IJEBM International Journal of Evidence-Based Medicine

International Journal of Evidence-Based Medicine
(eISSN 3083-1776)

Australasia Publishing Group

Reviewl Article

Cost-Effectiveness of Fixed-Dose Combination Polypills for Secondary Cardiovascular Disease Prevention: A Systematic Review

Obiageri Ihuarulam Okeoma[1], Adetunji Olawale Adediran[2], David O. Adeoti[3], Comfort Ohunene Matthew[4]

[1]*Department of Medical Laboratory Science, Faculty of Basic Medical and Applied Sciences, Trinity University, Yaba, Lagos, Nigeria*
[2]*Department of Internal Medicine, Faculty of Clinical Science, University College Hospital, Ibadan, Oyo State, Nigeria*
[3]*Department of Biomedical Engineering, Faculty of Chemical and Biomedical Engineering, University of New Haven, CT, USA*
[4]*Department of Clinical Pharmacy, Faculty of Pharmacy, University of Benin, Benin City, Nigeria*

Received: Mar 23, 2026
Accepted: Jul 07, 2026

Corresponding author's email: matthewcot94@gmail.com

Citation: Okeoma OI, Adediran AO, Adeoti DO, Matthew CO. Cost-Effectiveness of Fixed-Dose Combination Polypills for Secondary Cardiovascular Disease Prevention: A Systematic Review. International Journal of Evidence-Based Medicine. 2026;1(3):jebm010. https://doi.org/10.63946/jebm/18966

ABSTRACT

Background: Cardiovascular disease remains a leading cause of global morbidity and mortality, and long-term secondary prevention is often limited by poor adherence, pill burden, treatment costs, and health system barriers. Fixed-dose combination polypills may simplify treatment by combining multiple cardiovascular medicines into a single formulation, thereby improving adherence and reducing recurrent cardiovascular events.

Objective: This systematic review evaluated the cost-effectiveness of fixed-dose combination polypills compared with usual care, standard therapy, or separate monocomponents for secondary cardiovascular disease prevention across different healthcare and income settings.

Methods: The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. PubMed, Dimensions AI, ScienceDirect, and the Tufts Cost-Effectiveness Analysis Registry were searched for studies published between January 2015 and December 2025. Eligible studies included economic evaluations involving adults with established cardiovascular disease and reporting incremental cost-effectiveness ratios, cost per quality-adjusted life year, cost per disability-adjusted life year, cost savings, or related economic outcomes. Reporting quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards checklist.

Results: Fourteen records were included, comprising 13 full or partial economic evaluations and one Delphi consensus study with policy-relevant contextual interpretation. Most studies were conducted in high-income countries, particularly Spain, while evidence from low- and middle-income countries was limited. Fixed-dose combination polypills were generally reported as cost-effective or cost-saving, mainly driven by improved medication adherence, reduced pill burden, and prevention of recurrent cardiovascular events. Findings were also influenced by methodological factors such as analytic perspective and time horizon adopted across studies.

Conclusion: Fixed-dose combination polypills may offer economic value for secondary cardiovascular disease prevention, but broader implementation should be guided by local cost-effectiveness, affordability, budget impact, and real-world evidence, especially in low- and middle-income countries.

Keywords: Vent Polypill; Fixed-Dose Combination Therapy; Cost-Effectiveness; Cardiovascular Diseases; Secondary Prevention

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity worldwide, accounting for approximately 32% of all global deaths, with a substantial proportion of this burden occurring in low- and middle-income countries (LMICs) [1]. However, CVD also remains a major public health and economic challenge in high-income countries, where ageing populations, multimorbidity, hypertension, diabetes, and dyslipidaemia continue to increase the demand for long-term secondary prevention [2, 3]. Secondary prevention after myocardial infarction, stroke, or other established cardiovascular events is essential for reducing recurrent events, cardiovascular mortality, disability, and avoidable healthcare expenditure. Despite the availability of effective medicines, adherence to long-term secondary prevention remains suboptimal across many settings because patients are often required to take multiple medications, including antiplatelet agents, statins, and antihypertensive drugs [4, 5].

Poor adherence to secondary prevention therapy is an important barrier to effective cardiovascular risk reduction. In many LMICs, this problem is compounded by medicine costs, fragmented health systems, limited insurance coverage, and inconsistent access to essential medicines [3, 4]. In high-income countries, although access to medicines is generally better, long-term treatment persistence may still be affected by polypharmacy, ageing, comorbidities, treatment fatigue, and rising healthcare costs [4, 6]. These challenges have increased interest in simplified treatment strategies that can improve adherence while maintaining clinical effectiveness and affordability across different healthcare systems.

Fixed-dose combination cardiovascular polypill therapy has emerged as one such strategy. In this review, a fixed-dose combination polypill, hereafter referred to as an FDC polypill, is defined as a single-pill regimen that combines two or more cardiovascular preventive medicines, commonly including an antiplatelet agent, a statin, and one or more antihypertensive agents. By reducing pill burden and simplifying treatment regimens, FDC polypills have the potential to improve medication adherence, risk-factor control, and long-term cardiovascular outcomes [7, 8]. The inclusion of cardiovascular polypills in the World Health Organization Essential Medicines List in 2023 further reflects their potential relevance for health systems seeking scalable strategies for cardiovascular prevention, particularly in resource-constrained settings [9].

Although the clinical rationale for FDC polypills is strong, policy decisions require evidence not only on effectiveness but also on economic value. Economic evaluations are particularly important because the affordability, cost-effectiveness, and budget impact of polypill strategies may differ substantially across countries. Drug prices, healthcare utilisation costs, reimbursement systems, baseline cardiovascular risk, adherence patterns, and cost-effectiveness thresholds vary between high-income countries and LMICs. Consequently, evidence generated in one healthcare system cannot be assumed to apply directly to another without careful interpretation. Existing studies from high-income countries suggest that FDC polypills may be cost-effective or cost-saving when improved adherence and prevention of recurrent cardiovascular events are considered [2, 10]. However, evidence from LMICs remains comparatively limited, despite the high CVD burden and the potential policy relevance of simplified, affordable secondary prevention strategies in these settings.

Previous research has examined the clinical and economic implications of polypill therapy, but the available evidence remains heterogeneous in terms of study setting, model structure, perspective, time horizon, intervention composition, comparator, and outcome measure [11]. Some studies report incremental cost-effectiveness ratios expressed as cost per quality-adjusted life year (QALY) gained, whereas others report cost per disability-adjusted life year (DALY) averted, cardiovascular events prevented, or budgetary savings. This variation makes it necessary to synthesise the evidence systematically while distinguishing between findings from high-income countries and those from LMICs.

Therefore, this systematic review aims to synthesise and evaluate global evidence on the cost-effectiveness of FDC polypill therapy compared with usual care or separate monocomponents for secondary cardiovascular disease prevention. Specifically, the review assesses whether FDC polypills represent a cost-effective alternative to conventional multidrug regimens across different healthcare and income settings, and identifies the major factors influencing their economic value, including drug costs, adherence assumptions, healthcare perspective, time horizon, discounting, and local health system context. By presenting the evidence across both high-income countries and LMICs, this review provides a clearer basis for interpreting the potential role of FDC polypills in secondary CVD prevention while recognising the limits of generalisability across diverse health systems.

