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Review

Polypill for cardiovascular disease prevention: Systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Cardiovascular disease is the leading cause of death worldwide. Although many pharmacological agents exist, drug compliance and therapeutic goal achievement continue to be suboptimal. This meta-analysis aims to study the effectiveness of polypills in controlling blood pressure, dyslipidemia and in reducing future cardiovascular events.

Methods: We conducted a systematic search of electronic databases using pre-specified terms. Randomized clinical trials (RCT) comparing polypills (statin, antihypertensive agents, with or without aspirin) with the standard of care were included. Outcomes of interest were changes in [systolic blood pressure (SBP), diastolic blood pressure (DBP)] mmHg, [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C)] mg/dl, cardiovascular (CVD) mortality, and major adverse cardiovascular events (MACE).

Results: A total of 18 RCTs with 26,483 participants were included. The population had 55% males, with a mean age of 61.8 ± 7 years, and a mean BMI of 26.7 ± 4.2 kg/m^2. The mean follow-up was 15.0 ± 20 months. Compared with standard of care, polypill use was associated with a significant reduction of SBP (Mean Difference [MD] -6.39; [95%CI -9.21, −3.56] $p < 0.001$), DBP (MD -4.19, [95%CI -5.48, −2.89; $p < 0.001$], TC (MD -24.95, [95%CI -33.86, −16.04]; $p < 0.001$), and LDL-C (MD -27.92, [95%CI -35.39, −20.44]; $p < 0.001$). Polypill use was also associated with a significant reduction of CVD mortality (RR = 0.78; 95% CI (0.61, 0.99); $P = 0.04$) and MACE [RR = 0.76;95% CI (0.64, 0.91); $P = 0.002$].

Conclusion: This meta-analysis showed that compared to standard of care, polypill use was associated with a significant reduction of SBP, DBP, TC, LDL-C, and a significant reduction in fatal and non-fatal cardiovascular events.

1. Introduction

Cardiovascular disease (CVD) {coronary artery disease, stroke, and peripheral artery disease} remains the leading cause of significant morbidity, disability, and mortality worldwide [1]. According to the ongoing multinational Global Burden of Disease (GBD) study 2019, the burden of CVD from 1990 to 2019 has nearly doubled from 271 million to 523 million, and the number of CVD deaths has increased from 12.1 million to 18.6 million [1]. Moreover, in a nationally representative survey, the preventable fraction of cardiovascular mortality associated with complete elimination of elevated cholesterol levels, diabetes, hypertension, obesity, and smoking was ~50% in adults aged 45–79 from

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AE, adverse events; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; CVD mortality, cardiovascular mortality; CVD, cardiovascular disease; DBP, diastolic blood pressure; ESC, European society of cardiology; GBD, global burden of disease; IQR, interquartile range; LDL-C, low-density lipoprotein; MACE, major adverse cardiovascular events; MD, mean difference; MI, myocardial infarction; PROSPERO, International Prospective Register of Systematic Reviews; RCT, Randomized controlled trial; RR, risk ratio; SBP, systolic blood pressure; TC, total cholesterol.

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2009 to 2010 [2]. Primary and secondary prevention measures are hence urgently needed to control the CVD pandemic.

Although aggressive management of risk factors like hypertension and dyslipidemia can result in an impressive decline in CVD mortality, considerable challenges remain concerning adherence to multiple medications [3,4]. In the last two decades, polypill-based regimens (combination of generic versions of different classes of preventive medications) have emerged as an attractive and promising lower-cost strategy for reducing CVD burden [5–22].

Despite their popularity in developing countries, they are not available commercially in the United States due to limited data on reducing CVD events in the long term and the potential for more adverse events (AE). This meta-analysis aimed to determine the effect of polypill-based strategy on blood pressure and cholesterol levels and its subsequent impact on cardiovascular outcomes and to shed the light on tolerability and adherence.

2. Methods

This meta-analysis was completed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The analysis protocol registration number at the International Prospective Register of Systematic Reviews (PROSPERO) is CRD42021241704.

2.1. Study selection and eligibility criteria

Two authors (MM and MS) performed literature search and review, and disagreements were resolved via consultation with a third author (MO). We searched PubMed, Google scholar, and Cochrane databases from inception through January 2021 using the keywords "Polypill" OR "Polypills" OR "Fixed-Dose Combination Pills" AND "cardiovascular disease prevention" OR "heart disease prevention" OR "hypertension" OR "hyperlipidemia" OR "dyslipidemia." The search was limited to English language. The selection of studies followed a screening of titles and abstracts and a full-text review of potentially eligible studies for final determination.

