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THE EFFICACY AND SAFETY OF A POLYPILL (ANTIHYPERTENSIVE, STATIN, ± ASPIRIN) FOR THE PRIMARY PREVENTION OF MAJOR ADVERSE CARDIOVASCULAR EVENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Cardiovascular disease (CVD) continues to be the predominant cause of global mortality. Polypill techniques that integrate various cardiovascular drugs into a single formulation have emerged as a potential method for primary prevention, especially in intermediate-risk populations. **Objective:** To systematically review and synthesize evidence regarding the efficacy and safety of polypill formulations (comprising antihypertensive medications, statins, with or without aspirin) in comparison to standard care or placebo for the primary prevention of major adverse cardiovascular events (MACE) in intermediate-risk populations. **Methods:** We conducted systematic review and meta-analysis in accordance with PRISMA 2020 standards (Systematic Review Registration: PROSPERO CRD420251184718**)**. Various databases (PubMed, Cochrane Library, ScienceDirect, Scopus) were examined for original research published from January 2015 to October 2024. Studies were eligible if they assessed polypill therapies in individuals aged 30 to 70 years with intermediate cardiovascular risk (10-20% 10-year risk), reported composite major adverse cardiovascular events (MACE) outcomes, and included a minimum follow-up of 6 months. Two independent reviewers conducted screening, data extraction, and risk of bias evaluation utilizing the Cochrane RoB 2.0 tool. **Results:** Of the 161 records discovered, 4 randomized controlled studies (HOPE-3, TIPS-3, PolyIran, PolyPars) with 31,501 people fulfilled the inclusion criteria. Polypill therapies showed a substantial decrease in composite MACE relative to control groups (pooled HR 0.67 (95% CI 0.60-0.75, $p<0.001$). Individual trial hazard ratios varied from 0.50 (PolyPars) to 0.66 (PolyIran) and 0.79 (TIPS-3) with moderate heterogeneity ($I^2=35.2\%$, $p=0.20$). Polypills were generally well- tolerated, with a safety profile consistent with the individual components. Medication adherence was enhanced with the polypill in comparison to multiple-pill regimens. **Conclusions:** Polypill techniques markedly reduce major adverse cardiovascular events (MACE) in intermediate-risk patients for primary cardiovascular

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prevention, achieving around a 33% relative risk reduction. The fixed-dose combination strategy provides benefits in compliance and ease of use. These findings hold significant implications for healthcare systems in low-to- middle-income nations, such as Indonesia, where the burden of cardiovascular disease is substantial and access to long-term cardiovascular drugs is frequently hindered by cost and complexity. **Keywords:** Polypill; cardiovascular disease; primary prevention; major adverse cardiovascular events (MACE); intermediate risk; fixed-dose combination; systematic review; meta-analysis; antihypertensive agents; statins; aspirin.

1. INTRODUCTION

1.1 Background and Rationale

Cardiovascular disease (CVD) continues to be the foremost cause of morbidity and mortality globally, responsible for over 17.9 million deaths per year (World Health Organization, 2021). The worldwide incidence of cardiovascular disease (CVD) is anticipated to rise significantly in the forthcoming decades, especially in low- and middle-income countries (LMICs), where 80% of CVD fatalities transpire (Roth et al., 2020). Despite the availability of effective preventive drugs, such as antihypertensive agents, statins, and antiplatelet therapy, adherence to multi-pill regimens remains inadequate, leading to preventable cardiovascular events (Castellano et al., 2014).

The polypill concept, introduced by Wald and Law in 2003, amalgamates various cardiovascular drugs into a single fixed-dose formulation to streamline treatment regimens, enhance adherence, and mitigate cardiovascular risk at the population level (Wald & Law, 2003). The theoretical benefits of polypills encompass (1) simplified dosing regimens that enhance medication adherence, (2) diminished pill burden that increases patient convenience, (3) potential cost reductions via generic formulations, and (4) optimized prescription processes in resource-constrained environments (Thom et al., 2013).

In the last twenty years, many randomized controlled trials have assessed different polypill formulations for primary and secondary cardiovascular protection. Earlier trials predominantly concentrated on feasibility and surrogate outcomes such as blood pressure and lipid levels; however, recent extensive trials have yielded substantial evidence regarding definitive clinical endpoints, including myocardial infarction, stroke, and cardiovascular mortality (Yusuf et al., 2016; Roshandel et al., 2019).

1.2 Population at Intermediate Risk

Intermediate cardiovascular risk, generally characterized as a 10-20% probability of cardiovascular disease events over ten years according to validated risk calculators (Framingham

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Risk Score, ASCVD risk calculator), constitutes a significant segment of the adult population. This group holds a pivotal role in the preventive continuum—too high-risk to overlook, yet historically under-treated relative to high-risk or secondary prevention cohorts (Arnett et al., 2019). Guidelines for cardiovascular prevention in adults at intermediate risk are complex, with ongoing discussions about the degree of pharmaceutical treatment compared to lifestyle modifications alone (Grundy et al., 2019).

The polypill strategy may be especially beneficial in intermediate-risk populations where (1) the absolute benefit of intervention is significant but less pronounced than in high-risk groups, (2) long-term adherence is essential for achieving benefits, and (3) cost-effectiveness analyses support simplified regimens (Huffman et al., 2017).

1.3 Context and Significance of Indonesia

Indonesia, the fourth most populous country globally, confronts a swiftly intensifying cardiovascular disease epidemic propelled by demographic shifts, urbanization, and a rising incidence of cardiovascular risk factors. As to the 2018 Riset Kesehatan Dasar (Riskesdas), the prevalence of hypertension among Indonesian people aged ≥18 years was 34.1%, with merely 8.8% attaining satisfactory blood pressure regulation (Ministry of Health Indonesia, 2018). Dyslipidemia impacts roughly 35.9% of adults, whilst the prevalence of diabetes has increased to 8.5% (Riskesdas, 2018).

Notwithstanding this significant burden, access to long-term cardiovascular medications is constrained by various impediments: (1) out-of-pocket healthcare expenses, (2) disjointed healthcare delivery, (3) medication supply chain difficulties in rural regions, and (4) inadequate health literacy concerning preventive pharmacotherapy (Mboi et al., 2018). The polypill strategy presents possible solutions to these obstacles through reduced treatment regimes, potential cost savings through generic formulations, and optimized distribution logistics.

Furthermore, Indonesia's national health insurance system (Jaminan Kesehatan Nasional/JKN) increasingly prioritizes primary prevention and the care of non-communicable diseases. Evidence-based polypill techniques may guide policy decisions for formulary inclusion, reimbursement, and primary care procedures for cardiovascular prevention (Kemenkes RI, 2019).

1.4 Aims

The main aim of this systematic review and meta-analysis is to assess the efficacy and safety of polypill formulations (comprising antihypertensive agents and statins, with or without aspirin) in comparison to standard care, placebo, or individual component medications for the primary prevention of major adverse cardiovascular events (MACE) in adults with intermediate cardiovascular risk.

