Meta-Analysis on the Clinical Outcomes With Polypills for Cardiovascular Disease Prevention

Ramy Sedhom, MD, MSa, Mohamed Hamed, MDb, Weiyi Tan, MDc, Hend Mansoor, PhD, PharmDd, Liset Stoletniy, MDa, Mamas Mamas, BM BChe,f, Dmitry Abramov, MDa, Islam Y. Elgendy, MDg, and Ayman Elbadawi, MD, PhDc.

By Resident Ben Youssef Yesmine

Emergency Departement Of Monastir

Background:

- Cardiovascular disease (CVD) is the leading cause of death worldwide mainly because of aging and the increase of traditional CVD risk factors.
- Hypertension and elevated low-density lipoproteins (LDLs) are 2 of the most important risk factors for CVD , that's why the benefits of antihypertensives and statins in reducing major adverse cardiovascular and cerebrovascular events (MACCEs) are well established , however adherence to these treatements was very poor, therefore the concept of a polypill to better the adherence leading to the reduction of MACCE's.
- A polypill consists of a combination of :statin, aspirin, and 3 antihypertensives it was proposed 20 years ago.

Methods:

1/A computerized search of MEDLINE, EMBASE, and Cochrane databases was performed without language restriction through January 2023, using the terms “polypill” and “fixed-dose combination,” separately and in combination to identify RCTs that evaluated the outcomes of polypill therapy in CVD prevention.

2/*We included* RCTs that compared the clinical outcomes of polypill therapy versus control for CVD prevention. The control group could have included patients receiving a placebo or usual care.

3/*We included* RCTs evaluating the outcomes of polypills in patients with or without established CVD .

4/*We excluded* RCTs not reporting clinical outcomes and studies with a follow-up period of <1 year.

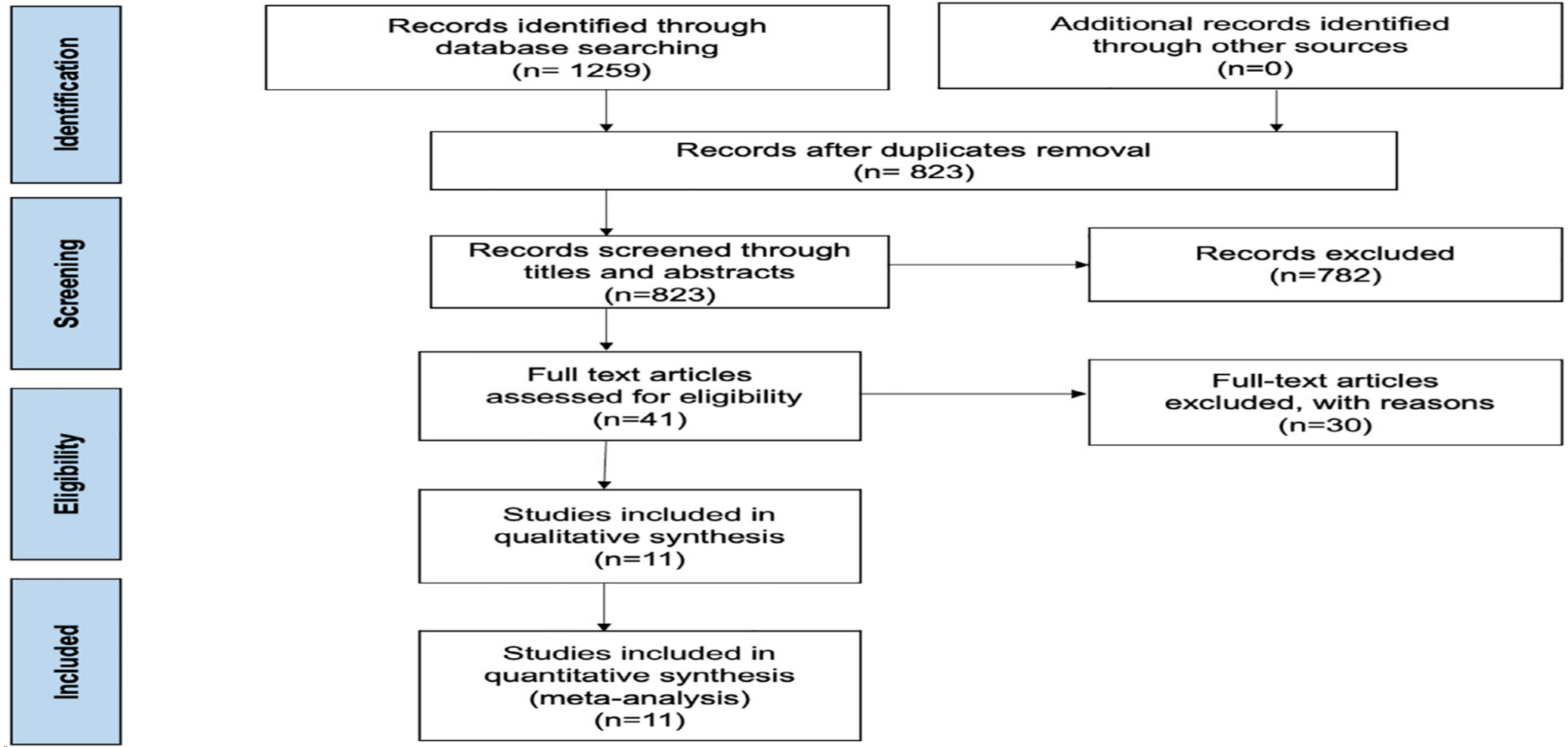
- The primary outcome of the study was the incidence of MACCEs as defined by each study.
- The secondary outcomes included the individual components of the primary outcome: adherence, serious adverse events, and major bleeding.