Inclusion criteria included (1) randomized controlled trial (RCT) design; (2) polypills or fixed-dose combination pills in one comparator arm (3) trials with at least four weeks duration (4) study should be reporting at least one of the outcomes of this meta-analysis.

We included RCTs of participants regardless of cardiovascular disease status (primary or secondary prevention). We excluded other types of studies (observation, retrospective, and prospective cohort studies). For studies with more than 2 arms and/or factorial design, we included the polypill or combination pills arm versus standard of care. Placebo arm was included if no standard of care was reported.

2.2. Outcome measures

The primary outcomes of interest were changes in: [SBP (mmHg), DBP (mmHg), LDL-C (mg/dl), TC (mg/dl)]. Secondary outcomes were cardiovascular (CVD) mortality defined as death secondary to myocardial infarction (MI), cerebrovascular accidents (CVA), heart failure, cardiac arrest or fatal ventricular arrhythmia; and major adverse cardiovascular events (MACE) defined as nonfatal MI or CVA, angina with evident ischemia, heart failure hospitalization, or coronary revascularization.

We reported the percentage of adherence, compliance, or discontinuation rate of polypills in the intervention arm. We also reported total or any AE, serious AE (leading to discontinuation, permanent harm, or hospitalization), dizziness/hypotension, gastric irritation/upset, muscle weakness/myopathy.

2.3. Data collection

Published data were extracted in a predefined table independently by two authors (MM & MS) and included trial design, baseline demographics, intervention, duration of follow-up, adherence rate, and clinical outcomes. Disagreements were resolved via consensus.

2.4. Risk of bias assessment

Two authors (MM & MS) conducted the risk of bias assessment for published data using the Cochrane Collaboration tool. Criteria assessed were random sequence generation, allocation concealment, blinding of participants and health care personnel, blinding of outcome assessment, incomplete outcome data, evidence of selective reporting, or other biases. Figs. S1, S2 (supplement).

2.5. Statistical analysis

Effect estimates were extracted from each study in the form of events in dichotomous data and mean or medians for continuous data. These were directly extracted from the article or calculated indirectly based on the available data presented in the text of the article.

Units for lipid profile were all standardized to mg/dl, using the online Omni calculator (https://www.omnicalculator.com/health/cholesterol-units), with rounding to one decimal.

The effect measures were pooled together using the random effects model to account for between-study variation. We calculated the pooled risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous data (CVD mortality, MACE, AE) and weighted mean difference (MD) and 95%CI for continuous data (change in SBP, DBP, LDL-C, and TC). Heterogeneity between studies was explored by Cochran Q statistic ($p < 0.05$) and I-squared (I^2) statistic. All statistical tests were two-sided, and P values ≤ 0.05 were considered significant.

In studies with zero events in both comparator groups, we added 1 unit to the numerator and denominator for both groups to avoid inestimable value in the software.

Furthermore, we have conducted several additional analyses: (a) sensitivity analysis by reporting the outcomes among primary and secondary prevention cohorts separately, and (b) sensitivity analysis by reporting the outcomes among trials using (aspirin-based regimens vs. non-aspirin-based regimens). All statistical analysis was conducted with RevMan version 5.4 Windows.

3. Results

3.1. Study trial designs

We identified 18 eligible RCTs fulfilling the inclusion criteria [5–22]. The trials included 26,483 participants with a mean age of 61.8 ± 7 years; 54.9% were males. Seven trials included patients with no cardiovascular disease (i.e., primary prevention) [5–11]. In contrast, four trials (PolyIran, UMPIRE, IMPACT& Kanyini GAP) enrolled patients with or at high risk of cardiovascular disease (primary & secondary prevention) [12,13,19,21]. One trial included nine arms of a varying number of fixed-dose components with no placebo arm: only the Polycap arm (the arm including a combination of statin, antihypertensives, and aspirin) was included as the active arm for this trial [10]. The comparator arm was the arm not including antihypertensives for blood pressure comparison, and the arm not containing lipid lowering agents for lipid profile comparisons. Eleven RCTs were double-blinded [5,7–10,14–18,22]. Two of the open-label RCTs had a crossover design, one trial had 2 arms [7], and another had 3 arms [20]. One RCT was a cluster-randomized trial nested in a cohort study [12]. seven trials were placebo-controlled with/or without lifestyle changes [7–10,14,17,20]. The rest were standard of care controlled.

In all the included trials, the polypill arm contained a statin

Table 1
Baseline characteristics of studies included in the meta-analysis.