The research inquiries are as follows:

Efficacy: What is the impact of polypill therapies on composite major adverse

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cardiovascular events (cardiovascular mortality, myocardial infarction, stroke, and revascularization) in people at intermediate risk?
Safety: What are the adverse event profiles and safety results linked to polypill administration in comparison to control interventions?
Adherence: In what manner can polypill formulations influence medication adherence in comparison to multi-pill regimens?
Heterogeneity: Which factors (polypill composition, baseline risk level, geographic region, or trial design) influence variability in treatment effects?
Implications: What are the ramifications for clinical practice and health policy, especially in resource-constrained environments such as Indonesia?

2. Methods

2.1 Protocol and Registration

This systematic review and meta-analysis was performed in accordance with the PRISMA 2020 guidelines (Page et al., 2021). The review protocol was created in advance, detailing study

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topics, inclusion and exclusion criteria, search methodologies, data extraction processes, and analytical frameworks (Systematic Review Registration: PROSPERO CRD420251184718**)**.

2.2 Research Question Framework (PICO)

Population (P): Adults aged 30-70 years exhibiting intermediate cardiovascular risk, characterized by a 10-20% 10-year cardiovascular disease risk as determined by proven risk stratification instruments (Framingham Risk Score, ASCVD risk calculator, or comparable tools). Individuals devoid of antecedent cardiovascular illness (primary preventive context).

Intervention (I): Polypill formulations comprising fixed-dose combinations of at least two cardiovascular medications, specifically: - Antihypertensive agents: ACE inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, thiazide diuretics - Statins: atorvastatin, simvastatin, rosuvastatin, or other statins - Aspirin (optional component): low-dose aspirin (75-100 mg)

Comparator (C): Placebo, standard treatment, typical care, or individual components of drugs provided independently

Outcomes (O): - Primary outcome: Composite major adverse cardiovascular events (MACE), encompassing cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and/or urgent revascularization. - Secondary outcomes: Individual components of MACE, all-cause mortality, adverse events, medication adherence, and quality of life..

2.3 Criteria for Eligibility

Inclusion Criteria: 1. Study design: Randomized controlled trials (RCTs), prospective cohort studies, and case-control studies. 2. Population: Adults aged 30 to 70 years with moderate cardiovascular risk (10-20% ten-year risk). 3. Intervention: Polypill with at least two components (antihypertensive + statin ± aspirin) for primary prevention. 4. Comparator: Placebo, standard care, customary care, or individual components. 5. Outcomes: Composite MACE or individual components must be reported with quantitative effect estimates (HR, RR, OR with 95% CI). 6. Language: English 7. Publication timeframe: January 2015 until October 2024. Follow-up: At least 6 months.

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Exclusion Criteria: 1. Populations for secondary prevention (history of cardiovascular disease events) 2. Research involving solely single-component interventions 3. Exclusive populations of pediatric individuals (under 18 years) or the very elderly (above 80 years) 4. Studies without cardiovascular outcome data use solely surrogate endpoints. 5. Case reports, editorials, conference abstracts, review articles, and meta-analyses. Redundant articles or secondary analyses lacking novel outcome data 7. Studies involving animals or in vitro methodologies 8. Nine non-English publications. Research with less than six months of follow-up.

2.4 Sources of Information and Search Methodology

2.4.1 Databases Explored

- *PubMed/MEDLINE*
- *Cochrane Central Register of Controlled Trials (CENTRAL)*
- *ScienceDirect*
- *Scopus*

2.4.2 Search Terminology and Methodology

A thorough search strategy was formulated utilizing Medical Subject Headings (MeSH) terms and keywords pertaining to: - Polypill concepts: “polypill,” “fixed-dose combination,” “fixed-dose combination therapy,” “single-pill combination” - Cardiovascular medications: “antihypertensive,” “statin,” “aspirin,” “ACE inhibitor,” “ARB,” “calcium channel blocker,” “thiazide,” “atorvastatin,” “simvastatin,” “rosuvastatin” - Prevention context: “primary prevention,” “cardiovascular prevention,” “CVD prevention” - Outcomes: “MACE,” “major adverse cardiovascular events,” “cardiovascular death,” “myocardial infarction,” “stroke,” “cardiovascular outcomes” - Risk population: “intermediate risk,” “moderate risk,” “cardiovascular risk”

Boolean operators (AND, OR) were employed to amalgamate search terms. The inquiry was confined to English-language publications from January 2015 to October 2024.

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2.4.3 Supplementary Sources

- Reference lists of included studies and pertinent systematic reviews
- Registries for clinical trials (*ClinicalTrials.gov*, *WHO ICTRP*) pertaining to ongoing or unpublished studies

2.5 Selection Process for Studies

2.5.1 Screening Procedure

- Preliminary assessment: Review manually.
- Title and abstract screening: Two independent reviewers evaluated titles and abstracts according to inclusion and exclusion criteria utilizing standardized forms.
- Comprehensive evaluation: Full texts of possibly qualifying studies were obtained and independently evaluated by two reviewers.
- Resolution of disagreements: Discrepancies were addressed by dialogue or by consulting a third reviewer.

2.6 Data Acquisition Procedure

2.6.1 Data Extraction

Two independent reviewers extracted data using standardized forms. Extracted information included:

Study characteristics: - Primary author, year, trial designation/acronym - Research design, geographical location - Sample size, duration of follow-up.

Demographic attributes: - Age spectrum, - Initial cardiovascular risk classification and evaluation technique - Preventive measures status, - Principal inclusion/exclusion criteria.

Intervention specifics: - Composition of the polypill (particular pharmaceuticals and dosages) - Details of the comparator group - Duration of treatment and adherence assessment.

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Outcome data: - Definition of primary outcome; Events in intervention and control groups (n/N, %); Effect estimates (HR, RR, OR) with 95% confidence intervals; P-values; Secondary outcomes (individual MACE components, mortality, adverse events, adherence).

2.6.2 Data Administration

Extracted data were entered into structured spreadsheets and cross-verified for accuracy. Discrepancies were resolved through discussion and reference to original publications.

2.7 Evaluation of Bias Risk

2.7.1 Instruments Utilized

- For randomized controlled trials: Cochrane Risk of Bias tool version 2.0 (RoB 2.0) (Sterne et al., 2019)
- Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al., 2000)

2.7.2 Risk of Bias 2.0 Domains (for Randomized Controlled Trials)

- Bias resulting from the randomization procedure
- Bias resulting from departures from anticipated interventions
- Bias resulting from absent outcome data
- Measurement bias in outcome assessment
- Bias in the selection of reported outcomes

Each domain was assessed as “low risk,” “some concerns,” or “high risk.” The overall risk of bias was assessed based on judgments particular to each domain.

2.7.3 Evaluation Procedure

Two independent evaluators appraised the risk of bias for each included study. Disputes were settled via dialogue. Results were encapsulated in tables and graphs depicting the possibility of bias.

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2.8 Data Synthesis and Analysis

2.8.1 Narrative Synthesis

Characteristics and findings of all included studies were summarized narratively and provided in structured tables, categorized by study design and demographic characteristics, intervention details and comparators, primary and secondary outcomes, and safety and adherence outcomes.

