An application to include fixed dose combinations in the WHO Model List of Essential Medicines for primary and secondary prevention of atherosclerotic cardiovascular diseases in adults

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1. Summary statement of the proposal for inclusion

Cardiovascular diseases are responsible for one third of deaths globally and the burden continues to rise. Member States need new strategies to achieve global goals, namely Sustainable Development Goal, Target 3.4 to reduce the risk of premature mortality from noncommunicable diseases by 1/3 by 2030. This goal will not be met without substantial reductions in the burden of premature cardiovascular disease, particularly ischemic heart disease and stroke. Most countries are not on track to meet Target 3.4.(1) Appendix 3 of the World Health Organization (WHO) Global Action Plan includes recommendations of cost effective interventions for people with and at high predicted risk for cardiovascular disease over the next 10 years, including antiplatelet, cholesterol and blood pressure lowering medications (CV2a, CV2b).

Current use of drugs to prevent and control atherosclerotic cardiovascular disease, including antiplatelet, cholesterol and blood pressure lowering drugs, remains exceedingly low over the past two decades despite high-quality evidence of their benefits as separate drug classes.(2–5) **Recent, high-quality evidence from large clinical trials provides new and compelling outcomes data on the favorable balance between benefits and harms of fixed-dose combination therapy, including statin and multiple blood pressure lowering medications with and without aspirin, for individuals with and at high risk for atherosclerotic cardiovascular disease**.(6) These data represent important developments in the science of fixed-dose combination therapy in the past few years. Recent transition state modelling conducted to support this application also demonstrates the major, potential health benefits of fixed-dose combination therapy among individuals eligible for pharmacotherapy (under review). These models estimate that use of fixed-dose combination therapy of statin and multiple blood pressure lowering drugs, with and without aspirin, among currently eligible individuals (i.e., individuals with and at high risk for atherosclerotic cardiovascular disease) could have an even greater reduction in cardiovascular disease mortality from 2023-2050 than widespread hypertension control or implementation of tobacco control policies alone (Table 1), and combined implementation of these strategies could prevention >200 million deaths. The greatest gains are expected in the population of individuals without prevalent cardiovascular disease (primary prevention), which has a 4-5-fold larger burden of fatal and non-fatal disease, respectively, compared with the population of individuals with prevalent cardiovascular disease (secondary prevention; unpublished data, Prospective Urban Rural Epidemiology Study).

Table 1. Comparison of the cumulative impact of different interventions on cardiovascular disease mortality.

Type of cardiovascular disease intervention	Cumulative cardiovascular disease deaths averted, 2023-2050
Primary + secondary prevention FDCs (with aspirin), 90% coverage*	140 million
Primary + secondary prevention FDCs (without aspirin), 90% coverage	120 million
Hypertension treatment, 80% coverage	61 million
Full implementation of WHO tobacco control policies by 2023	20 million

Note: Fixed-dose combination impact estimates come from a report under review at the time of application submission. The hypertension treatment impact estimate comes from a report by Pickersgill and

colleagues.(7) *The tobacco control impact estimate comes from Watkins and colleagues and includes the combined impact of all the population-level policies recommended in the MPOWER package.*(1) *Of course, tobacco control would reduce mortality from other causes like cancers and chronic respiratory diseases, so the total impact of tobacco control on all-cause mortality would be higher.*90% coverage is aspirational and aligned with the 90-90-90 target by UNAIDS and has been nearly achieved with diphtheria, pertussis, and tetanus vaccination worldwide and with ART for HIV with targeted efforts (data.worldbank.org).*

Reductions in non-fatal cardiovascular disease events, including myocardial infarctions and strokes, are estimated to be 3-4-fold greater than reductions in cardiovascular mortality alone based on the distribution of cardiovascular disease events estimated by the Global Burden of Disease and the Prospective Urban Rural Epidemiology Study.*(8,9) *Thus, widespread implementation and scale-up of fixed-dose combination therapy could have major public health gains even beyond achieving Target 3.4 of the UN Sustainable Development Goals.

Fixed-dose combinations of statins and blood pressure lowering drugs with and without aspirin, including fixed-dose combinations proposed herein, are also highly cost effective(10–12) and have increasing availability and marketing authorization; however, the current supply does not meet the current and projected demand. The recent inclusion of fixed-dose combinations for blood pressure lowering therapy in the 22nd Model List of Essential Medicines(13,14) stimulated their recommendation in the 2021 WHO hypertension guideline(15) and increased uptake through pooled and strategic procurement in Latin America.(16) This proposal represents a similar attempt at stimulating uptake of fixed-dose combination therapy at a large scale to meet the current and future challenges that the world faces due to atherosclerotic cardiovascular diseases.

This proposal seeks to add two fixed-dose combinations to the core list based on two clinical indications:

1. The combinations of: a) aspirin + simvastatin + ramipril + atenolol + hydrochlorothiazide, and b) atorvastatin + perindopril + amlodipine at pre-specified doses for the prevention of incident atherosclerotic cardiovascular disease among individuals with ≥10% predicted risk over 10 years (**primary prevention**),

2. The combination of aspirin + atorvastatin + ramipril at pre-specified doses for treatment of patients with existing atherosclerotic cardiovascular disease (**secondary prevention**).

These combinations are individual examples that are currently available in the market and do not represent a pharmacological class or therapeutic group. The medication classes included in these combinations are included in the Model List of Essential Medicines based on efficacy, safety, and cost-effectiveness. Recent high-quality trial data are included to support the use of fixed-dose combinations in primary and secondary prevention contexts, and the inclusion of these combinations is supported by trial evidence and availability.

Fixed-dose combinations can be feasibly implemented into health systems through the WHO HEARTS technical package, as has been demonstrated in varied settings, including in Mexico's public health sector by physicians(17), in Indonesia and Colombia by nonphysician health workers(18) and in a humanitarian setting by Médecins Sans Frontières in Lebanon.(19) Fixed-dose combination can thus help to equitably reduce the impact of cardiovascular disease globally by simplifying

treatment options and expanding accessibility across economic levels, both *across and within countries*.

2. Consultation with WHO technical department(s)
Dr. Taskeen Khan, Medical Officer, Cardiovascular Disease (CVD) programme implementation, Non Communicable Disease (NCD) management unit at the WHO headquarters in Geneva, Switzerland.

Dr. Benedikt Huttner, Secretary, 23rd WHO Expert Committee on the Selection and Use of Essential Medicines at the WHO headquarters in Geneva, Switzerland.

3. Other organization(s) consulted and/or supporting the submission
Please see supporting letters from the World Heart Federation and its members among other organizations in the Supplemental Appendix 9.

4. Key information for the proposed medicine(s)
4.1 International non-proprietary name (INN, generic name) of the medicine

- Atorvastatin
- Simvastatin
- Perindopril
- Ramipril
- Amlodipine
- Atenolol
- Hydrochlorothiazide
- Acetylsalicylic acid (non-INN: the WHO establishes that aspirin does not have INN because this name was already in wide use when the INN system began, and it was a well-established name)

4.2 Anatomical therapeutic chemical (ATC) code of the medicine

INN	ATC code
Simvastatin, acetylsalicylic acid, ramipril, atenolol, hydrochlorothiazide	C10BX
Atorvastatin, perindopril, amlodipine	C10BX11
Atorvastatin, acetylsalicylic acid, and ramipril	C10BX06

4.3 Dosage form(s) and strength(s) of the proposed medicine(s)
These are summarized in the Table below.

Combinations	Strength(s) in mg	Formulation
Acetylsalicylic acid, simvastatin, ramipril, atenolol, hydrochlorothiazide	100/20/5/50/12.5	Tablet
Atorvastatin, perindopril, amlodipine	20/5/5	Tablet
	20/10/10	Tablet
	40/5/5	Tablet
	40/10/10	Tablet
Acetylsalicylic acid, atorvastatin, ramipril	100/40/2.5	Tablet
	100/40/5	Tablet
	100/40/10	Tablet
	100/20/2.5	Tablet
	100/20/5	Tablet
	100/20/10	Tablet

4.4 Indication(s)

Primary prevention: Adults at high-risk for an incident cardiovascular disease event, based on 10-year predicted risk of 10% or greater as outlined in Appendix 3 of the WHO Global Action Plan (CV2a, CV2b), which outlines recommendations of cost-effective interventions. Individuals with type 2 diabetes or those that are 40 years and older and with concomitant essential hypertension would also generally be eligible for fixed-dose combination therapy based on recommendations in the WHO HEARTS technical package.(20) The indications listed below are commonly included as conditions among individuals who are at high predicted risk for atherosclerotic cardiovascular disease as outlined in the WHO HEARTS technical package.

Indication	ICD-11
Essential hypertension	BA00
Hypercholesterolemia	5C80.0
Type 2 diabetes mellitus	5A11

Secondary prevention: Adults with a prior cardiovascular disease event (myocardial infarction, coronary revascularization, or stroke).

Indication	ICD-11
Ischemic heart diseases/chronic ischemic heart disease	
Old myocardial infarction	BA50
Coronary atherosclerosis	BA52
Other specified chronic ischemic heart disease	BA5Y
Chronic ischemic heart disease, unspecified	BA5Z
Stroke	
Cerebral ischemic stroke	8B11
Other atherosclerosis	
Atherosclerotic chronic arterial occlusive disease	BD40

5. Proposal for an individual medicine or representative of a pharmacological class/therapeutic group

While the individual components of the proposed fixed-dose combination may be representative of their respective pharmacological class or therapeutic group, this proposal does not seek a square box listing given previous concerns identified by previous Model List of Essential Medicines reviewers to specify the combinations under review. It may be appropriate to update this listing in the future based on available data and marketing authorization for new fixed-dose combinations for primary and secondary prevention of atherosclerotic cardiovascular disease.

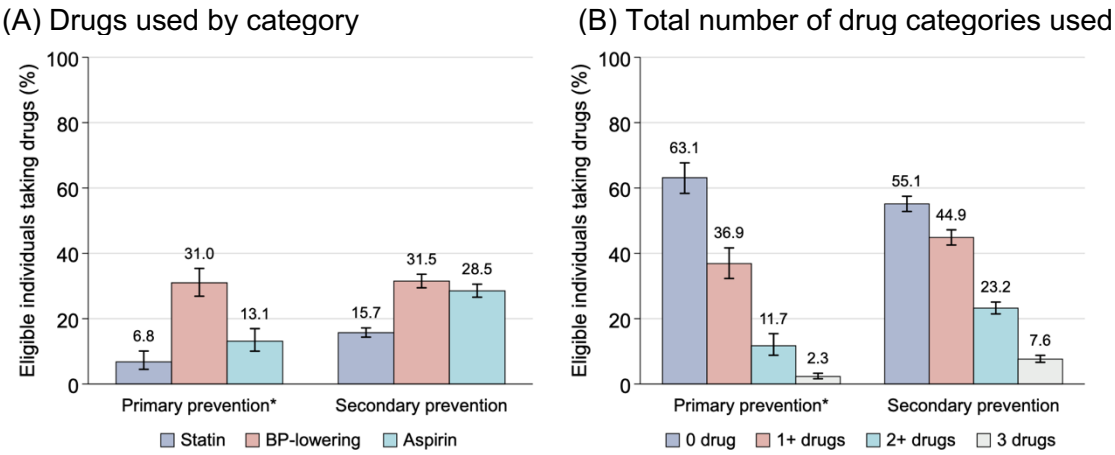
6. Information supporting the public health relevance

6.1 Rationale

Cardiovascular disease is the leading cause of deaths globally, which is largely driven by underlying atherosclerosis and ischemic heart disease, in particular.(21) Clinical practice guidelines recommend pharmacotherapy with cholesterol and blood pressure lowering drugs for individuals with prevalent disease (secondary prevention) and for individuals at high-risk for incident disease (primary prevention). Antiplatelet therapy (aspirin) is also recommended for individuals with prevalent disease (secondary prevention). Pharmacotherapy is recommended in the WHO's Global Action Plan for patients with and at high risk for cardiovascular disease based on decades of experience and evidence supporting these drug classes (CV2a, CV2b). Thus, medicines in each of these drug classes have long been included in recent WHO's Model Lists of Essential Medicines on their efficacy, safety, and cost effectiveness, both for patients with prevalent cardiovascular disease, as well as those at high risk for incident disease.(22) This risk-based approach is a central feature of the WHO HEA**R**TS technical package for country-level implementation.(20)

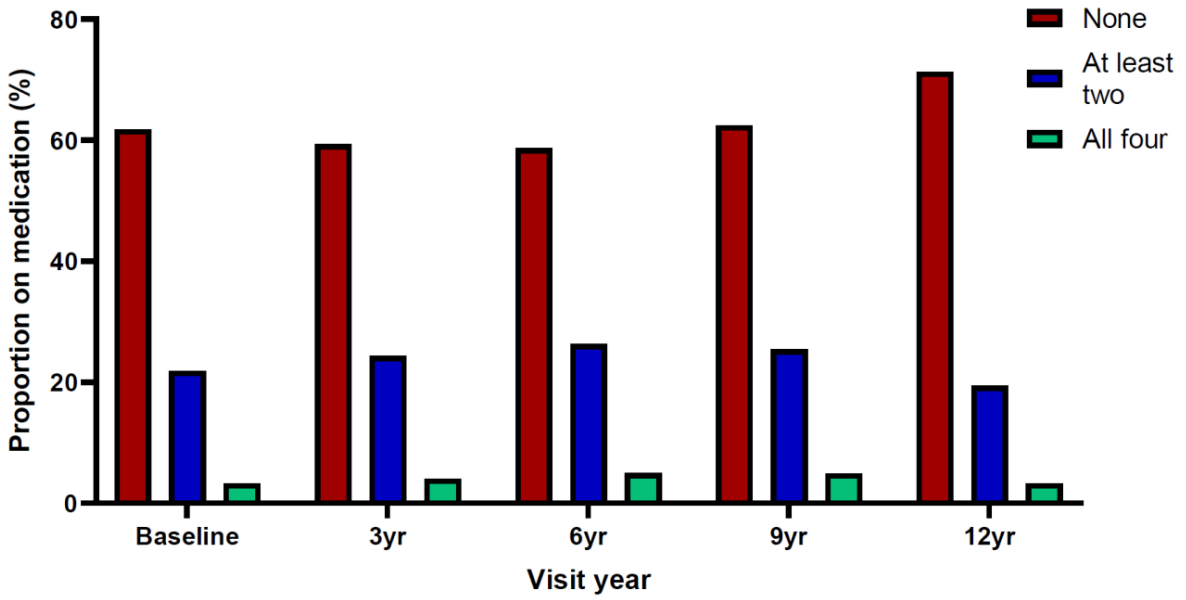
Despite the large burden of disease and availability of effective medications, uptake of individual medicines has been(5), and unfortunately remains, very low. For example, data from 40 demographic health surveys in low- and middle-income countries (2013-2019) synthesized by the Global Health & Population Project on Access to Care for Cardiometabolic Disease (HPACC) show <10% of eligible adults using recommended pharmacotherapy (statin, blood pressure lowering drug, and aspirin) based on either high-risk (≥20% predicted risk over 10 years) primary prevention or secondary prevention indications (Figure 1, includes data from accepted and pending publication).(2,3) These rates are strikingly similar to those reported in the PURE study in 2011.(5) Updated unpublished data from the PURE study show little change in the use of these drugs during the subsequent period in an analysis of data from 21 high-, middle-, and low-income countries (Figure 2). Optimal pharmacotherapy rates are also low in high-income countries, such as the United States, where nationally representative data demonstrate that only 1 out of every 4 American adults with prevalent disease take the combination of antiplatelet, statin, and blood pressure lowering therapy for secondary prevention of atherosclerotic cardiovascular disease.(23,24) **Thus, the current approach of using individual medications to prevent and control cardiovascular disease at scale has been and continues to be *woefully* *inadequate*.**

Figure 1. Treatment with statins, BP-lowering drugs, and aspirin among eligible individuals for the primary and secondary prevention of cardiovascular disease in 40 low- and middle-income countries.



**Primary prevention refers to individuals without cardiovascular disease and predicted cardiovascular disease risk >20%. Error bars represent 95% CIs. The sample includes non-pregnant individuals aged 40-69 years from the following countries (survey year): Afghanistan (2018), Algeria (2016-17), Armenia (2016), Azerbaijan (2017), Bangladesh (2018), Belarus (2016), Benin (2015), Bhutan (2014), Botswana (2014), Burkina Faso (2013), Ecuador (2018), Eswatini (2014), Ethiopia (2015), Georgia (2016), Guyana (2016), Iran (2016), Iraq (2015), Jordan (2019), Kenya (2015), Kiribati (2015), Kyrgyzstan (2013), Lebanon (2017), Moldova (2013), Mongolia (2019), Morocco (2017), Myanmar (2014), Nauru (2015-16), Nepal (2019), Solomon Islands (2015), Sri Lanka (2014), St. Vincent & the Grenadines (2013), Sudan (2016), Tajikistan (2016), Timor-Leste (2014), Tokelau (2014), Turkmenistan (2018), Tuvalu (2015), Uganda (2014), Vietnam (2015), Zambia (2017). Of note, surveys in Burkina Faso, Kyrgyzstan, Myanmar, and Tokelau had data limited to individuals aged 40-64 years.*

Figure 2. Longitudinal rates of medication use (aspirin, statins, beta-blockers, and ACE inhibitors) among all participants with prevalent cardiovascular disease (i.e., secondary prevention), including baseline and during follow-up from 17 countries in the Prospective Urban Rural Epidemiology (PURE) Study (unpublished data).The figure shows little improvement in the use of these proven medications over a 12 year period. The lack of change in the use of these medications is consistently observed in high-, middle-, and low-income countries (data not shown).