-Study name -follow up - Sample size	-Design -Prevention status	Polypill Ingredients (mg)	Age years mean (SD)	Male n (%)	SBP/DBP mmHg mean (SD)	Type 2 DM n (%)	LDL-C mg/dl mean (SD)	BMI Kg/m^2 mean (SD)	Smoker n (%)
-Chul Oh et al. 2018 (TELSTA-YU) −8 weeks −203 patients	-Double blind, Parallel -2nd prevention	Telmisartan 80 Rosuvastatin 20	61.2 (10.6)	150 (73.9)	151 (12.4)/ 90(9.4)	126 (62.1)	144 (28.6)	25.7 (2.8)	53 (26)
-Hong S J et al. 2019 −8 weeks −144 patients	-Double blind, Parallel -2nd prevention	Telmisartan Amlodipine 80/10 + Rosuvastatin 20	66.8 (9.6)	33 (22.9)	147 (12.4)/X	15 (10.4)	154 (32.6)	26.9 (3.2)	
-Lafeber et al. 2014 (TEMPUS) −6-8 weeks −78 patients	-Open label Cross over -2nd prevention	Aspirin 75, Simvastatin 40 lisinopril 10 HCTZ 12.5	67 (8)	66 (85)	132(14)/ 73(9)		85 (23.2)	27.5 (3.7)	12 (16)
-Lee H Y et al. 2017 −8 weeks −143 patients	-Double blinded, Parallel -2nd prevention	Losartan 100 Amlodipine 5, Rosuvastatin 20	59.9 (8.3)	107 (74.8)	143(14)/ 95(7)		153.5 (32)	26.8 (3.3)	
-Munoz et al. 2019 −12 weeks −303 patients	-Open label, Parallel -1st prevention	Amlodipine 2.5, Atorvastatin 10, losartan 25, HCTZ 12.5	56(6)	121 (40)	140 (17.5)/ 83(8)	39 (12.8)	113 (34.5)	30.8 (8.4)	145 (48)
-Patel et al. 2015 (Kanyini Gap) −18 months −623 patients	-Open label, Parallel -1st & 2nd prevention	Aspirin 75 Simvastatin 40 Lisinopril 10 Atenolol 50 OR HCTZ 12.5	63.5 (12.6)	392 (63)	143(20)/ 81(12)	341 (54.7)	92.6 (37)		205 (33)
-POLYIRAN 2019 −60 months −6838 patients	-Cluster randomized trial nested in cohort -1st & 2nd prevention	Aspirin 81 Atorvastatin 20 HCTZ 12.5 Enalapril 5/valsartan 40	59.5	3398 (49.7)	131/79	1029 (15)	117.1	26.5	321 (5)
-UMPIRE trial 2013 −15 months −2004 patients	-Open label, Parallel - 1st & 2nd prevention	Aspirin 75 Simvastatin 40 Lisinopril 10 Atenolol50 OR HCTZ 12.5	61.8 (10.6)	1642 (82)	137.4 (21)/ 78(12)	564 (28)	91.5 (34)	27 (4.7)	275 (14)
-Yusuf et al. 2021 −55 months −5713 patients	-Double blinded, factorial design -1st prevention	Aspirin 75 Simvastatin 40 Atenolol 100 HCTZ 25 Ramipril 10	63.9 (6.6)	2688 (47)	144.5 (17)/ 84(10)	2095 (36.7)	120.7 (40.7)	25.8 (4.7)	512 (9)
-Wald et al. 2012 −12 weeks −84 patients	-Double blinded -Cross over trial -1st prevention	Amlodipine 2.5 Losartan 25 HCTZ 12.5 Simvastatin 40	59 (51–77)	64 (74)	143(16)/ 86(10)		143 (34)	28 (4)	8(9)
-Selak et al. 2014 (IMPACT) −12 months −513 patients	-Open label, Parallel -1st & 2nd prevention	Aspirin 75 Simvastatin 40 Lisinopril 10 Atenolol 50 OR HCTZ 12.5	62(8)	326 (63.5)	144(20)/ 83(11)	218 (43)	98.5 (31)	33 (7)	77 (15)
-Malekzadeh et al. 2010 −12 months −475 patients	-Double blinded, Parallel -1st prevention	Aspirin 81 Atorvastatin 20 Enalapril 2.5 HCTZ 12.5	59 (7)	317 (66.7)	127.5 (17)/ 80(10)		116 (26)	26.2 (4.3)	101 (21)
-Neutel et al. 2009 (CUSP) −8 weeks −123 patients	-Double blinded, Parallel -2nd prevention	Amlodipine 5 Atorvastatin 20	53 (10.6)	66 (53.6)	146.5 (10)/ 91(7)		134 (23)	30.7 (6.7)	
-collaborative group study 2011 −12 weeks −378 patients	-Double blinded, Parallel -1st prevention	Aspirin 75 Simvastatin 20 Lisinopril 10 HCTZ 12.5	61.4 (7.2)	305 (80.7)	134 (13.5)/ 80(9)		141 (35)		153 (40.5)
-Indian Polycap study (TIPS) 2009 −12 weeks −2053 patients	-Double blinded, Parallel, 9 arms -1st prevention	Aspirin 100 Simvastatin 20 Ramipril 5 Atenolol 50 HCTZ 12.5	54 (7.9)	1152 (56)	134.4 (12)/ 85(8)	696 (34)	116 (31)	26.3 (4.5)	276 (13.4)
-Grimm et al. 2010 (TOGETHER) −6 weeks −244 patients	-Double blinded, Parallel, - 2nd prevention	Amlodipine 5 Atorvastatin 10–20	56 (29–82)	123 (50.4)	SBP 132.6 (12)		129.5 (23)		74 (30.3)
-Soliman et al. 2011 (WHO study) −3 months −216 patients	-Open label, Parallel -1st prevention	Aspirin 75 Simvastatin 20 Lisinopril 10 HCTZ 12.5	59.1 (7.2)	59 (27.3)	165.2 (18)			24.3 (1.1)	