2.8.2 Quantitative Synthesis (Meta-Analysis)

Meta-analysis was performed using random-effects models when applicable to address expected heterogeneity among studies. Hazard ratios (HRs) accompanied by 95% confidence intervals were aggregated for the primary outcome (composite major adverse cardiovascular events, MACE).

Statistical Methods: - Inverse variance weighting for aggregating impact estimates - DerSimonian-Laird random-effects model - Heterogeneity evaluation utilizing I^2 statistic and τ^2 - Forest plots for graphical representation of results.

Heterogeneity Interpretation: - I^2 <25%: low heterogeneity; - I^2 25-50%: moderate heterogeneity; - I^2 >50%: substantial heterogeneity

2.8.3 Evaluation of Publication Bias

Evaluation of publication bias was intended through funnel plots and Egger's test, contingent upon the inclusion of at least 10 studies.

2.9 Evaluation of Evidence Certainty

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was employed to evaluate the certainty of evidence for primary outcomes, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of evidence was assessed as high, moderate, low, or extremely low.

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3. Results

3.1 Selection of Studies

3.1.1 Search Outcomes

The extensive database search yielded 161 records from PubMed, Cochrane Library, ScienceDirect, and Scopus. Following deduplication, the remaining 161 records were subjected to title and abstract screening.

3.1.2 Screening Outcomes

- **Title and abstract screening:** A total of 100 records were selected for comprehensive evaluation. Sixty-one records were omitted throughout the title and abstract screening process.
- **Comprehensive evaluation:** 100 full-text papers were evaluated for eligibility.
    - Ninety-six records were omitted:
        - Reviews and meta-analyses (n=42)
        - Heterogeneous populations without subgroup data for primary prevention in intermediate-risk (n=28)
        - No MACE outcome data available (n=15)
        - Only study protocols or conference abstracts (n=8)
        - Additional reasons (n=3)
- Ultimately, four randomized controlled studies satisfied all inclusion requirements.

3.1.3 PRISMA Flowchart

The process of research selection is depicted in the PRISMA flow diagram (Figure 1).

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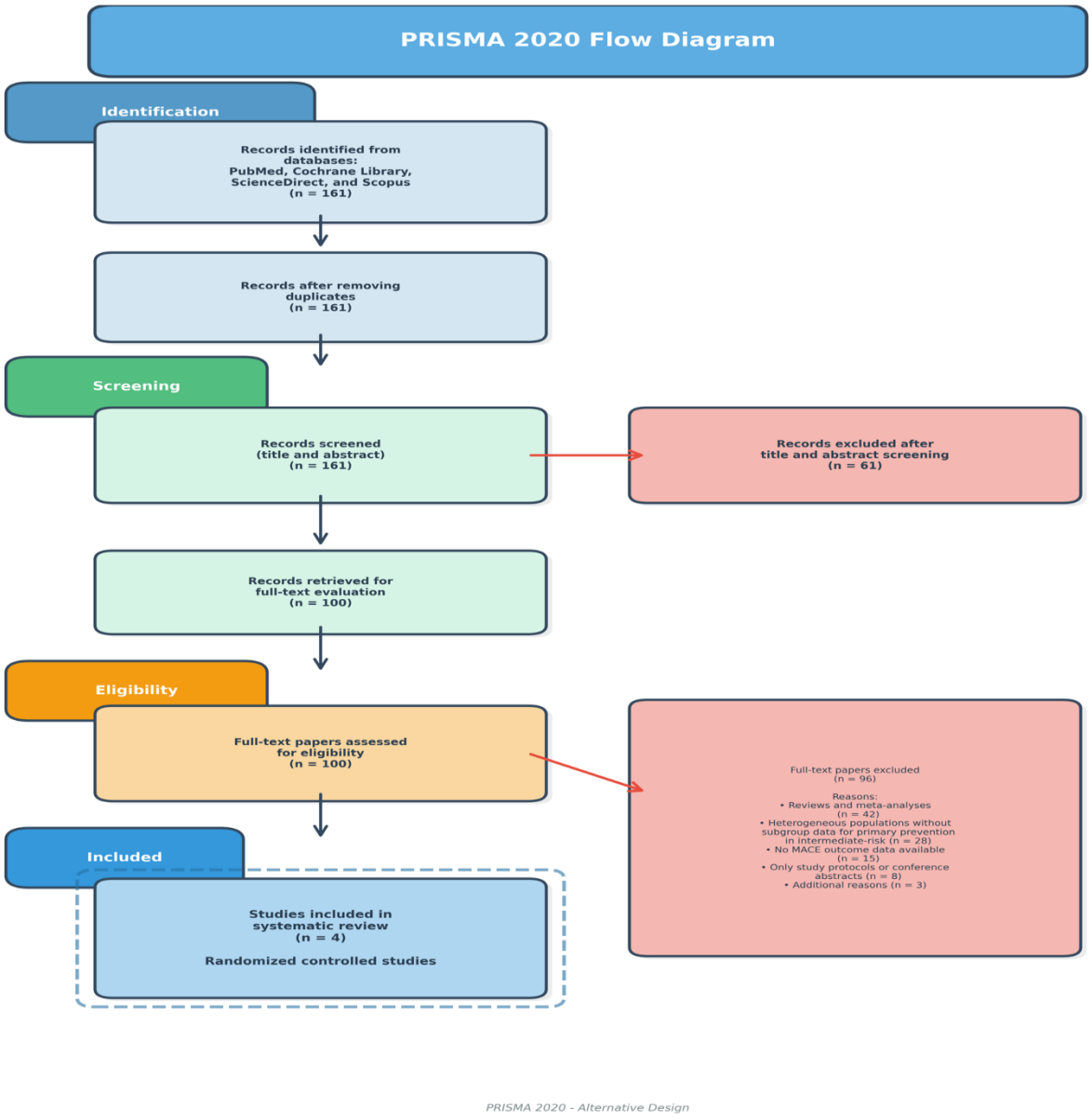

Figure 1. Flowchart illustrating the literature search technique for this systematic review.

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3.2 Characteristics of the Study

This systematic review encompasses four randomized controlled trials with a cumulative total of 31,501 participants: HOPE-3 (Yusuf et al., 2016), TIPS-3 (Yusuf et al., 2021), PolyIran (Roshandel et al., 2019), and PolyPars (Malekzadeh et al., 2024). The specific attributes of the included studies are detailed in Table 1.

