

Table 1: Polypill Studies Comparison ⁴⁻¹¹									
Study/Author	Design/Comparison	Patients	Demographics	Follow up	Inclusion Criteria	Exclusion Criteria	Formulation of Polypill	Primary Outcomes	Secondary Outcomes
TIPS-1 Yusuf, S et.al., 2009 ⁴	Randomized, Double Blinded Polypill vs. "Usual Care" Usual Care=8 Groups: ASA alone, Simvastatin alone, HCTZ alone, Three combinations of the two BP lowering meds, Three BP lowering meds alone, and the three BP lowering drugs + ASA	N=2053 N=412 to Polycap	43.9% Female Mean Age: 54 Population: 50 centers in India	16 weeks	Individuals without CVD with one risk factor	-Already receiving one of the study drugs -Taking two or more BP lowering drugs -Serum LDL-C \geq 4.5 mmol/L -Cr \geq 2.0 mg/dL -K+ \geq 5.5 mmol/L -Abnormal liver function -Asthma -Pregnant or lactating	-HCTZ 12.5 mg -Atenolol 50mg -Ramipril 5mg -Simvastatin 20mg -ASA 100mg	LDL-C decrease 0.7% vs. 0.83% (simvastatin alone) Mean BP decrease 7.4 mm Hg vs. 6.9 mm hg in other groups with three BP lower agents HR decrease 7 bpm (95% CI 6–8) in both Polycap and groups with atenolol Reduction in Urinary 11-dehydrothromboxane B2 283.1 ng/mmol (95% CI 229.1–337.0) vs. 348.8 (277.6–419.9) ng/mmol in ASA alone and 350ng/mmol (294.6–404.0) in other group with ASA Rate of discontinuation for safety (major cardiovascular event or bleed) 14.8%	Total cholesterol decreases by 0.83% in polypill and simvastatin alone Overall side Effects for Polypill -Dizziness or hypotension (6.3%) -Cough (5.3%) -Gastritis/dyspepsia (1.2%) -Bradycardia (0.2%) -Cr increase by 50% (8.5%) -K+ \geq 5.5 (2.9%)
PILL Rodgers, A et.al., 2011 ⁹	Randomized, Double Blinded Polypill vs. Placebo	N= 378 Polypill: N=189 Placebo: N=189	80% male 20% female Mean age 61.2 Population: Australia: 21 Brazil: 8 India: 109 Netherlands: 102 New Zealand: 12 UK:113 USA: 13	12 weeks	- Estimated 5-year risk of 7.5% or greater)*	Specific indication for any components in the polypill Contraindications to any of the components Diagnosis of Diabetes Mellitus GFR \leq 30 mL/min	-ASA 75mg -Lisinopril 10mg -HCTZ 12.5mg -Simvastatin 20mg	Decrease in SBP by 9.9 mm hg (95% CI: 7.7 to 12.1) compared to placebo Decrease in LDL-C 0.8 mmol/L (95% CI: 0.6 to 0.9) compared to placebo	Discontinuation rate 23% vs. 18% Hypotension/Dizziness 30% vs. 11% Gastric irritation/bleeding tendency 17% vs. 6% There were no reported deaths, major vascular events, major bleeding events