(continued on next page)

Table 1 (*continued*)

-Study name -follow up - Sample size	-Design -Prevention status	Polypill Ingredients (mg)	Age years mean (SD)	Male n (%)	SBP/DBP mmHg mean (SD)	Type 2 DM n (%)	LDL-C mg/dl mean (SD)	BMI Kg/m^2 mean (SD)	Smoker n (%)
-Yusuf et al. (HOPE-3) 2016 −67 months −6348 patients	-double blind,2 × 2 Factorial -1st prevention	Rosuvastatin 10 Candesartan 16, HCTZ 12.5	65.7 (6.3)	3405 (53.6)	138 (14.7)/ 82(9.3)	363 (5.7)	127.5 (36.5)	27.1 (4.8)	1780 (28)
Totals: ***26,483 patients***	**Follow up (months)** **15 ± 20**		***61.8 (7)***	***14,537 (54.9)***	***137.5 (15)/ 82(8.7)***	***5486 (20.7)***	***118 (33)***	***26.7 (4.2)***	***3992 (15)***

BMI = body mass index.
HCTZ = hydrochlorothiazide.
LDL-C = low density lipoprotein cholesterol.
M(SD) = mean (standard deviation).
SBP/DBP = systolic blood pressure/diastolic blood pressure.

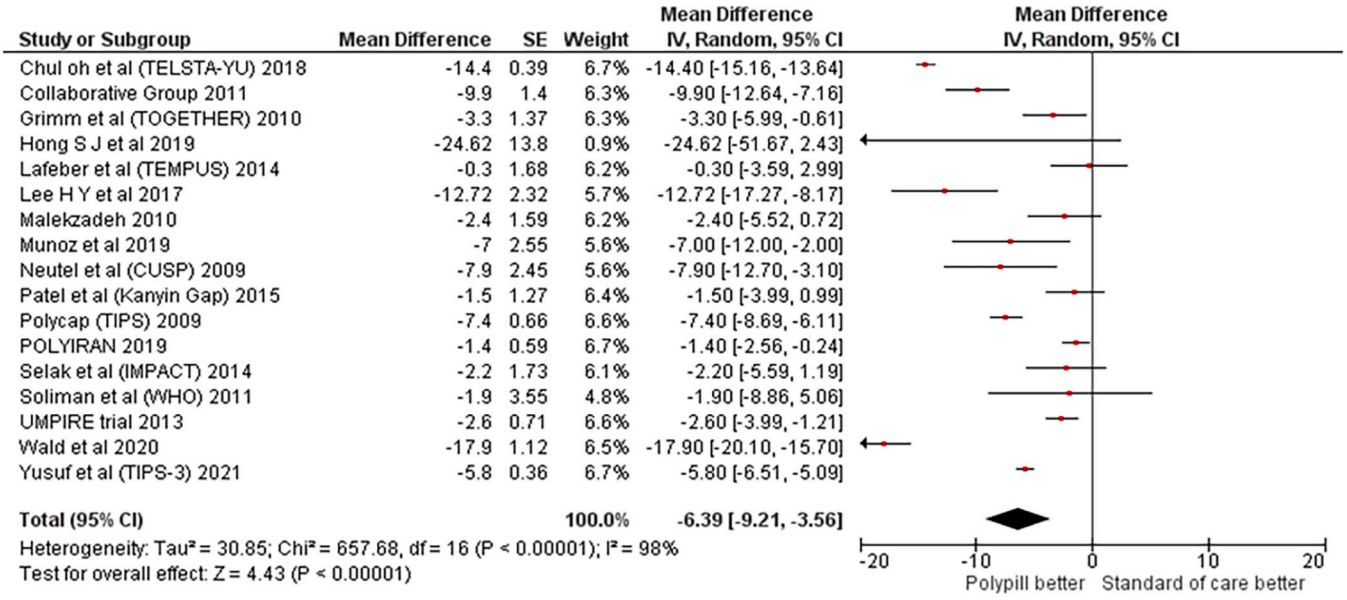

Fig. 1. Clinical outcome; change in systolic blood pressure (SBP) from baseline.