5/Studies were classified into low risk, unclear risk, or high risk.

6/The analysis was performed using an intention-to-treat model.

Results :

The final analysis included 11 RCTs with a total of 25,389 patients; 12,791 patients were in the polypill arm, and 12,598 patients were in the control arm. **The follow-up period** ranged from 1 to 5 years.



1 RCT included patients with established CVD, 6RCTs included patients with and without CVD, 4 RCTs included patients without established CVD.

Table 2
Baseline characteristics of the studies population

Study		Age in years, mean (+/- SD)	Female	BMI kg/m^2, mean (SD)	Hypertension	Diabetes	Smoking	Established CVD
SECURE	*FDC*	75.8 (6.7)	31%	27.4 (4.4)	77%	42%	51.2%	100%
	Control	76.1 (6.5)	31%	27.5 (4.3)	78.8%	43.2%	51.4%	100%
PolyIran-Liver	*FDC*	58.6 (6.3)	49.7%	28.1 (25.1-31.7)*	52.6%	22.1%	18.4%	18.3%
	Control	59.4 (6.9)	47.5%	28.1 (25.2-31.2)*	56.1%	21.1%	23.9%	13.5%
TIPS-3	*FDC*	63.8 (6.5)	52.1%	25.8 (4.6)	83.4%	36.5%	9.5%	0
	Control	64.1 (6.8)	53.3%	25.6 (4.6)	83%	37.1%	8.1%	0
PolyIran	*FDC*	59.3 (59-59.6)*	51.5%	26.6 (26.3-27)*	49%	14.5%	3.9%	11.3%
	Control	59.7 (59.4-60.1)*	49.1%	26.4 (26.1-26.8)*	49.6%	15.6%	5.4%	10.2%
Muñoz et al.	*FDC*	56 (6)	56%	31.3 (8.5)	42%	-	44%	0
	Control	56 (6)	64%	30.4 (8.4)	43%	-	52%	0
HOPE-3	*FDC*	65.7 (6.3)	46.1%	27.2 (4.8)	37.7%	6.2%	28%	0
	Control	65.7 (6.3)	46.7%	27.1 (4.7)	38.3%	5.3%	28.1%	0
Kanyini GAP	*FDC*	63.4 (12.5)	36.7%	-	-	59.5%	34.8%	58.8%
	Control	63.7 (12.7)	37.3%	-	-	54.8%	31.2%	63.4%
IMPACT	*FDC*	62 (8)	39%	33 (7)	-	44%	29%	45%
	Control	62 (8)	34%	33 (7)	-	41%	32%	46%
UMPIRE	*FDC*	62.1 (10.4)	18.5%	27 (4.6)	92.4%	28.2%	54%	-
	Control	61.6 (10.8)	17.7%	26.9 (4.7)	93.5%	28%	50.3%	-
CRUCIAL	*FDC*	60 (10)	46.6%	28.7 (5.2)	-	42.6%	40.5%	-
	Control	60.3 (10)	49.5%	28.9 (5)	-	42%	36.5%	-
Malekzadeh et al.	*FDC*	59 (6.5)	37.8%	26.4 (4.3)	-	-	19.1%	0%
	Control	59.1 (7.3)	28.6%	26 (4.2)	-	-	23.5%	0%