Fixed-dose combination therapy is a strategy that has been successfully used to reduce treatment gaps in other conditions, which supports the rationale for this application. For example, fixed-dose combination therapy is widely recommended for the management of hypertension, HIV, hepatitis C, and malaria based on efficacy,

safety, and cost effectiveness. **Data from large randomized trials show that fixed-dose combinations have substantial benefits by reducing the risk of cardiovascular disease events (nearly 50% relative risk reduction), including fatal and non-fatal myocardial infarction and stroke and need for revascularization in primary (6) and secondary prevention settings.(25) Fixed dose combinations improve risk factor control and adherence.(6,26) They are safe(6) and cost effective.(10)**

Fixed-dose combinations with two blood pressure lowering medications are also included in the 2021 WHO hypertension guidelines.(22) Accordingly, the 22nd WHO Model List of Essential Medicines includes multiple combinations for each condition, including 4 combinations for hypertension. A major downstream benefit of inclusion of blood pressure lowering fixed-dose combination therapy into the 2021 Model List of Essential Medicine has been listing, bulk procurement, and increased availability of these combinations by the Pan American Health Organization Strategic Fund for implementation in the HEARTS in the Americas program, which includes 26 countries and >2,100 health centers.(16,27)

6.2 Target populations

Based on the burden and totality of evidence, the proposal includes two clinical indications for fixed-dose combination therapy:

1. High-risk primary prevention, defined as a predicted 10-year risk of ≥10% of atherosclerotic cardiovascular disease
2. Secondary prevention in patients with prevalent atherosclerotic cardiovascular disease

In both indications, which represent a risk continuum, the respective components of the proposed fixed-dose combinations are already recommended in international guidelines and included in the WHO Model List of Essential Medicines and in Appendix 3 of the WHO Global Action Plan for Noncommunicable Diseases.

6.3 Alternative medicines currently included on the Model Lists for the proposed indications

The individual drug classes included in the proposed fixed-dose combination (e.g., statin, angiotensin converting enzyme inhibitor, calcium channel blocker, antiplatelet) are all included in the WHO Model List of Essential Medicines.

7. Treatment details

7.1 Dosage regimen and duration of treatment

Dosage regimen	Route of administration	Frequency	Duration
Primary prevention Aspirin (100 mg), Simvastatin (20), Ramipril (5), Atenolol (50), and Hydrochlorothiazide (12.5)	Oral	Once a day	Lifelong

Atorvastatin (20/40 mg), Perindopril (5/10), and Amlodipine (5,10)			
Secondary prevention Aspirin (100 mg), Atorvastatin (40/20), and Ramipril (2.5/5/10)	Oral	Once a day	Lifelong

These combinations are proposed based on supporting trial data(6,25) and widespread availability and marketing authorization for the proposed indications.

7.2 Requirements to ensure appropriate use of the medicine(s)

For patients considering or taking statins, baseline liver function and lipid levels are recommended, though relative benefits of statins have been observed across all lipid and risk levels in the Cholesterol Treatment Trialists' Collaboration.(28) Serial lipid monitoring 6-12 weeks after initiation (and annually thereafter) is recommended for patients taking statins,(29) though statin trial data suggest a longer interval for monitoring stable patients could better detect true changes in lipids, which could also lower costs.(30) For patients considering or taking angiotensin converting enzyme inhibitors, the WHO 2021 hypertension guideline recommend monitoring renal function and serum potassium "when starting or changing dose, if testing is readily available and does not delay treatment".(15) These laboratory diagnostic tests are included in the WHO Model List of Essential Diagnostics. For patients considering or taking aspirin for secondary prevention of atherosclerotic cardiovascular disease, no specific laboratory monitoring is recommended. The proposed fixed-dose combinations are contraindicated in women who are pregnant or breastfeeding, similar to the contraindications of the individual components.

7.3 Recommendations in existing WHO guidelines

WHO recommends that all people who have had a cardiovascular disease event should be treated with blood pressure-lowering therapy, statin, and aspirin, as well as being offered lifestyle advice (Supplemental Appendix 1). The WHO HEARTS technical package provides examples of these medications based on scientific evidence, once daily suitability, common usage and availability and include: ACE inhibitors (e.g., lisinopril, ramipril, perindopril), thiazide-like diuretics (e.g., chlorthalidone or indapamide sustained release with an option to use hydrochlorothiazide if first two are not available) and calcium channel blockers (amlodipine) as blood pressure-lowering therapies.(20) Statins listed included simvastatin and atorvastatin as an alternative.(20) For patients at high-risk for cardiovascular disease events, including individuals at high cardiovascular disease risk or with type 2 diabetes mellitus with hypertension, WHO recommends treatment with statin and single pill combination of blood pressure lowering therapy in the WHO HEARTS technical package and 2021 hypertension guideline, respectively.(15,20,31)

7.4 Recommendations in other current clinical guidelines

Statins and blood pressure lowering drugs are also recommended for all people with a history of atherosclerotic cardiovascular disease in all guidelines,

including those from Europe(29,32), the US(29), Japan(33), Brazil(34), Australia(35), and many other regions with additional support from the World Heart Federation.(36) These medications are also recommended for individuals at high predicted risk for incident atherosclerotic cardiovascular disease, including individuals with type 2 diabetes mellitus 40 years and older.(37) These medications are typically recommended to be used lifelong to prevent incident or recurrent atherosclerotic cardiovascular disease events. Antiplatelet therapy is also recommended for individuals with prevalent atherosclerotic cardiovascular disease, but there is no consensus yet regarding its use in primary prevention indications. For example, the 2022 United States Preventive Services Task Force gives aspirin a Grade C for individuals aged 40-59 years old with 10% or greater 10-year predicted risk for incident atherosclerotic cardiovascular disease.(38)

8. Review of benefits: summary of evidence of comparative effectiveness

8.1 Systematic literature search

The Cochrane Collaboration has previously synthesized results from all published randomized trials evaluating fixed-dose combination strategy of at least one blood pressure lowering and one lipid lowering drug in primary and secondary prevention of atherosclerotic cardiovascular disease in 2014 and 2017.(26,39) Additional randomized trials providing long-term data on clinical outcomes have been published since these earlier systematic reviews providing the rationale for this systematic review update that we have conducted to support this application.(25,40–42) These data are supported by an individual participant data meta-analysis of 3 large trials published by the Polypill Trialists' Collaboration.(6) We have also identified the 2022 publication of a systematic review and study-level meta-analysis of fixed-dose combination therapy, though this latter review was not inclusive of all published trials.(43) Thus, this review represents the most updated synthesis on the state-of-the-evidence across the continuum of risk for cardiovascular disease.

Study question

What is the effect size and quality of evidence of fixed-dose combination therapy on all-cause mortality, fatal and non-fatal atherosclerotic cardiovascular disease (ASCVD) events, and adverse events in people with or a high risk for ASCVD?

Literature search and study selection

This systematic review protocol was designed according to the participants, interventions, comparators, outcomes, timing, setting, and study design format, and the prespecified protocol was prospectively registered (PROSPERO CRD42021229735).(44) This systematic review is an update to a previous Cochrane Collaboration review published in 2017, and we followed guidelines published by the Cochrane Collaboration to synthesize the effects of interventions.(26,45)

We reviewed the original search strategy and conducted search updates on December 4, 2020 and April 4, 2022 (Supplemental Appendix 2). The updated searches captured studies published since 2016 when the last search was done for the Cochrane Collaboration 2017 systematic review. We conducted the searches on MEDLINE (Ovid), Cochrane Library (Wiley), EMBASE (Elsevier), CINAHL Plus with Full Text (EBSCOhost), and Web of Science (Thomson Reuters). We sought additional studies from ClinicalTrials.gov and the WHO International Clinical Trial Registry Platform. We did not impose restrictions on language, geography, or

publication type. Search results were uploaded to EndNote and subsequently Covidence for deduplication and screening. An experienced information specialist performed all searches. We contacted study authors of included trials when necessary to identify information we might have missed, and reference lists of included articles were checked for additional studies.

Eligibility criteria

We included randomized controlled trials evaluating fixed-dose combination therapy with at least one blood pressure lowering drug and one lipid-lowering drug compared to usual care, placebo, or active drug therapy in adults 18 years and older with no restriction regarding presence of atherosclerotic cardiovascular disease. The co-primary outcomes were fatal or non-fatal atherosclerotic cardiovascular disease endpoints (myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, angina or angiographically-defined ischemic heart disease, stroke, transient ischemic attack, carotid endarterectomy or peripheral artery disease), all-cause mortality, and adverse events. Secondary outcomes included systolic blood pressure, low-density lipoprotein (LDL) cholesterol, adherence, discontinuation, and health-related quality of life.

Study selection and data extraction

Five authors reviewed the title and abstract of each paper and retrieved potentially relevant references in duplicate. Following this initial screening, we obtained full-text reports of potentially relevant studies and four authors independently selected studies in duplicate to be included in the review using predetermined inclusion criteria.(44) Three review authors independently extracted key data in duplicate using a structured data extraction form including details of the study design, participant characteristics, study setting, intervention, comparator, outcome data, outcome assessment, adverse effects, and methodological quality from each of the included studies. Any disagreements regarding study inclusion or extracted data were resolved by consensus or through review with another author.

Risk of bias and quality of evidence assessment

Three review authors independently assessed risk of bias in duplicate using the revised Cochrane Risk of Bias Tool for randomized trials with disagreements resolved by discussion. Two authors evaluated the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework using the GRADE checklist, which addresses issues related to internal and external validity.(46) We report the absolute and relative effects, quality of evidence, and specific reason(s) applied for downgrading the overall quality of evidence.

Statistical analysis

We report pooled dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs) using a fixed-effect meta-analysis when heterogeneity was low to low-moderate (I^2 <50%). We express continuous data as mean differences (MDs) with 95% CIs. We closely examined the level at which randomization occurred for the same outcome. In the event of substantial clinical, methodological, or statistical heterogeneity (I^2 ≥50%), we either did not conduct a meta-analysis or we performed a random-effect meta-analysis with cautious interpretation of results as a pooled effect estimate. We identified heterogeneity (inconsistency) through visual inspection

of forest plots and by using a standard Chi² test with a significance level of α = 0.1. In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis. If we included more than 10 studies investigating a particular outcome, then we used funnel plots and regression-based Egger test to assess small-study effects and publication bias.(47)

We attempted to contact study authors to obtain missing data. We closely assessed participant attrition rates including withdrawals, loss to follow-up, and drop-outs. We used the average of reported standard deviations from studies for a certain outcome to impute standard deviation values for studies that did not report standard deviations or if we failed to obtain it from study authors for the same outcome.

We report the effect of fixed-dose combination therapy on key outcomes separately for primary prevention (populations where 15% or less had pre-existing atherosclerotic cardiovascular disease) versus secondary prevention. We had pre-determined to stratify these results based on substantial heterogeneity that we observed between these trial groups, particularly related to pharmacotherapy among comparator groups. We report results from the largest prevention trial, SECURE(25), separately due to the substantial heterogeneity due to populations and comparator groups observed in trials with mixed primary and secondary populations with 15% or greater with prevalent atherosclerotic cardiovascular disease. We also report pre-specified subgroup results from patients with prevalent cardiovascular disease from the PolyIran trial(41), which were separately reported. We conducted sensitivity analyses to report results for trials that include more than 500 participants, three-drug or more fixed-dose combination therapies, and usual care as the comparator group. Statistical analyses were done using R 4.0.5 (R Project for Statistical Computing).

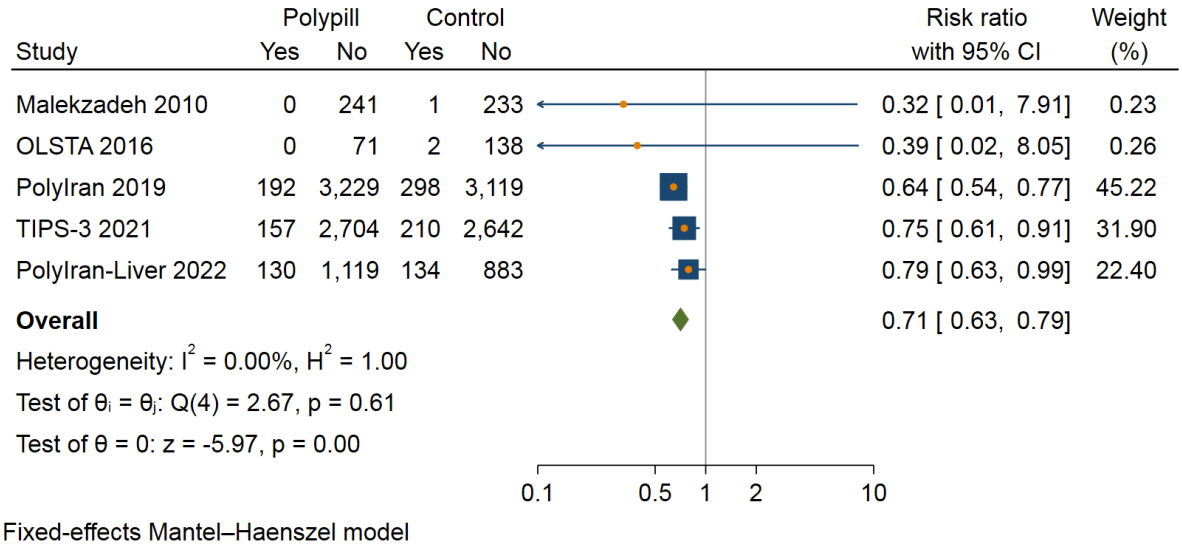
8.2 Summary of available evidence for comparative effectiveness

Building on a 2017 Cochrane review update that included 13 trials and 9,059 participants(26), this systematic review update provides relevant data to support this application (unpublished). The search strategy is shown in Supplemental Appendix 2, and the PRISMA flowchart is shown in Supplemental Appendix 3. Results from 13 new clinical trials (n=18,277 additional participants) over the past 6 years, including 3 large outcomes trials (PolyIran(41), TIPS-3(42), SECURE(25)) published in the last 3 years, have strengthened the evidence base for fixed-dose combination therapy to a total of **26 trials** and **27,336 participants** (note: only 16 trials [n=26,567 participants] were identified in a 2022 systematic review(43)). The characteristics of included studies are reported in Supplemental Appendix 4. An individual participant data meta-analysis of 3 large, outcome-driven primary prevention trials (n=18,162 participants) has also been reported by the Polypill Trialists' Collaboration(6), including PolyIran(41), TIPS-3(42), and HOPE-3(48). The risk of bias across the included trials was low (Supplemental Appendix 5).

<u>Primary prevention</u>

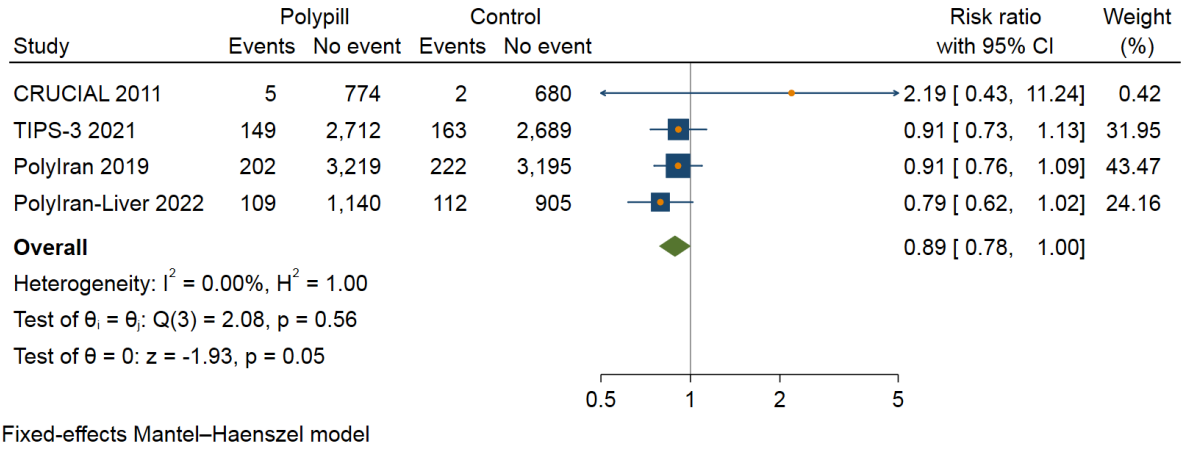
For high-risk primary prevention, there is **high-quality evidence** that fixed-dose combination therapy **reduces the risk of fatal and nonfatal major adverse cardiovascular events by 29%** (6.1% versus 8.4%, RR=0.71, 95% CI: 0.63, 0.79, I^2=0%) based on the study level meta-analysis (Figure 3).