(Rosuvastatin, simvastatin, or atorvastatin) and at least two antihypertensive drugs (calcium channel blocker, beta-blocker, ACEI/ARB, or diuretic). In 10 RCTs [5,8–13,19–21], the polypill arm included low-dose aspirin (75–100 mg) in addition to a statin and at least two antihypertensive drugs.

Nine RCTs reported MACE [5,6,8,9,12,13,19,21,22], and eight reported CVD mortality [5,6,9,12,13,18,19,22].

3.2. Baseline characteristics

Mean (SD) data of participants were as follows: SBP/DBP was 137.5 (15)/82(8.7) mmHg; LDL-C was 118 (33) mg/dl, and BMI was 26.7(4.2) kg/m^2. About 21% were diabetic and 15% were current or ex-smokers. A total of 29% reported taking antihypertensive and/or lipid lowering medications at the time of enrollment. The mean duration of follow-up was 15.0 (20) months. Table 1 shows the baseline patient characteristics.

3.3. Primary outcomes

3.3.1. Effect on BP control

Compared with standard of care, polypill use was associated with a significant reduction of SBP (mmHg) [mean difference (MD)-6.39; 95% CI (−9.21, −3.56); $p < 0.001$] Fig. 1, and DBP (mmHg) [MD -4.19, 95% CI (−5.48, −2.89) $p < 0.001$] Fig. S3.

3.3.2. Effect on lipid control

Polypill use, compared with standard of care, was associated with a significant reduction of LDL-C (mg/dl) [MD -27.92, 95% CI (−35.39, −20.44) p < 0.001] Fig. 2, and TC (mg/dl) [MD -24.95, 95% CI (−33.86, −16.04); p < 0.001] Fig. S4.

3.4. Secondary outcomes

3.4.1. Effect on CVD mortality and MACE

Compared with the standard of care, polypill use was associated with a significant reduction of CVD mortality [RR = 0.78; 95% CI (0.61, 0.99); $P = 0.04$] and MACE [RR = 0.76;95% CI (0.64, 0.91); $P = 0.002$] Figs. 3 & 4.

3.5. Sensitivity analyses

Based on the sensitivity analyses, the favorable effects of polypills on blood pressure and lipid control remained significant in patients both with and without existent cardiovascular disease (primary vs. secondary

