (IV, Random, 95% CI)	-0.70 [-0.98, -0.41]
3 Total cholesterol: primary prevention trials	7	2147	Mean Difference (IV, Random, 95% CI)	-0.92 [-1.18, -0.65]
4 Total cholesterol: secondary prevention trials	4	4417	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.49, 0.17]
5 Total cholesterol: comparator as usual care	5	4620	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.44, 0.12]
6 Total cholesterol: placebo or inactive control	4	1148	Mean Difference (IV, Random, 95% CI)	-0.83 [-0.99, -0.67]

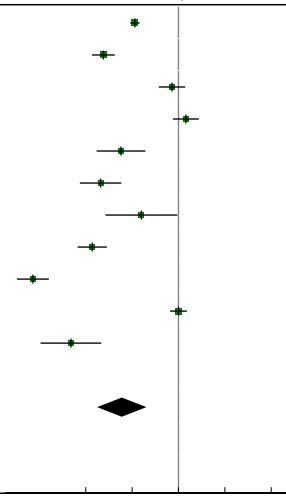
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Total cholesterol: 3+ drugs only	8	4792	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.80, -0.16]
8 Total cholesterol: 2 drugs	3	1773	Mean Difference (IV, Random, 95% CI)	-0.94 [-1.50, -0.38]

Analysis 4.1. Comparison 4 Lipids, Outcome 1 Total cholesterol.

Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-0.4 (0.5)	657	0 (0.5)		9.59%	-0.47[-0.52,-0.42]
CUSP 2009	63	-0.7 (0.3)	60	0.1 (0.4)		9.43%	-0.81[-0.93,-0.69]
IMPACT 2014	242	-0.2 (0.8)	239	-0.1 (0.8)		9.36%	-0.07[-0.21,0.07]
Kanyini GAP 2014	261	4.4 (0.8)	254	4.3 (0.8)		9.37%	0.08[-0.06,0.22]
Malekzadeh 2010	241	-0.9 (1.5)	234	-0.3 (1.4)		8.79%	-0.62[-0.88,-0.36]
PILL 2011	189	-1 (1.2)	189	-0.1 (1)		9.01%	-0.84[-1.06,-0.62]
Soliman 2009	99	-1.4 (1.2)	104	-1 (1.6)		7.99%	-0.4[-0.79,-0.01]
TIPS 2009	375	-0.7 (0.9)	189	0.2 (0.9)		9.31%	-0.93[-1.09,-0.77]
TOGETHER 2010	118	-1.5 (0.7)	115	0.1 (0.6)		9.25%	-1.57[-1.74,-1.4]
UMPIRE 2013	1002	-0.1 (1)	1002	-0.1 (1)		9.51%	0[-0.09,0.09]
Wald 2012	86	-1.2 (1.2)	86	0 (1)		8.4%	-1.16[-1.49,-0.83]
Total ***	**3436**		**3129**			**100%**	**-0.61[-0.88,-0.35]**

Heterogeneity: Tau^2=0.19; Chi^2=441.55, df=10(P<0.0001); I^2=97.74%

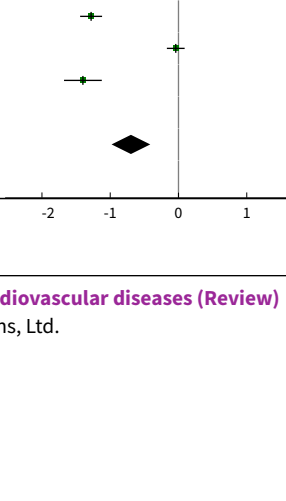
Test for overall effect: Z=4.51(P<0.0001)



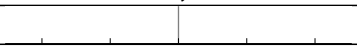
Analysis 4.2. Comparison 4 Lipids, Outcome 2 LDL cholesterol.

Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-0.7 (0.7)	657	0.1 (0.8)		8.61%	-0.73[-0.81,-0.65]
CUSP 2009	63	-1 (0.4)	59	0.1 (0.7)		8.28%	-1.16[-1.37,-0.95]
FOCUS 2014	350	0.1 (1.4)	345	0.1 (0.8)		8.4%	0.08[-0.09,0.25]
IMPACT 2014	242	-0.2 (0.7)	239	-0.2 (0.6)		8.54%	-0.05[-0.17,0.07]
Kanyini GAP 2014	261	2.2 (0.7)	254	2.2 (0.7)		8.53%	0[-0.12,0.12]
Malekzadeh 2010	241	-0.6 (0.6)	234	-0.1 (1)		8.48%	-0.45[-0.59,-0.31]
OLSTA 2016	61	1.9 (0.7)	36	4 (1.1)		7.39%	-2.1[-2.5,-1.7]
PILL 2011	189	-0.9 (1)	189	-0.2 (1)		8.33%	-0.75[-0.94,-0.56]
TIPS 2009	375	-0.7 (0.8)	189	0 (0.8)		8.49%	-0.72[-0.86,-0.58]
TOGETHER 2010	118	-1.3 (0.6)	115	0 (0.7)		8.43%	-1.28[-1.44,-1.12]
UMPIRE 2013	1002	-0.1 (1.5)	1002	-0.1 (1.5)		8.51%	-0.04[-0.17,0.09]
Wald 2012	86	-1.4 (1)	86	0 (0.9)		8.01%	-1.4[-1.68,-1.12]
Total ***	**3748**		**3405**			**100%**	**-0.7[-0.98,-0.41]**

Heterogeneity: Tau^2=0.24; Chi^2=496.2, df=11(P<0.0001); I^2=97.78%



Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=4.82(P<0.0001)							



Analysis 4.3. Comparison 4 Lipids, Outcome 3 Total cholesterol: primary prevention trials.

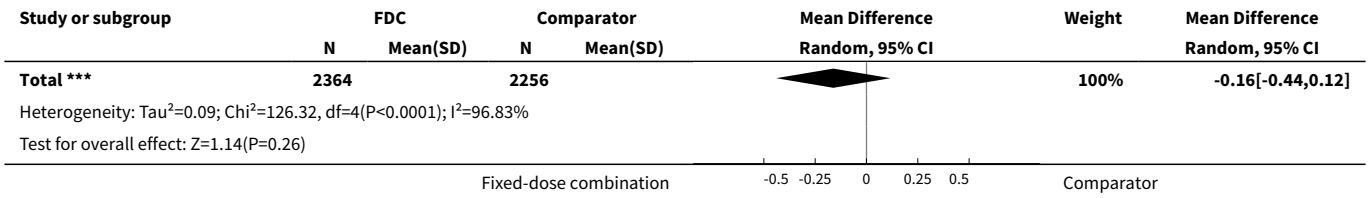
Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CUSP 2009	63	-0.7 (0.3)	59	0.1 (0.4)		15.7%	-0.81[-0.93,-0.69]
Malekzadeh 2010	241	-0.9 (1.5)	234	-0.3 (1.4)		14.02%	-0.62[-0.88,-0.36]
PILL 2011	189	-1 (1.2)	189	-0.1 (1)		14.57%	-0.84[-1.06,-0.62]
Soliman 2009	99	-1.4 (1.2)	104	-1 (1.6)		12.07%	-0.4[-0.79,-0.01]
TIPS 2009	375	-0.7 (0.9)	189	0.2 (0.9)		15.37%	-0.93[-1.09,-0.77]
TOGETHER 2010	118	-1.5 (0.7)	115	0.1 (0.6)		15.21%	-1.57[-1.74,-1.4]
Wald 2012	86	-1.2 (1.2)	86	0 (1)		13.04%	-1.16[-1.49,-0.83]
Total ***	**1171**		**976**			**100%**	**-0.92[-1.18,-0.65]**
Heterogeneity: Tau^2=0.11; Chi^2=71, df=6(P<0.0001); I^2=91.55%							
Test for overall effect: Z=6.76(P<0.0001)							

Analysis 4.4. Comparison 4 Lipids, Outcome 4 Total cholesterol: secondary prevention trials.