Figure 3. Forest plot of the effect of fixed-dose combination therapy on **major cardiovascular events** in primary prevention**.**



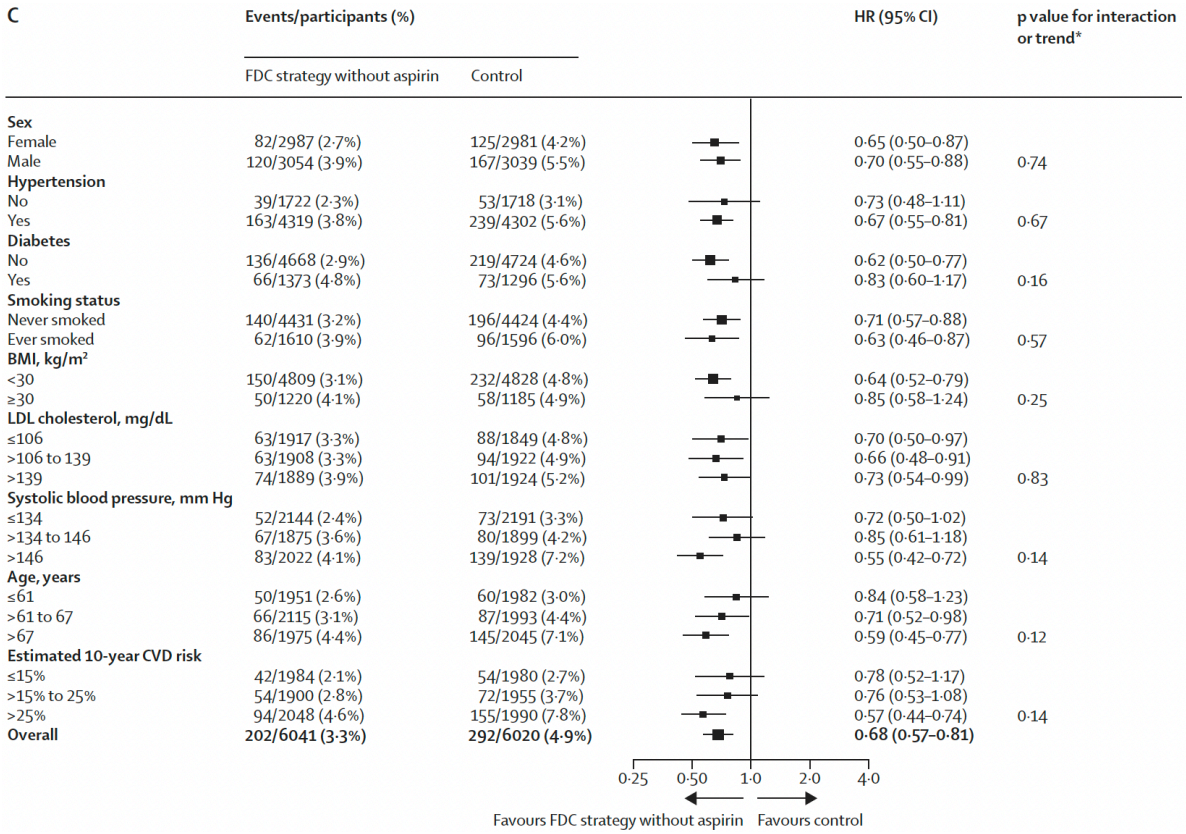
There is also **high-quality evidence** that fixed-dose combination therapy **reduces the risk of all-cause mortality by 11%** (5.6% versus 6.3%, RR=0.89, 95% CI: 0.78, 1.00, I^2=0%) based on the study level meta-analysis (Figure 4).

Figure 4. Forest plot of the effect of fixed-dose combination therapy on **all-cause mortality** in primary prevention**.**



These results are further corroborated with individual participant data meta-analysis conducted by the Polypill Trialists' Collaboration, which demonstrated an overall 38% reduction in the risk of cardiovascular death, myocardial infarction, stroke, or arterial revascularization (3.0% versus 4.9%, HR=0.62, 95% CI: 0.53, 0.73).(6) Results were similar for fixed-dose combinations that did not include aspirin (3.3% versus 4.9%, HR=0.68, 95% CI: 0.57, 0.81), with no evidence of heterogeneity across tertiles of baseline predicted risk levels or other characteristics (Figure 5).

Figure 5. Forest plot of the effect of fixed-dose combination therapy on **major cardiovascular events** in primary prevention across pre-specified subgroups in the Polypill Trialists' Collaboration.



A separate analysis of fixed-dose combination of blood pressure lowering + statins + aspirin versus placebo indicates a nearly 50% relative risk reduction in cardiovascular disease events (HR = 0.53 [95% CI: 0.41, 0.67]).(6)

Fixed dose combination therapy led to reduction in risk factors, including a weighted mean difference of -8.08 mmHg (95% CI: -10.83, -5.34) in systolic blood pressure (Figure 6) and -1.06 mmol/L (95% CI: -1.36, -0.76) in LDL cholesterol (Figure 7). These study-level meta-analytic estimates have substantial heterogeneity, but have a similar direction and magnitude of effect to estimates from an individual participant data meta-analysis of large polypill trials by the Polypill Trialists' Collaboration (mean [95% CI] difference in systolic blood pressure: -4.7 mmHg [-4.2, -5.2] and LDL cholesterol: -0.59 mmol/L [-0.55, -0.62], Figure 8). Thus, there is **high quality evidence that fixed-dose combinations reduce systolic blood pressure and LDL cholesterol** compared to high quality usual care or placebo. Expected benefits in a general population context may be even greater given the very low baseline treatment rates as reported in Sections 1 and 6.

Figure 6. Forest plot of the effect of fixed-dose combination therapy on **systolic blood pressure (mm Hg)** in primary prevention.

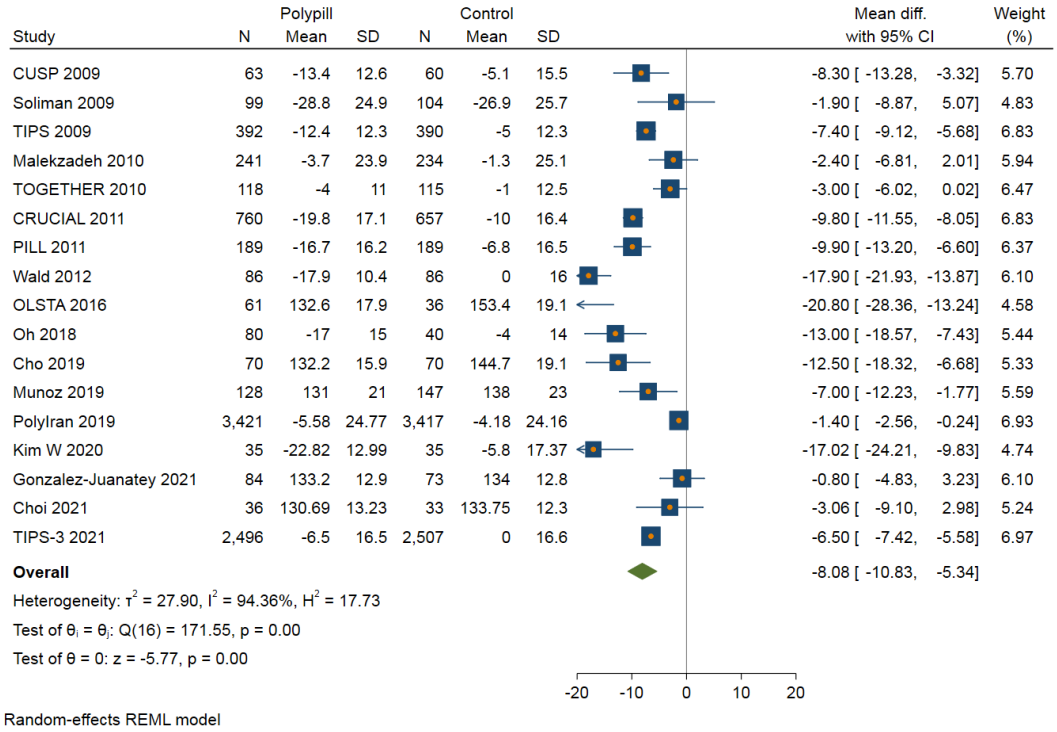


Figure 7. Forest plot of the effect of fixed-dose combination therapy on **LDL cholesterol (mmol/L)** in primary prevention.

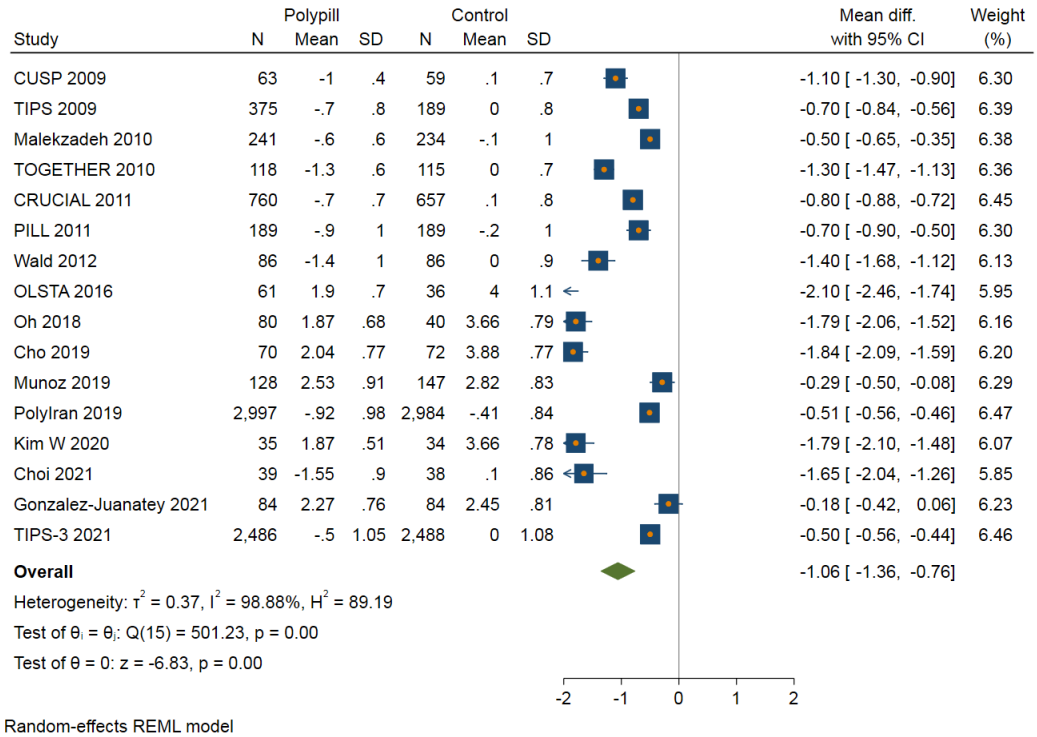


Figure 8. Effect of fixed-dose combination therapy on **SBP** and **LDL cholesterol** in primary prevention in trials reported by the Polypill Trialists' Collaboration.

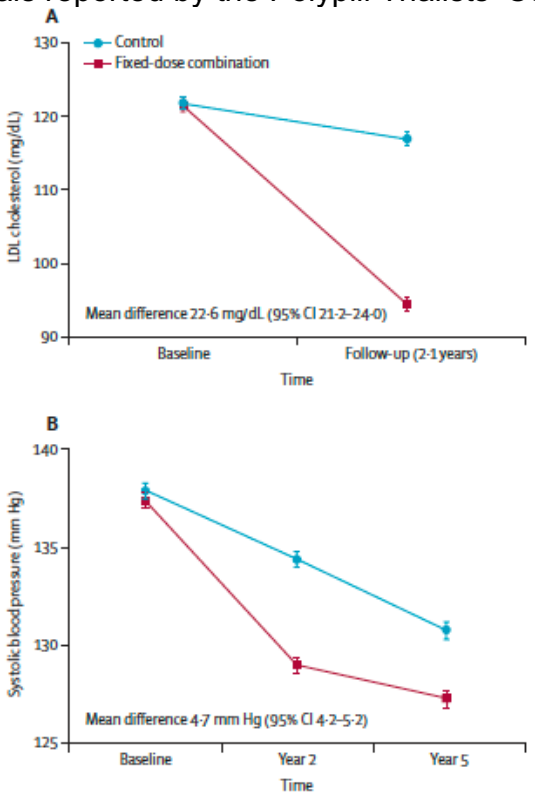


Figure 1: **Changes in LDL cholesterol (A) and systolic blood pressure (B) with a fixed dose combination treatment strategy compared to control**
Data are presented for participants with complete data on LDL cholesterol (n=10 867) and systolic blood pressure (n=16 366) at the reported timepoints. The follow-up for LDL cholesterol was reported at a mean of 2·1 years across trials. Mean difference in LDL of 22·6 mg/dL corresponds to 0·58 mmol/L. Systolic blood pressure was 5·4 mm Hg lower in the fixed-dose combination strategy group at 2 years and 3·5 mm Hg lower at 5 years.

<u>Exclusively secondary prevention population</u>

For secondary prevention, the SECURE trial (n=2499 participants) is the only adequately powered clinical trial to evaluate the effect of fixed-dose combination therapy on cardiovascular outcomes.(25) The SECURE trial demonstrated a 24% lower risk of the composite of cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization (9.5% versus 12.7%, HR=0.76, 95% CI, 0.60, 0.96) using the fixed-dose combinations of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg) compared with high quality usual care. Reductions in cardiovascular disease events were likely due to improvements in adherence, which were higher in the fixed-dose combination therapy group (74.1% versus 63.2% at 24 months, RR=1.17; 95% CI, 1.10, 1.25). In the PolyIran trial, 737 participants had cardiovascular disease at baseline, and among this subgroup, fixed-dose combination therapy reduced the rate of major adverse cardiovascular events by a similar direction and magnitude of effect to the primary trial results, with no evidence of an interaction based on baseline disease status (adjusted HR=0.80, 95% CI: 0.57, 1.12, $p_{interaction}$=0.19). Thus, there is **high-quality evidence that fixed-dose combinations reduces the risk of major adverse cardiovascular events in exclusively secondary prevention populations.**

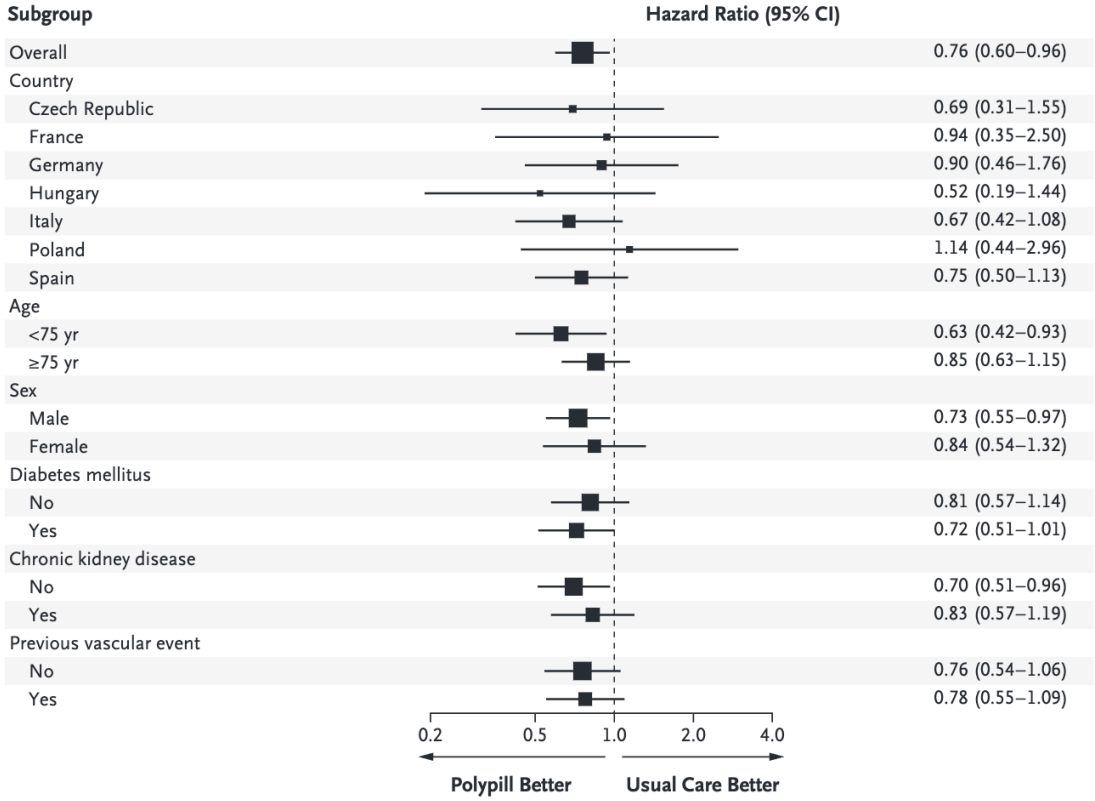
Mixed primary and secondary prevention trial populations

Inclusion of other trials with at least 15% of participants with prevalent cardiovascular disease (including SECURE) shows substantial heterogeneity with results likely being driven by a small number of events from trials that were not designed to evaluate the effect of fixed-dose combination therapy on clinical outcomes (Supplemental Appendix 6). Thus, these results do not seem to be reliable and estimates for secondary prevention should be derived from exclusively secondary prevention populations reported in SECURE and PolyIran.

8.3 Assessment of applicability of the available evidence across diverse populations and settings

Beyond use of the individual drug classes for decades all around the world, trials of fixed-dose combination therapy for prevention and control of atherosclerotic cardiovascular disease have been conducted in >30 countries across a range of WHO regions and categories based on factors such as per capita income (Supplemental Appendix 4).(26) The combination of aspirin + ramipril + atorvastatin has also been demonstrated to be feasibly implemented and acceptable in patients with prevalent cardiovascular disease in a humanitarian setting in Lebanon(19), bolstering the case for its use. Data from the SECURE trial show that there is no evidence of heterogeneity of effect based on country (Figure 9).(25) The HOPE-4 cluster randomized trial (n=30 clusters, n=1371 participants) also showed the feasibility, effectiveness, and safety of delivering the combination of angiotensin receptor blocker + statin in patients without prior cardiovascular disease through non-physician health workers in Colombia and Malaysia.(18) These health workers were supported by computer-based simplified management algorithms, and the study intervention showed a 43% relative risk reduction in predicted risk (-6.4% (95% CI: -8.0, -4.8) in the control group and -11.2% (95% CI: -12.9, -9.5) in the intervention group driven by 11.5 mm Hg (95% CI: -14.9, -8.0) greater reduction in systolic blood pressure, and a 0.41 mmol/L (95% CI: -0.6, -0.2) reduction in LDL.

