A Polypill for Primary Prevention of Cardiovascular Disease: The International Polycap Study (TIPS)-3

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On behalf of the TIPS-3 Investigators

Disclosures

Prem Pais:

- Institutional research support from Wellcome Trust and Cadila Pharmaceuticals, Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada

Salim Yusuf:

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Polypill Hypothesis

- Risk factors have a graded relationship with CVD risk
- Statins, β-blockers, ACE i and aspirin collectively reduce CVD risk by 75% in secondary prevention (Yusuf, Lancet 2001)
- **Wald and Law hypothesized 80% RRR for MI and Stroke (BMJ, 2003)**
  - Combination of 3 BP lowering drugs at ½ dose should reduce SBP by 18 mmHg: 40% RRR in **MI and stroke**
  - Statins reduce LDL-C by 1.8 mmol/L: 40% RRR in **MI and stroke**
  - Aspirin: 25% RRR in **MI and stroke**
  - Hcy Lowering: 20% risk reduction in **MI and stroke**

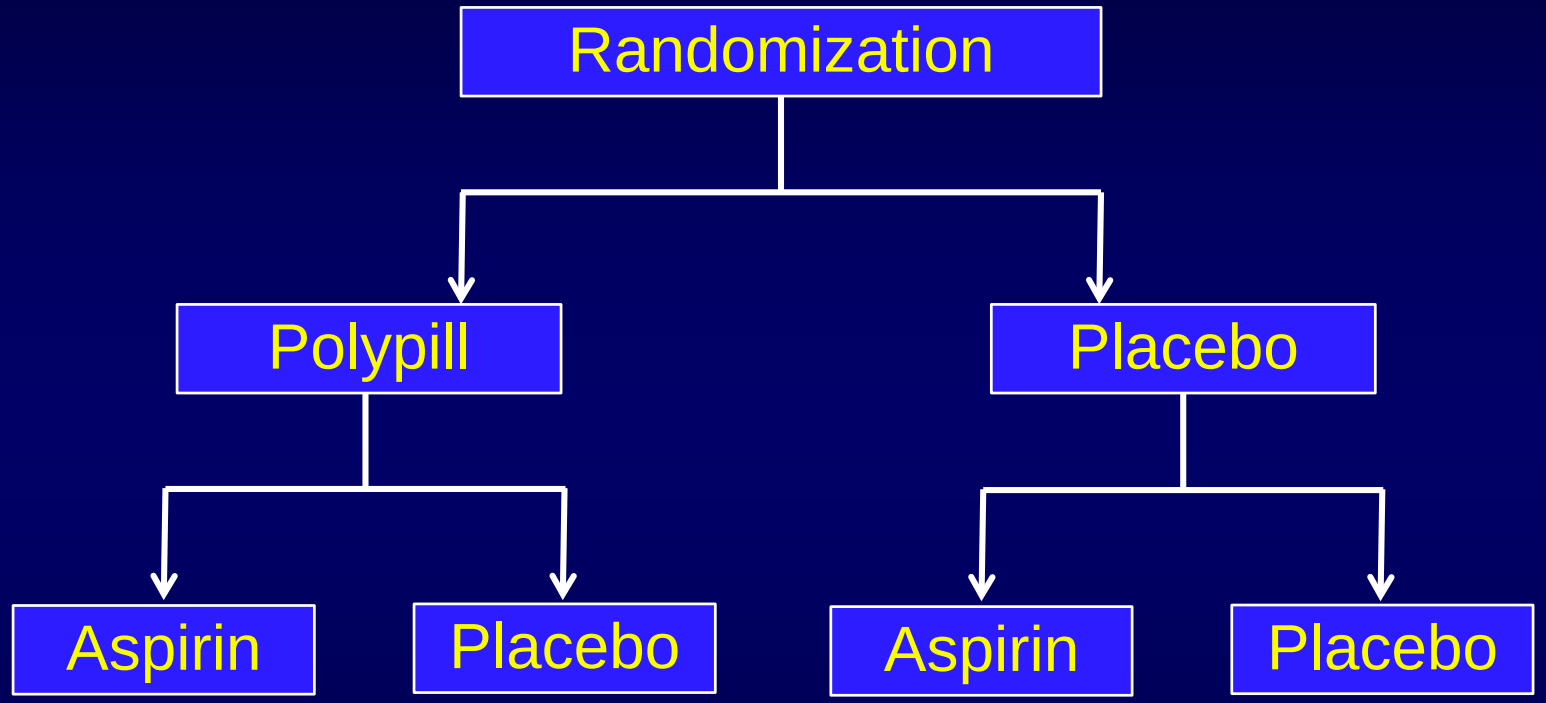
Objectives and Primary Outcomes

To determine whether:

1. **Polypill** reduces the composite of CVD events* compared to its **placebo**
2. **Aspirin** reduces the composite of CV death, MI or stroke compared to its **placebo**
3. **Polypill plus aspirin** reduces composite of CVD events* compared to **double placebo**

**Major CVD (CV death, non-fatal stroke, non-fatal MI), heart failure, resuscitated cardiac arrest, or arterial revascularization*

TIPS-3: Factorial RCT



Polypill: atenolol 100 mg + ramipril 10 mg + HCTZ 25 mg + simvastatin 40 mg capsule daily

Aspirin: 75 mg daily

Statistical Considerations

- Placebo event rate at 5 yrs of 6%
- Projected non-adherence: 20%
- 35% RRR with 5000 people: 80% power

Pre-specified analyses:

- Intention to treat
- Total events (first and recurrent events)
- *Sensitivity analysis:* censoring events 30 days after discontinuation of blinded treatment due to non-medical reasons e.g. inability to resupply drugs

Eligibility Criteria

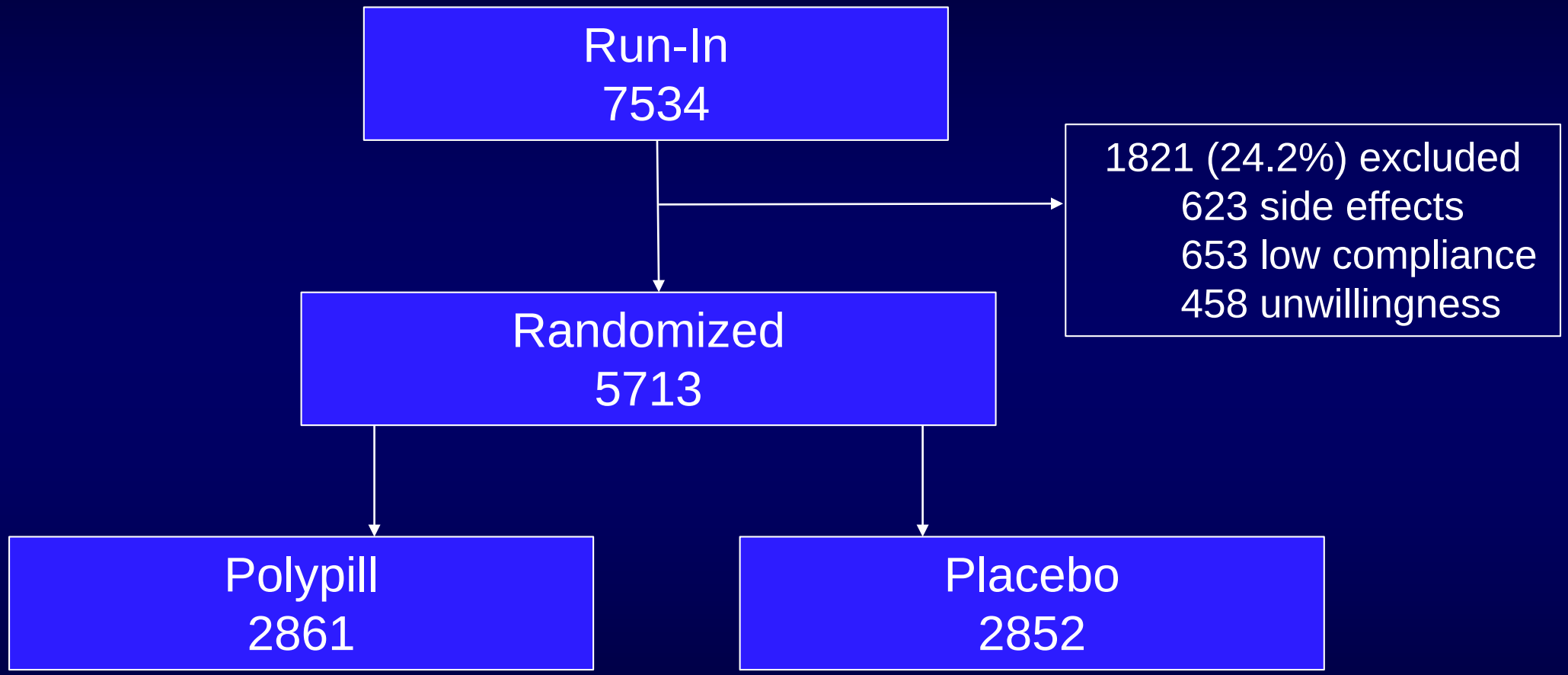
Inclusion (CVD Risk >1.0%/yr):