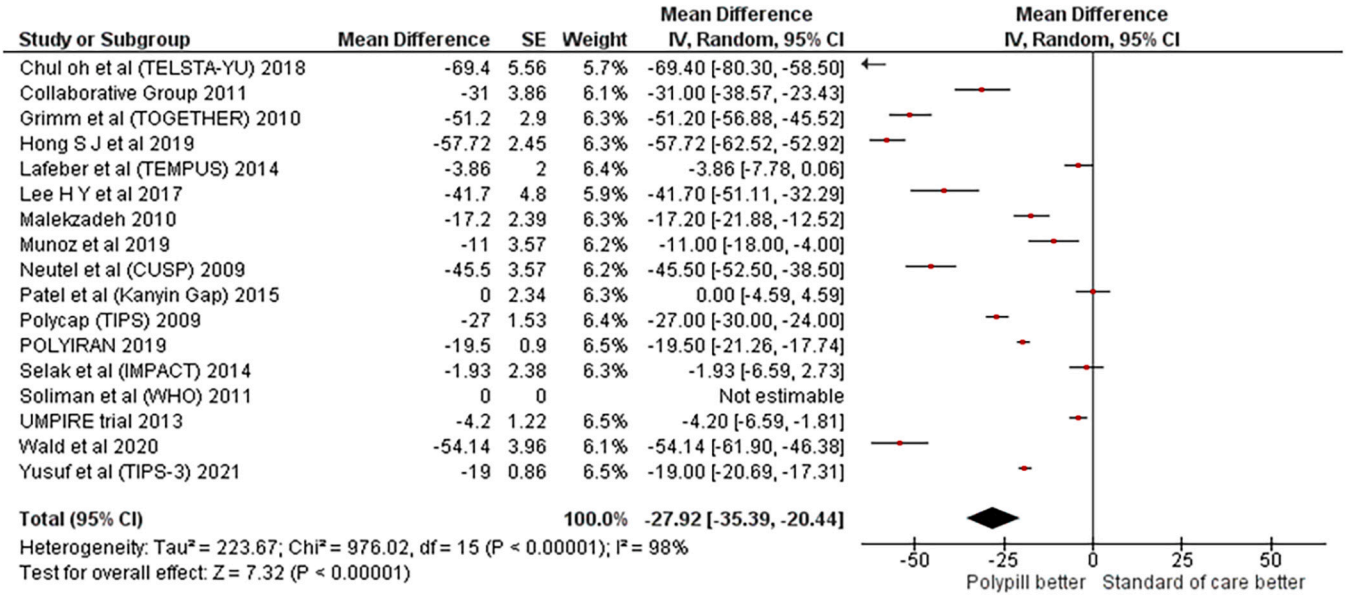

Fig. 2. Clinical outcome; change in low density lipoprotein cholesterol (LDL-C) from baseline.

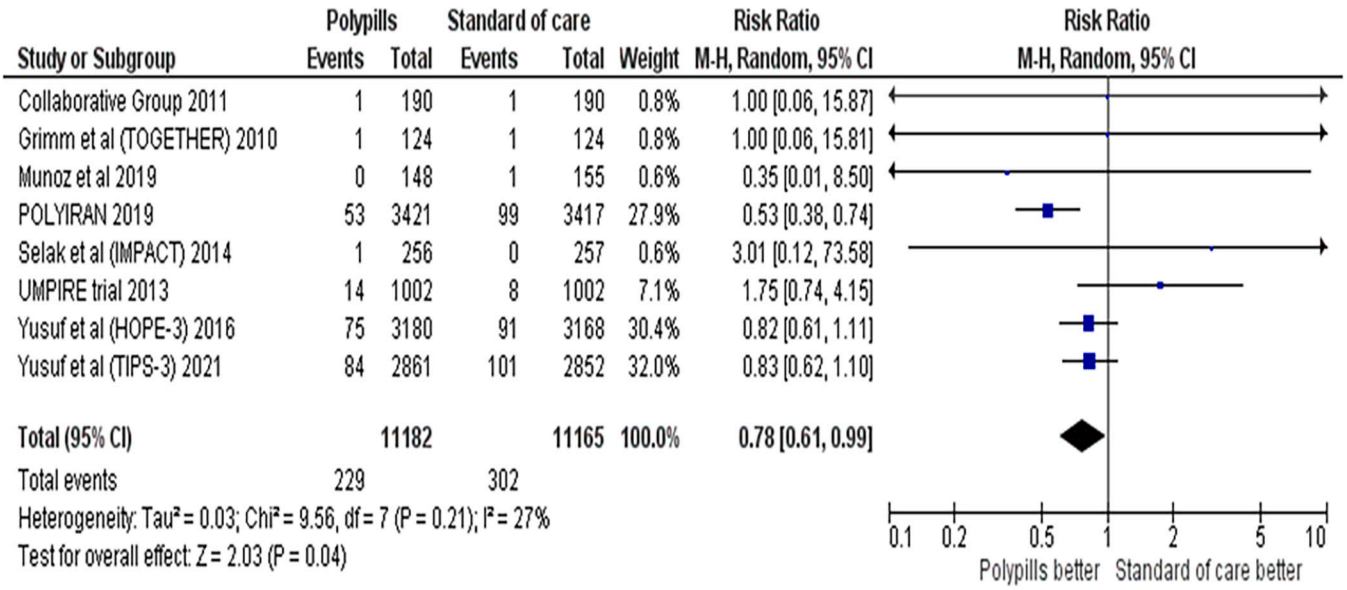

Fig. 3. Clinical outcome; effect on cardiovascular (CVD) mortality.

prevention): SBP "primary prevention cohort" [MD-7.83;95% CI (−11.21, −4.45), $P < 0.001$], SBP "secondary prevention cohort" [MD -6.67;95% CI (−12.43, −0.92), $P = 0.02$], TC "primary prevention cohort" [MD -29.65;95% CI (−39.80,-19.50), $P < 0.001$], TC " secondary prevention cohort" [MD -24.82; 95% CI (−38.10,-11.55),$P < 0.001$] Figs. S5a, b, S6a, b respectively. Also, this effect was significant regardless of aspirin inclusion (aspirin-based vs. non-aspirin-based regimens): SBP "aspirin receiving cohort" [MD -3.74; 95% CI (−5.59, −1.89), $P < 0.001$], SBP "non-aspirin receiving cohort" [MD -11.02; 95% CI (−15.31,-6.74), $P < 0.001$], TC "aspirin receiving cohort" [MD -13.19; 95% CI (−24.71,-1.68), $P = 0.02$], TC "non-aspirin receiving cohort" [MD -38.22; 95% CI (−47.73,-28.71), $P < 0.001$] Figs. S7a, b, S8a, b respectively.