Figure 9. Forest plot of the effect of fixed-dose combination therapy on major adverse cardiovascular events among pre-specified subgroups in the SECURE trial, including by participant's country.(25)



A subgroup analysis from a 2022 systematic review demonstrated lower rates of major adverse cardiovascular events in groups randomized to fixed-dose combination therapy in low- and middle-income countries (RR=0.67 [95% CI: 0.56, 0.79]) compared with high-income countries (RR=1.04 [95% CI: 0.69, 1.58]), likely demonstrating the influence of the comparator group's background treatment rate.(43)

Fixed dose combination therapy in mixed primary and secondary prevention led to reduction in risk factors, including a weighted mean difference of -1.23 mm Hg (95% CI: -2.10, -0.36) in systolic blood pressure (Figure 10) and 0.02 mmol/L (95% CI: -0.06, 0.03) in LDL cholesterol (Figure 11). The difference in systolic blood pressure has no statistical heterogeneity so is considered **high quality evidence** against a well-treated comparison group. The estimate for LDL cholesterol has moderate heterogeneity, and thus the data supporting this risk factor difference is **moderate quality** compared to high quality usual care. Expected benefits in a general population context would be greater given the very low baseline treatment rates as reported in Sections 1 and 6.

Figure 10. Forest plot of the effect of fixed-dose combination therapy on **systolic blood pressure** in mixed primary and secondary prevention.

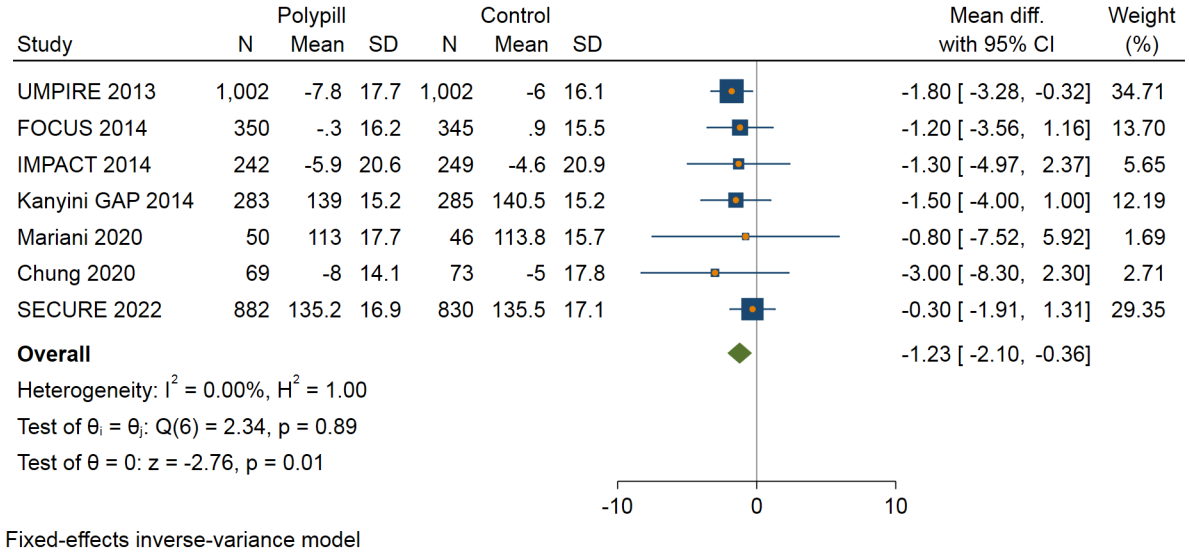
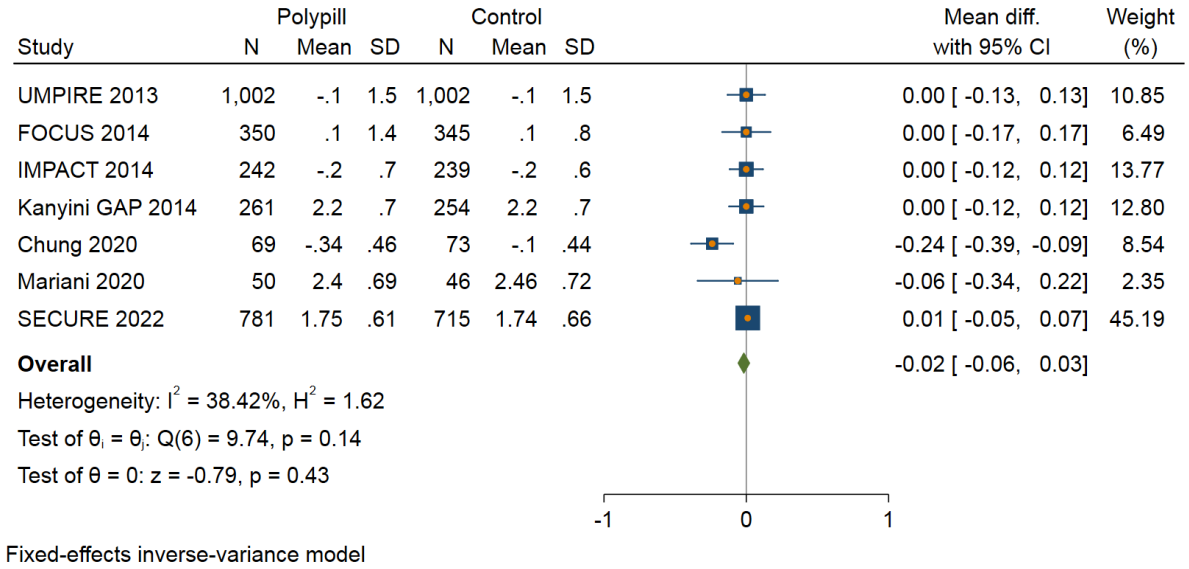


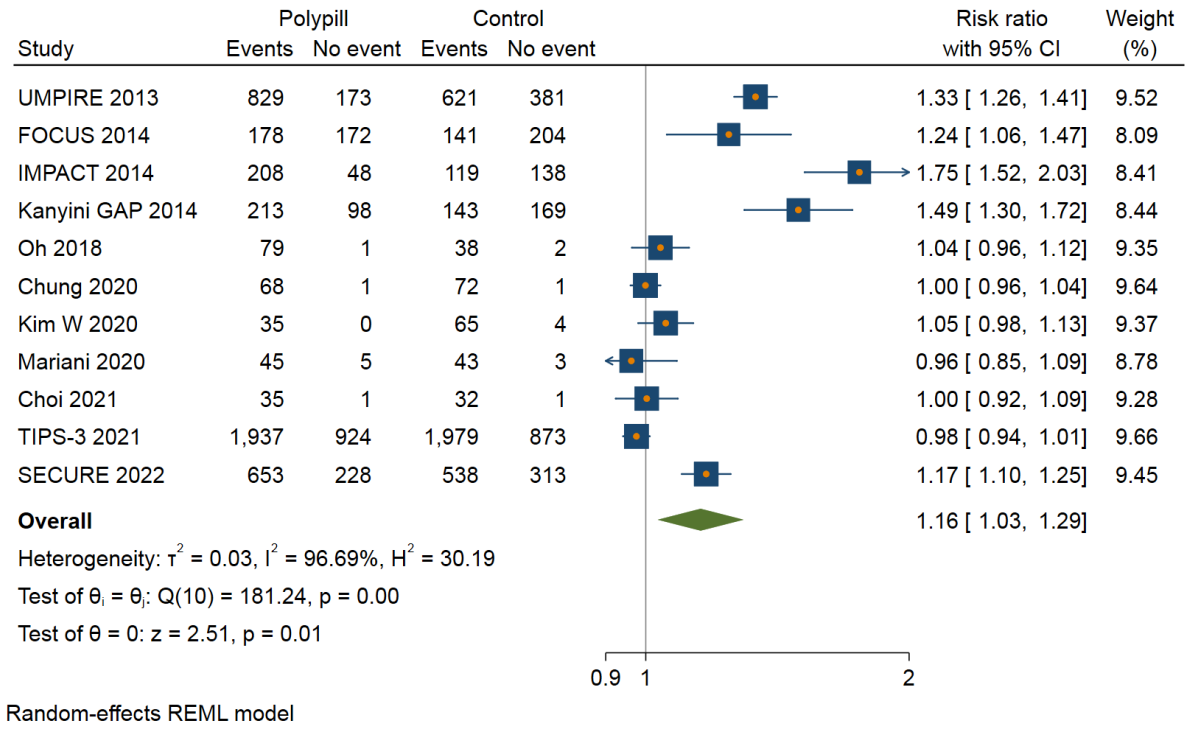
Figure 11. Forest plot of the effect of fixed-dose combination therapy on **LDL cholesterol** in mixed primary and secondary prevention.



Subgroup and additional secondary analyses

Results were similar across pre-specified subgroups, including large trials (n>500 participants), 3+ drugs, and usual care (Supplemental Appendix 6). There were no differences in health-related quality of life (n=3 trials, n=2,109 participants, Supplemental Appendix 7). Adherence rates were reported in 11 trials and were higher among patients randomized to fixed-dose combination therapy (RR=1.16, 95% CI: 1.03, 1.29, I^2=97%, Figure 12), though there was substantial heterogeneity for this outcome, which has inherent limitations to assess the true effect on adherence, especially among an unselected population rather than among clinical trial participants who typically have higher adherence rates than the general population. Expected benefits in a general population context may be ***even greater*** given the very low baseline treatment rates as reported in Sections 1 and 6.

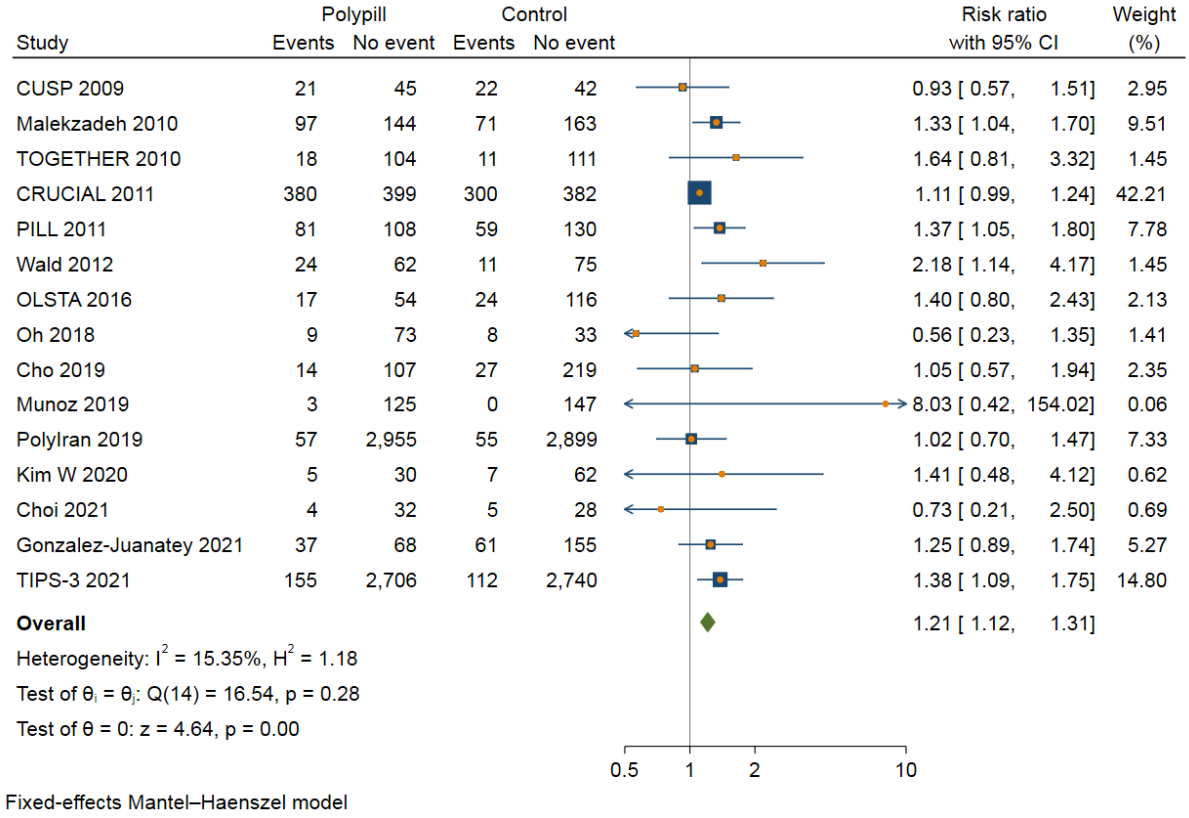
Figure 12. Forest plot of the effect of fixed-dose combination therapy on **adherence** rates.



9. Review of harms and toxicity: summary of evidence of comparative safety

The main mechanism of effect of fixed-dose combinations is to increase adherence, so expectedly, because of increased exposure to the included drugs, fixed-dose combinations **increase the risk of adverse events by 21%** (11.6% versus 9.6%, RR = 1.21 95% CI: 1.12, 1.31, I^2=15%, high-quality evidence) in primary prevention trials (Figure 13). There was no evidence of funnel plot asymmetry (Supplemental Appendix 8).

Figure 13. Forest plot of the effect of fixed-dose combination therapy on **any adverse events** in primary prevention trials.



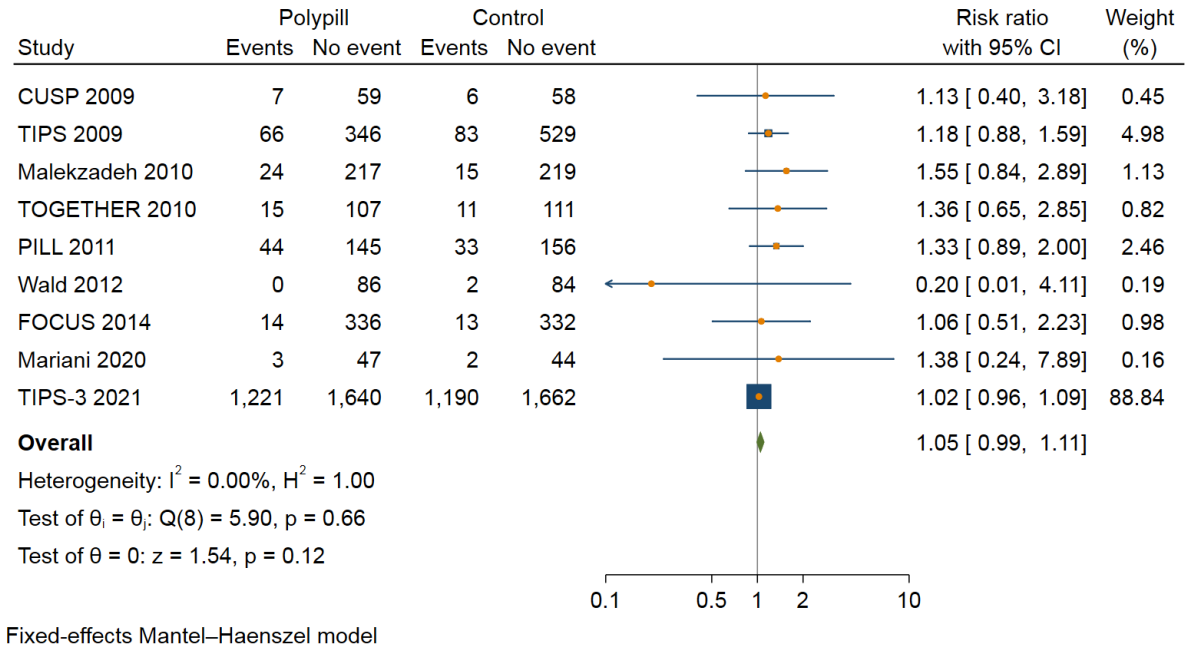
Importantly, most adverse events were mild and reversible, such as dizziness or muscle aches, as well as consistent with increased exposure to the included drugs, which are currently included in the WHO Model List of Essential Medicines. These data are corroborated by the individual participant data meta-analysis, which was restricted to patients with a primary prevention indication (Table 2). Data from the largest secondary prevention trial (SECURE(25)), show no difference in adverse events between the fixed-dose combination therapy and usual care groups.