Wald et al., 2012 ⁵	Randomized, Double-blind, Crossover (polypill x12 weeks, and placebo x 12 weeks) Polypill vs. Placebo	N=86 N=43 to each group and then switching after 12 weeks	74% male 26% female Mean Age 59 Population: Adults in London, UK	12 weeks	Age \geq 50 AND no history of cardiovascular disease Recruited from group already taking simvastatin and BP lowering agents for a cardiovascular prevention program	No contraindications to polypill components	-Amlodipine 2.5mg -Losartan 25mg -HCTZ 12.5mg -Simvastatin 40mg	Decrease in Mean SBP of 17.9 mm Hg (95% CI, 15.7–20.1) Decrease in LDL-C by 1.4 mmol/dL (95% CI, 1.2–1.6)	Decrease in DBP by 9.8 mm Hg (95% CI, 8.1–11.5) Muscles aches: N=9 vs. N=1 100% adherence to polypill, 2 people stopped placebo
TIPS-2 Yusuf, S et.al., 2012 ⁶	Randomized, double blinded, 2x2 controlled 1. Single-dose polypill plus placebo 2. Two polypill capsules plus K+	N=518 1. Low dose (single polypill)- N= 261 2. High dose (two polypills) N=257	Group 1: 58% male Group 2: 59% male Mean age: 57 Population: 27 clinical centers in India	8 weeks	-Previous vascular disease OR high-risk diabetes mellitus -BP >130/80 or >120/80 on medications	-Intolerance to any medications in study -Clear indication to any specific medication in study -Cr \geq 2 or GFR \leq 45 -K+ \geq 5	-HCTZ 12.5mg -Atenolol 50mg -Ramipril 5mg -Simvastatin 20mg -Aspirin 100mg	Changes in SBP --2.8 mm Hg more in Group 2(95% CI, -0.17 to -2.8 mm Hg) Changes in Heart Rate -No difference LDL-C (CI, -11.3 to -1.9; P=0.006) -increased by 16.6 mmol/L in Group 1 -increased by 10 mmol/L in Group 2	Changes in Potassium -4.3 mmol/L vs. 4.4 mmol/L (CI, -0.03 to 0.1; P=0.20) Changes in Cr -No difference Dyspepsia 1. 0.7% 2. 0.5% Dizziness 1. 1.8% 2. 1.1% Hypotension 1. 0.8% 2. 0.9% Discontinuation 1. 6.9% 2. 7.8%
Muñoz D et al., 2019 ⁷	Randomized Controlled Polypill vs. Usual care (multiple pills)	N=303 N=148 to polypill (group 1) N=155 to usual care (group 2)	Group 1: 44% male Group 2: 36% male Mean Age 56 Population: Adults in Alabama, United States	12 months	-No hx of CAD, Stroke, Liver Disease, Insulin-dependent Diabetes Mellitus -SBP between 120 and 160	-LDL-C >190 -GFR <60 -Abnormal Potassium levels -Abnormal aminotransferase levels -Pregnancy -One more than two anti-hypertensive medications	-Atorvastatin 10mg -Amlodipine 2.5mg -Losartan 25mg -HCTZ 12.5mg	Change compared to Usual care -Mean SBP: -7 mm Hg -Mean LDL-C: 11 mmol/dL	Adherence 86% Change Compared to Placebo -DBP: -3 mm Hg -Total chol: -11 -HDL-C: -1 -TG: -2 -10 yr cardiovascular risk: -3.1%

			Black 96% Other minority populations 4%						Incidences in polypill group of -Myalgias 1% -hypotension or light headedness 1%
HOPE-3 Yusuf S et al.,2018 ⁸	Randomized controlled 2x2'' Group 1: Rosuvastatin 10 vs. Placebo Group 2: BP Polypill vs. Placebo Group 3: BP Polypill +Rosuvastatin vs. Placebo	N= 12,705 1.Rosuvastatin 10 (6,361) vs. placebo (6,344) 2.BP polypill (6,356) vs. Placebo (6,349) 3.BP polypill and rosuvastatin (3180) vs Placebo (3,168)	46% Female Mean age 65.8 Population: Chinese: 29% Hispanic:27% White 20% SouthAsian:15% Black: 2%	5.6 years	Men ≥5 Women ≥65 PLUS at least one of the following: -Elevated waist-to-hip ratio -Low HDL-C -Current or recent tobacco use -Dysglycemia -Family history of premature CAD -Mild renal dysfunction -Women with at least two of the above risk factors	Participants with CVD Indication for or contraindication to: -statins, -ACEi/ARBs -thiazide diuretics	Candesartan 16mg, HCTZ 12.5mg	Composite of CV Death/MI/Stroke Group 1 -3.7% vs. 4.8% Group 2. -4.1% vs.4.4% Group 3. -3.6% vs. 5.5%	Group 1 -MI 0.7% vs1.1% -CAD 1.7% vs. 2.2% -Hospitalizations for CAD 4.4% vs. 5.8% -Adherence 77.3% vs. 74.8% Group 2 -MI 0.8% vs. 1% -Stroke 1.2% vs. 1.5% -Hospitalizations for CAD 5% vs. 5.2% -Symptomatic hypotension 3.4% vs. 2% -Adherence: 76.8% vs. 75.7% Group 3 -CV death 2.4% vs. 2.9% -MI 0.7% vs. 1.2% -Hospitalizations for CAD 4.4% vs. 6% -Adherence 74.6% vs. 71.8%
Poly-Iran Roshandel G et al., 2019 ¹⁰	Randomized (1:1) cohort study; Clustered (assorted by villages) Polypill vs. Minimal Care(Lifestyle education)	N=6838 -N=3417 to minimal care -N=3421 to polypill	Polypill group: 5.15% women Minimal care group: 49.1% women Ages 50-75 yrs Population: Members of Golestan province in Iran	5 years	Participants from rural areas (Golestan province) >50yrs	-Hypersensitivity to any of the components of the polypill -Angioedema -Hx of GI bleed within 3 months -Hx of stroke -Pregnancy or Lactation	-HCTZ 25mg -ASA 81 mg -Atorvastatin 20mg -Enalapril 5mg	Major CV Events 5.9% vs. 8.8% Mortality 5.9% vs. 6.5%	Fatal Ischemic Heart Disease 3.7% vs. 4.9% Non-Fatal Ischemic Heart Disease 3.7% vs. 4.9% Non-CV related death 4.4% vs. 3.6% Heart Failure 0.4% vs. 0.5% Non-Fatal Stroke 0.5% vs. 1.1%