CVD = cardiovascular disease; FDC = fixed-dose combination; IQR = interquartile range; SD = standard deviation.
* Median (IQR).

Polypill therapy was associated with a lower risk of MACCE (5.8% vs 7.7%; RR 0.78; 95% confidence interval [CI] 0.67 to 0.91)

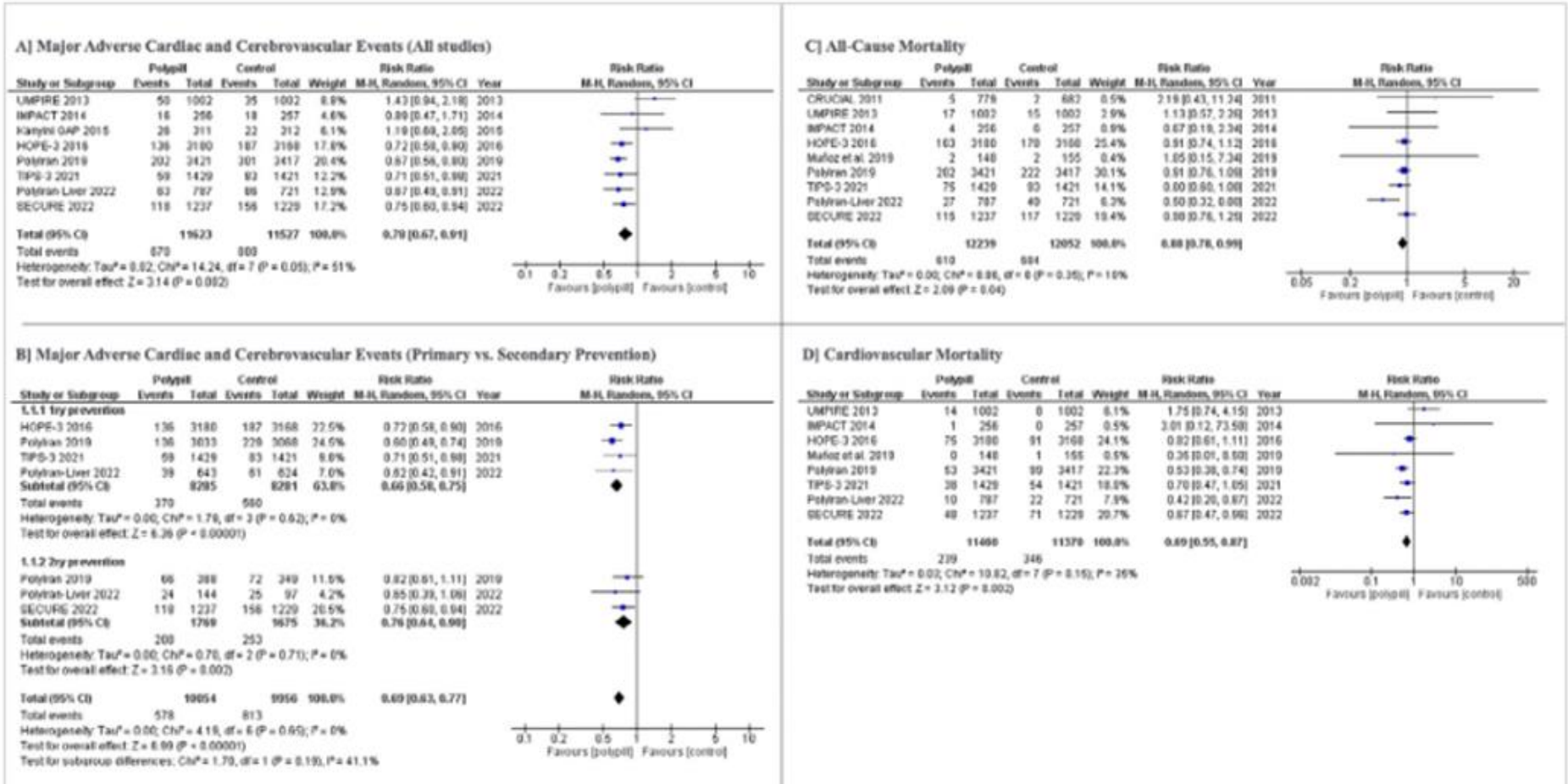


Figure 2. Forest plot for *(A)* Overall MACCE, *(B)* MACCE in primary vs secondary prevention, *(C)* All-cause mortality, and *(D)* Cardiovascular mortality. M-H = Mantel-Haenszel.

Polypill therapy was associated with a lower risk of all-cause mortality cardiovascular mortality myocardial stroke and cardiovascular hospitalizations

There was no difference between both groups in the incidence of heart failure and revascularization