3.6. Adherence, compliance, and adverse effects

A total of 16 trials reported the percentage of adherence, compliance, or discontinuation rate of polypill arm [6–14,16,18–21]. The pooled mean (SD) of adherence/compliance was 88.0±7.8%.

AE analysis showed no statistical difference between polypill versus standard of care group regarding total AE, serious AE, GI upset/irritation, or muscle weakness/myopathy [RR 1.21; 95% CI (0.99, 1.49); $P = 0.07$], [RR 1.08;95% CI (0.97, 1.21); $P = 0.15$], [RR 0.99; 95% CI (0.68, 1.46); $P = 0.97$], [RR 1.67; 95%CI (0.46, 6.04); $P = 0.43$], respectively, Fig. S9. (supplement) However, dizziness/hypotension was significantly more reported in polypill group than standard of care [RR 1.58;95% CI (1.16, 2.15); $P = 0.003$], Fig. S9. (supplement).

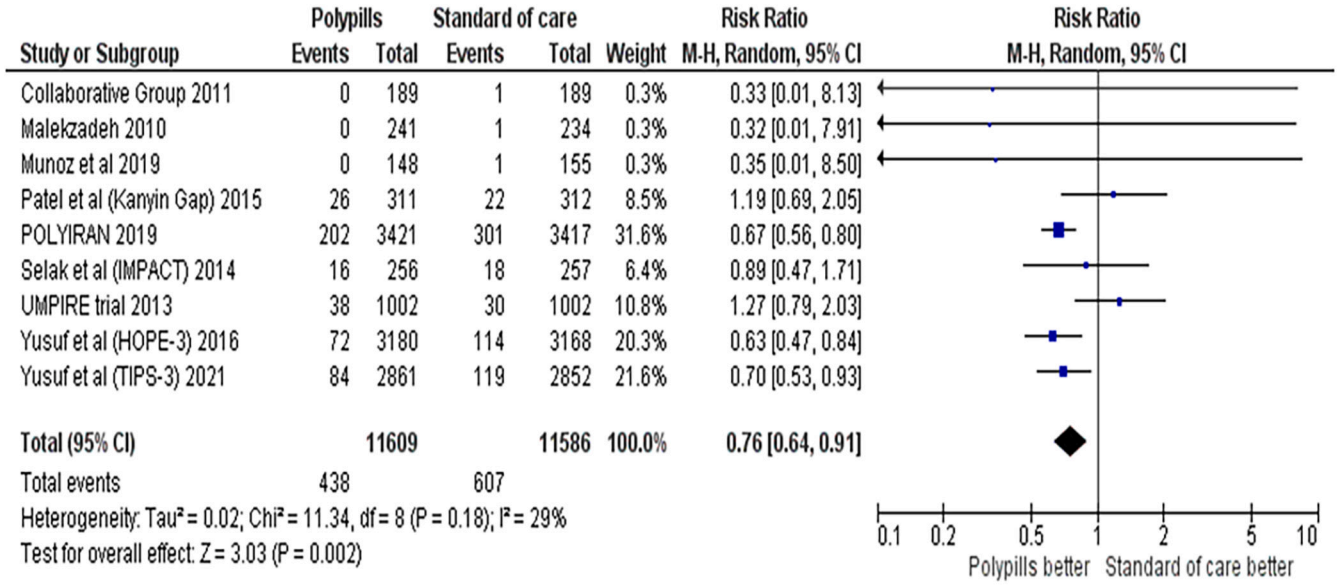

Fig. 4. Clinical outcome: effect on major adverse cardiovascular events (MACE).

4. Discussion

CVD and its sequelae are one of the major contributors to morbidity and mortality worldwide. The last decade showed a noticeable increase in interest in polypills or fixed-dose combination pills with the premise of maximizing adherence and compliance to reduce disease burden [23–25]. Our meta-analysis is the largest analysis so far summarizing polypills effects in RCTs. We found that a polypill comprised of a statin, two antihypertensive agents with or without aspirin significantly improved BP control, blood lipid control and lowered fatal and non-fatal cardiovascular events.