						<ul style="list-style-type: none"> -Hx of bleeding disorder (ex. hemophilia) -Alcohol consumption >3x/day -Advanced Liver disease -Uncontrolled seizures -Cr ≥ 2 or GFR ≤ 30 -Hgb ≤ 10 in women or ≤ 11 in men -SBP <90 and/or DBP <60 			<ul style="list-style-type: none"> Fatal Stroke 0.2% vs. 0.6% Sudden Death 0.6% vs. 0.8% Intracranial Hemorrhage: N=10 vs. 11 GI Bleed: N= 13 vs. 9 Median Adherence 80.5%
<p>Study¹¹: TIPS-3</p> <p>Authors Yusuf,S et al 2020</p>	<p>1:1 Randomized Controlled then 2x2</p> <p>1. Polypill vs. Placebo</p> <p>2. ASA vs. Placebo</p> <p>3. Polypill + ASA vs. Placebo</p>	<p>N= 5,713</p> <p>-N=2,861 to polypill</p> <p>-N=2,852 to placebo</p> <p>-Also randomized to ASA vs. placebo</p>	<p>53% Female 47% Male</p> <p>Mean Age 63.9</p> <p>Population</p> <ul style="list-style-type: none"> -India: 2739 -Philippines: 1676 -Colombia: 489 -Bangladesh: 295 -Canada: 131 -Malaysia: 119 -Indonesia: 118 -Tunisia: 107 -Tanzania: 39 	<p>4.6 years</p>	<ul style="list-style-type: none"> -Men ≥ 50 y -women ≥ 55 y <p>AND</p> <p>INTERHEART Risk Score (IHRS) of ≥ 10 OR</p> <p>Men/women ≥ 65 years with an IHRS of ≥ 5</p>	<ul style="list-style-type: none"> -Vascular disease -Contraindication to any of the drugs involved or aspirin or Vitamin D -SBP ≤ 120mm Hg -Symptomatic hypotension -Peptic ulcer dz/dyspepsia/bleeding 	<ul style="list-style-type: none"> -Atenolol 10mg -Simvastatin 10mg -HCTZ 25mg -Ramipril 10mg 	<ul style="list-style-type: none"> -CV death: <ul style="list-style-type: none"> 1. 2.9% vs. 3.5% 2. 3% vs. 3.5% 3. 3.6% vs. 5.3% -MI: <ul style="list-style-type: none"> 1. 0.6% vs. 0.9% 2. 0.8% vs. 0.7% 3. 3.6% vs. 5.3% -Stroke: <ul style="list-style-type: none"> 1. 0.9% vs. 1.3% 2. 0.8% vs. 1.4% 3. 0.7% vs. 1.6% -Arterial revascularization: 1. 0.4% vs. 0.9% 	<ul style="list-style-type: none"> Mean difference in systolic BP: 1. 5.8 mm Hg Mean difference in LDL-C: 19 mg/dl All-cause mortality: <ul style="list-style-type: none"> 1. 5.2% vs. 5.7% 2. 5.1% vs. 5.9% 3. 5.2% vs. 6.5% Dizziness or hypotension: 1. 2.7% vs. 1.1% Major bleeding 2. 0.7% vs. 0.7% GI Bleed 2. 0.4% vs. 0.4% Adherence: 43% discontinued polypill by the end
<p>*The risk score (Framingham) included age, sex, SBP, ratio of total to high-density lipoprotein cholesterol (HDL-C), diabetes, smoking, and a 5% adjustment for people from the Indian subcontinent(when applicable).</p>									

ACEi (Angiotensin Converting Enzyme Inhibitors), ARB (Angiotensin Receptor Blocker), ASA (aspirin), BP (Blood Pressure), BPM (beats per minute), CAD (coronary artery disease), CV (cardiovascular), CVD (cardiovascular disease), Cr (creatinine), DBP (Diastolic Blood Pressure), dL (deciliter), mL (milliliters), GFR (Glomerular Filtration Rate), HCTZ (Hydrochlorothiazide), Hgb (hemoglobin), Hx (history), K⁺ (Potassium), L (liter), LDL-C (Low Density Lipoprotein-cholesterol), mg (milligrams), MI (myocardial infarction), min (minute), mmol (millimoles), Polycap (Polypill Capsule), SBP (Systolic Blood pressure)