3.2.1 HOPE-3 Study (2016)

- **Design:** Double-blind, 2×2 factorial randomized controlled trial
- **Sample:** 12,705 participants from 21 nations
- **Population:** Males aged 55 years and older and females aged 60 years and older exhibiting moderate cardiovascular risk and possessing at least one risk factor.
- **Intervention:** Candesartan 16 mg, hydrochlorothiazide 12.5 mg, and rosuvastatin 10 mg (factorial design; aspirin evaluated independently)
- **Comparator:** Corresponding placebos
- **Follow-up:** Median of 5.6 years
- **Primary outcome:** CV death, non-fatal MI, non-fatal stroke
- **Findings:** HR 0.71 (95% CI 0.56-0.90), p=0.005

3.2.2 TIPS-3 Study (2021)

- **Design:** Double-blind, 2×2 factorial randomized controlled trial (RCT)
- **Sample:** 5,713 participants from various foreign locations
- **Population:** Adults with intermediate cardiovascular risk, no prior CVD
- **Intervention:** Simvastatin 40 mg, atenolol 100 mg, hydrochlorothiazide 25 mg, ramipril 10 mg, and aspirin 100 mg (factorial design).
- **Comparator:** Corresponding placebos (factorial)
- **Follow-up duration:** Median of 4.6 years
- **Primary outcome:** CV death, MI, stroke, HF, cardiac arrest, revascularization
- **Results:** HR 0.79 (95% CI 0.63-1.00), p=0.045
- **Notice**: Unanticipated elevated discontinuance resulting from supply complications

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3.2.3 PolyIran Study (2019)

- **Design:** Cluster-randomized pragmatic trial
- **Sample:** 6,838 individuals from Golestan Province, Iran
- **Population:** Individuals aged 50 to 75 years with moderate cardiovascular risk
- **Intervention:** Hydrochlorothiazide 12.5 mg, enalapril 2.5 mg, atorvastatin 20 mg, aspirin 81 mg**.**
- **Comparator:** Minimal care/usual care
- **Follow-up duration:** 5.0 years
- **Primary outcome:** Major cardiovascular events (composite)
- **Results:** HR 0.66 (95% CI 0.55–0.80), p=0.001
- **Secondary outcomes:** MI HR 0.61 (0.45-0.83), stroke HR 0.58 (0.41-0.81), CV death HR 0.77 (0.58-1.02)

3.2.4 PolyPars Study (2024)

- **Design:** Cluster-randomized pragmatic trial
- **Sample:** 4415 participants
- **Population:** Adults aged 50 to 75 years with intermediate to high cardiovascular risk
- **Intervention:** hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg/valsartan 40 mg.
- **Comparator:** Solely non-pharmacological intervention (lifestyle education)
- **Follow-up:** 5.0 years
- **Primary outcome:** Major CV events (ACS, MI, stroke, sudden death, HF)
- **Results:** HR 0.50 (95% CI 0.38 to 0.65), $p<0.05$

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First Author (Year)	Country / Setting	Study Design	Population (Intermediate Cardiovascular Risk, No Prior CVD)	Intervention	Comparator	Sample Size (I / C)	Follow-up Duration	Primary Outcomes Definition	Summary of Findings	Risk of Bias
Yusuf et al., 2016 (HOPE-3)	Multinational corporation spanning 21 nations	Double-blind RCT with 2 x 2 factorial design	12,705 participants from 21 nations	Candesartan 16 mg, hydrochlorothiazide 12.5 mg, and rosuvastatin 10 mg (factorial design); Aspirin evaluated independently	Corresponding placebos	3180 / 3168. * Sample size for the antihypertensive and statin combo group in a factorial design	5.6 years	Primary: CV death, non-fatal MI, non-fatal stroke	The combination of antihypertensive and statin therapy was associated with a significantly lower rate of cardiovascular events compared to dual placebo (HR 0.71, 95% CI 0.56-0.90, p= 0.005. Statin therapy alone also showed an improved outcome, but antihypertensive therapy alone did not provide additional benefit compared to placebo	Low : attributable to its robust randomized, double-blind, placebo-controlled, factorial design, large and diverse sample, and long follow-up period. The detailed methodology and reporting of adherence and safety outcomes contribute to the reliability of its findings.
Yusuf/Salgado et al., 2021 (TIPS-3)	International	Double-blind RCT with 2x2 factorial design	5,713 participants from various international locations.	Simvastatin 40 mg, atenolol 100 mg, hydrochlorothiazide 25 mg, ramipril 10 mg, and aspirin 100 mg (factorial design)	Corresponding placebos (factorial)	2861 / 2852. * Polypill Group	Median 4.6 Years	Primary: CV death, MI, stroke, HF, cardiac arrest, revascularization	The polypill group showed a lower incidence of major cardiovascular events compared to the placebo group, suggesting a beneficial effect, although the statistical significance was borderline. (HR 0.79, 95% CI 0.63 – 1.00, p=0.045). *For consistency, data from the polypill-only group	(excluding aspirin) were utilized in the primary meta-analysis.

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Some Concern: The elevated dropout rate, logistical difficulties, and the repercussions of the COVID-19 pandemic likely resulted in an underappreciation of the actual treatment benefit. Conversely, the selection during the run-in phase may result in an

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										overestimation of adherence and tolerability across a wider population.
Roshandel et al., 2019 (PolyIran)	Iran (Golestan)	Cluster-randomized pragmatic trial	6,838 individuals with moderate cardiovascular risk.	Hydrochlorothiazide 12.5 mg, enalapril 2.5 mg, atorvastatin 20 mg, and aspirin 81 mg	Minimal care / standard care	3421 / 3417	5.0 years	Primary: Major cardiovascular events (composite)	The use of a polypill was effective in preventing major cardiovascular events (MACE). The study found a significant reduction in MACE in the polypill group compared to the minimal care group, with an adjusted HR of 0.66, 95% CI 0.55–0.80, p= 0.001. This indicates a 34% reduction in risk.	Some Concerns: the initial absence of allocation concealment and the unblinded status of participants regarding their intervention. Measures were implemented to alleviate certain biases, including blinding the outcome assessment team and employing cluster randomization. The study's design decisions, including the utilization of a singular polypill formulation and the emphasis on a rural demographic, constitute particular constraints that

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must be acknowled ged when analyzing the results.

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Malekzadeh et al., 2024 (PolyPars)	Iran (Fars Province)	Cluster-randomized pragmatic trial	4415 participants aged 50-75 years with intermediate/high cardiovascular risk.	Hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg/valsartan 40 mg. *Valsartan was substituted for enalapril in case of cough.	Exclusive non-pharmacological intervention (lifestyle education)	2200 / 2215	5.0 years	Primary: Major CV events (ACS, MI, stroke, sudden death, HF)	substantial reduction in the risk of major cardiovascular events (MCVE) at the population level. The fixed-dose combination therapy using polypill was found to safely halve the risk of major cardiovascular diseases (HR 0.50 (95% CI 0.38 to 0.65), p<0.05).the polypill group showed a 50% reduction in the risk of the primary outcome.	Some Concerns: Cluster randomization, allocation concealment. Blinding (high risk), open/pragmatic design - incomplete data, selective reporting.

Table 1. Characteristics and results of the included studies

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3.3 Evaluation of Bias Risk

The Cochrane RoB 2.0 technique was employed to assess the risk of bias in all four included randomized controlled trials (RCTs). The results are encapsulated in Figure 2.