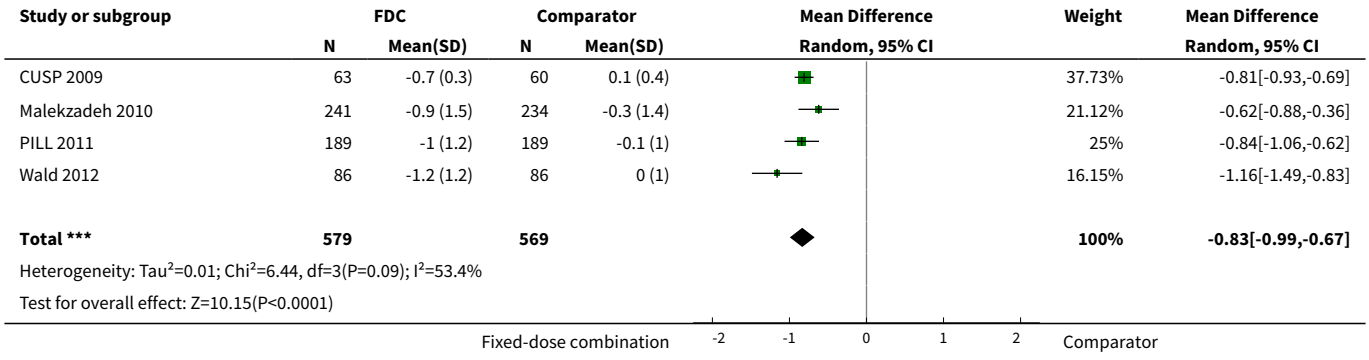
Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-0.4 (0.5)	657	0 (0.5)		31.23%	-0.47[-0.52,-0.42]
IMPACT 2014	242	-0.2 (0.8)	239	-0.1 (0.8)		29.73%	-0.07[-0.21,0.07]
Kanyini GAP 2014	261	4.4 (8.1)	254	4.3 (0.8)		8.29%	0.08[-0.91,1.07]
UMPIRE 2013	1002	-0.1 (1)	1002	-0.1 (1)		30.74%	0[-0.09,0.09]
Total ***	**2265**		**2152**			**100%**	**-0.16[-0.49,0.17]**
Heterogeneity: Tau^2=0.09; Chi^2=95.54, df=3(P<0.0001); I^2=96.86%							
Test for overall effect: Z=0.95(P=0.34)							

Analysis 4.5. Comparison 4 Lipids, Outcome 5 Total cholesterol: comparator as usual care.

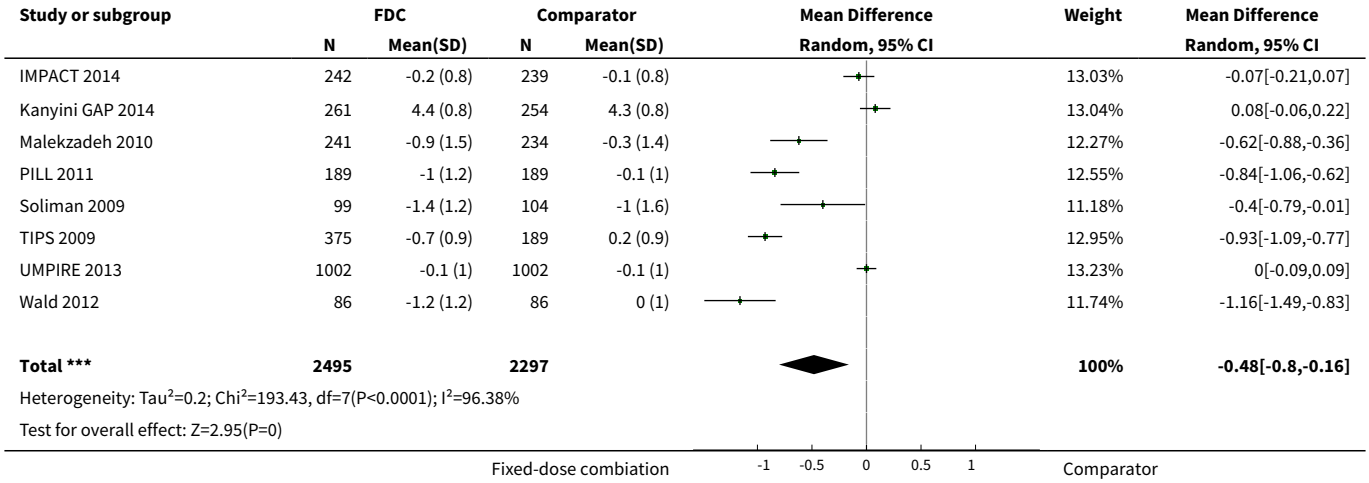
Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
CRUCIAL 2011	760	-0.4 (0.5)	657	0 (0.5)		21.75%	-0.47[-0.52,-0.42]
IMPACT 2014	242	-0.2 (0.8)	239	-0.1 (0.8)		20.72%	-0.07[-0.21,0.07]
Kanyini GAP 2014	261	4.4 (0.8)	254	4.3 (0.8)		20.75%	0.08[-0.06,0.22]
Soliman 2009	99	-1.4 (1.2)	104	-1 (1.6)		15.37%	-0.4[-0.79,-0.01]
UMPIRE 2013	1002	-0.1 (1)	1002	-0.1 (1)		21.41%	0[-0.09,0.09]