Methodology

Research Question

The central research question guiding this review was: *What is the cost-effectiveness of fixed-dose combination polypill therapy compared with usual care or separate monocomponents for secondary cardiovascular disease prevention across different healthcare and income settings?* The PICO framework was used to define the review question and eligibility criteria [12, 13]. The population comprised adults with established cardiovascular disease; the intervention was fixed-dose combination cardiovascular polypill therapy; the comparator was usual care or separate monocomponents; and the outcomes were economic outcomes, including incremental cost-effectiveness ratios (ICERs), cost per quality-adjusted life year (QALY), cost per disability-adjusted life year (DALY), cost savings, and cardiovascular events prevented.

Study Design and Protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [14]. The review focused on economic evaluations of fixed-dose combination polypills for secondary cardiovascular disease prevention. The review protocol was not prospectively registered in PROSPERO. However, the review question, eligibility criteria, information sources, search strategy, screening process, and data extraction framework were defined before final study selection.

Information Sources and Search Strategy

A literature search was conducted on 6 February 2026 using four information sources: PubMed, Dimensions AI, ScienceDirect, and the Tufts Cost-Effectiveness Analysis Registry. These sources were selected because they provide coverage of biomedical, clinical, multidisciplinary, and health economic literature relevant to cardiovascular prevention and cost-effectiveness analysis. PubMed was searched for biomedical and clinical studies, Dimensions AI and ScienceDirect were searched for multidisciplinary and open-access research articles, while the Tufts CEA Registry was searched because of its specific focus on cost-effectiveness and cost-utility studies.

The search covered studies published from January 2015 to December 2025. This date range was selected to capture contemporary evidence following increasing global interest in fixed-dose combination cardiovascular therapy and to maintain consistency with the database filters applied during the search. Search terms combined keywords and controlled vocabulary related to cardiovascular disease, secondary prevention, fixed-dose combination therapy, polypill therapy, and economic evaluation. The PubMed search used Medical Subject Headings (MeSH) and free-text terms because MeSH-based searching improves retrieval of relevant biomedical literature and reduces irrelevant search results [16]. Boolean operators were used to combine search concepts.

The main search terms included “cardiovascular disease,” “heart disease,” “secondary prevention,” “polypill,” “fixed-dose combination,” “cost-effectiveness,” “economic evaluation,” “cost-utility,” “ICER,” “QALY,” and “DALY.” Database-specific filters were applied where relevant. PubMed, ScienceDirect, and Dimensions AI searches were limited to English-language human studies within the review period. Free full text or open-access filters were applied where available because only retrievable full-text articles could be assessed against the eligibility criteria and quality appraisal framework. The Tufts CEA Registry search was not filtered because the yield was manageable and the available registry filters were not sufficiently aligned with the specific eligibility criteria of this review. Therefore, all Tufts records retrieved from the search were manually screened using the same inclusion and exclusion criteria applied to the other information sources. The full search strategy, search yield, filters applied, and final yield for each information source are presented in Table 1.

Table 1: Search Strategy

Databases	Search strings	Search yield	Filters applied	Final yield
PubMed	("Cardiovascular Diseases"[MeSH] OR "heart disease" OR "cardiovascular") AND ("Polypill" OR "fixed dose combination" OR "fixed-dose combination") AND ("Secondary Prevention" OR "post-event") AND ("Cost-Effectiveness" OR "economic evaluation" OR "cost utility" OR "cost DALY" OR "cost QALY" OR "incremental cost-effectiveness")	31	2015-2025, Free full text, English, Humans	10

Databases	Search strings	Search yield	Filters applied	Final yield
Sciencedirect	("cardiovascular disease") AND ("polypill" OR "fixed dose combination") AND ("secondary prevention") AND ("economic evaluation" OR "cost effectiveness" OR "cost utility" OR "cost DALY" OR "cost QALY")	249	2015-2025, Research article, English, open access	18
Dimensions Ai	("cardiovascular disease" OR "heart disease") AND ("polypill" OR "fixed dose combination") AND ("secondary prevention") AND ("economic evaluation" OR "cost effectiveness" OR "cost utility" OR "cost DALY" OR "cost QALY")	31	2015-2025, Article, open access	17
Tufts CEA Registry	("cardiovascular disease" OR "heart disease") AND ("polypill" OR "fixed dose combination") AND ("secondary prevention") AND ("economic evaluation" OR "cost effectiveness" OR "cost utility" OR "cost DALY" OR "cost QALY")	60	Nil	

Eligibility Criteria

Studies were included if they involved adults with established cardiovascular disease and evaluated a fixed-dose combination cardiovascular polypill for secondary prevention. Eligible comparators included usual care, standard therapy, or monotherapy and were used as reported in the original studies. These terms were not treated as identical interventions; rather, they reflected the comparator definitions adopted by each included economic evaluation. Studies were required to report at least one economic outcome relevant to decision-making, including ICER, cost per QALY, cost per DALY, cost savings, budget impact, or cardiovascular events prevented. Eligible study designs included model-based economic evaluations, trial-based economic evaluations, cost-effectiveness analyses, cost-utility analyses, and budget impact analyses.

Studies were excluded if they were reviews, editorials, commentaries, protocols, methodological papers, or studies focused only on primary prevention. Studies that did not report economic outcomes relevant to cost-effectiveness decision-making were also excluded. Expert consensus or Delphi studies were not included in the main economic evaluation synthesis. Where such studies provided policy-relevant economic interpretation directly related to fixed-dose combination polypills for secondary cardiovascular disease prevention, they were discussed separately as contextual evidence.

Study Selection and Data Extraction

All retrieved records were imported into Zotero, and duplicates were removed. The full study selection process is as detailed in the PRISMA flow diagram (Figure 1). Two reviewers independently screened titles and abstracts against the eligibility criteria. Full texts of potentially eligible studies were then assessed independently by the same reviewers. Disagreements were resolved through discussion.

Inter-rater agreement was assessed using Cohen's kappa and is reported in the supplement file. Agreement was substantial for title and abstract screening, with a Cohen's kappa value of 0.75, and substantial to almost perfect for full-text eligibility assessment, with a Cohen's kappa value of 0.82. These values indicate acceptable consistency between reviewers during the study selection process.

Data were extracted using a standardized extraction form. Extracted information included author, year of publication, country or region, income setting, study population, intervention, comparator, study design, economic evaluation type, model type, perspective, time horizon, discount rate, cost inputs, outcome measures, ICERs, cost per QALY, cost per DALY, cost savings, sensitivity analysis findings, funding source, and conflict-of-interest disclosures.

It is worth noting that Economic results were extracted and presented as reported in the original studies. Costs and incremental cost-effectiveness ratios were not converted to a common currency or adjusted to a single price year; therefore, absolute cost estimates should not be interpreted as directly comparable across studies.