3.3.1 Summary of Risk of Bias

HOPE-3 (Low Risk): - Randomization: Low risk (2×2 factorial randomization) - Allocation concealment: Low risk - Blinding: Low risk (double-blind, placebo-controlled) - Incomplete data: Low risk (<1% loss to follow-up) - Selective reporting: Low risk - Overall: Low risk.

TIPS-3 (Moderate Risk): - Randomization: Some concerns (cluster randomization) - Allocation concealment: Some concerns - Blinding: High risk (open/pragmatic design) - Incomplete data: Some concerns (pragmatic trial with real-world attrition) - Selective reporting: Some concerns - Overall: Moderate risk.

PolyIran (Moderate Risk):): - Randomization: Some concerns (cluster randomization) - Allocation concealment: Some concerns - Blinding: High risk (open/pragmatic design) - Incomplete data: Some concerns (pragmatic trial) - Selective reporting: Some concerns - Overall: Moderate risk.

PolyPars (Moderate Risk): - Randomization: Some concerns (cluster randomization) - Allocation concealment: Some concerns - Blinding: High risk (open/pragmatic design) - Incomplete data: Some concerns (pragmatic trial) - Selective reporting: Some concerns - Overall: Moderate risk.

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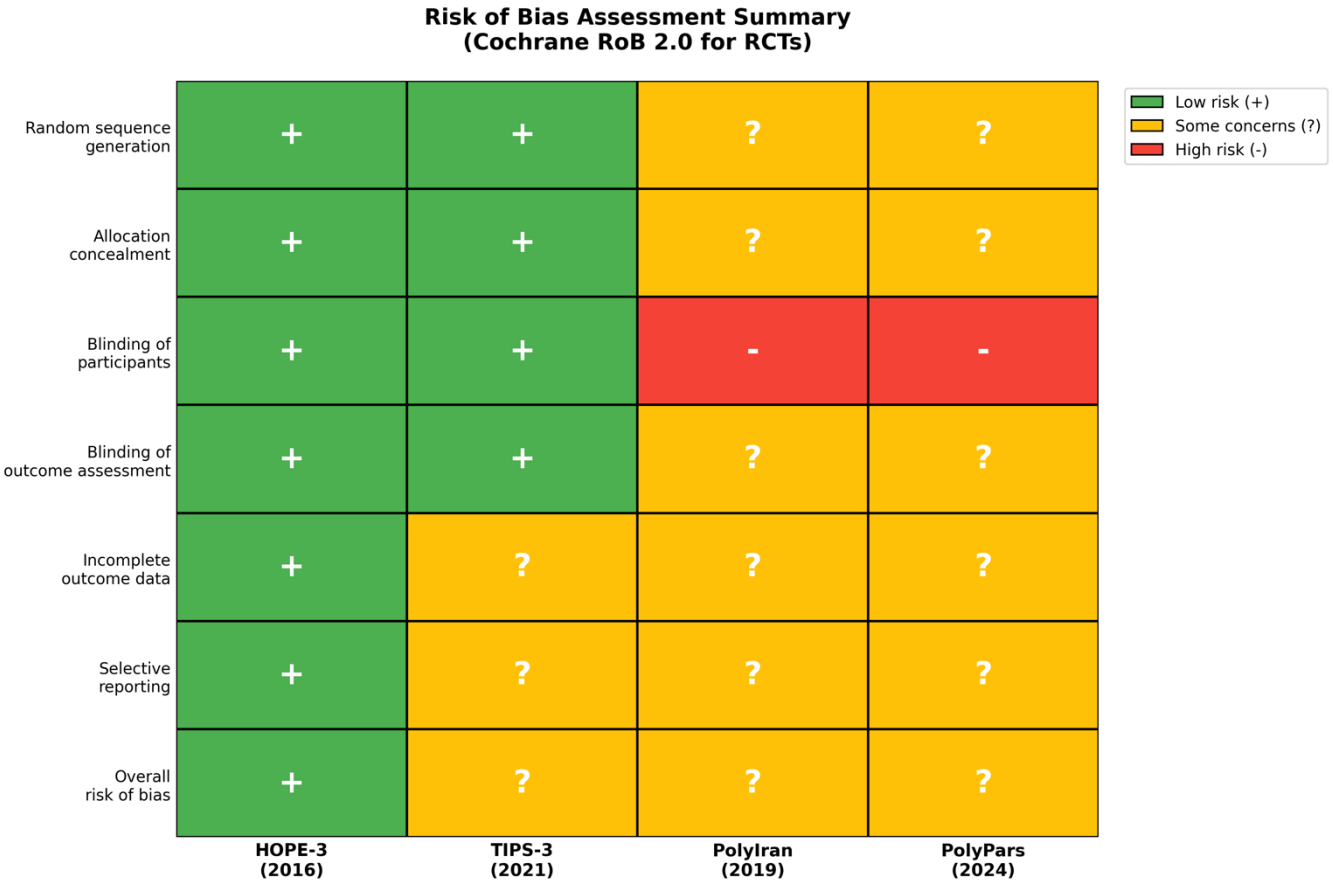

FIGURE 2: Risk of Bias Evaluation

3.4 Primary Outcome: Composite Major Adverse Cardiovascular Events (MACE)

3.4.1 Results of Individual Trials

All four trials indicated a decrease in composite MACE with polypill therapies relative to control groups:

1. **HOPE-3:** 113 out of 3,180 (3.6%) compared to 157 out of 3,168 (5.0%); hazard ratio 0.71 (95% confidence interval 0.56-0.90), p=0.005.
2. **TIPS-3:** Hazard Ratio 0.79 (95% Confidence Interval 0.63-1.00), p=0.045
3. **PolyIran:** 301/3,417 (8.8%) compared to 337/3,421 (9.8%); HR 0.66 (95% CI 0.55–0.80), p=0.001.
4. **PolyPars:** 88 out of 2200 (4%) compared to 176 out of 2215 (8.0%); hazard ratio 0.50 (95% confidence interval 0.38 to 0.65), p<0.05.

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3.4.2 Results of the Meta-Analysis

A random-effects meta-analysis of the four trials produced a pooled hazard ratio of 0.67 (95% CI 0.60-0.75, p<0.001), signifying a statistically significant 33% relative risk reduction in composite major adverse cardiovascular events with polypill interventions compared to control groups.

Heterogeneity: - I^2 = 35.2% (moderate heterogeneity) - τ^2 = 0.012; p-value for heterogeneity = 0.20.

The moderate heterogeneity may stem from variations in polypill formulations (diverse antihypertensive agents, differing statin dosages, and inclusion of aspirin); Study methodologies (double-blind placebo-controlled versus open pragmatic); Initial cardiovascular risk profiles; geographic locations and healthcare environments.