Table 2. Adverse events in Polypill Trialists' Collaboration individual participant data meta-analysis.(6)

	Control	Fixed-dose combination strategy	p value
Effects potentially related to statin or blood pressure lowering medication			
Participants included in analysis	9088	9074	..
Muscle pain	787 (8·7%)	634 (7·0%)	<0·0001
Dizziness	834 (9·2%)	1060 (11·7%)	<0·0001
Death due to renal cause	7 (0·1%)	5 (0·1%)	0·77
Reported non-fatal renal failure or death due to renal cause	41 (0·5%)	44 (0·5%)	0·75

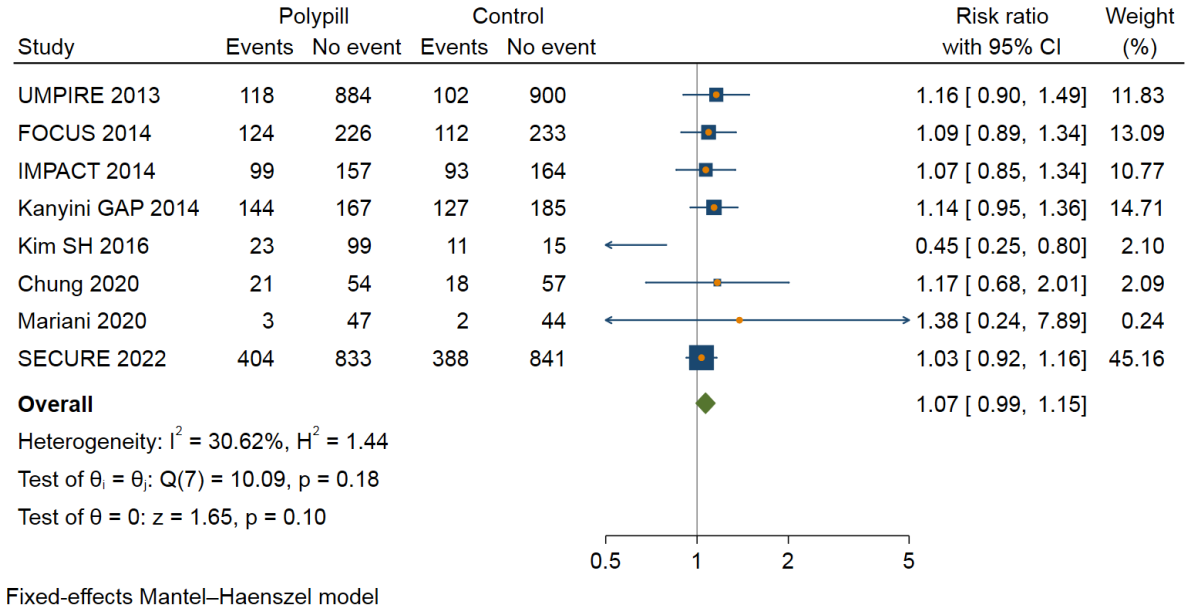
Discontinuation rates were similar between groups among the 9 trials that reported this information (RR=1.05%, 95% CI: 0.99, 1.11, I^2=0%, Figure 14).

Figure 14. Forest plot of the effect of fixed-dose combination therapy on **discontinuation rates**.



For secondary prevention trials, there is **moderate quality evidence** that fixed-dose combinations **increases the risk of adverse events by 7%** (27.5% versus 25.9%, RR = 1.07 95% CI: 0.99, 1.15, I^2=30%, Figure 15). The quality of evidence is downgraded due to heterogeneity and thus the true effect may be primarily determined by the treatment rate in the comparator group.

Figure 15. Forest plot of the effect of fixed-dose combination therapy on **adverse events** in secondary prevention trials.



10. Summary of available data on comparative cost and cost-effectiveness

10.1 Price and affordability

For this application, we invited Emerging Leaders from the World Heart Federation Salim Yusuf Emerging Leaders Programme from 12 countries (based on interest and capacity) to collect primary data on market authorisation and retail price of fixed dose combinations in their home countries. The Emerging Leaders are a network of early career researchers and practitioners with demonstrated commitment to reducing mortality and morbidity from cardiovascular disease globally. Countries included: Bangladesh, India, Nepal, Iraq, Nigeria, Cameroon, Mauritius, Sweden, Spain, Argentina, Colombia, and Mexico. Emerging Leaders responded to a survey asking whether any polypills were authorised for marketing in their countries, and if so, whether they could be found in the nearest large public and private pharmacies to their place of residence and their cost. We combined these data with other country-level data on availability, cost, and market authorization. (Market authorization is discussed in Section 11 below.)

Fixed dose combinations were stocked by private pharmacies visited in four included countries: Spain, Mauritius, India, and Argentina. No public pharmacies visited stocked any combination for primary or secondary prevention of cardiovascular disease. The type of combinations available in private pharmacies, their price (in USD) and affordability are shown in Table 3. Affordability was defined using the WHO/Health Action International standards, according to which a drug is "affordable" if the cost of one month's supply is lower than the lowest daily wage of a government worker in that area. Most combinations found in this survey were affordable in the local context.

Table 3. Affordability of fixed dose combinations stocked in private pharmacies in four countries.

Country	Type	Brand	Marketed by	Price/ tab (USD)	Cost for 1 month supply (USD)	Minimum Daily wage (USD)	Number of days' wages
Proposed formulations							
Spain	Aspirin + Atorvastatin + Ramipril	Trinomia	Ferrer	0.74	22.20	32.66	0.68
India	Aspirin + Atorvastatin + Ramipril	Ramitorva	Zydus Lifesciences	0.04	1.26	5.41	0.23
India	Aspirin + Simvastatin + Ramipril + Atenolol + Hydrochlorothiazide	Polycap	Cadila	0.34	10.14	5.41	1.87
Alternative formulations							
Mauritius	Atorvastatin + Perindopril Arginine + Amlodipine	Triveram	Servier	0.88	26.46	9.52	2.78
India	Metoprolol + Atorvastatin + Ramipril	Lifepill 3 Metpure	Zydus Lifesciences Emcure	0.13	4.04	5.41	0.75
India	Aspirin + Atorvastatin + Ramipril +	CV Pill Lifepill 4	Torrent	0.12	3.60	5.41	0.67

	Metoprolol	Zycad	Zydus Lifesciences Zydus Lifesciences				
India	Losartan + Atorvastatin + Aspirin + Atenolol	Starpill	Cipla	0.17	5.22	5.41	0.96
Argentina	Rosuvastatin + Candesartan + Hydrochlorothiazide	Polilep	Lepetit	0.31	9.30	7.64	1.21

10.2 Cost-effectiveness

Primary prevention

The cost-effectiveness of fixed-dose combinations as a primary prevention strategy was examined in the 2020 systematic review by Jahangiri et al (30). The review identified 14 studies that evaluated cost-effectiveness for primary prevention. The study populations varied but, in general, included healthy adults aged 30 years or older with high risk of cardiovascular disease without a history of cardiovascular events. Fixed-dose combinations in all 14 studies contained at least one statin and two blood pressure lowering drugs, and aspirin was included in 7 studies. Twelve of the 14 studies had “no therapy” as the comparator, and 7 studies focused on cost-effectiveness. Fixed-dose combination was cost-effective in 5 studies(49–53), of which it was dominant in 2 studies. In the study by Ferket et al.(51), fixed-dose combination therapy was not cost-effective in one of the five scenarios, while being totally dominant in the other four. It was not cost-effective in the study by Zomer et al.(54) Price was the key determinant of cost-effectiveness, followed by the effect of age and risk for cardiovascular disease.

A 2021 economic analysis based on The International Polycap Study 3 (TIPS-3) trial reported the regional variations in cost implications of fixed-dose combinations as a primary prevention strategy.(12) Fixed-dose combinations contained statins and multiple blood-pressure lowering drugs with or without aspirin. Over the 4.6 years of the trial, the use of fixed-dose combinations was associated with a higher mean total cost per patient in lower-middle- and upper-middle-income countries but was cost neutral in high-income countries (dominant strategy). The difference in costs per patient between fixed-dose combinations and placebo over the trial period was USD$291 in lower-middle-income countries, USD$1068 in upper-middle-income countries, and USD$48 in high-income countries, with similar findings for combinations with aspirin (compared with a double placebo). These results were partly driven by higher drug costs in low- and middle-income countries and the lower costs of procedures or hospitalizations for myocardial infarction or stroke, which also can be reduced by fixed-dose combination therapy. Nevertheless, when estimated using monthly household capacity to pay or a threshold of 4% of the gross national income per capita, fixed-dose combination therapy was affordable in all groups.

Secondary prevention

A systematic review studies conducting a full economic evaluation of fixed-dose combination therapy containing aspirin, statin, and at least 1 blood pressure lowering drug for atherosclerotic cardiovascular disease secondary prevention was conducted in 2020 by Jahangiri et al.(10) The review found 12 studies that focused on combinations for secondary prevention of CVD. The study populations included

adults aged 30 years and older with at least one non-fatal coronary heart disease event and indication for secondary prevention treatment. In six studies, fixed-dose combination therapy was cost-effective(55–59), in four studies, it was dominant, meaning it was both clinically superior and cost-saving. Only one study concluded that it was not cost-effective, but could possibly become cost-effective, and potentially cost-saving, if its price was reduced to less than $100 USD per month.(60) Price was the leading determinant of cost-effectiveness.

A 2021 abstract reported a cost-effectiveness analysis of the proposed fixed-dose combination of aspirin, atorvastatin, and ramipril used in a secondary prevention population in Portugal using a Markov model.(61) The study reported an incremental cost effectiveness ratio of €5,130/life year gained for the overall population, €5,768/life year gained for women and €4,884/life year gained for men. The incremental cost-utility ratio was €5,332/quality-adjusted life year (QALY) gained in total, €5,817/QALY gained for women and €5,137/QALY gained for men. If a willingness-to-pay threshold of €30,000/QALY gained was assumed, the there was an estimated likelihood of 76.1% that the combination was cost-effective and 27.8% that it was cost saving compared to usual care. All of these estimates are consistent with therapies considered an “effective intervention” or a “best buy” according to thresholds set by the WHO.

11. Regulatory status, market availability, and pharmacopeial standards

11.1 and 11.2 Regulatory status and marketing availability of the proposed medicine(s)

Primary prevention

The proposed formulation of acetylsalicylic acid 100 mg, simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg is manufactured by Cadila, India and is authorized for marketing for primary prevention under the name Polycap in India and Zambia.

An additional proposed formulation is the fixed-dose combination of atorvastatin (20/40mg), perindopril (5/10), and amlodipine (5/10) is manufactured by Servier Laboratories, France, and is authorized for marketing for primary prevention under the names Triveram and Lipertance in **51 countries**: Armenia, Belgium, Bulgaria, Cambodia, Antigua and Barbuda, Bahamas, Barbados, Cuba, Dominica, Dominican Republic, Grenada, Haiti, Jamaica, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Trinidad and Tobago, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Croatia, Chechia, Estonia, Finland, France, Germany, Ghana, Greece, Ireland, Italy, Ivory Coast, Kazakhstan, Latvia, Lithuania, Luxembourg, Madagascar, Mauritius, Myanmar, Paraguay, Philippines, Poland, Portugal, Russia, Slovakia, Slovenia, Switzerland, Vietnam. This combination is proposed based on its widespread marketing authorization and availability, recognizing that a large portion of the data supporting this application for primary prevention are derived from the aforementioned combination of .

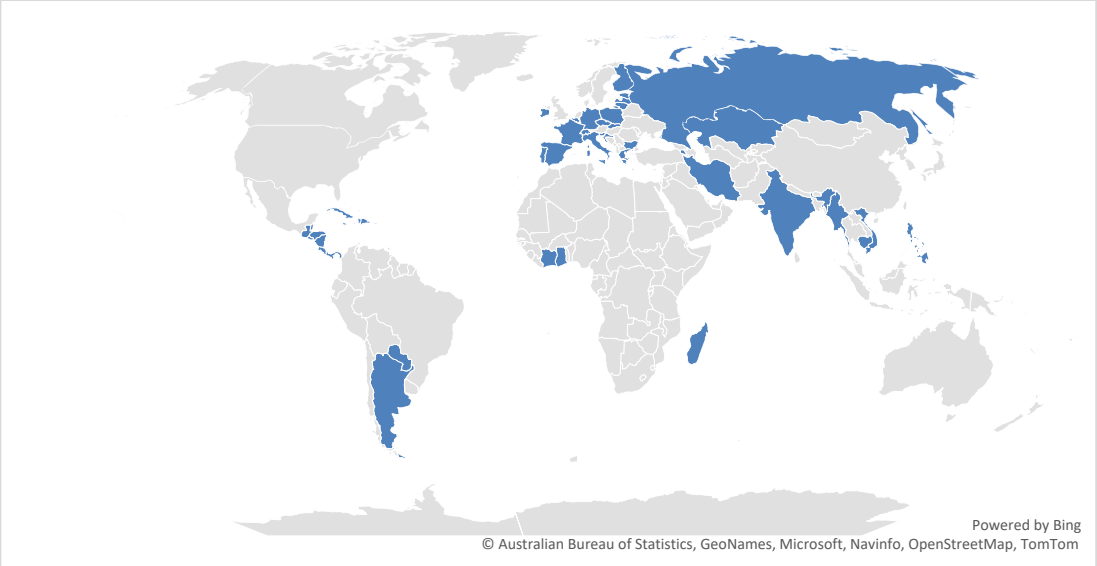
Secondary prevention

The proposed formulation of acetylsalicylic acid, atorvastatin, ramipril is manufactured by Ferrer Internacional, S.A. of Spain and is authorized for marketing for secondary prevention under the names CNIC Polypill, Trinomia, Sincronium, and Iltria in **26 countries** worldwide – Mexico, Chile, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras; Austria, Belgium, Germany, Greece, Ireland, Portugal, Serbia, Spain; Armenia, Belarus, Bosnia-Herzegovina, Georgia, Jordan,

Kazakhstan, Kosovo, Moldova, Montenegro, Ukraine, and Uzbekistan, with plans to launch in Lebanon.

It is also manufactured by Zydus Lifesciences, India under the name Ramitorva and is authorized for marketing in India. The map (Figure 16) shows countries where at least one fixed-dose combination for atherosclerotic cardiovascular disease prevention and control has received marketing authorization (blue). Countries in grey indicate those where data are not available.

Figure 16. Countries where at least one fixed-dose combination has received marketing authorization (blue).



11.2 Pharmacopeial standards

Each of the drug substances listed in Section 4 has a monograph in both European and United States Pharmacopoeias.

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Supplemental Appendices.

Supplemental Appendix 1. WHO preventive medication and lifestyle advice recommendations for people who have had a previous cardiovascular disease event.

Blood pressure-lowering therapy	"BP reduction should be considered in all patients with established CHD, particularly with BP >140/90 mm Hg. Lifestyle factors (particularly high alcohol intake) should be addressed first and if BP is still above 140/90 mm Hg, drug treatment indicated. When beta-blockers and ACE inhibitors cannot be given, or in cases where BP remains high, treatment with a thiazide diuretic is likely to reduce risk of recurrent vascular events. A target BP of 130/80-85 mm Hg is appropriate" "ACE inhibitors are recommended in all patients following myocardial infarction" "Treatment with beta-blockers is recommended in all patients with a history of myocardial infarction and those with CHD who have developed major left ventricular dysfunction leading to heart failure" "BP reduction should be considered in all patients with previous TIA or stroke to a target of <130/<80-85 mm Hg"
Statins	"Treatment with statins is recommended for all patients with established CHD. Treatment should be continued in the long term, probably lifelong. Patients at high baseline risk are particularly likely to benefit." "Treatment with a statin should be considered for all patients with established CeVD, especially if they also have evidence of established CHD."
Aspirin	"All patients with established CHD should be treated with regular aspirin in the absence of clear contraindications. Treatment should be initiated early and continued lifelong" "All patients with a history of TIA or stroke presumed due to cerebral ischaemia or infarction should be treated with long-term (probably lifelong) aspirin in the absence of clear contraindications"
Tobacco smoking	• Strong encouragement and support to stop smoking by a health professional • Advise to stop other forms of tobacco use • Offer nicotine replacement therapy to those who smoke ≥10 cigarettes/day • Advise non-smokers to avoid exposure to second-hand tobacco smoke as much as possible
Unhealthy diet	• Reduce total fat intake to <30% and saturated fat to <10% of calories • Eliminate / reduce intake of trans-fatty acids as much as possible

	• Most dietary fat should be polyunsaturated (up to 10% of calories) or monounsaturated (10-15% of calories) • Reduce daily salt intake by at least one-third, and if possible, to <5 g or <90 mmol /day • Encouragement to eat at least 400g a day of a range of fruits and vegetables, as well as whole grains and pulses
Physical inactivity	• Regular light-to-moderate intensity physical activity • Offer supervised exercise programmes where feasible
Overweight / obesity	• Advise weight loss through the combination of a reduced energy diet and increased physical activity
>3 units of alcohol/ day	• Advise to reduce alcohol consumption

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

CVD event defined as angina, myocardial infarction, stroke, transient ischaemic attack, peripheral vascular disease, coronary revascularization or carotid endarterectomy

Source: World Health Organization. Prevention of cardiovascular disease. Pocket guidelines for assessment and management of cardiovascular risk. Geneva: World Health Organization, 2007.

Supplemental Appendix 2: Search documentation details.