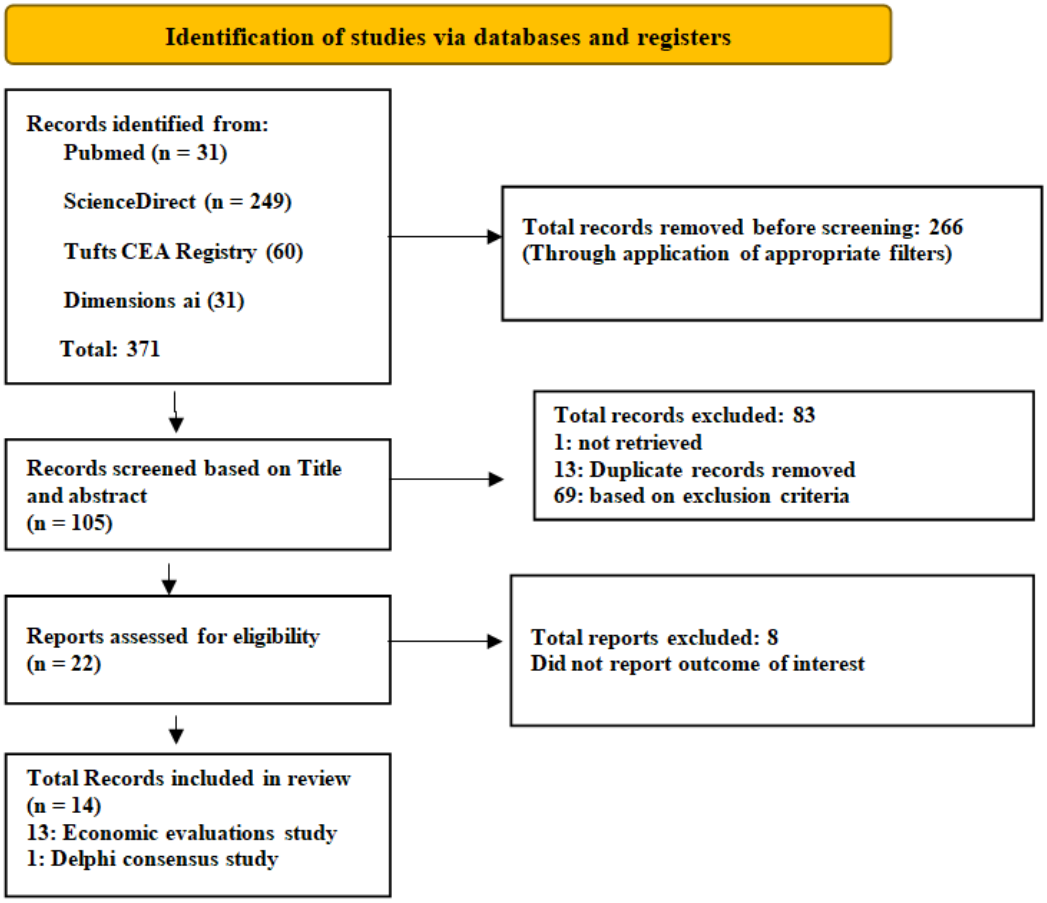

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram

Contextual Evidence from Delphi Consensus

Piñeiro et al. (2025) [21] was considered separately from the main economic evaluation synthesis because it was a Delphi consensus study rather than a formal cost-effectiveness or cost-utility analysis. The study was retained as contextual evidence because it provided expert consensus on the clinical, implementation, and policy relevance of the cardiovascular polypill in secondary prevention. Its findings were used only to support interpretation of implementation relevance and were not included in the comparison of incremental cost-effectiveness ratios, cost per quality-adjusted life year, cost per disability-adjusted life year, or cost-saving estimates.

Quality Appraisal

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used to appraise the reporting quality, completeness, and transparency of the included economic evaluations [17]. CHEERS was considered appropriate for this review because the included studies were health economic evaluations, and the checklist provides a structured framework for assessing whether key components of economic evaluation reporting were adequately described, including title, abstract, study perspective, comparators, time horizon, discounting, outcome measurement, cost estimation, analytical methods, uncertainty, heterogeneity, funding, and conflicts of interest.

Each included study was assessed against the CHEERS items. A score of 1 was assigned when the item was fully reported, 0.5 when the item was partially reported or unclear, and 0 when the item was not reported. Items that were not applicable to a particular study design were marked as not applicable and excluded from the denominator when calculating percentage scores. Studies scoring above 85% were classified as having excellent reporting quality, those scoring 70–85% as very good reporting quality, those scoring 50–69% as good reporting quality, and those scoring below 50% as poor reporting quality.

The full item-level CHEERS quality assessment table is provided in the supplementary file. The appraisal was used to support interpretation of reporting completeness and transparency across studies rather than to exclude studies solely on the basis of reporting score.

Data Synthesis

Due to heterogeneity in study settings, model structures, comparators, perspectives, time horizons, discount rates, cost inputs, and outcome measures, meta-analysis was not appropriate. A narrative synthesis was therefore conducted [15]. Findings were organised by country income setting, economic

evaluation type, perspective, time horizon, and outcome measure. Study-level economic outcomes, including ICERs, cost per QALY, cost per DALY, cost savings, threshold values, and sensitivity analysis findings, were summarised in structured tables where reported. Sources of heterogeneity were examined narratively, including differences in healthcare system context, drug costs, adherence assumptions, model structure, discounting, and comparator choice. Publication bias was considered qualitatively by examining the direction of findings, funding disclosures, selective reporting, and the limited availability of unpublished economic evaluations.

Results

Overview of the Included Studies

A total of 14 records were included in the evidence synthesis. Of these, 13 were full or partial economic evaluations of fixed-dose combination (FDC) polypills for secondary cardiovascular disease (CVD) prevention, while one study, Piñeiro et al. (2025) [21], was a Delphi consensus study that provided policy-relevant expert interpretation on the economic and implementation value of the cardiovascular polypill but was not treated as a full economic evaluation. The included evidence covered both high-income countries and low- and middle-income countries (LMICs), reflecting the revised global scope of this review.

Most of the full economic evaluations used model-based approaches, particularly Markov models and microsimulation models. Other studies used observational cost-effectiveness approaches [22, 27] or within-trial economic evaluation [24]. The studies generally compared an FDC polypill, most commonly containing aspirin, atorvastatin, and ramipril, with usual care, standard care, multiple monotherapies, or separate monocomponents. The main outcomes reported included incremental cost-effectiveness ratios (ICERs), cost per quality-adjusted life year (QALY), cost per disability-adjusted life year (DALY), life-years gained, cardiovascular events prevented, and cost savings.

The geographic distribution of the evidence was uneven. A substantial proportion of the studies were conducted in high-income European settings, particularly Spain, with additional evidence from the United Kingdom [19], Portugal [26], Greece [30], and the United States [28]. Evidence from LMICs was more limited and was mainly represented by multicountry modelling evidence from China, India, Mexico, Nigeria, and South Africa [20], and trial-based economic evidence from India [24]. Therefore, although the review provides global evidence, the interpretation of findings for LMICs requires caution because most included studies were generated in high-income health systems.

Table 2: General Characteristics of the Included Studies

Study ID	Country/Region	Income Setting	Study Design/ Model	Study Population	Sample Size/Modelled Cohort	Intervention	Polypill Composition	Comparator	Perspective	Time Horizon	Cost Measurement	Discount Rate Reporting
Rubio G. et al. (2021) [18]	Spain	High-income	Markov cost-effectiveness model	Adults with previous cardiovascular events	1,000	CNIC-polypill	Aspirin + atorvastatin + ramipril	Monotherapy	National Health System	Lifetime	Costs in 2020 Euros per QALY, LY	Partially reported
Gaziano et al. (2025) [11]	Spain	High-income	Decision-analytic Markov model	Secondary prevention patient	Modelled cohort not clearly	CV-polypill	Acetylsalicylic acid + atorva	Standard care	Spanish healthcare	Lifetime	Public sector costs, ICER	Reported