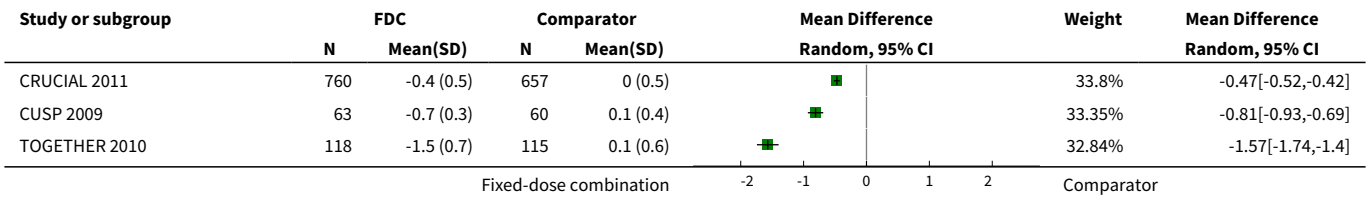
Analysis 4.6. Comparison 4 Lipids, Outcome 6 Total cholesterol: placebo or inactive control.



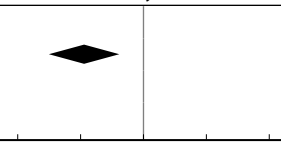
Analysis 4.7. Comparison 4 Lipids, Outcome 7 Total cholesterol: 3+ drugs only.



Analysis 4.8. Comparison 4 Lipids, Outcome 8 Total cholesterol: 2 drugs.



Study or subgroup	FDC N	FDC Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Total ***	**941**		**832**			**100%**	**-0.94[-1.5,-0.38]**
Heterogeneity: Tau^2=0.24; Chi^2=159.25, df=2(P<0.0001); I^2=98.74%							
Test for overall effect: Z=3.31(P=0)							

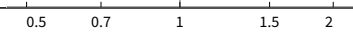


Comparison 5. Adherence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adherence	4	3835	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.26, 1.65]
2 Adherence: usual care as comparator	3	3140	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.35, 1.49]
3 Adherence: comparator provision of individual drugs	1	695	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.06, 1.47]

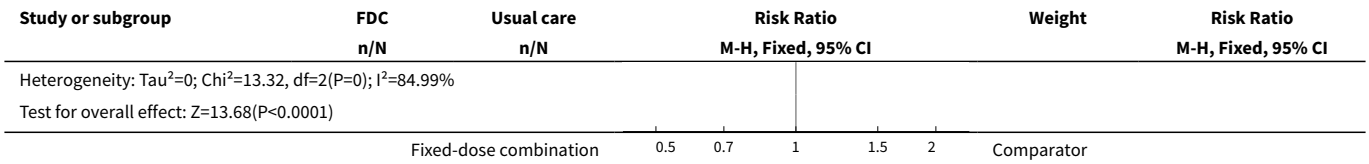
Analysis 5.1. Comparison 5 Adherence, Outcome 1 Adherence.

Study or subgroup	FDC n/N	Usual care n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
FOCUS 2014	178/350	141/345		21.87%	1.24[1.06,1.47]
IMPACT 2014	208/256	119/257		23.59%	1.75[1.52,2.03]
Kanyini GAP 2014	213/311	143/312		23.76%	1.49[1.3,1.72]
UMPIRE 2013	829/1002	621/1002		30.78%	1.33[1.26,1.41]
Total (95% CI)	**1919**	**1916**		**100%**	**1.44[1.26,1.65]**
Total events: 1428 (FDC), 1024 (Usual care)					
Heterogeneity: Tau^2=0.01; Chi^2=14.82, df=3(P=0); I^2=79.76%					
Test for overall effect: Z=5.36(P<0.0001)					