Database Search Overview (Initial search 12/04/2020)

Database searched	Date Searched	Results
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to December 03, 2020	12/04/2020	1220
Cochrane Database of Systematic Reviews Issue 12 of 12, December 2020 (Wiley)	12/04/2020	23
Cochrane Central Register of Controlled Trials Issue 12 of 12, December 2020 (Wiley)	12/04/2020	941
EMBASE (Elsevier)	12/04/2020	4050
CINAHL Plus with Full Text (EBSCOhost)	12/04/2020	353
Web of Science (Thomson Reuters)	12/04/2020	504
Total		**7089**
Total after deduplication		**5881**

Database Search Overview (Updated search 4/4/2022)

Database	Searched	Results
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to April 04, 2022	4/4/2022	719
Cochrane Database of Systematic Reviews Issue 4 of 12, April 2022 (Wiley)	4/4/2022	6
Cochrane Central Register of Controlled Trials Issue 3 of 12, March 2022 (Wiley)	4/4/2022	84
EMBASE (Elsevier)	4/4/2022	1585
CINAHL Plus with Full Text (EBSCOhost)	4/4/2022	53
Web of Science (Thomson Reuters)	4/4/2022	393
Total		2840
Total after deduplication		2826

Link to results on ClinicalTrials.gov (Last searched 11-25-2020)
https://clinicaltrials.gov/ct2/results?cond=cardiovascular+OR+hypertension+OR+dyslipidemia+OR+hyperlipidemia+OR+hypercholesterolemia&term=polypill+OR+%22fixed+dose%22+OR+%22drug+combination%22+OR+%22drug+combinations%22&type=Intr&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=

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

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 3, 2022
Search Strategy:

#	Searches	Results
1	exp Cardiovascular Diseases/	2416196

2	(cardio* or cardia* or heart* or coronary* or angina* or ventric* or myocard* or pericard* or isch?em* or emboli* or arrhythmi* or thrombo* or "atrial fibrillat*" or tachycardi* or endocardi* or ASCVD).tw.	2698876
3	(sick adj sinus).tw.	2299
4	exp Stroke/	138391
5	(stroke or stokes or cerebrovasc* or "cerebral vascular" or apoplexy).tw.	309809
6	(brain adj2 accident*).tw.	172
7	((brain* or cerebral or lacunar) adj2 infarct*).tw.	27066
8	exp Hypertension/	256918
9	(hypertensi* or "peripheral arter* disease*").tw.	450730
10	((high or increased or elevated) adj2 "blood pressure").tw.	33963
11	exp Hyperlipidemias/	66549
12	(hyperlipid* or hyperlip?emia* or hypercholesterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*).tw.	79035
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	3904461
14	Drug Combinations/	73815
15	(polypill* or policap or polycap or quintapill or single-pill* or single-tablet* or "combination pill*" or "combination tablet*" or "red heart pill*").tw.	2656
16	((multi* or several) adj2 (ingredient* or component*)).tw.	23659
17	(single adj2 (pill* or tablet*) adj2 comb*).tw.	387
18	14 or 15 or 16 or 17	98924
19	13 and 18	14045
20	(randomized controlled trial or controlled clinical trial).pt.	607392
21	(randomi?ed or placebo or trial or groups or randomly).ab.	2945622
22	drug therapy.fs.	2256741
23	20 or 21 or 22	4871464
24	exp animals/ not humans.sh.	4762182
25	23 not 24	4233545
26	19 and 25	7463
27	limit 26 to yr="2016 -Current"	1220

The Cochrane Library
ID Search Hits
#1 MeSH descriptor: [Cardiovascular Diseases] explode all trees 107983
#2 (cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard* OR pericard* OR isch?em* OR emboli* OR arrhythmi* OR thrombo* OR "atrial fibrillat*" OR tachycardi* OR endocardi* OR ASCVD):ti,ab,kw 302742
#3 sick NEAR sinus 358
#4 MeSH descriptor: [Stroke] explode all trees 9883
#5 (stroke OR stokes OR cerebrovasc* OR "cerebral vascular" OR apoplexy):ti,ab,kw 63466
#6 (brain NEAR/2 accident*):ti,ab,kw 182
#7 ((brain* OR cerebral OR lacunar) NEAR/2 infarct*):ti,ab,kw 4935
#8 MeSH descriptor: [Hypertension] explode all trees 18032
#9 (hypertensi* OR "peripheral arter* disease*"):ti,ab,kw 64837
#10 ((high OR increased OR elevated) NEAR/2 "blood pressure"):ti,ab,kw 5434
#11 MeSH descriptor: [Hyperlipidemias] explode all trees 6414
#12 (hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*):ti,ab,kw15487

#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 382959
#14 MeSH descriptor: [Drug Combinations] this term only 11534
#15 (polypill* OR policap OR polycap OR quintapill OR single-pill* OR single-tablet* OR "combination pill*" OR "combination tablet*" OR "red heart pill*"):ti,ab,kw 1409
#16 ((multi* OR several) NEAR/2 (ingredient* OR component*)):ti,ab,kw 2119
#17 (single NEAR/2 (pill* OR tablet*) NEAR/2 comb*):ti,ab,kw 213
#18 #14 OR #15 OR #16 OR #17 14754
#19 #13 AND #18 3212
#20 #19 with Cochrane Library publication date Between Jan 2016 and Dec 2020 964

Embase

No. Query	Results
#22 **#21** AND [2016-2021]/py	**4,050**
#21 **#19** AND **#20**	**7,453**
#20 **'crossover procedure'**:de OR **'double-blind procedure'**:de OR **'randomized controlled trial'**:de OR **'single-blind procedure'**:de OR **random***:de,ab,ti OR **factorial***:de,ab,ti OR **crossover***:de,ab,ti OR ((**cross** NEXT/1 **over***):de,ab,ti) OR **placebo***:de,ab,ti OR ((**doubl*** NEAR/1 **blind***):de,ab,ti) OR ((**singl*** NEAR/1 **blind***):de,ab,ti) OR **assign***:de,ab,ti OR **allocat***:de,ab,ti OR **volunteer***:de,ab,ti	**2,678,615**
#19 **#13** AND **#18**	**38,698**
#18 **#14** OR **#15** OR **#16** OR **#17**	**196,827**
#17 (**single** NEAR/2 (**pill*** OR **tablet***) NEAR/2 **comb***):ti,ab,kw	**675**
#16 ((**multi*** OR **several**) NEAR/2 (**ingredient*** OR **component***)):ti,ab,kw	**30,149**
#15 **polypill***:ti,ab,kw OR **policap**:ti,ab,kw OR **polycap**:ti,ab,kw OR **quintapill**:ti,ab,kw OR **'single pill*'**:ti,ab,kw OR **'single tablet*'**:ti,ab,kw OR **'combination pill*'**:ti,ab,kw OR **'combination tablet*'**:ti,ab,kw OR **'red heart pill*'**:ti,ab,kw	**4,304**
#14 **'drug combination'**/de	**163,151**
#13 **#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12**	**6,072,184**
#12	**105,269**

hyperlipid*:ti,ab,kw OR **hyperlip?emia***:ti,ab,kw OR **hypercholesterol***:ti,ab,kw OR **hypercholester?emia***:ti,ab,kw OR **hyperlipoprotein?emia***:ti,ab,kw OR **hypertriglycerid?emia***:ti,ab,kw

169,142

#11
'hyperlipidemia'/exp

51,413

#10
((**high** OR **increased** OR **elevated**) NEAR/2 **'blood pressure'**):ti,ab,kw

740,614

#9
hypertensi*:ti,ab,kw OR **'peripheral arter* disease*'**:ti,ab,kw

796,582

#8
'hypertension'/exp

42,746

#7
((**brain*** OR **cerebral** OR **lacunar**) NEAR/2 **infarct***):ti,ab,kw

273

#6
(**brain** NEAR/2 **accident***):ti,ab,kw

497,268

#5
stroke:ti,ab,kw OR **stokes**:ti,ab,kw OR **cerebrovasc***:ti,ab,kw OR **'cerebral vascular'**:ti,ab,kw OR **apoplexy**:ti,ab,kw

341,390

#4
'cerebrovascular accident'/exp

3,546

#3
(**sick** NEAR/1 **sinus**):ti,ab,kw

3,777,368

#2
cardio*:ti,ab,kw OR **cardia***:ti,ab,kw OR **heart***:ti,ab,kw OR **coronary***:ti,ab,kw OR **angina***:ti,ab,kw OR **ventric***:ti,ab,kw OR **myocard***:ti,ab,kw OR **pericard***:ti,ab,kw OR **isch?em***:ti,ab,kw OR **emboli***:ti,ab,kw OR **arrhythmi***:ti,ab,kw OR **thrombo***:ti,ab,kw OR **'atrial fibrillat*'**:ti,ab,kw OR **tachycardi***:ti,ab,kw OR **endocardi***:ti,ab,kw OR **ascvd**:ti,ab,kw

4,668,283

#1
'cardiovascular disease'/exp

EMBASE.com RCT filter from Cochrane:
Source: Lefebvre C, Eisinga A, McDonald S, Paul N. Enhancing access to reports of randomized trials published world-wide - the contribution of EMBASE records to the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. Emerging Themes in Epidemiology 2008; 5:13.

CINAHL Plus with Full Text

#	Query	Results
S22	S19 AND S20	353

	Limiters - Published Date: 20160101-20201231	
S21	S19 AND S20	1,165
S20	(MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (CONTROL W5 GROUP) OR MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES) OR AB (CLUSTER W3 RCT)) NOT ((MH ANIMALS+ NOT MH HUMAN) OR (MH (ANIMAL STUDIES) NOT MH (HUMAN)) OR (TI (ANIMAL MODEL) NOT MH (HUMAN)))	772,521
S19	(S14 OR S15 OR S16 OR S17) AND (S13 AND S18)	3,798
S18	S14 OR S15 OR S16 OR S17	18,760
S17	single N2 (pill* OR tablet*) N2 comb*	218
S16	(multi* OR several) N2 (ingredient* OR component*)	4,352
S15	polypill* OR policap OR polycap OR quintapill OR single-pill* OR single-tablet* OR "combination pill*" OR "combination tablet*" OR "red heart pill*"	951
S14	(MH "Drug Combinations")	13,888
S13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	961,624
S12	hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*	26,751
S11	(MH "Hyperlipidemia+")	21,063
S10	(high OR increased OR elevated) N2 "blood pressure"	9,756
S9	hypertensi* OR "peripheral arter* disease*"	123,973
S8	(MH "Hypertension+")	81,466
S7	(brain* OR cerebral OR lacunar) N2 infarct*	14,582
S6	brain N2 accident*	70
S5	stroke OR stokes OR cerebrovasc* OR "cerebral vascular" OR apoplexy	139,076
S4	(MH "Stroke+")	71,607
S3	sick N1 sinus	807
S2	cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard* OR pericard* OR	713,329

	isch?em* OR emboli* OR arrhythmi* OR thrombo* OR "atrial fibrillat*" OR tachycardi* OR endocardi* OR ASCVD	
S1	(MH "Cardiovascular Diseases+")	607,341

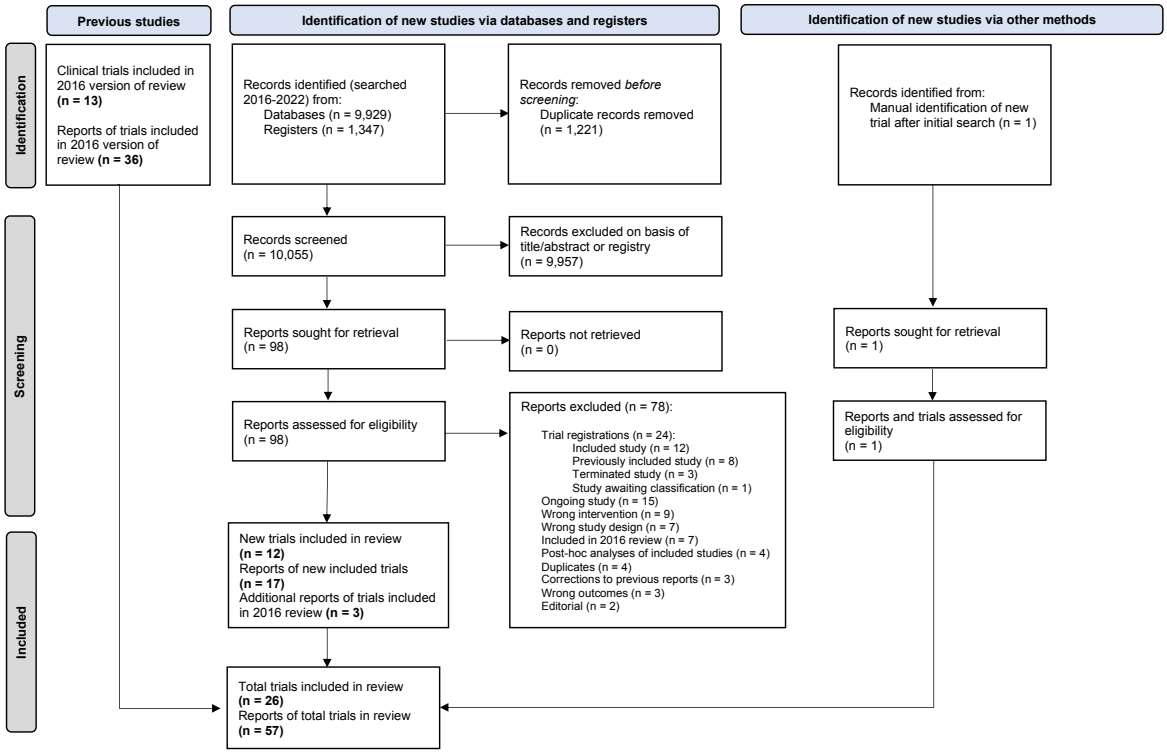
CINAHL RCT filter:
Glanville et al. See: Glanville J, Dooley G, Wisniewski S, Foxlee R, Noel-Storr A. Development of a search filter to identify reports of controlled clinical trials within CINAHL Plus. Health Information & Libraries Journal. 2019 Mar;36(1):73-90.

Web of Science

5 502
#4
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2016-2020
# 4 1,255
#3 AND #2 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 3 3,948,057
TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 2 74,590
TS=(polypill* OR policap OR polycap OR quintapill OR single-pill* OR single-tablet* OR "combination pill*" OR "combination tablet*" OR "red heart pill*") OR TS=((multi* OR several) NEAR/2 (ingredient* OR component*)) OR TS=(single NEAR/2 (pill* OR tablet*) NEAR/2 comb*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 1 3,772,086
TS=(cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard* OR pericard* OR isch?em* OR emboli* OR arrhythmi* OR thrombo* OR "atrial fibrillat*" OR tachycardi* OR endocardi* OR ASCVD) OR TS=(sick NEAR/1 sinus) OR TS=(stroke OR stokes OR cerebrovasc* OR "cerebral vascular" OR apoplexy) OR TS=(brain NEAR/2 accident*) OR TS=((brain* OR cerebral OR lacunar) NEAR/2 infarct*) OR TS=(hypertensi* OR "peripheral arter* disease*") OR TS=((high OR increased OR elevated) NEAR/2 "blood pressure") OR TS=(hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

RCT Filters used by Cochrane ENT
Retrieved from
https://ent.cochrane.org/sites/ent.cochrane.org/files/public/uploads/rct_filters.pdf on 4 December 2020

Supplemental Appendix 3. PRISMA flow diagram.



Supplemental Appendix 4. Characteristics of included studies.

Study/ Design	Participants (N)	Polypill Intervention	Comparator	Key Outcomes	Timing	Setting
CUSP 2009 Two-group RCT	N = 130 Primary prevention	1. Amlodipine 5 mg + atorvastatin 20 mg and counseling on diet, exercise, smoking cessation	Placebo and counseling on diet, exercise, smoking cessation	SBP, DBP LDL-C	8 weeks	United States
Soliman 2009 Two-group RCT	N = 216 Primary prevention	1. Aspirin 75 mg + simvastatin 20 mg + lisinopril 10 mg + hydrochlorothiazide 12.5 mg	Usual care	SBP Total cholesterol	3 months	Sri Lanka
TIPS 2009 Nine-group RCT	N = 2053 Primary prevention	1. Hydrochlorothiazide 12.5 mg + atenolol 50 mg + ramipril 5 mg + simvastatin 20 mg + aspirin 100 mg	1. Aspirin 100 mg 2. Hydrochlorothiazide 12.5 mg 3. Simvastatin 20 mg 4. Hydrochlorothiazide 12.5 mg + ramipril 5 mg 5. Hydrochlorothiazide 12.5 mg + atenolol 50 mg 6. Ramipril 5 mg + atenolol 50 mg 7. Hydrochlorothiazide 12.5 mg + ramipril 5 mg + atenolol 50 mg 8. Hydrochlorothiazide 12.5 mg + ramipril 5 mg + atenolol 50 mg + aspirin 100 mg	LDL-C SBP, DBP HR Urinary 11-dehydrothromboxane B2 Discontinuation	12 weeks	India
TOGETHER 2010 Two-group RCT	N = Primary prevention	1. Amlodipine 5 mg or 10 mg + atorvastatin 20 mg and therapeutic lifestyle changes	Amlodipine 5 mg or 10 mg and therapeutic lifestyle changes	SBP, DBP LDL-C Adverse events	6 weeks	United States
Malekzadeh 2010 Two-group RCT	N = 475 Primary prevention	1. Aspirin 81 mg + enalapril 2.5 mg + atorvastatin 20 mg + hydrochlorothiazide 12.5 mg	Placebo	MACE LDL-C SBP, DBP Adverse events	12 months	Iran
CRUCIAL 2011 Two-group cluster RCT	N = 1461 Primary prevention	1. Amlodipine 5 mg or 10 mg + atorvastatin 10 mg or 20 mg	Usual care including therapeutic lifestyle counseling	All-cause mortality SBP, DBP LDL-C Total cholesterol Adverse events	12 months	Costa Rica, Croatia, Czech Republic, Dominican Republic, Indonesia, Jordan,