				s with MI	reported		statin + ramipril		perspective		per QALY	
Becerra et al. (2015) [19]	United Kingdom	High-income	Markov model	MI patients	Modelled cohort not clearly reported	FDC polypill	Aspirin 100 mg + atorvastatin 20 mg + ramipril 2.5/5/10 mg	Multiple monotherapy	National Health System	10 years	£8200 per QALY gained	Partially reported
Lin et al. (2019) [20]	China, India, Mexico, Nigeria, South Africa	Mixed LMIC settings	Microsimulation model	Adults with atherosclerotic CVD	1,000	Polypill	Aspirin 75 mg + lisinopril 10 mg + atenolol 50 mg + simvastatin 40 mg	Usual care	Public sector	5 years	ICER per DALY averted, country-specific costs	Reported
Piñeiro et al. (2025) [21]	Global, 19 countries	Mixed settings	Delphi consensus	Secondary prevention patients	Not applicable	CV-polypill	Acetylsalicylic acid/ASA + atorvastatin + ramipril	Usual care	Not applicable	Not applicable	N/A	Reported
Cordero et al. (2023) [22]	Spain	High-income	Observational retrospective economic study	Secondary prevention patients with IHD	1,614	CNIC-polypill	Aspirin + atorvastatin + ramipril	Monotherapy	Spanish National Health System	2 years	Cost savings, event rates	Reported
González-Domínguez et al.	Spain	High-income	Markov cost-utility model	Secondary prevention patients with	1,000	CNIC-polypill	Acetylsalicylic acid 100 mg + atorvastatin	Monotherapy	Spanish National Health	Lifetime	Cost per QALY gained, ICER	Reported

(2023) [23]				IHD or stroke			20/40 mg + ramipril 2.5/5/10 mg		System			
Singh et al. (2018) [24]	India	LMIC	Within-trial cost-effectiveness analysis	Patients requiring secondary CVD prevention	Trial population not clearly stated in extracted table	Polypill	Aspirin + statin + two blood pressure-lowering drugs	Usual care	Health system	5 years	Public sector costs	Not applicable
Barrios et al. (2017) [25]	Spain	High-income	Markov model	Post-MI patients	Modelled cohort not clearly reported	Polypill	Aspirin 100 mg + atorvastatin 20 mg + ramipril 10 mg	Monotherapy	Spanish National Health System	10 years	Costs in Euros per QALY	Reported
Aguiar et al. (2022) [26]	Portugal	High-income	Markov cost-utility model	Patients with coronary heart disease or stroke	1,000	CNIC-polypill	Acetylsalicylic acid 100 mg + atorvastatin 20/40 mg + ramipril 2.5/5/10 mg	Separate monocomponents	National Health System	Lifetime	€1557 per QALY gained	Reported
Dalmau et al. (2024) [27]	Spain	High-income	Observational economic study	Secondary prevention patients with IHD	1,080	CNIC-polypill	Acetylsalicylic acid 100 mg + atorvastatin 20/40 mg + ramipril	Monotherapy	Spanish National Health System	2 years	€2317–€2407 cost savings	Reported

							2.5/5/10 mg					
Gaziano et al. (2019) [28]	United States	High-income	Markov microsimulation model	Adults with IHD or stroke	NHANES-based population	Polypill	Aspirin 81 mg + atenolol 50 mg + ramipril 5 mg + simvastatin 40 mg, atorvastatin 80 mg, or rosuvastatin 40 mg	Usual care	Health sector, societal, payer	Lifetime	$20,073 per QALY (Polypill I), $21,818 per QALY (Polypill II), cost savings from societal perspective	Partially reported
Arrabal et al. (2015) [29]	Spain	High-income	Markov model	Adults with MI requiring secondary prevention	Modelled cohort not clearly reported	Polypill	Aspirin 100 mg + atorvastatin 20 mg + ramipril 10 mg	Multiple monotherapy	Spanish healthcare system	10 years	Costs in Euros, cost per QALY gained	Reported
Ntaios et al. (2019) [30]	Greece	High-income	Markov model with budget impact analysis	Adults with IHD/post-MI	1,000	CNIC-polypill	Acetylsalicylic acid + ramipril + atorvastatin	Monotherapy	Greek National Health System	Lifetime for cost-effectiveness; 5 years for budget impact	€2,926/QALY, cost savings per event prevented	Reported

Quality Appraisal

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used to assess the reporting quality, completeness, and transparency of the included studies [17]. The appraisal focused on whether key components of economic evaluation reporting were clearly described, including study perspective, population, comparators, time

horizon, discounting, costs, outcomes, model assumptions, analytical methods, uncertainty, heterogeneity, funding, and conflicts of interest.

Overall, reporting quality was high across most included studies. Eleven studies scored above 85%, indicating excellent reporting quality. Three studies scored between 70% and 85%, indicating very good reporting quality [24, 28, 30]. Lower scores were mainly due to incomplete reporting of currency year and conversion, unclear assumptions, incomplete conflict-of-interest reporting, or limited detail on discounting.

It is important to note that CHEERS was used in this review to assess reporting completeness and transparency, not to assess clinical risk of bias. The full item-level CHEERS quality assessment is provided in the supplementary file.

Table 3: Summary of CHEERS Reporting Quality Scores

Study ID	CHEERS Score	Reporting Quality Category	Main Reporting Limitations
Rubio G. et al. (2021) [18]	94%	Excellent	Discount rate partially reported
Gaziano et al. (2025) [11]	96%	Excellent	Minor limitations only
Becerra et al. (2015) [19]	87.5%	Excellent	Currency/conversion and assumptions partially reported
Lin et al. (2019) [20]	96%	Excellent	Currency/conversion not fully reported
Piñeiro et al. (2025) [21]	96%	Excellent	Delphi design limits its status as a full economic evaluation
Cordero et al. (2023) [22]	96%	Excellent	Minor limitations only
González-Domínguez et al. (2023) [23]	96%	Excellent	Minor limitations only
Singh et al. (2018) [24]	75%	Very good	Some model-related items not applicable; conflict of interest not fully reported
Barrios et al. (2017) [25]	96%	Excellent	Currency/conversion not fully reported
Aguiar et al. (2022) [26]	96%	Excellent	Minor limitations only
Dalmau et al. (2024) [27]	91.6%	Excellent	Minor limitations only
Gaziano et al. (2019) [28]	85.4%	Very good	Discount rate and conflict-of-interest reporting partially complete
Arrabal et al. (2015) [29]	87.5%	Excellent	Introduction and currency/conversion reporting incomplete
Ntaios et al. (2019) [30]	79.2%	Very good	Introduction, funding source, and conflict-of-interest reporting incomplete

Cost-Effectiveness of Polypills

The included economic evaluations generally reported favourable cost-effectiveness findings for FDC polypills in secondary cardiovascular disease prevention. Across high-income settings, FDC polypills were commonly found to be cost-effective compared with usual care, standard care, monotherapy, or separate monocomponents. However, the magnitude of cost-effectiveness varied by setting, comparator, model assumptions, drug costs, perspective, and time horizon, as summarised in Table 4.

Among high-income country studies, evidence from Spain was particularly prominent, with most studies reporting favourable economic outcomes. These findings suggest that the CNIC-polypill may offer good economic value within the Spanish healthcare system,

particularly when improved adherence and reduction in recurrent cardiovascular events are considered. However, because several included studies were conducted within the same national health system, these findings should not be interpreted as universally transferable across all settings.

Evidence from other high-income countries also supported the potential cost-effectiveness of FDC polypills. Becerra et al. (2015) [19] reported favourable cost-effectiveness in the United Kingdom over a 10-year time horizon. Aguiar et al. (2022) [26] reported favourable outcomes over a lifetime horizon in Portugal, while Ntaios et al. (2019) [30] also used a lifetime horizon for cost-effectiveness analysis in Greece. In the United States, Gaziano et al. (2019) [28] adopted a lifetime horizon and reported ICERs of $20,073 per QALY for one strategy and $21,818 per QALY for another, with additional cost savings observed from a societal perspective.