- Men ≥ 50 yrs and women ≥ 55 yrs with an IHRS ≥ 10, or men and women ≥ 65 yrs with an IHRS of ≥5

Key Exclusion:

- Vascular disease

Flow Diagram



Mean follow-up 4.6 years

Vital status: 99.2%, clinical outcomes: 98.9%

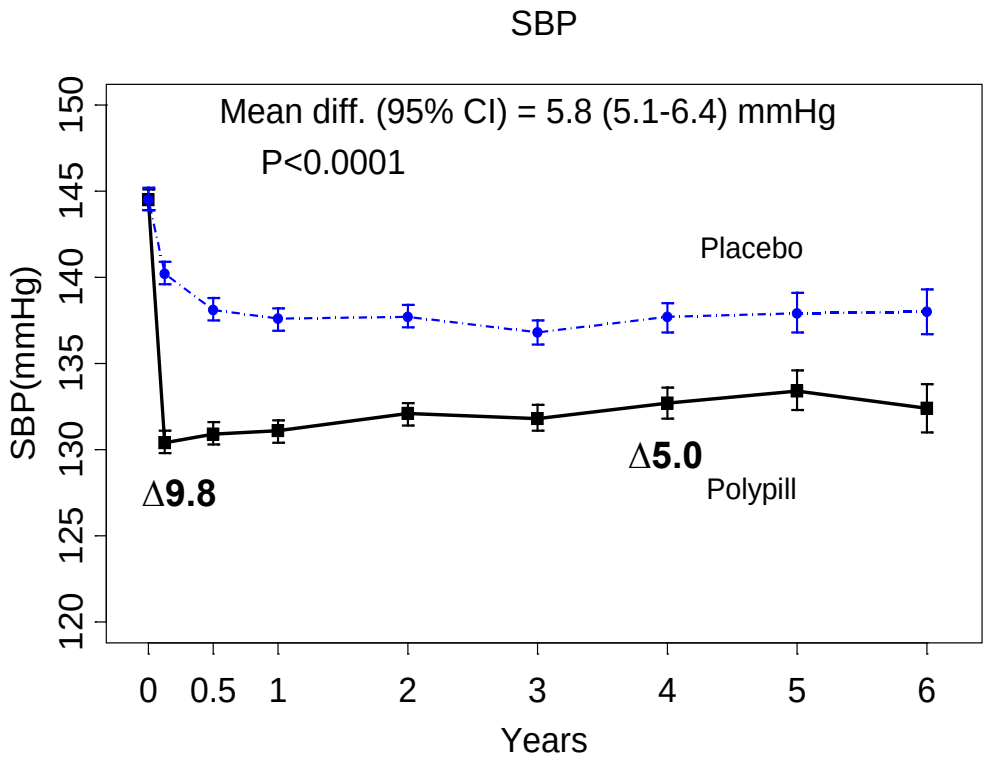
Randomization by Country

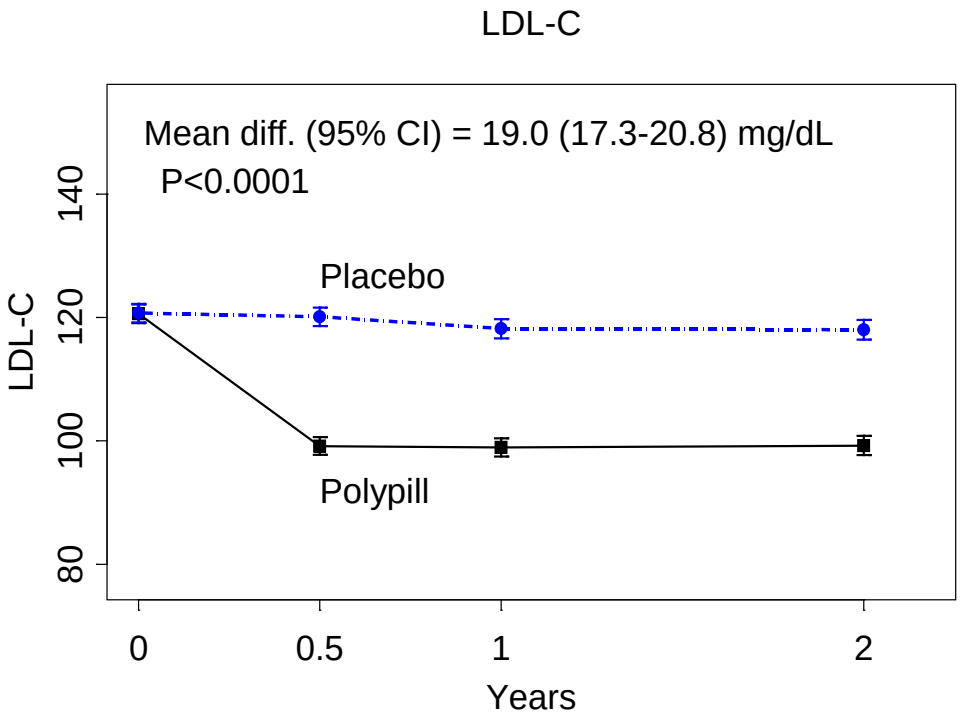
	N Rand
India	2739
Philippines	1676
Colombia	489
Bangladesh	295
Canada	131
Malaysia	119
Indonesia	118
Tunisia	107
Tanzania	39
Total	5713