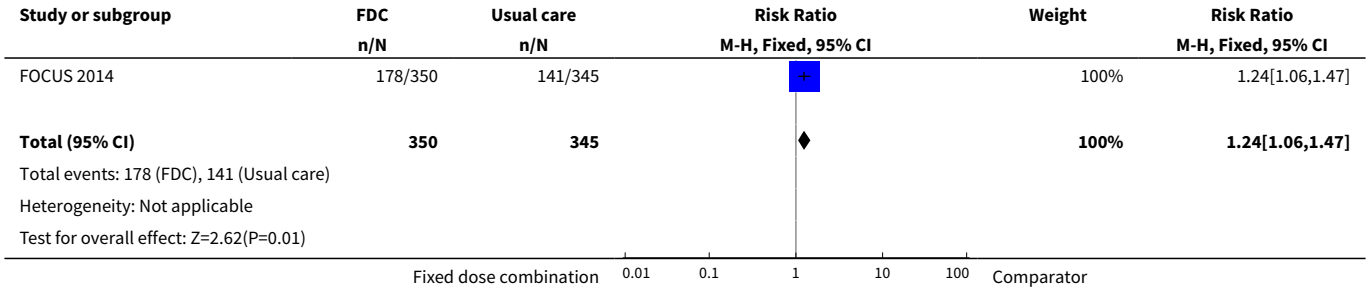


Analysis 5.2. Comparison 5 Adherence, Outcome 2 Adherence: usual care as comparator.

Study or subgroup	FDC n/N	Usual care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
IMPACT 2014	208/256	119/257		13.46%	1.75[1.52,2.03]
Kanyini GAP 2014	213/311	143/312		16.18%	1.49[1.3,1.72]
UMPIRE 2013	829/1002	621/1002		70.37%	1.33[1.26,1.41]
Total (95% CI)	**1569**	**1571**		**100%**	**1.42[1.35,1.49]**
Total events: 1250 (FDC), 883 (Usual care)					



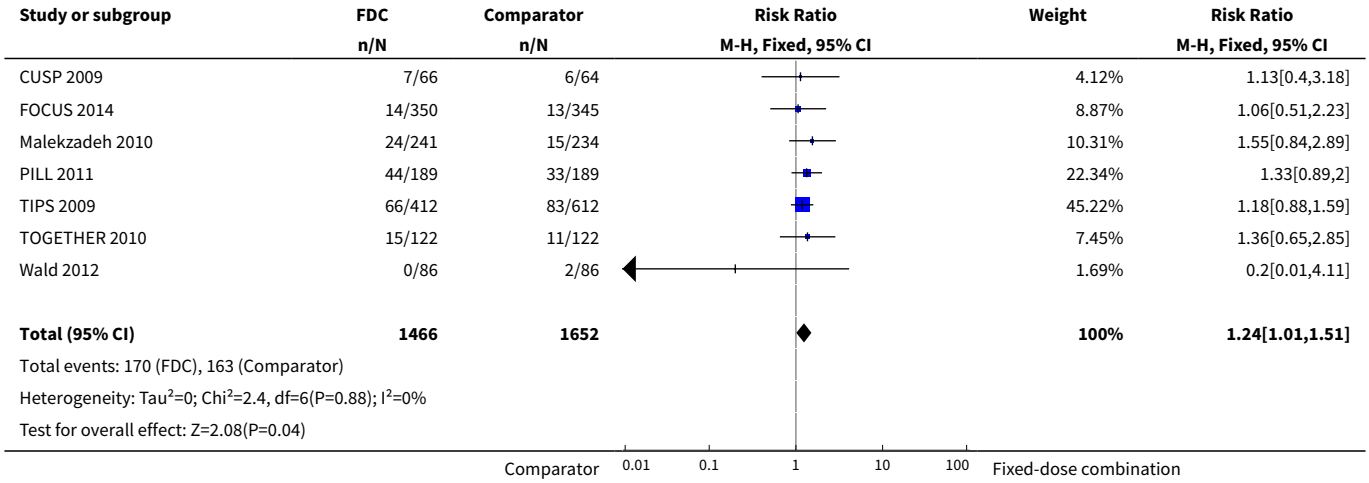
Analysis 5.3. Comparison 5 Adherence, Outcome 3 Adherence: comparator provision of individual drugs.