Evidence from low- and middle-income countries was more limited but generally favourable. Lin et al. (2019) [20] applied a 5-year time horizon across multiple LMIC settings (China, India, Mexico, Nigeria, and South Africa) and reported ICERs of approximately $1,000–$2,000 per DALY averted, suggesting that FDC polypills may be economically attractive in resource-constrained settings. Singh et al. (2018) [24] also used a 5-year time horizon in India and reported favourable within-trial economic outcomes. However, the smaller number of LMIC studies means that conclusions should be interpreted cautiously, particularly given differences in drug pricing, health system capacity, affordability, and implementation feasibility across settings.

Table 4: Study-Level Economic Outcomes

Study ID	Country/Region	Comparator	Main Economic Outcome Reported	Time Horizon	Main Result
Rubio G. et al. (2021) [18]	Spain	Monotherapy	Cost per QALY/life-year gained	Lifetime	Favourable cost-effectiveness for CNIC-polypill
Gaziano et al. (2025) [11]	Spain	Standard care	ICER and major adverse cardiovascular events	Lifetime	Cost-effective from the Spanish healthcare perspective
Becerra et al. (2015) [19]	United Kingdom	Multiple monotherapy	Cost per QALY and events avoided	10 years	Approximately £8,200 per QALY gained
Lin et al. (2019) [20]	China, India, Mexico, Nigeria, South Africa	Usual care	Cost per DALY averted	5 years	Approximately $1,000–$2,000 per DALY averted
Piñeiro et al. (2025) [21]	Global	Usual care	Expert consensus on implementation and economic value	Not applicable	Contextual expert support; not a full economic evaluation
Cordero et al. (2023) [22]	Spain	Monotherapy	Cost savings and event rates	2 years	Cost-saving findings reported in observational analysis
González-Domínguez et al. (2023) [23]	Spain	Monotherapy	Incremental QALYs and ICER	Lifetime	Favourable cost-utility findings
Singh et al. (2018) [24]	India	Usual care	Cost per QALY and event rates	5 years	Favourable within-trial cost-effectiveness

Study ID	Country/Region	Comparator	Main Economic Outcome Reported	Time Horizon	Main Result
Barrios et al. (2017) [25]	Spain	Monotherapy	Events prevented and ICER	10 years	Cost-effective in post-MI secondary prevention
Aguiar et al. (2022) [26]	Portugal	Separate monocomponents	ICER, life-years, and QALYs	Lifetime	€1,557 per QALY gained
Dalmau et al. (2024) [27]	Spain	Monotherapy	Cost savings and recurrent MACE	2 years	€2,317–€2,407 cost savings reported
Gaziano et al. (2019) [28]	United States	Usual care	ICER, QALYs, life-years, budget impact	Lifetime	$20,073–$21,818 per QALY; societal cost savings
Arrabal et al. (2015) [29]	Spain	Multiple monotherapy	Cost per QALY/life-year gained	10 years	Favourable cost-effectiveness reported
Ntaios et al. (2019) [30]	Greece	Monotherapy	Cost per QALY and budget impact	Lifetime for cost-effectiveness; 5 years for budget impact	€2,926 per QALY gained

Note: Economic outcomes are reported in the currencies, price years, time horizons, perspectives, and comparator frameworks used in the original studies. Costs and ICERs were not adjusted for inflation or converted to a common currency year. Direct comparison of absolute ICER values across studies is therefore methodologically inappropriate because results may be influenced by time horizon, discount rate, analytic perspective, comparator definition, country-specific costs, and willingness-to-pay thresholds.

Factors Affecting Cost-Effectiveness of Polypills

Several factors influenced the cost-effectiveness of FDC polypills across the included studies. The most consistent drivers were drug cost, adherence improvement, cardiovascular events prevented, health system perspective, and duration of follow-up. Studies generally found that polypills became more economically attractive when they improved adherence and reduced recurrent cardiovascular events, especially myocardial infarction, stroke, hospitalisation, and revascularisation.

Drug cost was an important determinant of ICERs. Where the FDC polypill was priced competitively relative to separate monocomponents, the intervention was more likely to be cost-effective or cost-saving [24, 26, 27]. Conversely, where drug acquisition costs were higher, cost-effectiveness depended more heavily on the assumed magnitude of adherence improvement and event reduction [20, 28].

Adherence was another central driver. The simplified dosing structure of the FDC polypill was associated with improved medication adherence, which translated into better risk-factor control and fewer recurrent cardiovascular events in several models [18, 19, 24, 28]. However, because adherence effects were often modelled rather than directly observed over long periods, the magnitude of this benefit remains an important source of uncertainty.

The healthcare system context also shaped economic outcomes. In high-income countries, the polypill may reduce costs by preventing expensive hospital-based cardiovascular events [11, 19, 22, 27]. In LMICs, the potential value of polypills may be substantial because of high CVD burden and low adherence, but affordability, medicine availability, procurement systems, and patient out-of-pocket costs may strongly influence real-world cost-effectiveness [20, 24].

Perspective and Time Horizon in Economic Evaluations

The analytic perspective varied across studies and influenced the reported economic value of polypills. Several studies adopted a national health

system or healthcare payer perspective, focusing mainly on direct medical costs, including drug costs, outpatient care, hospitalisation, and cardiovascular event management [18, 19, 30]. Gaziano et al. (2019) [28] considered health sector, payer, and societal perspectives, allowing wider assessment of cost savings. Singh et al. (2018) [24] adopted a health system perspective in the Indian setting.

Time horizons also varied. Some studies used short or medium time horizons, such as 2 years [22, 27], 5 years [20, 24], or 10 years [19, 25, 29], while others used lifetime horizons [18, 11, 23, 30]. Studies with longer time horizons generally reported more favourable cost-effectiveness because they captured long-term prevention of recurrent cardiovascular events, mortality reduction, and accumulated QALY or life-year gains. Shorter time horizons were more conservative because they captured fewer downstream benefits.

Discount rate reporting was generally adequate but not uniform. Most studies reported discounting, while some reported it partially or did not provide sufficient detail in the extracted information [18, 19, 28]. This variation should be considered when comparing ICERs across studies, because differences in discounting can meaningfully affect long-term modelled cost-effectiveness estimates.

Geographic Distribution and Generalisability of Findings

The review identified a clear geographic imbalance in the evidence base. Spain accounted for a large share of the included studies [11, 22, 25, 27]. These studies consistently reported favourable economic findings for FDC polypills, but they were conducted within a relatively similar healthcare and reimbursement environment. Therefore, while the Spanish evidence is important, it should not be overgeneralised to other countries without considering differences in drug prices, treatment pathways, health system financing, and cost-effectiveness thresholds.

The non-Spanish high-income evidence from the United Kingdom [19], Portugal [26], Greece [30], and the United States [28] also suggested favourable economic value, although these studies used different models, comparators, and thresholds. LMIC evidence was comparatively limited, with the strongest multicountry evidence coming from Lin et al. (2019) [20] and trial-based evidence from India [24]. This imbalance means that the findings support the potential economic value of FDC polypills globally, but stronger country-specific evidence is still needed for LMIC policy decisions.

Heterogeneity Across Included Studies

Substantial heterogeneity was observed across the included studies. This heterogeneity is related to differences in study design, model structure, population characteristics, intervention composition, comparator, economic perspective, time horizon, discounting, outcome measure, and local cost inputs. Markov models and microsimulation approaches dominated the evidence base, but observational and trial-based economic evaluations were also included [22, 24, 27].