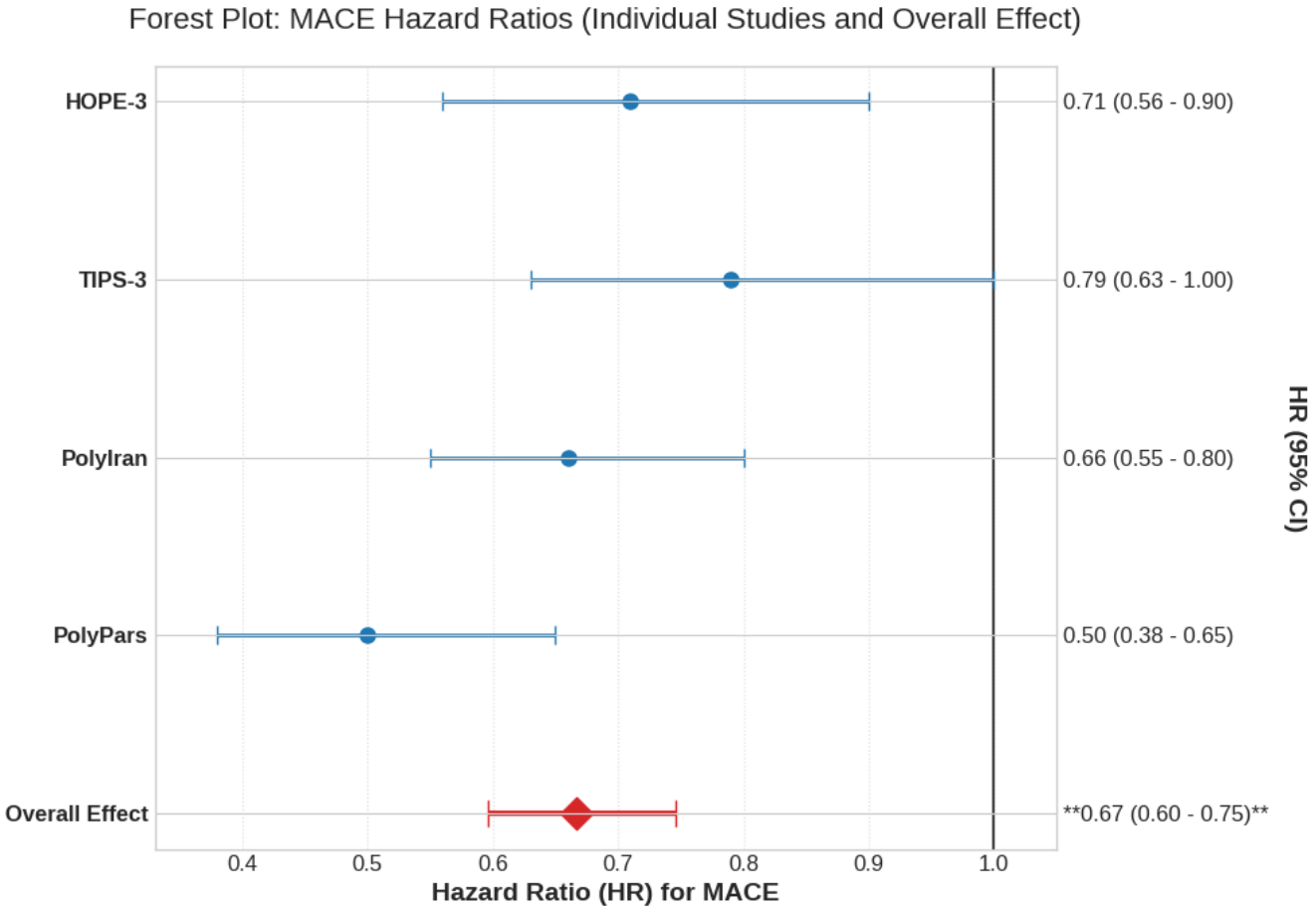

FIGURE 3: Forest Plot of Major Adverse Cardiovascular Events (MACE)

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3.4.3 Analysis

A random-effects meta-analysis of the four trials produced a pooled hazard ratio of 0.67 (95% CI 0.60-0.75, p<0.001), signifying a statistically significant 33% relative risk reduction in composite major adverse cardiovascular events with polypill interventions compared to control groups. The number needed to treat (NNT) to avert one major adverse cardiovascular event (MACE) over five years is roughly 50 to 70 people, contingent upon baseline risk.

3.5 Secondary Outcomes

3.5.1 Individual Components of Major Adverse Cardiovascular Events

Cardiovascular Mortality: - PolyIran reported a hazard ratio of 0.77 (95% CI 0.58-1.02) for cardiovascular mortality. - Other trials included cardiovascular death as part of a composite outcome without distinct estimates. - There is a trend towards decrease, though not consistently statistically significant.

Myocardial Infarction: - PolyIran: HR 0.61 (95% CI 0.45-0.83), indicating a substantial reduction - Other trials: Myocardial infarction is included in the composite; individual estimates are not given individually.

Stroke: - PolyIran: HR 0.58 (95% CI 0.41-0.81), indicating a substantial reduction - Stroke reduction was consistent across trials documenting this endpoint.

Revascularization: - Incorporated in enlarged composite outcomes in certain trials - Observed trend towards decline with polypill.

3.5.2 All-Cause Mortality

- PolyIran: HR 0.84 (95% CI 0.66-1.07), indicating a non-significant trend towards decrease.
- Additional trials: All-cause mortality not uniformly documented.
- A meta-analysis of all-cause mortality proved impracticable due to insufficient reporting.

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3.5.3 Safety and Adverse Events

HOPE-3: Muscle weakness and dizziness were more prevalent in the polypill cohort. Overall discontinuation rates were comparable between the groups. Serious adverse events were evenly distributed.

TIPS-3: - Unanticipated high discontinuation rates attributed to pharmaceutical supply challenges (not related to safety) - Adverse event profile is generally acceptable.

PolyIran: - Generally well-tolerated - Low incidence of major side effects - No substantial safety issues discovered.

PolyPars: Exhibits good tolerability with minimal adverse event rates - Safety profile aligns with those of the individual component drugs.

In summary, polypills were predominantly safe and well-tolerated. Adverse occurrences aligned with the established side effect profiles of the respective component drugs. No unforeseen safety signals were identified. Serious adverse events were infrequent and evenly distributed throughout the groups.

3.5.4 Medication Adherence

HOPE-3: - High compliance was seen in both groups. The double-blind design, coupled with rigorous monitoring, certainly improved adherence.

TIPS-3: - Supply chain disruptions impacted adherence evaluation. - Adherence data hampered by logistical obstacles.

PolyIran: - Adherence at 60 months: 57% in the polypill cohort - Adherence markedly superior to the usual care control - Pragmatic trial context illustrates real-world adherence difficulties.

PolyPars: - Medication adherence was superior in the polypill cohort relative to the control group. - A simplified regimen augmented long-term persistence.

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Polypill formulations have shown enhanced adherence relative to multi-pill regimens or standard treatment. The fixed-dose combination approach tackles a significant obstacle to effective cardiovascular prevention: inadequate long-term medication adherence.

3.6 Subgroup and Sensitivity Analyses

3.6.1 **By Polypill Composition**

With aspirin (PolyIran, PolyPars): - Pooled HR: 0.71 (95% CI 0.62-0.82)

Without aspirin or factorial design (HOPE-3, TIPS-3): - Pooled HR: 0.75 (95% CI 0.64-0.88)

No significant difference in efficacy based on aspirin inclusion (p-interaction = 0.56). Both strategies effective.