Comparison 6. Discontinuation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation	7	3118	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.01, 1.51]

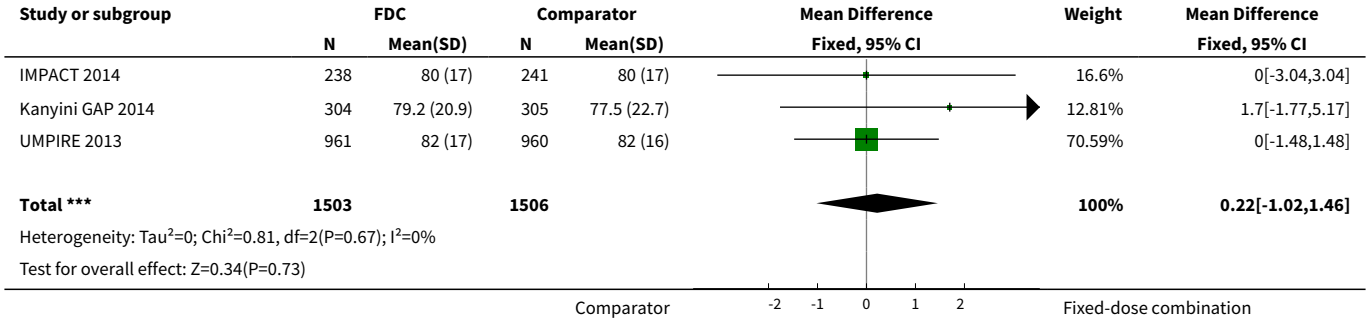
Analysis 6.1. Comparison 6 Discontinuation, Outcome 1 Discontinuation.



Comparison 7. Health-related quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 EQ-5D health state	3	3009	Mean Difference (IV, Fixed, 95% CI)	0.22 [-1.02, 1.46]

Analysis 7.1. Comparison 7 Health-related quality of life, Outcome 1 EQ-5D health state.



ADDITIONAL TABLES

Table 1. Polypill content by trial

Study	Polypill contents (dose)	Comparator
CRUCIAL 2011	Amlodipine 5 mg to 10 mg Atorvastatin 10 mg[a]	Usual care
CUSP 2009	Amlodipine 5 mg Atorvastatin 20 mg	Placebo
FOCUS 2014	Aspirin 100 mg Ramipril 2.5 mg, 5 mg, or 10 mg Simvastatin 40 mg	Individual components: Aspirin 100 mg Ramipril 2.5 mg, 5 mg, or 10 mg Simvastatin 40 mg
IMPACT 2014	Aspirin 75 mg Atenolol 50 mg Lisinopril 10 mg Simvastatin 40 mg or Aspirin 75 mg Hydrochlorothiazide 12.5 mg	Usual care

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

	Lisinopril 10 mg Simvastatin 4 0mg	
Kanyini GAP 2014	Aspirin 75 mg Atenolol 50 mg Lisinopril 10 mg Simvastatin 40 mg or Aspirin 75 mg Hydrochlorothiazide 12.5 mg Lisinopril 10 mg Simvastatin 40 mg	Usual care
Malekzadeh 2010	Aspirin 81 mg Atorvastatin 20 mg Enalapril 2.5 mg Hydrochlorothiazide 12.5 mg	Placebo
OLSTA 2016	Olmesartan 40 mg Rosuvastatin 20 mg	1. Olmesartan 40 mg, 2. rosuvastatin 20 mg, or 3. 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 100 mg 2. Aspirin 100 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg 3. Hydrochlorothiazide 12.5 mg 4. Hydrochlorothiazide 12.5 mg, atenolol 50 mg 5. Hydrochlorothiazide 12.5 mg, ramipril 5 mg

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

		6. Hydrochlorothiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg 7. Ramipril 5 mg, atenolol 50 mg, or 8. Simvastatin 20 mg
TOGETHER 2010	Amlodipine 5 mg to 10 mg Atorvastatin 10 mg	Amlodipine 5 mg, 10 mg
UMPIRE 2013	Aspirin 75 mg Atenolol 50 mg Lisinopril 10 mg Simvastatin 40 mg or Aspirin 75 mg Hydrochlorothiazide 12.5 mg Lisinopril 10 mg Simvastatin 40 mg	Usual care
Wald 2012	Amlodipine 2.5 mg Hydrochlorothiazide 12.5 mg Losartan 25 mg Simvastatin 40 mg	Placebo

[a]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)

Appendix 3. Search strategies 2016

CENTRAL/DARE/HTA/NHS EDD

#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 2013 to 2016

MEDLINE OVID

Cochrane sensitivity-maximising RCT filter applied (Handbook 2011)

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 (2013* or 2014* or 2015* or 2016*).ed.

62 60 and 61

Embase OVID

Cochrane RCT filter (Handbook 2011)

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 (2013* or 2014* or 2015* or 2016*).em.