Outcome measures also differed. Some studies reported cost per QALY gained [19, 26, 28, 30], others reported cost per DALY averted [20], while some reported cardiovascular events prevented, recurrent major adverse cardiovascular events, or cost savings [22, 27]. These differences limited the feasibility of quantitative meta-analysis and justified the use of narrative synthesis.

Comparator choice was another source of heterogeneity. Some studies compared FDC polypills with usual care or standard care [11, 20, 24, 28], while others compared them with monotherapy or separate monocomponents [18, 19, 22, 30]. Because usual care and monotherapy may differ across health systems, direct comparison of ICERs across countries should be made cautiously.

Certainty and Limitations of the Economic Evidence

The certainty of the economic evidence was influenced by the predominance of model-based studies, differences in model assumptions, and limited direct evidence from LMICs. While most studies reported favourable economic outcomes, many relied on assumptions about long-term adherence, recurrent event reduction, treatment persistence, and health utility gains. These assumptions are reasonable within model-based economic evaluation but introduce uncertainty when applying the findings to real-world settings.

Evidence from observational studies and within-trial analyses provided useful real-world or trial-based support [22, 24, 27], but these studies were fewer than model-based evaluations. The Delphi consensus study by Piñeiro et al. (2025) [21] was useful for implementation interpretation but was not considered equivalent to a formal economic evaluation. Overall, the evidence suggests that FDC polypills are likely to be cost-effective in several settings, but certainty is stronger for high-income countries than for LMICs.

Publication Bias and Selective Reporting

Publication bias could not be assessed quantitatively because the included studies differed substantially in setting, design, comparator, outcome

measure, currency, price year, and ICER reporting. A funnel plot or pooled meta-analysis was therefore not appropriate. However, qualitative assessment suggested that publication bias and selective reporting remain possible concerns.

Funding and conflict-of-interest reporting were generally available but not complete in all studies. In particular, some studies had incomplete reporting of funding sources or conflicts of interest [24, 28, 30]. These limitations should be considered when interpreting the consistency of favourable findings across the evidence base. The possibility of selective publication of positive economic findings was therefore acknowledged as a limitation of this review.

Most included studies reported favourable cost-effectiveness results, and studies with positive findings, particularly those that are industry-funded or investigator-initiated around a specific marketed formulation, may be more likely to reach publication. Therefore, the consistently favourable direction of findings should be interpreted with appropriate caution.

Discussion

Main Findings

This systematic review evaluated the cost-effectiveness of fixed-dose combination (FDC) polypills for secondary cardiovascular disease (CVD) prevention across different healthcare and income settings. The included evidence generally suggests that FDC polypills may be cost-effective or cost-saving compared with usual care, standard therapy, monotherapy, or separate monocomponents. Across the included studies, favourable economic findings were mainly driven by improved adherence, reduced pill burden, prevention of recurrent cardiovascular events, and potential reductions in long-term healthcare costs.

However, the strength of this evidence differs across settings. Evidence from high-income countries, particularly Spain, was more abundant and consistently favourable. Evidence from LMICs was comparatively limited, with the strongest LMIC evidence coming from the multicountry modelling study by Lin et al. (2019) [20] and the within-trial economic evaluation by Singh et al. (2018) [24]. Therefore, while the findings support the potential economic value of FDC polypills globally, the evidence should be interpreted cautiously when applied to LMICs because local medicine prices, health system capacity, insurance coverage, procurement mechanisms, and patient affordability may differ substantially across countries.

The review also found considerable methodological heterogeneity across studies. Included studies differed in model structure, comparator, intervention composition, analytic perspective, time horizon, discount rate reporting, and outcome measures. Some studies reported ICERs or cost per QALY gained [19, 26, 28, 30], others reported cost per DALY averted [20], while some reported cost savings or cardiovascular events prevented [22, 27]. This heterogeneity justified the use of narrative synthesis rather than quantitative meta-analysis.

Comparison with Existing Literature

The findings of this review are broadly consistent with previous literature suggesting that FDC polypills can improve adherence and may offer good economic value in cardiovascular prevention. Espinosa et al. (2024) [31] reported that polypill therapy has potential value in cardiovascular prevention because it simplifies treatment and may improve adherence compared with conventional multi-drug regimens. This aligns with the present review, where adherence improvement was one of the most frequently reported drivers of cost-effectiveness.

Similarly, Jahangiri et al. (2022) [32] reviewed the cost-effectiveness of polypills in both primary and secondary prevention of CVD and found that the economic attractiveness of polypill strategies was largely linked to improved compliance, lower treatment complexity, and reduced cardiovascular events. These findings support the results of included studies such as Becerra et al. (2015) [19], Lin et al. (2019) [20], and Gaziano et al. (2019) [28], where improved adherence assumptions contributed substantially to favourable economic outcomes.

Lamy et al. (2024) [33] examined cost-effectiveness in the context of primary prevention rather than secondary prevention. Therefore, its findings should not be interpreted as directly equivalent to the evidence synthesised in this review. Nevertheless, it provides contextual support for the broader economic rationale of fixed-dose combination cardiovascular therapy, particularly where reduced pill burden and improved adherence are expected to improve long-term outcomes. The distinction between primary and secondary prevention remains important because patients with established CVD have higher baseline risk and may derive different absolute benefits from preventive therapy.

Nansseu et al. (2018) [34] highlighted the feasibility and implementation challenges of fixed-dose combination therapy in LMICs, including affordability, medicine availability, local policy support, and health system readiness. These concerns are consistent with the present review, which found that LMIC evidence remains limited and that economic results from high-

income countries cannot be transferred directly to resource-constrained settings without local adaptation.

Relevance and Implementation of Study Findings

The findings of this review have important implications for policy and clinical practice, but they should be applied with caution. The evidence suggests that FDC polypills may be a useful strategy for improving adherence and reducing recurrent cardiovascular events in secondary prevention. The inclusion of cardiovascular polypills in the World Health Organization Essential Medicines List in 2023 further supports their relevance as a potentially scalable intervention in cardiovascular prevention [9].

For policymakers, the findings support consideration of FDC polypills as part of secondary CVD prevention strategies, particularly where poor adherence, high pill burden, and recurrent cardiovascular events contribute substantially to healthcare costs. However, decisions about formulary inclusion, insurance reimbursement, or large-scale implementation should be based on local economic evaluation, affordability analysis, and budget impact assessment. This is especially important in LMICs, where health system financing, procurement systems, out-of-pocket payments, and drug availability may influence whether polypills are genuinely accessible and cost-effective.

For clinicians, FDC polypills may offer a practical option for patients who struggle with complex multidrug regimens, particularly older adults and patients with comorbidities. However, clinical use should still consider individual patient needs, contraindications, drug tolerability, dose flexibility, and availability of alternative regimens.

Future Research Directions

Future research should prioritise country-specific and region-specific economic evaluations of FDC polypills for secondary CVD prevention, particularly in LMICs. Although the current evidence suggests potential economic value, there remains limited direct evidence from resource-constrained settings. Future studies should use local data on medicine prices, treatment adherence, cardiovascular event rates, healthcare utilisation, patient out-of-pocket costs, and cost-effectiveness thresholds.

More real-world evidence is also needed. Many included studies relied on model-based assumptions about long-term adherence, event reduction, and survival benefits. Longitudinal observational studies and pragmatic trials would help determine whether the adherence and economic benefits predicted in models are achieved in routine practice. Future studies should also report discount rates, time horizons, model assumptions, sensitivity analyses, funding sources, and conflicts of interest more completely to improve transparency and comparability.