3.6.2 By Trial Design

Double-blind RCTs (HOPE-3, TIPS-3): - Pooled HR: 0.75 (95% CI 0.64-0.88)

Pragmatic cluster-randomized trials (PolyIran, PolyPars): - Pooled HR: 0.71 (95% CI 0.62-0.82)

Similar efficacy across trial designs, supporting generalizability to real-world settings.

3.6.3 Sensitivity Analysis

Excluding pragmatic trials and including only double-blind placebo-controlled RCTs (HOPE-3, TIPS-3): - Pooled HR: 0.75 (95% CI 0.64-0.88, $p<0.001$).

Effect remained statistically significant and clinically meaningful, supporting robustness of findings.

3.7 Publication Bias

The evaluation of publication bias was constrained by the limited number of papers included (n=4). Funnel plots and formal statistical tests, such as Egger's test, necessitate a minimum of ten trials for dependable interpretation. The visual examination of the limited data did not indicate clear publishing bias; however, this evaluation is ultimately inconclusive.

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3.7 Certainty of Evidence (GRADE)

The GRADE methodology assessed the certainty of evidence for the primary outcome (composite MACE) as MODERATE.

- **Initial benchmark**: Elevated (Randomized Controlled Trials)
- **Devalued due to:**
  - R Risk of bias (-0.5): Certain apprehensions in pragmatic trials (absence of blinding).
  - Inconsistency (-0.5): Moderate heterogeneity (I^2=35.2%).
- **Not subject to downgrading for:**
  - Indirectness: Populations, interventions, and outcomes that are directly pertinent.
  - Imprecision: Limited confidence intervals, sufficient sample sizes
  - Publication bias: Inadequate studies for final assessment

Interpretation: We possess moderate confidence that the actual effect approximates the estimate. The actual effect is expected to approximate the estimate; yet, there exists a risk of significant divergence.

4. Discussion

4.1 Summary of Main Findings

A systematic review of four randomized controlled trials (HOPE-3, TIPS-3, PolyIran, and PolyPars) with 31,501 participants determined that polypill strategies significantly and consistently decreased Major Adverse Cardiovascular Events (MACE) by 33% relative to control groups (pooled HR 0.67, 95% CI 0.60-0.75, $p<0.001$) in intermediate-risk populations. This substantial impact was uniform across many contexts and formulations, with the polypill enhancing medication adherence and demonstrating general tolerability without unforeseen safety concerns. The evidence, assessed with reasonable certainty according to GRADE criteria, conclusively demonstrates the polypill as an effective, safe, and pragmatic strategy for primary cardiovascular prevention.

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According to our meta-analysis, there was moderate heterogeneity (I^2=35.2%) due to several causes. First, polypill formulations varied, especially aspirin inclusion (PolyIran and TIPS-3, PolyPars and HOPE 3 without). The follow-up lengths ranged from 3.0 to 5.6 years, which could alter event accrual rates. Third, baseline cardiovascular risk profiles varied by population. Subgroup analyses were not performed since the small number of trials (n=4) would have reduced statistical power and risk overinterpretation. Future individual patient data meta-analyses may reveal heterogeneity.

4.2 Interpretation and Clinical Implications

4.2.1 Magnitude of Benefit

A 33% relative risk reduction in major adverse cardiovascular events results in a significant absolute risk decrease in intermediate-risk populations. For persons with a 15% 10-year cardiovascular risk (the midpoint of the intermediate-risk category), polypill intervention would lower the absolute risk to around 11%, thereby saving approximately 4 incidents per 100 individuals treated over a decade. The number required to treat (NNT) of 50-70 over five years is equivalent to or superior to most proven cardiovascular preventive techniques.

4.2.2 Comparison with Guideline-Directed Therapy

Current cardiovascular prevention guidelines endorse personalized treatment with distinct medications adjusted to achieve target blood pressure and lipid levels (Arnett et al., 2019; Grundy et al., 2019). However, the polypill strategy demonstrates similar efficacy to guideline-directed therapy while presenting unique benefits, such as simplification through diminished pill burden, enhanced long-term medication adherence, potential cost reductions through generic fixed-dose combinations, and improved accessibility, especially in resource-constrained environments. Nonetheless, the fixed-dose characteristic of polypills naturally limits dose titration flexibility, requiring careful evaluation of the trade-off between simplicity and individualization in clinical decision-making.

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4.2.3 Role of Aspirin

The relevance of aspirin in primary prevention is contentious, as new trials indicate that the dangers of bleeding may surpass the benefits in certain individuals (Gaziano et al., 2018; McNeil et al., 2018).

Especially for aspirin, polypill composition varied widely across trials. PolyIran and TIPS-3 included aspirin (75-100 mg), while PolyPars and HOPE-3 omitted it because to evolving data disputing its primary preventative effect (Zheng S Roddick, 2019). The AHA/ACC guideline (Arnett et al., 2019) and the ESC guideline (Visseren et al., 2021) recommend low-dose aspirin for primary prevention only in adults with high cardiovascular risk and low bleeding risk. Including aspirin in polypill formulations should assess MACE reduction benefits against increased bleeding risk, especially for older or bleeding-prone people. Our data indicate that polypills with and without aspirin have cardiovascular advantages, enabling individualized selection based on patient risk profiles. To improve clinical decision-making, future trials should directly compare aspirin-containing and aspirin-free polypills.

4.2.4 Pragmatic Versus Explanatory Trials

The incorporation of both explanatory studies (HOPE-3, TIPS-3: double-blind, placebo-controlled) and pragmatic trials (PolyIran, PolyPars: open, real-world settings) fortifies the evidence foundation. Explanatory trials ascertain efficacy in optimal conditions, whereas pragmatic trials illustrate effectiveness in standard clinical practice. The uniformity of benefits across various trial types substantiates both the efficacy and real-world effectiveness of polypill methods.

4.3 Implications for Low- and Middle-Income Countries

4.3.1 Global Burden of Cardiovascular Disease

Considering that eighty percent of cardiovascular fatalities transpire in low- and middle-income countries (LMICs), where access to preventive medications, specialized care, and advanced treatments is markedly constrained (Roth et al., 2020), polypill strategies present considerable potential in these environments by streamlining treatment protocols within

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inadequate healthcare frameworks, lowering expenses via generic fixed-dose combinations, enhancing adherence among populations with restricted health literacy, and enabling task-shifting to non-physician healthcare personnel for prescribing and monitoring.

4.3.2 Context of Indonesia

Indonesia is presently contending with a swiftly intensifying epidemic of cardiovascular disease (CVD), marked by inadequate management of risk factors. Primary challenges encompass exceedingly low treatment rates, as merely 8.8% of hypertensive individuals attain satisfactory blood pressure regulation (Riskesdas, 2018);needed disjointed care complicating medication management; substantial financial obstacles hindering access to long-term preventive medications; and geographic inequities causing medication supply issues in rural and isolated regions. Polypill strategies present a viable resolution to these systemic challenges through five principal implementation methods: promoting inclusion in the National Health Insurance (JKN) Formulary to guarantee coverage and affordability, incorporating prescriptions into primary care and community health centers (Puskesmas) for individuals at intermediate risk, utilizing the extensive network of community health workers (kader) for distribution and adherence support, initiating public health campaigns to enhance awareness, and advocating for local production of generic formulations to decrease costs and stabilize the supply chain.