69 67 and 68

ISI Web of Science

RCT filter adapted from Cochrane RCT filter.

25 #24 AND #23, from 2013 to 2016

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)

Clinical Trials Register Searches

clinicaltrials.gov
clinicaltrials.gov/ct2/home

Advanced Search

Search Terms: polypill OR "fixed dose" OR "drug combination" OR "drug combinations"

Study Type: Interventional Studies

Conditions: cardiovascular OR hypertension OR dyslipidemia OR hyperlipidemia OR hypercholesterolemia

WHO ICTRP
apps.who.int/trialsearch/

polypill AND cardiovascular OR polypill AND hypertension OR polypill AND dyslipidemia OR polypill AND hyperlipidemia OR polypill AND hypercholesterolemia OR fixed dose AND cardiovascular OR fixed dose AND hypertension OR fixed dose AND dyslipidemia OR fixed dose AND hyperlipidemia OR fixed dose AND hypercholesterolemia OR drug combination AND cardiovascular OR drug combination AND hypertension OR drug combination AND dyslipidemia OR drug combination AND hyperlipidemia OR drug combination AND hypercholesterolemia OR drug combinations AND cardiovascular OR drug combinations AND hypertension OR drug combinations AND dyslipidemia OR drug combinations AND hyperlipidemia OR drug combinations AND hypercholesterolemia

WHAT'S NEW

Date	Event	Description
12 January 2017	New search has been performed	The searches were re-run on 19 September 2016. Differences between 2014 review and 2017 update: Title changed from cardiovascular disease to atherosclerotic cardiovascular disease for greater clarity in the target disease of combinations with at least one blood pressure-lowering drug and one lipid-lowering drug.
6 January 2017	New citation required but conclusions have not changed	Four additional trials reported in this update compared with 2014 review. No change in the overall direction and magnitude of effects with the addition of these additional trials. More ongoing trials identified.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development or update of the protocol. For this update, Ehete Bahiru screened titles and abstracts, assessed studies for inclusion and exclusion, extracted data, and edited the update. Angharad de Cates screened titles and abstracts, assessed studies for inclusion and exclusion, extracted data, contacted authors, and drafted the original review. Matthew Farr and Morag Jarvis screened titles and abstracts, assessed studies for inclusion and exclusion, and extracted data for the original review. Mohan Palla screened titles and abstracts and assessed studies for inclusion and exclusion for the update. Karen Rees supervised the title screening and data extraction for the initial review and contributed to writing the original review and to editing of the update. Shah Ebrahim assisted in analyses and interpretation and contributed to writing of the review. Mark Huffman contacted study authors, screened titles and abstracts, assessed studies for inclusion and exclusion, extracted data, performed the analyses, and drafted the review and update.

DECLARATIONS OF INTEREST

Mark Huffman has received grant support from Cochrane to support the production of this update. Dr. Huffman also receives grant support from World Heart Federation to serve as senior program advisor for its Emerging Leaders program, which is supported by Boehringer Ingelheim and Novartis and has been supported by AstraZeneca and Bupa. Dr. Huffman has also received travel support from the World Heart Federation for its polypill satellite meeting at the World Congress of Cardiology and Cardiovascular Health in 2016.

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

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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.

Differences between 2014 review and 2017 update

In the 2017 update, cardiovascular disease has been changed to atherosclerotic cardiovascular disease for greater clarity in the target disease of combinations with at least one blood pressure-lowering drug and one lipid-lowering drug. We also moved discontinuation rates from the primary outcome section, where it was reported under adverse events, to an individual secondary outcome. The rationale for this change was two-fold: 1) investigator-defined adverse event rates did not necessarily include discontinuation rates, and 2) discontinuation

rates could not be reported when the comparator group was usual care. We included trials with active single drug comparators but not trials comparing different fixed-dose combinations. We have also removed the dose subgroup analysis because most fixed-dose combinations included moderate doses of either blood pressure-lowering drugs, lipid-lowering drugs, or both.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticholesteremic Agents [*administration & dosage] [adverse effects]; Antihypertensive Agents [*administration & dosage] [adverse effects]; Aspirin [*administration & dosage] [adverse effects]; Blood Pressure [drug effects]; Cardiovascular Diseases [mortality] [*prevention & control]; Cause of Death; Cholesterol [blood]; Drug Combinations; Placebo Effect; Platelet Aggregation Inhibitors [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male; Middle Aged