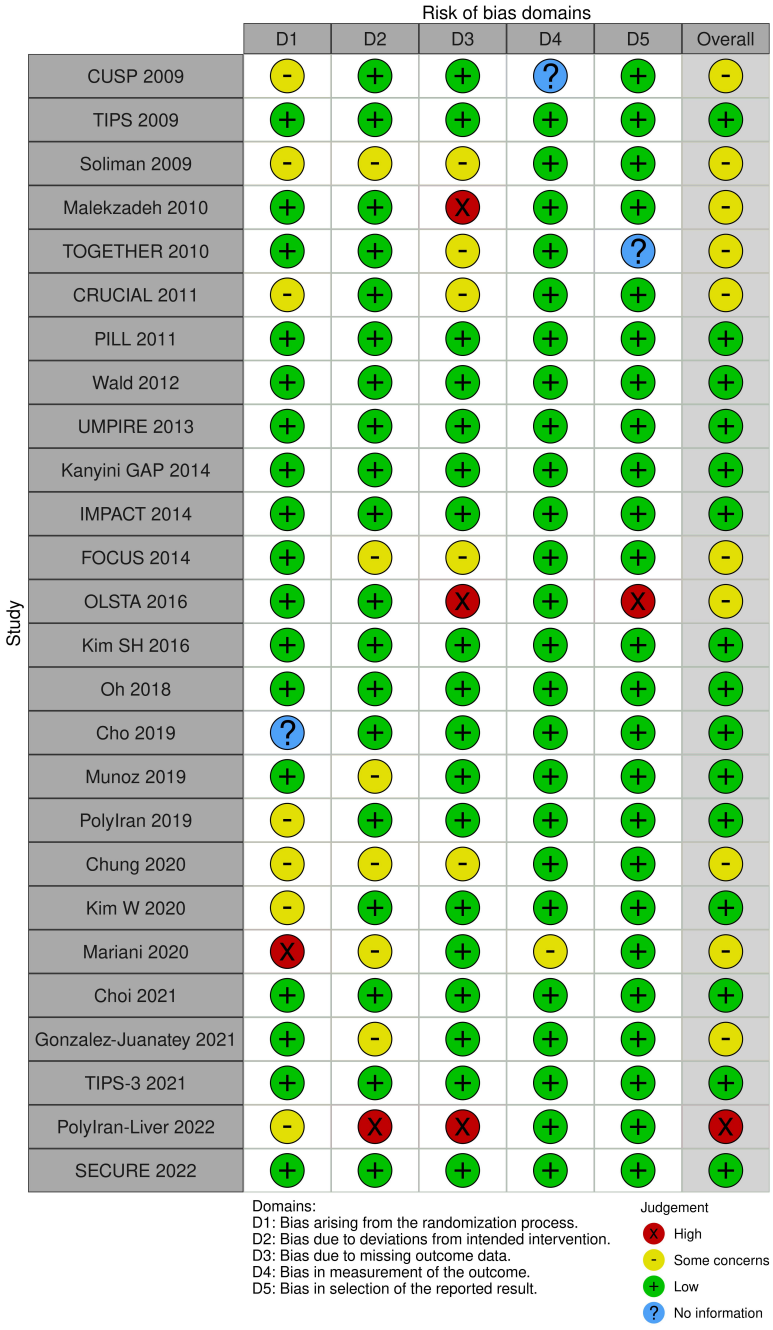
						Kuwait, Lebanon, Malaysia, Mexico, Panama, Philippines, South Korea, Russia, Taiwan, Thailand, Turkey, UAE, Venezuela
PILL 2011 Two-group RCT	N = 378 Primary prevention	1. Aspirin 75 mg + lisinopril 10 mg + hydrochlorothiazide 12.5 mg + simvastatin 20 mg	Placebo	SBP LDL-C Discontinuation	12 weeks	Australia, Brazil, India, Netherlands, New Zealand, United Kingdom, United States
Wald 2012 Two-group crossover RCT	N = 86 Primary prevention	1. Amlodipine 2.5 mg + losartan 25 mg + hydrochlorothiazide 12.5 mg + simvastatin 40 mg	Placebo	SBP, DBP LDL-C	12 weeks	England
UMPIRE 2013 Two-group RCT	N = 2004 Mixed secondary prevention	1. Aspirin 75 mg + simvastatin 40 mg + lisinopril 10 mg + atenolol 50 mg OR hydrochlorothiazide 12.5 mg	Usual care	All-cause mortality MACE Adherence SBP LDL-C	15 months	India, Europe
Focus 2014 Two-group RCT	N = 695 Secondary prevention	1. Aspirin 100 mg + simvastatin 40 mg + ramipril 2.5 mg or 5 mg or 10 mg	Drugs given individually: Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5 mg or 5 mg or 10 mg	All-cause mortality MACE Adherence SBP, DBP LDL-C Adverse events	9 months	Italy, Spain, Argentina, Paraguay
Kanyini GAP 2014 Two-group RCT	N = 623 Mixed secondary prevention	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	Usual care	All-cause mortality MACE SBP Total cholesterol Adherence	18 months	Australia
IMPACT 2014 Two-group RCT	N = 513 Mixed secondary prevention	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	Usual care	All-cause mortality MACE Adherence SBP, DBP LDL-C	12 months	New Zealand

OLSTA 2016 Factorial four-group RCT	N = 162 Primary prevention	1. Olmesartan 40 mg + rosuvastatin 20 mg	Monotherapy with: 1. Olmesartan 40 mg OR 2. Rosuvastatin 20 mg OR 3. Placebo	MACE LDL-C DBP	8 weeks	Korea
Kim SH 2016 Factorial four-group RCT	N = 230 Mixed secondary prevention	1. Irbesartan 300 mg + atorvastatin 40 mg OR 2. Irbesartan 300 mg + atorvastatin 80 mg	Monotherapy with: 1. Irbesartan 300 mg OR 2. Atorvastatin 40 mg OR 3. Atorvastatin 80 mg OR 4. Placebo	LDL-C DBP Adverse events	8 weeks	Korea
Oh 2018 Four-group RCT	N = 210 Primary prevention	1. Telmisartan 80 mg + rosuvastatin 20 mg	Monotherapy with: 1. Telmisartan 80 mg OR 2. Rosuvastatin 20 mg OR 3. Placebo	SBP, DBP LDL-C Adverse events	8 weeks	Korea
Cho 2019 Three-group RCT	N = 219 Primary prevention	1. Candesartan 32 mg + rosuvastatin 20 mg	Monotherapy with: 1. Candesartan 32 mg OR 2. Rosuvastatin 20 mg	SBP, DBP LDL-C Total cholesterol Adverse events	8 weeks	Korea
Munoz 2019 Two-group RCT	N = 303 Primary prevention	1. Atorvastatin 10 mg + amlodipine 2.5 mg + losartan 25 mg + hydrochlorothiazide 12.5 mg	Usual care: participants were offered routine care at the Franklin Primary Health Center and from their PCP	SBP LDL-C Adherence Adverse events	12 months	United States
PolyIran 2019 Two-group cluster RCT	N = 6838 Primary prevention	1. Hydrochlorothiazide 12.5 mg + aspirin 81 mg + atorvastatin 20 mg + enalapril 5 mg OR 2. Hydrochlorothiazide 12.5 mg + aspirin 81 mg + atorvastatin 20 mg + valsartan 40 mg	Minimal care: healthy lifestyle education on diet, weight, smoking, opium	MACE All-cause mortality SBP, DBP LDL-C Adherence Adverse events	5 years	Iran
Chung 2020 Two-group RCT	N = 150 Mixed secondary prevention	1. Olmesartan 20 mg + rosuvastatin 5 mg OR 2. Olmesartan 20 mg + rosuvastatin 10 mg OR 3. Olmesartan 20 mg + rosuvastatin 20 mg OR 4. Olmesartan 40 mg + rosuvastatin 20 mg	Usual regimen with angiotensin receptor blocker and statin as individual drugs with comparable efficacy to the polypill	Adherence SBP, DBP LDL-C	6 months	Korea
Kim W 2020 Three-group RCT	N = 106 Primary prevention	1. Rosuvastatin 20 mg + amlodipine 10 mg	Monotherapy with: 1. Amlodipine 10 mg OR	SBP LDL-C Total cholesterol	8 weeks	Korea

			2. Rosuvastatin 20 mg	Adverse events		
Mariani 2020 Two-group RCT	N = 100 Secondary prevention	1. Aspirin 100 mg + simvastatin 40 mg + atenolol (50 or 100 mg) + ramipril (5 or 10 mg)	Aspirin 100 mg, Simvastatin 40 mg, Atenolol (50 or 100 mg), Ramipril (5 or 10 mg) as separate pills	Adherence SBP Total cholesterol Adverse events	6 months	Argentina
Choi 2021 Two-group RCT	N = 80 Primary prevention	1. Telmisartan 80 mg + Rosuvastatin (10 or 20 mg)	Monotherapy with: 1. Telmisartan 80 mg	SBP, DBP	16 weeks	Korea
Gonzalez-Juanatey 2021 Three-group RCT	N = 321 Primary prevention	1. Atorvastatin 40 mg + ramipril 10 mg + aspirin 100 mg	Monotherapy with: 1. Ramipril 10 mg OR 2. Atorvastatin 40 mg	SBP, DBP LDL-C Total cholesterol Adverse events	4 weeks	United States
TIPS-3 2021 2-by-2-by-2 factorial design RCT	N = 5713 Primary prevention	1. Simvastatin 40 mg + atenolol 100 mg + hydrochlorothiazide 25 mg + ramipril 10 mg	Placebo	All-cause mortality MACE SBP LDL-C Total cholesterol Adherence Adverse events	4.6 years	India, Bangladesh, Philippines, Malaysia, Indonesia, Colombia, Canada, Tanzania, Tunisia
Polylran-Liver 2022 Two-group pragmatic RCT, consent after randomization	N = 1508 Primary prevention	1. Aspirin 81 mg + hydrochlorothiazide 12.5 mg + atorvastatin 20 mg + valsartan 40 mg	Usual care	All-cause mortality MACE (Primary outcomes reported for randomized population)	5 years	Iran
SECURE 2022 Two-group RCT	N = 2499 Secondary prevention	1. Aspirin 100 mg + ramipril (2.5 or 5 or 10 mg) + atorvastatin (20 or 40 mg)	Usual care	All-cause mortality MACE SBP, DBP LDL-C Adherence Adverse events	3 years	Spain, Italy, France, Germany, Poland, Czech Republic Hungary

*Primary prevention: population where 15% or less participants had pre-existing ASCVD
*Mixed secondary prevention: population where >15% participants had pre-existing ASCVD
*Secondary prevention: population where 100% participants had pre-existing ASCVD
ASCVD=atherosclerotic cardiovascular disease; HCTZ=hydrochlorothiazide; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; PCP: primary care physician; RCT: randomized clinical trial; MACE: major cardiovascular events

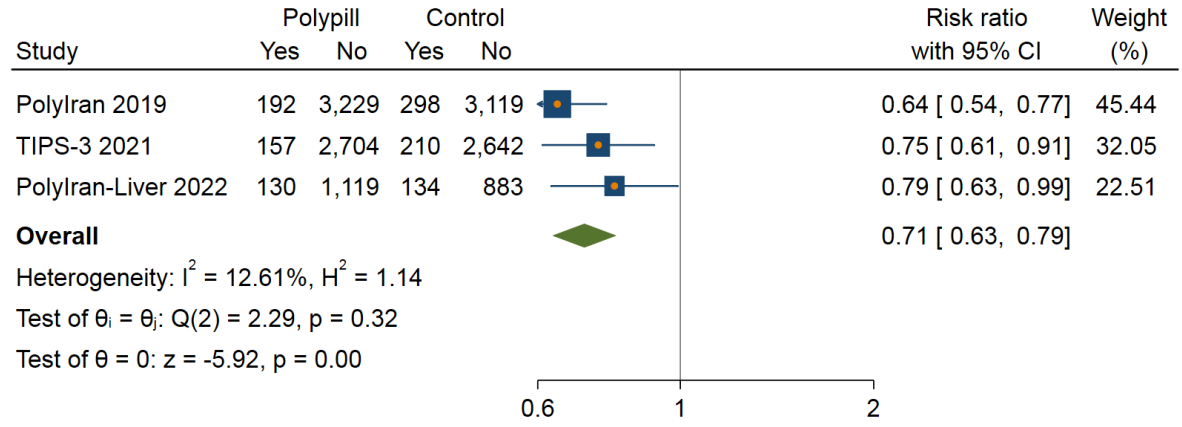
Supplemental Appendix 5. Risk of bias assessment for included studies.



Supplemental Appendix 6. Subgroup analyses.

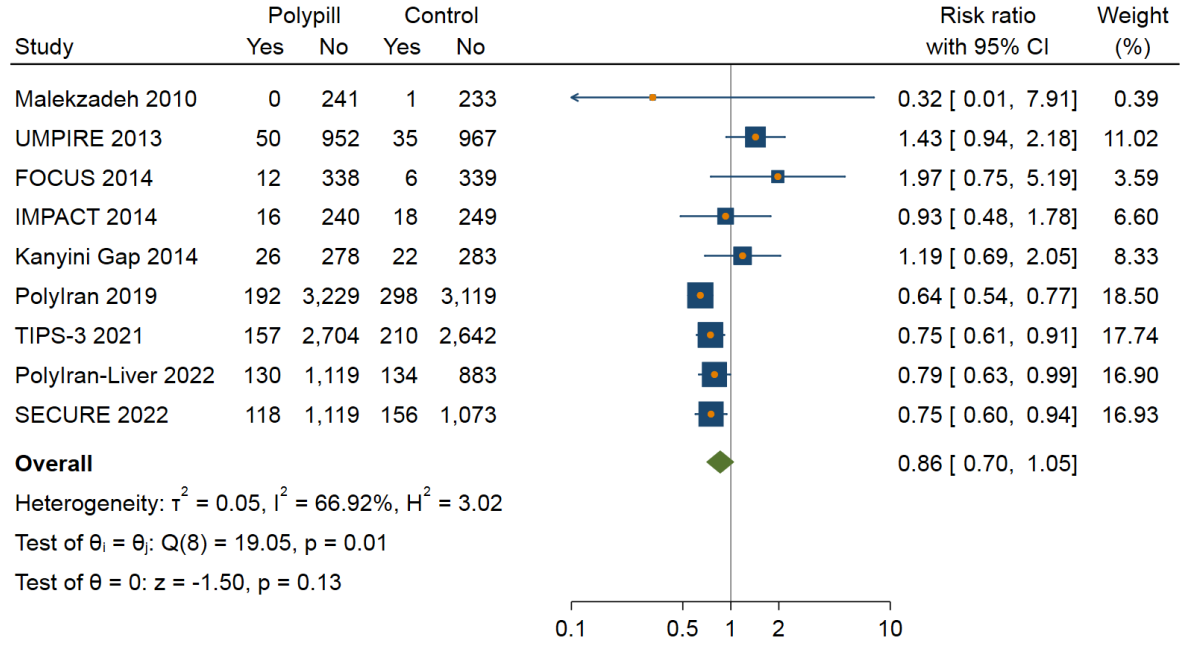
1. Fatal and non-fatal atherosclerotic cardiovascular disease events

Supplemental Analysis 1.1. Fatal and non-fatal ASCVD events: Primary prevention trials with >500 participants.



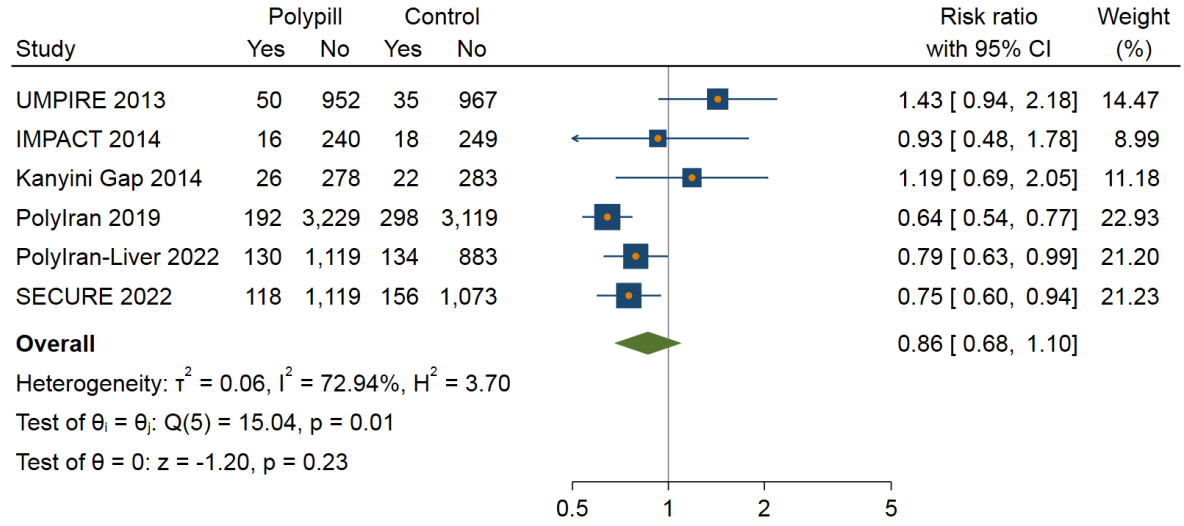
Fixed-effects Mantel–Haenszel model

Supplemental Analysis 1.2: Fatal and non-fatal ASCVD events: 3+ drugs for all included trials.