In addition, future economic evaluations should examine budget impact, affordability, equity, and implementation feasibility. Cost-effectiveness alone may not be sufficient for policy decisions, especially in LMICs where even cost-effective interventions may remain unaffordable without subsidy, insurance coverage, or procurement reform. Distributional cost-effectiveness analysis may also be useful for assessing whether FDC polypills reduce or widen inequalities in access to secondary prevention.

Strengths and Limitations

This systematic review provides a comprehensive synthesis of the cost-effectiveness evidence on fixed-dose combination (FDC) polypills for secondary cardiovascular disease prevention. A key strength of the study lies in its inclusion of evidence from both high-income countries and low- and middle-income settings, allowing for a broad assessment of economic value across diverse healthcare systems. The review followed a structured and transparent methodology consistent with PRISMA 2020 guidelines and applied the CHEERS checklist to evaluate the reporting quality of included economic evaluations. In addition, key economic dimensions such as perspective, time horizon, discounting, comparator structure, and uncertainty were systematically examined to enhance interpretability of findings.

Several limitations should also be acknowledged. The review protocol was not prospectively registered in PROSPERO, which represents a transparency limitation; however, all core methodological components, including eligibility criteria, search strategy, and data extraction procedures, were predefined prior to study selection.

The inclusion of Piñeiro et al. (2025) [21] as a Delphi consensus study was intentional but distinct from the main evidence base. It was treated as contextual evidence only, rather than a formal economic evaluation, to support interpretation of implementation and policy relevance without affecting the core cost-effectiveness synthesis.

The evidence base was also geographically skewed, with a substantial proportion of studies originating from Spain and relying on the CNIC-polypill formulation. This concentration, together with incomplete reporting of funding relationships in some studies, limits the ability to fully exclude potential sponsor influence within this subgroup.

Furthermore, evidence from low- and middle-income countries remains limited, despite the high burden of cardiovascular disease in these settings. Most

included studies were model-based and therefore dependent on assumptions regarding long-term adherence, clinical effectiveness, costs, and health utilities, which introduces uncertainty into the findings.

Additional limitations relate to heterogeneity across studies in terms of time horizon, discounting, perspective, comparator definitions, and outcome measures, which prevented quantitative synthesis. Publication bias could not be formally assessed due to methodological heterogeneity and lack of a common effect measure, although the predominance of favourable findings suggests possible underrepresentation of less positive results. Finally, only selected databases were searched, meaning that some relevant studies indexed elsewhere may not have been captured.

Despite these limitations, the review provides a structured and policy-relevant synthesis of available evidence and highlights important gaps for future research, particularly in low-resource settings.

Conclusion

This systematic review found that fixed-dose combination (FDC) polypills may represent a cost-effective strategy for secondary cardiovascular disease (CVD) prevention across different healthcare and income settings. Most included economic evaluations reported favourable outcomes, including cost savings, acceptable incremental cost-effectiveness ratios, cost per QALY gained, cost per DALY averted, and reductions in recurrent cardiovascular events. The main factors driving these findings were improved medication adherence, reduced pill burden, lower or comparable drug costs, and prevention of costly cardiovascular events.

However, the findings should be interpreted with caution. The evidence base was dominated by studies from high-income countries, particularly Spain, while direct evidence from low- and middle-income countries remained limited. In addition, many studies were model-based and relied on assumptions about long-term adherence, cardiovascular event reduction, costs, utilities, time horizons, and discounting. Differences in healthcare systems, drug pricing, reimbursement structures, affordability, and implementation capacity also limit the direct transferability of findings across countries.

Overall, the available evidence supports the potential economic value of FDC polypills for secondary CVD prevention, but it does not justify uniform implementation across all settings without local assessment. Policymakers considering polypill adoption should evaluate country-specific cost-effectiveness, budget impact, medicine affordability, procurement systems, patient access, and health system readiness. Further real-world economic evaluations, especially from LMICs, are needed to strengthen the evidence base and guide context-specific implementation decisions.

Supplementary Materials

Supplementary file available via: https://www.jebm.org/suppfile/765/Supplement-file-jebm010.pdf

Acknowledgements

Competing Interests: All the authors declare that they have no conflict of interest.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: All the resources consulted in the review are provided in the reference section.

Funding: No funding of any kind was received.

Authors' Contributions: This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Disclosure of AI Use: To improve language and readability, ChatGPT was utilized during the preparation of this manuscript. The authors critically reviewed, edited, and approved all AI-generated text and take full responsibility for the accuracy and integrity of the published work.

References

1. World Health Organization. Cardiovascular diseases (CVDs) [Internet]. 2025 [cited 2026 Feb 6]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Abreu-Silva EO de, Siepmann M, Siepmann T. Polypills in the Management of Cardiovascular Risk—A Perspective. J Clin Med. 2024 Sep 15;13(18):5487. doi: 10.3390/jcm13185487

3. Joseph P, Avezum Á, Ramasundarahettige C, Mony PK, Yusuf R, Kazmi K, et al. Secondary Prevention Medications in 17 Countries Grouped by Income Level (PURE): A Prospective Cohort Study. J Am Coll Cardiol. 2025 Feb 11;85(5):436–47. doi: 10.1016/j.jacc.2024.10.121
4. Laranjo L, Lanas F, Sun MC, Chen DA, Hynes L, Imran TF, et al. World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease: 2023 Update. Glob Heart. 2024 Jan 22;19(1):8. doi: 10.5334/gh.1278
5. Ogungbe O, Byiringiro S, Adedokun-Afolayan A, Seal SM, Himmelfarb CRD, Davidson PM, et al. Medication Adherence Interventions for Cardiovascular Disease in Low- and Middle-Income Countries: A Systematic Review. PPA. 2021 Apr 29;15:885–97. doi: 10.2147/PPA.S296280
6. Schwalm JD, Joseph P, Leong D, Lopez-Lopez JP, Onuma O, Bhatt P, et al. Cardiovascular disease in the Americas: optimizing primary and secondary prevention of cardiovascular disease. Lancet Reg Health Am. 2025 Feb 1;42:100964. doi: 10.1016/j.lana.2024.100964
7. Lopez-Lopez JP, Gonzalez AM, Lanza P, Lopez-Jaramillo P. Benefits of the Polypill on Medication Adherence in the Primary and Secondary Prevention of Cardiovascular Disease: A Systematic Review. Vasc Health Risk Manag. 2023 Sep 12;19:605–15. doi: 10.2147/VHRM.S421024
8. Salim H, Musmar B, Saifi M, Ayyad M, Ruzieh M, Azar J, et al. The Impact of Polypill on Adherence and Cardiovascular Outcomes: A Comprehensive Systematic Review with Meta-Analysis. Curr Cardiol Rev. 2024;20(2):e230124225968. doi: 10.2174/011573403X283174240110025442
9. O'Riordan M. Polypills Added to List of WHO's Essential Medicines [Internet]. TCTMD.com; 2023 [cited 2026 Feb 6]. Available from: https://www.tctmd.com/news/polypills-added-list-whos-essential-medicines
10. Birla S, Angural A, Madathumchalil A, Shende RV, Shastry SV, Mahadevappa M, et al. Redefining the polypill: pros and cons in cardiovascular precision medicine. Front Pharmacol. 2023 Sep 19;14:1268119. doi: 10.3389/fphar.2023.1268119
11. Gaziano T, Castellano JM, Dymond A, Looby A, Mealing S, Owen R, et al. Cost-effectiveness of the CV-polypill strategy versus standard care for secondary cardiovascular prevention in Spain: an analysis based on the SECURE trial. Lancet Reg Health Eur. 2025 Aug;55:101348. doi: 10.1016/j.lanepe.2025.101348
12. Hosseini MS, Jahanshahlou F, Akbarzadeh MA, Zarei M, Vaez-Gharamaleki Y. Formulating research questions for evidence-based studies. J Med Surg Public Health. 2024 Apr 1;2:100046. doi: 10.1016/j.glmedi.2023.100046
13. Johns C. Library Guides: Systematic Reviews: Question frameworks (e.g PICO) [Internet]. [cited 2026 Feb 6]. Available from: https://plymouth.libguides.com/systematicreviews/question
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71
15. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version. 2006 Apr 1;1(1):b92. doi: 10.13140/2.1.1018.4643
16. Mao Y, Lu Z. MeSH Now: automatic MeSH indexing at PubMed scale via learning to rank. J Biomed Semant. 2017 Apr 17;8(1):15. doi: 10.1186/s13326-017-0123-3
17. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMC Med. 2013 Mar 25;11(1):80. doi: 10.1186/1741-7015-11-80
18. Rubio G, Araujo F, Aguiar C, Carcedo D, Abreu-Oliveira TP, Paz S, et al. Cost-effectiveness of a cardiovascular polypill