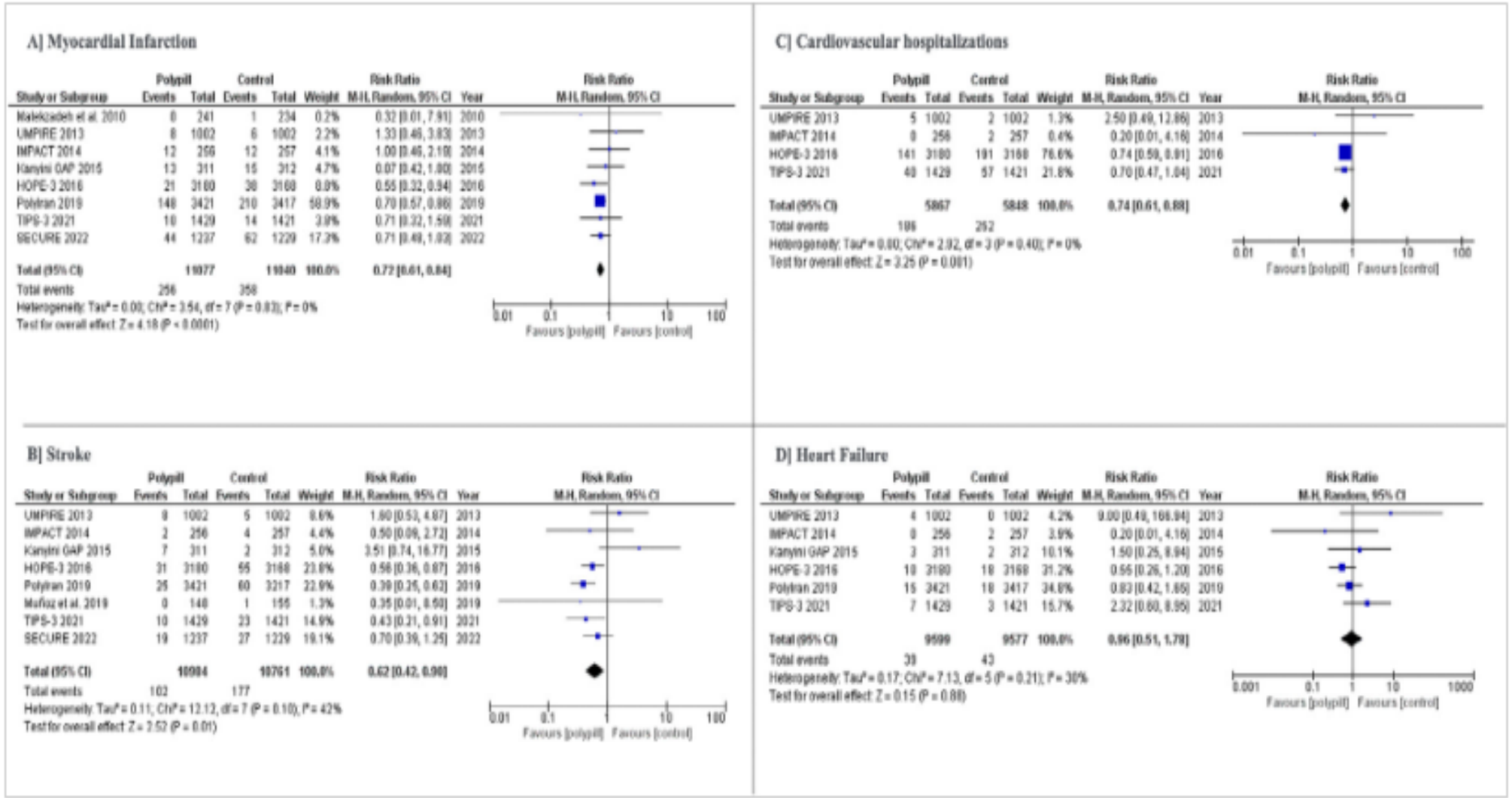


Figure 3. Forest plot for *(A)* myocardial infarction, *(B)* stroke, *(C)* cardiovascular hospitalizations, and *(D)* heart failure. M-H = Mantel-Haenszel.

Polypill therapy was associated with higher adherence

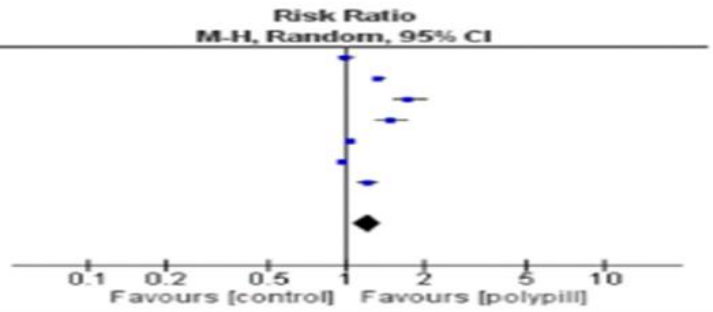
There was no difference between both groups in the incidence of adverse events and risk of major bleeding

A] Adherence

Study or Subgroup	Polypill Events	Polypill Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Malekzadeh et al. 2010	214	241	208	234	14.8%	1.00 [0.94, 1.06]	2010
UMPIRE 2013	829	961	621	960	15.0%	1.33 [1.26, 1.41]	2013
IMPACT 2014	208	256	119	257	12.5%	1.75 [1.52, 2.03]	2014
Kanyini GAP 2015	213	304	143	305	12.7%	1.49 [1.30, 1.72]	2015
HOPE-3 2016	2245	3180	2140	3168	15.3%	1.05 [1.01, 1.08]	2016
TIPS-3 2021	1937	2861	1979	2852	15.3%	0.98 [0.94, 1.01]	2021
SECURE 2022	653	1237	538	1229	14.4%	1.21 [1.11, 1.31]	2022
Total (95% CI)		**9040**		**9005**	**100.0%**	**1.21 [1.08, 1.37]**	
Total events	6299		5748				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 174.39$, $df = 6$ ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: $Z = 3.26$ ($P = 0.001$)