Contemporary large-scale data on the efficacy of polypills are limited. Two prior meta-analyses have examined this issue and reached promising, yet underpowered conclusions. In a meta-analysis in 2012, Elley et al. showed a statistically significant reduction in SBP, DPB, TC, and LDL-C with polypill compared to control with a mean difference of −9.19, −4.99, −1.22, and − 1.02, respectively [23]. However, this analysis included only 6 studies with a total sample size of 2218 patients and restricted their inclusion to patients without cardiovascular diseases. Another meta-analysis by Bahiru et al. ($n = 9059$ patients) showed that polypills were superior to standard of care in achieving BP and cholesterol control but did not improve all-cause mortality [RR 1.10 95% CI (0.64, 1.89)] and fatal and non-fatal atherosclerotic CVD events [RR 1.26;95% CI (0.95, 1.66)] [24]. Our meta-analysis included a large number of contemporary studies with a sample size of 26,483 patients and hence is more powered to provide convincing evidence on this vital question.

A significant barrier to adherence to guideline-directed medical therapy is the use of multiple medications, which polypill use overcomes [25]. Taking one polypill instead is more attractive to patients regarding compliance and affordability. Gaziano and colleagues showed in their cost-effectiveness model that polypill use has a favorable cost profile, with a reduction of health-related costs for both patients and payers [26]. Multiple similar studies also concluded that polypill is a cost-effective strategy for the population on multiple medications to modify cardiovascular risk factors [27,28]. Despite that, polypills are not yet approved in the US due to limited evidence from adequately powered RCTs. We believe that higher compliance and adherence to pharmacotherapy and lifestyle modifications are vital in controlling BP, lipid profile, and subsequent cardiovascular events. This probably explains the significant results of our analysis.

Selak et al., in their meta-analysis, showed that patients randomized to polypills have significantly improved achievement of European Society of Cardiology (ESC) targets of BP, LDL, and antiplatelet therapy compared to standard of care [25]. Their finding, among other studies, hypothesizes that polypills improve adherence, compliance, and subsequent target achievement. Our analysis showed polypill tolerability and compliance of more than 88%, which is promising data that call for conducting more extensive global studies on patients on multiple medications.

A major concern of polypill use in the US is regarding safety and AE. Being combined of multiple different ingredients, it might be hard to adjust polypill dose or regimen according to AE and patient tolerability. Our analysis showed non-different AE between polypill and standard of care regarding total and serious AE, GI upset/irritation, or muscle weakness/myopathy. Noteworthy, dizziness/hypotension was noted more in the polypill group, probably due to the inclusion of two antihypertensive medications taken at once, compared to standard of care where medicines are usually taken separately at different times during the day. Despite that, our analysis showed an adherence rate > 88%. Further longitudinal studies are needed to weigh the risk/benefit ratio and find a more tolerable yet effective polypill regimen.

Our sensitivity analysis showed consistent significant results regardless of aspirin inclusion in polypill-based regimens. Although this does not negate the value of aspirin, it goes in line with the recently raised debate about the importance of aspirin in primary prevention and the need for individualized risk-benefit assessment [29]. Of note, our analysis did not focus on patients with a known history of cardiovascular events, for whom aspirin is still indicated for secondary prevention, per current guidelines [30].

4.1.1. *Strength & limitations*

Our study is the largest so far summarizing RCTs of polypills or fixed-dose combination pill role in CVD prevention. We included international, multi-continent studies with a broad range of population and risk factors worldwide. Hard and clinically relevant endpoints are reported. We believe our results are clinically significant with good generalizability to a wide range of clinical settings.

Our study also has numerous limitations. The heterogeneity between

trials was large, with different methodologies and outcomes reported. Duration of follow-up was widely variable and ranged from 6 weeks to 65 months. Also, various studies reported different standards of care and practices. Noteworthy, three large trials (TIPS3, PolyIran, HOPE-3) represented 57% of the entire cohort, and a limited number of studies reported all the outcomes of this analysis [10,12,22]. Finally, we used summary-level data, not individual-level data, and so interpretation should be cautious.

5. Conclusion

This meta-analysis showed that compared to standard of care, polypills were associated with significant reductions of SBP, DBP, TC, and LDLs over a mean follow-up of 15 months. It also showed a noticeable reduction of fatal and non-fatal cardiovascular events. The effects mentioned above are similar in both patients with and without CVD. Polypills are non-inferior to standard of care in clinical outcomes with improved adherence and no major safety concerns. These findings warrant further testing, especially in a population with low adherence.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.04.085.

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Conflict of interest

Authors report no relevant conflict of interest.

Author's contribution

MM: conceptulization, data curation, formal analysis, original draft writing
MO: formal analysis, soft ware supevision, original draft writing
BK: project administration, software supervision, review and editing
MS: data curation, original draft writing
AL: supervision, visualization, review and editing
MA: Conceptuilization, project administration, review and editing

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