strategy (aspirin, atorvastatin, ramipril) for the secondary prevention of cardiovascular disease based on real life improvement in risk factor control. Eur J Prev Cardiol. 2021 May 11;28(1). doi: 10.1093/eurjpc/zwab061.447

19. Becerra V, Gracia A, Desai K, Abogunrin S, Brand S, Chapman R, et al. Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. BMJ Open. 2015 May 9;5(5):e007111. doi: 10.1136/bmjopen-2014-007111
20. Lin JK, Moran AE, Bibbins-Domingo K, Falase B, Pedroza Tobias A, Mandke CN, et al. Cost-effectiveness of a fixed-dose combination pill for secondary prevention of cardiovascular disease in China, India, Mexico, Nigeria, and South Africa: a modelling study. Lancet Glob Health. 2019 Oct;7(10):e1346–58. doi: 10.1016/S2214-109X(19)30339-0
21. Piñeiro D, González-Juanatey JR, Abreu A, Alvarez EG, Ponte-Negretti C, Weisser B, et al. The Polypill (Acetyl Salicylic Acid, Atorvastatin, and Ramipril) Paradigm Shift in Secondary Prevention: Global Expert Delphi Consensus. Glob Heart. 2025;20(1):83. doi: 10.5334/gh.1466
22. Cordero A, Dalmau González-Gallarza R, Masana L, Fuster V, Castellano JM, Ruiz Olivar JE, et al. Economic Burden Associated with the Treatment with a Cardiovascular Polypill in Secondary Prevention in Spain: Cost-Effectiveness Results of the NEPTUNO Study. Clinicoecon Outcomes Res. 2023;15:559–71. doi: 10.2147/CEOR.S396290
23. González-Domínguez A, Durán A, Hidalgo-Vega Á, Barrios V. Cost-effectiveness of the CNIC-Polypill versus separate monocomponents in cardiovascular secondary prevention in Spain. Rev Clin Esp (Engl Ed). 2023 Aug 1;223(7):414–22. doi: 10.1016/j.rceng.2023.06.007
24. Singh K, Crossan C, Laba TL, Roy A, Hayes A, Salam A, et al. Cost-effectiveness of a fixed dose combination (polypill) in secondary prevention of cardiovascular diseases in India: Within-trial cost-effectiveness analysis of the UMPIRE trial. Int J Cardiol. 2018 Jul 1;262:71–8. doi: 10.1016/j.ijcard.2018.03.082
25. Barrios V, Kaskens L, Castellano JM, Cosin-Sales J, Ruiz JE, Zsolt I, et al. Usefulness of a Cardiovascular Polypill in the Treatment of Secondary Prevention Patients in Spain: A Cost-effectiveness Study. Rev Esp Cardiol (Engl Ed). 2017 Jan 1;70(1):42–9. doi: 10.1016/j.rec.2016.05.009
26. Aguiar C, Araujo F, Rubio-Mercade G, Carcedo D, Paz S, Castellano JM, et al. Cost-Effectiveness of the CNIC-Polypill Strategy Compared With Separate Monocomponents in Secondary Prevention of Cardiovascular and Cerebrovascular Disease in Portugal: The MERCURY Study. J Health Econ Outcomes Res. 2022;9(2):134–46. doi: 10.36469/001c.39768
27. Dalmau R, Cordero A, Masana L, Ruiz E, Sicras-Mainar A, González-Juanatey JR. The CNIC-polypill (acetylsalicylic acid, atorvastatin, and ramipril), an effective and cost-saving secondary prevention strategy compared with other therapeutic options in patients with ischaemic heart disease. Eur Heart J Open. 2024 Mar;4(2):oeae027. doi: 10.1093/ehjopen/oeae027
28. Gaziano TA, Pandya A, Sy S, Jardim TV, Ogden JM, Rodgers A, et al. Modeling the cost effectiveness and budgetary impact of Polypills for secondary prevention of cardiovascular disease in the United States. Am Heart J. 2019 Aug;214:77–87. doi: 10.1016/j.ahj.2019.04.020
29. Arrabal N, Kaskens L, Garcia-Alonso F, Gracia A. A Polypill Intervention To Improve Adherence For Secondary Cardiovascular Disease Prevention In Spain: A Cost-Effectiveness Study. Value Health. 2015 Nov 1;18(7):A393–4. doi: 10.1016/j.jval.2015.09.883
30. Ntaios G, Vemmos K, Papapetrou P, Zafeiri S, Rubio G. Economic evaluation of the CNIC Polypill for the secondary prevention of cardiovascular events in Greece –a cost-effectiveness and budget impact analysis. Value Health. 2019 Nov 1;22:S550. doi: 10.1016/j.jval.2019.09.778
31. Espinosa EVP, Matute EM, Sosa Guzmán DM, Khasawneh FT. The Polypill: A New

Alternative in the Prevention and Treatment of Cardiovascular Disease. J Clin Med. 2024 May 29;13(11):3179. doi: 10.3390/jcm13113179 PubMed PMID: 38892892; PubMed Central PMCID: PMC11172978.

32. Jahangiri R, Rezapour A, Malekzadeh R, Olyaeemanesh A, Roshandel G, Motevalian SA. Cost-effectiveness of fixed-dose combination pill (Polypill) in primary and secondary prevention of cardiovascular disease: A systematic literature review. PLoS One. 2022;17(7):e0271908. doi: 10.1371/journal.pone.0271908
33. Lamy A, Tong W, Joseph P, Gao P, Huffman MD, Roshandel G, et al. Cost effectiveness analysis of a fixed dose combination pill for primary prevention of cardiovascular disease from an individual participant data meta-analysis. eClinicalMedicine. 2024 Jul 1;73:102651. doi: 10.1016/j.eclinm.2024.102651
34. Nansseu JR, Tankeu AT, Kamtchum-Tatuene J, Noubiap JJ. Fixed-dose combination therapy to reduce the growing burden of cardiovascular disease in low- and middle-income countries: feasibility and challenges. J Clin Hypertens (Greenwich). 2018 Jan;20(1):168–73. doi: 10.1111/jch.13162