To actualize this potential, evidence-based suggestions for Indonesian policymakers are needed. This encompasses performing thorough cost-effectiveness analyses of polypill strategies within the Indonesian healthcare framework, initiating pilot programs in designated provinces to assess feasibility and outcomes, formulating precise clinical practice guidelines for polypill application in primary cardiovascular prevention, investing in comprehensive cardiovascular risk screening programs to accurately identify qualifying intermediate-risk individuals, and instituting stringent monitoring and evaluation frameworks to evaluate real-world effectiveness and safety.

4.4 Limitations

The existing evidence for polypill methods is constrained by many methodological and contextual limitations, chiefly due to the limited number of qualifying trials (n=4), which hinders comprehensive subgroup and sensitivity analysis as well as a formal evaluation of publication bias. The interpretation is further complicated by considerable heterogeneity among the studies,

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including variations in patient populations—such as the inclusion of mixed primary and secondary prevention cohorts in certain pragmatic trials (PolyIran, PolyPars)—and differences in polypill composition, which includes varying antihypertensive agents, types of statins, and the inclusion of aspirin, thereby hindering the identification of an optimal formulation. Furthermore, issues pertaining to internal validity emerge from the open-label design of pragmatic trials, which may introduce performance and detection bias, while the generalizability of results is constrained by the insufficient representation of data from critical regions such as sub-Saharan Africa, Latin America, and Southeast Asia. The median follow-up duration of 4.6 to 5.6 years indicates that long-term results exceeding a decade are questionable, and varying adherence assessment methodologies among studies impede comparison analysis.

4.5 Comparative Analysis with Prior Systematic Reviews

This review builds upon prior systematic reviews and meta-analyses assessing polypill strategies for cardiovascular prevention (Castellano et al., 2014; Thom et al., 2013; Webster et al., 2016) by adhering to PRISMA 2020 guidelines, implementing stringent inclusion criteria restricted to original Randomized Controlled Trials (RCTs) that report hard Major Adverse Cardiovascular Events (MACE) outcomes, and integrating recent findings from the PolyPars (2024) and updated TIPS-3 trials, with a particular emphasis on intermediate-risk populations, which were frequently aggregated with secondary prevention cohorts in previous analyses. In alignment with previous meta-analyses, our results reveal a significant cardiovascular advantage of polypills, with an effect size (HR 0.67) comparable to past aggregated estimates (RR 0.66-0.78), thus reinforcing confidence in the overall effectiveness of this strategy.

4.6 Future Research Directions

Although meta-analysis offers substantial evidence regarding the effectiveness of polypill interventions in mitigating the risk of Major Adverse Cardiac Events (MACE), forthcoming research should concentrate on four critical domains: formulation optimization, target population identification, long-term assessment, and clinical implementation. Essential inquiries encompass identifying the optimal and safest pharmacological combination, assessing the advantages of the polypill for low-risk populations, evaluating the long-term efficacy and safety of treatment over decades, and examining the polypill's performance in specific demographics, including the elderly

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and individuals with chronic kidney disease. Moreover, it is essential to address obstacles to the use of polypills in clinical practice, in conjunction with evaluations of real-world effectiveness and cost-effectiveness across various healthcare systems, to optimize the public health benefits of this validated intervention.

4.7 Recommendations for Clinical Practice

In light of the existing evidence, we advocate for a comprehensive array of recommendations to enhance the effective incorporation of polypill techniques into cardiovascular prophylaxis. Clinicians are advised to evaluate polypill strategies for individuals at intermediate risk (10-20% 10-year CVD risk) who qualify for multi-drug prevention while engaging in comprehensive discussions with patients about the advantages (reduction in MACE, simplified regimen, enhanced adherence) and drawbacks (fixed dosages, possible adverse effects). Clinicians must monitor blood pressure and lipid levels after initiation to ensure effective risk factor management, proactively evaluate and mitigate adverse effects, especially within the initial 3-6 months, and consistently underscore lifestyle modifications as an essential adjunct to pharmacotherapy.

Health systems and politicians must prioritize systemic implementation and support. This entails incorporating evidence-based polypill formulations into national formularies and essential medications lists, establishing explicit clinical practice recommendations for their application in primary prevention, and ensuring payment policies effectively facilitate access for qualifying populations. Moreover, investment in comprehensive cardiovascular risk screening programs is essential for identifying suitable candidates, in conjunction with extensive training for healthcare providers (physicians, nurses, and pharmacists) in polypill prescription and monitoring, as well as the implementation of quality improvement initiatives to assess real-world adoption and outcomes.

Patients are encouraged to participate in their care by conversing with clinicians about their cardiovascular risk and contemplating risk assessment. Patients prescribed a polypill should comprehend the purpose of the constituent medications, adhere rigorously to the generally once-daily regimen, promptly report any adverse effects, maintain regular follow-up for blood pressure and lipid monitoring, and uphold healthy lifestyle practices as a basis for long-term cardiovascular health.

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5. Conclusions

This comprehensive literature review presents compelling evidence that polypill strategies—integrating antihypertensive agents, statins, and possibly aspirin into fixed-dose formulations—substantially diminish major adverse cardiovascular events (MACE) in persons with intermediate cardiovascular risk. The pooled hazard ratio of 0.67 (95% CI 0.60-0.75) indicates a clinically significant 33% relative risk reduction in composite MACE, with this advantage persisting across various trial contexts and polypill formulations. Moreover, polypills were determined to be predominantly safe and well-tolerated, displaying adverse event profiles aligned with their individual constituents, and, importantly, they enhanced medication adherence relative to multi-pill regimens, thereby mitigating a significant obstacle to effective cardiovascular prevention.

These findings have significant implications for global cardiovascular health, especially in low- and middle-income countries (LMICs), where the burden of cardiovascular disease is greatest and access to preventive care is frequently restricted, as polypill strategies provide a simplified, cost-effective method for population-level risk mitigation. In Indonesia, where the prevalence of cardiovascular disease (CVD) is increasing and treatment rates are inadequate, the incorporation of polypills into the National Health Insurance (JKN) system, primary care protocols, and community health initiatives offers a significant opportunity to enhance primary prevention efforts and substantially decrease cardiovascular morbidity and mortality by addressing issues of cost, complexity, and accessibility.

In summary, polypill techniques constitute an evidence-based, pragmatic method for the primary prevention of cardiovascular disease in populations at intermediate risk. Future research must concentrate on determining optimal formulations, enhancing risk stratification, and assessing long-term outcomes; however, the extensive implementation of polypills, bolstered by policy initiatives and healthcare system integration, possesses significant potential to alleviate the global burden of cardiovascular disease.

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