Random-effects REML model

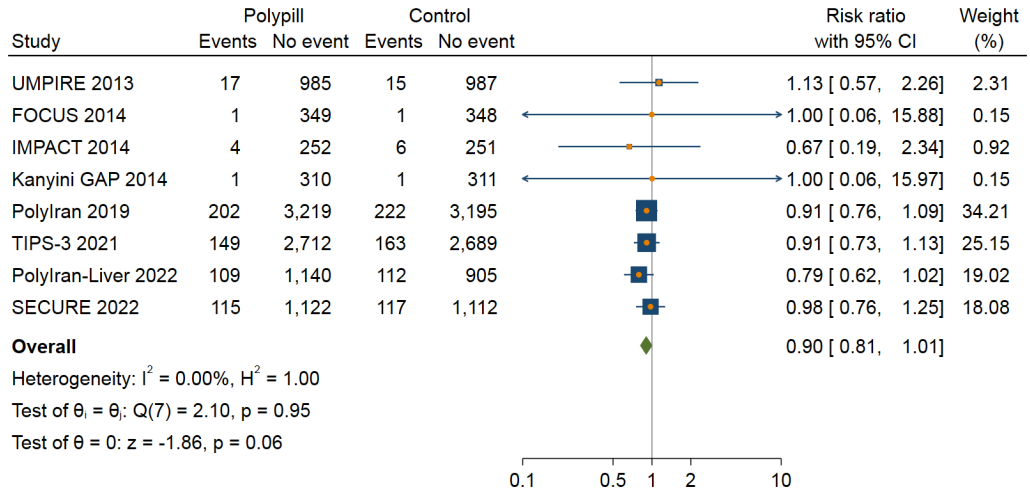
Supplemental Analysis 1.3: Fatal and non-fatal ASCVD events: Comparator as usual care.



Random-effects REML model

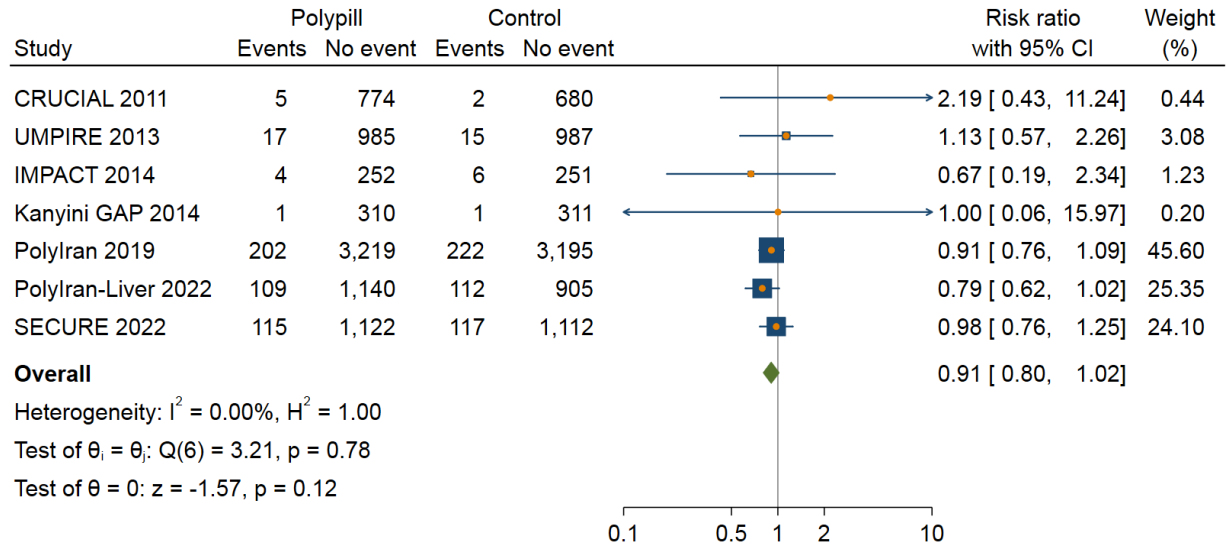
2. All-cause mortality

Supplemental Analysis 2.1. All-cause mortality: 3+ drugs.



Fixed-effects Mantel–Haenszel model

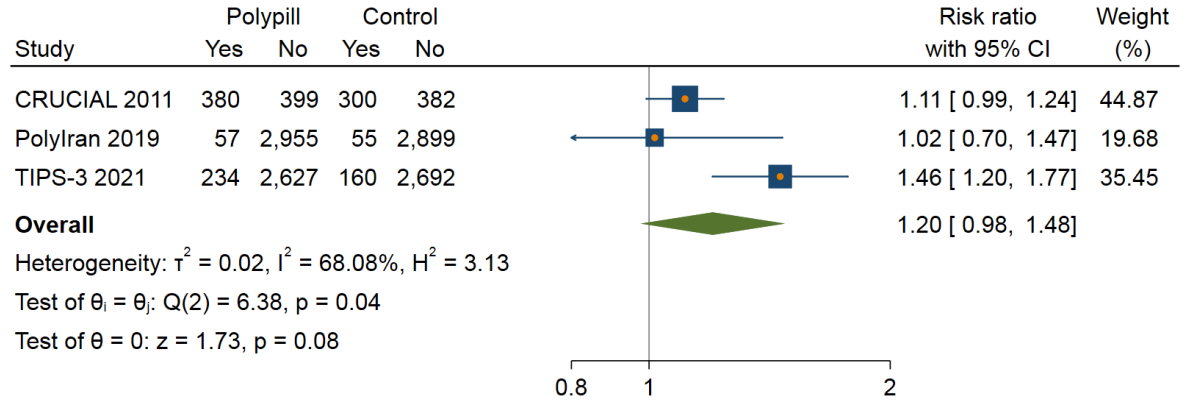
Supplemental Analysis 2.2. All-cause mortality: Comparator as usual care.



Fixed-effects Mantel–Haenszel model

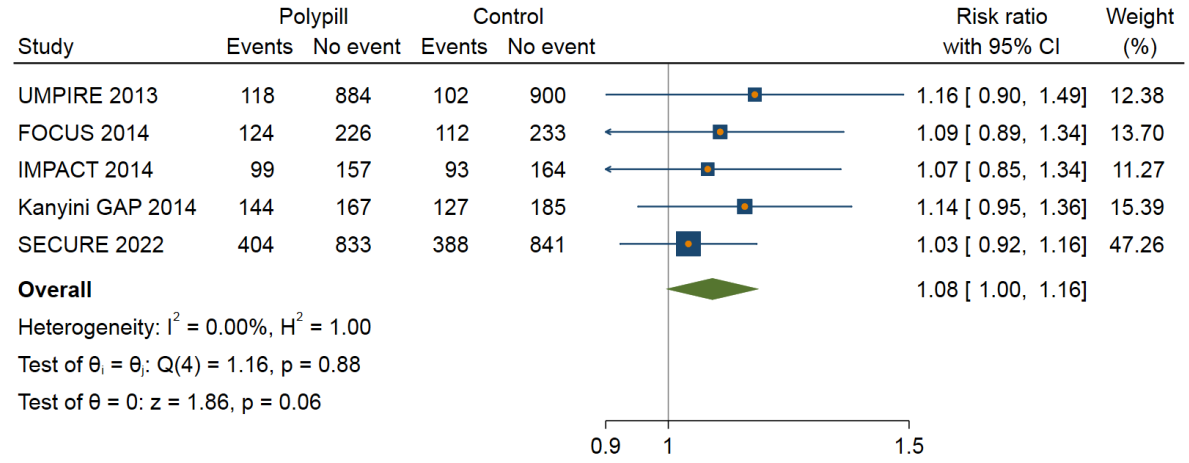
3. Adverse events

Supplemental Analysis 3.1. Adverse events: Trials >500 participants in primary prevention.



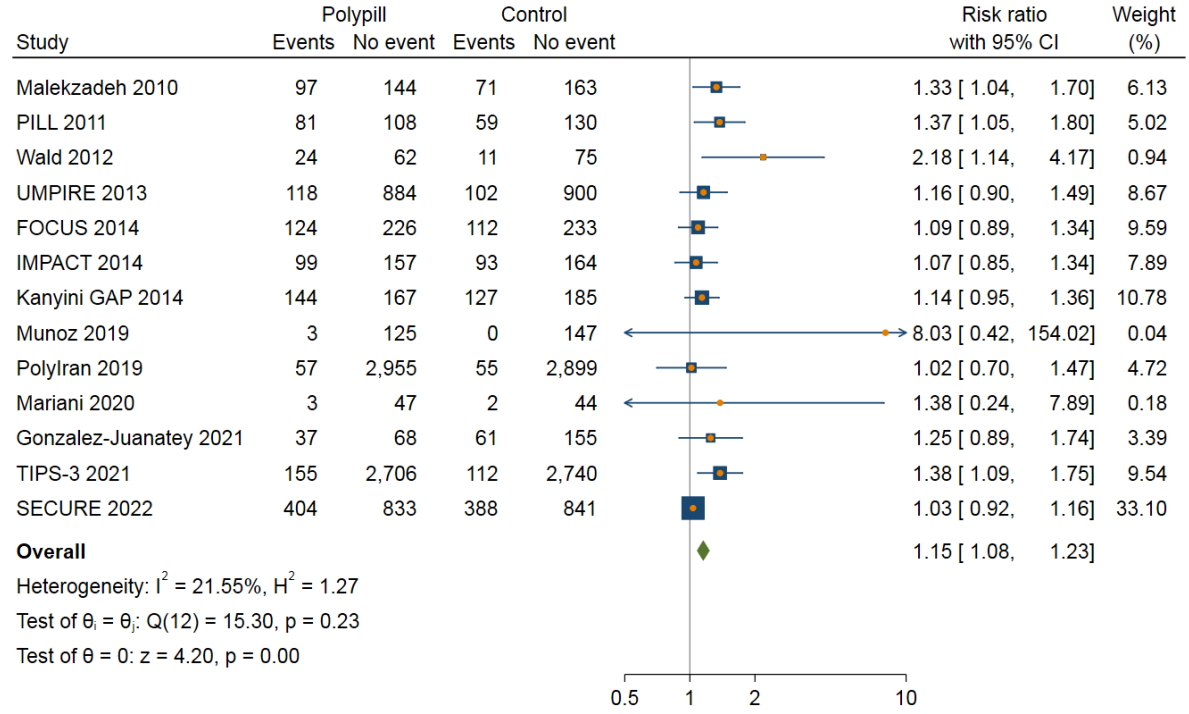
Random-effects REML model

Supplemental Analysis 3.2 Adverse events: Trials >500 participants in mixed primary and secondary prevention trials.



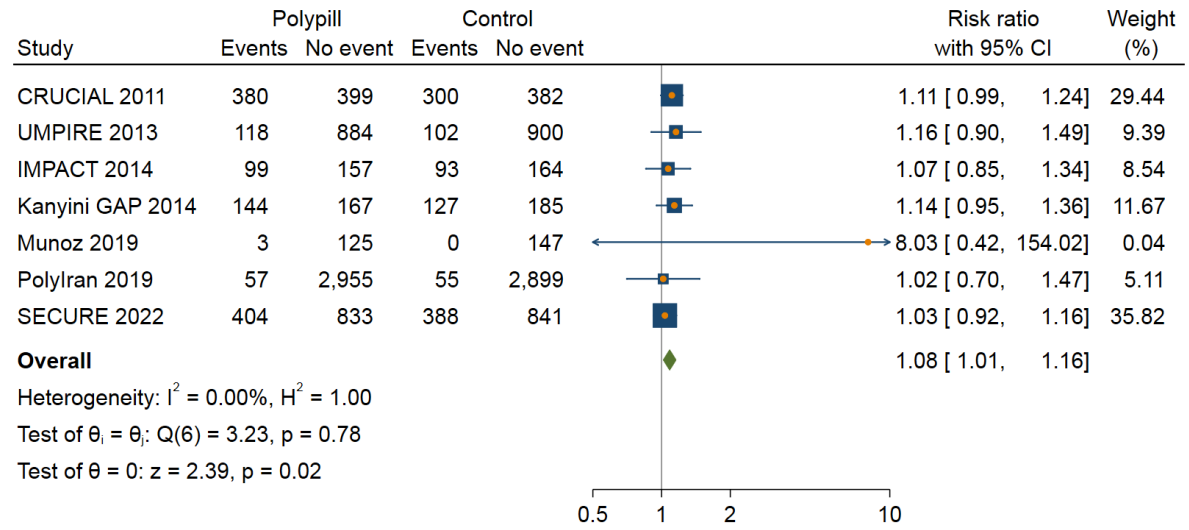
Fixed-effects Mantel–Haenszel model

Supplemental Analysis 3.3. Adverse events: 3+ drugs.

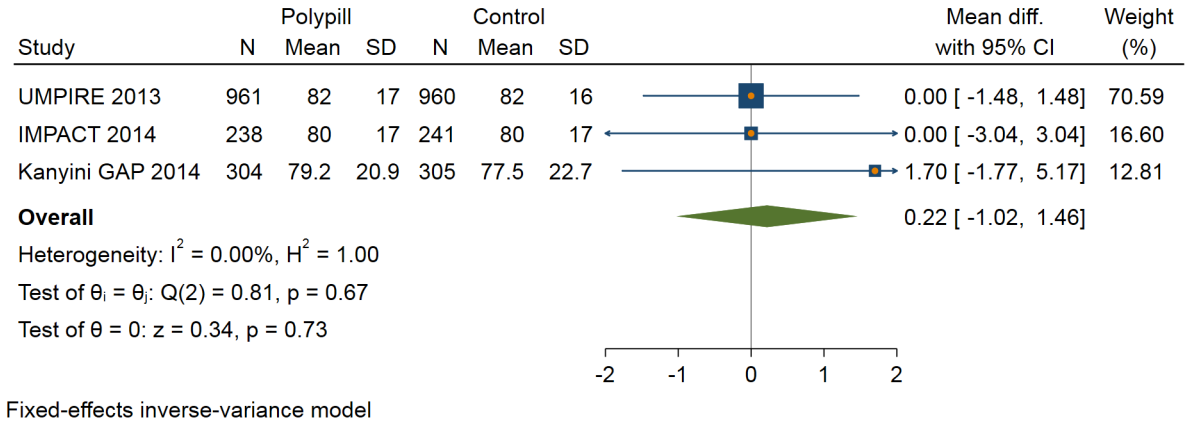


Fixed-effects Mantel–Haenszel model

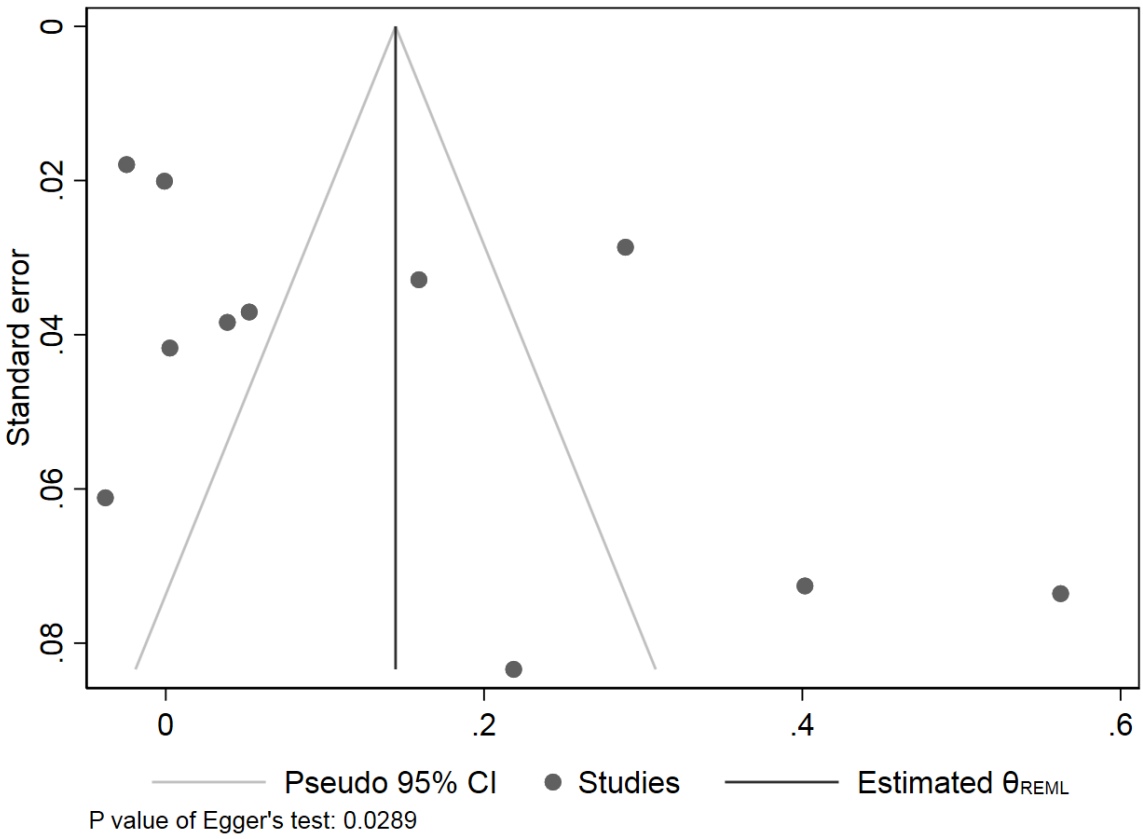
Supplemental Analysis 3.4. Adverse events: Comparator as usual care.



Supplemental Appendix 7. Difference in health-related quality of life: EQ-5D health state.



Supplemental Appendix 8. Funnel plot for adherence among primary, mixed, and secondary prevention trials.



Funnel plots were not created for other co-primary outcomes because there were less than 10 trials for primary and secondary prevention indications for fatal and nonfatal cardiovascular disease events and all-cause mortality.

Supplemental Appendix 9. Letters of Support.

Forthcoming.