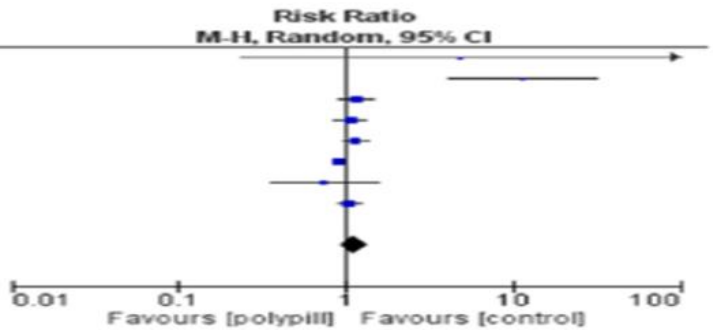


B] Adverse Events

Study or Subgroup	Polypill Events	Polypill Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Malekzadeh et al. 2010	2	241	0	234	0.4%	4.86 [0.23, 100.60]	2010
CRUCIAL 2011	52	779	4	682	3.0%	11.38 [4.14, 31.30]	2011
UMPIRE 2013	118	1002	102	1002	16.0%	1.16 [0.90, 1.49]	2013
IMPACT 2014	99	256	93	257	16.9%	1.07 [0.85, 1.34]	2014
Kanyini GAP 2015	144	311	127	312	18.5%	1.14 [0.95, 1.36]	2015
HOPE-3 2016	697	3180	757	3168	21.1%	0.92 [0.84, 1.00]	2016
TIPS-3 2021	12	1429	16	1421	5.0%	0.75 [0.35, 1.57]	2021
SECURE 2022	237	1237	224	1229	19.0%	1.05 [0.89, 1.24]	2022
Total (95% CI)		**8435**		**8305**	**100.0%**	**1.12 [0.93, 1.36]**	
Total events	1361		1323				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 31.61$, $df = 7$ ($P < 0.0001$); $I^2 = 78\%$

Test for overall effect: $Z = 1.19$ ($P = 0.24$)



C] Major Bleeding

Study or Subgroup	Polypill Events	Polypill Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
IMPACT 2014	4	256	0	257	1.0%	9.04 [0.49, 166.96]	2014
Polyiran 2019	23	3421	20	3417	24.5%	1.15 [0.63, 2.09]	2019
TIPS-3 2021	9	1429	12	1421	11.8%	0.75 [0.32, 1.76]	2021
SECURE 2022	57	1237	49	1229	62.7%	1.16 [0.80, 1.68]	2022
Total (95% CI)		**6343**		**6324**	**100.0%**	**1.12 [0.83, 1.50]**	
Total events	93		81				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.88$, $df = 3$ ($P = 0.41$); $I^2 = 0\%$

Test for overall effect: $Z = 0.75$ ($P = 0.46$)

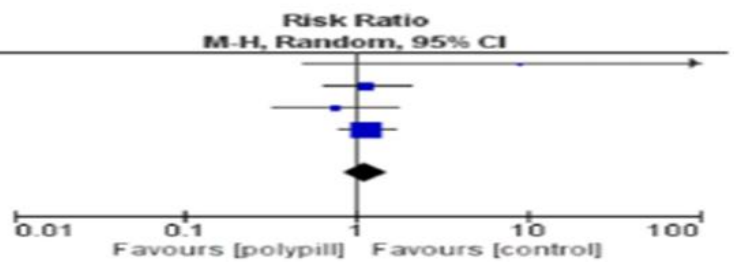


Figure 4. Forest plot for *(A)* adherence, *(B)* adverse events, and *(C)* major bleeding. M-H = Mantel-Haenszel.

Discussion : In this meta-analysis of 11 RCTs including 25,389 patients, we evaluated the role of polypill therapy in CVD prevention :

1/Polypill therapy was associated with a lower incidence of cardiac events compared with placebo or usual-minimal care.

2/The observed reduction of MACCEs with the polypill strategy was consistent across the included studies.

3/Polypill therapy was associated with a higher degree of adherence.

4/There was no difference between both groups in the incidence of major bleeding or other adverse events.

5/Statins were included in all RCTs , they have been shown to reduce the risk of MACCE in both primary and secondary prevention.

6/Moreover, a meta-analysis of 25 trials found that in patients with established CVD but without hypertension, antihypertensive therapy was associated with decreased risk of MACCEs.

7/The use of aspirin in primary CVD prevention is controversial with recent data showing that although aspirin reduces the risk of nonfatal myocardial infarction, it is not associated with lower mortality risk and significantly increases the risk of major bleeding

Conclusion :

- In this meta-analysis of RCTs, a polypill strategy was associated with a lower incidence of MACCEs. This benefit was consistent for both primary and secondary prevention.
- A polypill strategy was not associated with a higher incidence of adverse events and was associated with a higher degree of adherence.
- These findings support the widespread use of a polypill strategy in patients at higher risk or with CVD.

The present analysis has several limitations :

1/There was high degree of heterogeneity for the primary study outcome.

2/The components of the polypill, the definition of the control arm, and the follow-up period varied across the included studies.

3/There were variabilities in the included studies in the inclusion criteria, components of the polypill, and end point definition.

4/There were insufficient data across the included studies to pool the treatment effects for polypills versus control approaches on cardiovascular risk factors.

Thank you for your attention !