Baseline Characteristics

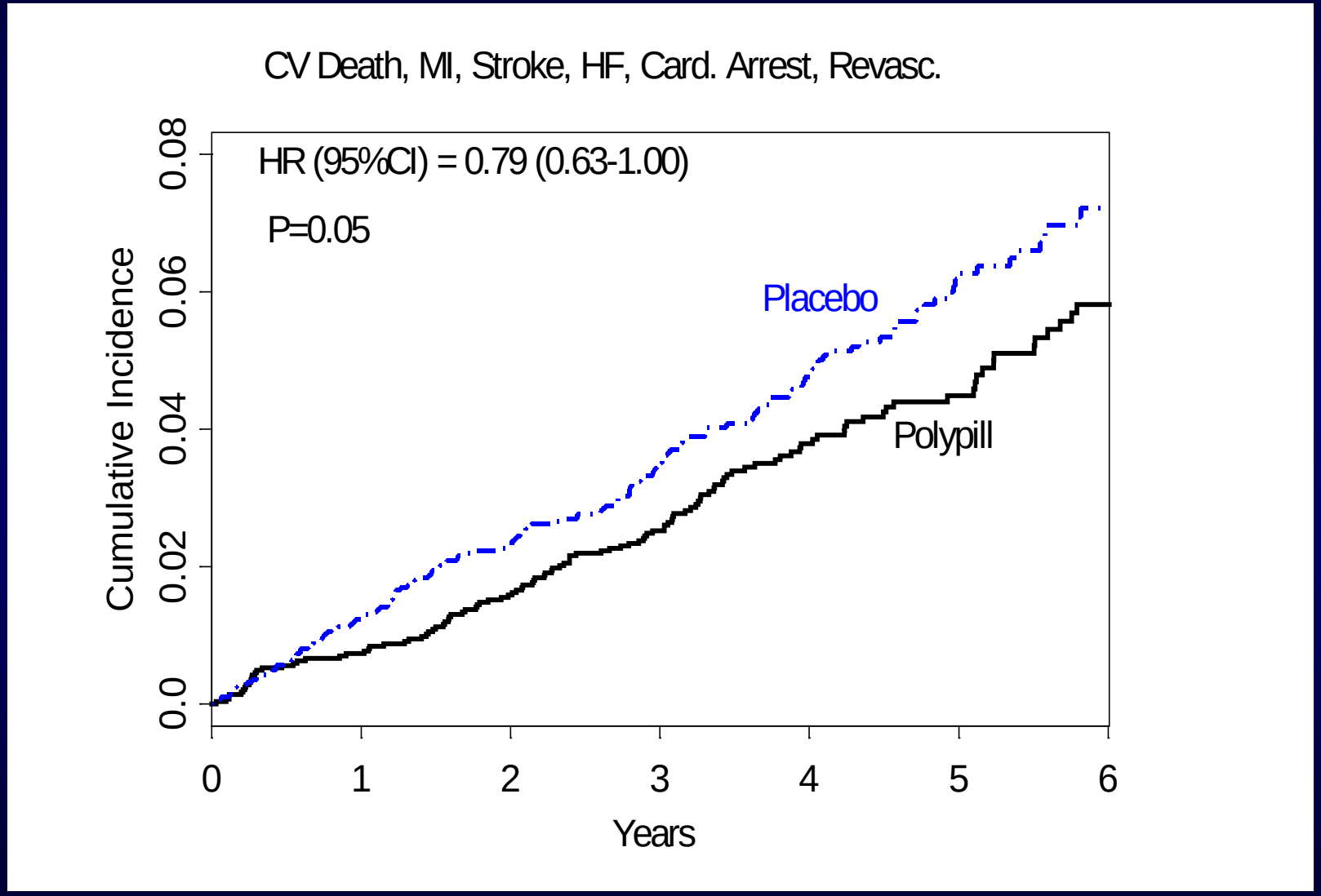
	Polypill N = 2,861	Placebo N=2,852
Age, yrs	63.9	63.9
Female (%)	53.2	52.7
HTN or SBP > 140 (%)	83.6	84.1
DM or Glucose > 126 mg/dL (%)	37.2	36.1
Smoker (%)	9.1	8.9
SBP, mmHg	144.5	144.5
Total cholesterol, mg/dL	196.1	196.2
LDL, mg/dL	120.6	120.7
Mean IH Risk score	18.0	17.9

Polypill vs Placebo: Risk Factor Changes





Polypill vs Placebo: Primary Outcome



Polypill vs Placebo: Clinical Outcomes

Outcomes	Polypill (N= 2,861) (%)	Placebo N=2,852 N (%)	Hazard Ratio (95% CI)	P-value
Primary	126 (4.4)	157 (5.5)	0.79 (0.63-1.00)	0.050
Secondary				
CV death, MI, Stroke	111 (3.9)	139 (4.9)	0.79 (0.61-1.01)	0.062
Primary + angina	132 (4.6)	164 (5.8)	0.79 (0.63-1.00)	0.049
First + Recurrent Primary Events	138	179	0.76 (0.60-0.97)	0.028
Mortality	149 (5.2)	163 (5.7)	0.90 (0.72-1.13)	0.371

Polypill vs Placebo: Clinical Outcomes

Components of the primary and secondary outcomes	Polypill (N=2,861) N (%)	Placebo (N=2,852) N (%)	Hazard Ratio (95% CI)
CV death	84 (2.9)	101 (3.5)	0.82 (0.61-1.09)
MI	17 (0.6)	26 (0.9)	0.66 (0.36-1.22)
Stroke	26 (0.9)	36 (1.3)	0.71 (0.43-1.18)
HF	12 (0.4)	10 (0.4)	1.19 (0.51-2.74)
Cardiac arrest	1(0)	0 (0)	-
Revascularization	12 (0.4)	25 (0.9)	0.48 (0.24-0.95)
Angina	17 (0.6)	22 (0.8)	0.77 (0.41-1.44)

Adherence

1. Mean contrast between polypill and placebo groups was 80% for BP lowering medications and 82% for statins
2. Non-adherence for polypill and placebo similar:
   - 19% at 2 years
   - 32% at 4 years
   - 43% at study end
     - 15% delays in drug supply
     - 5% side effects
3. Similar results for aspirin and combination

Sensitivity Analysis Accounting for Non-adherence

	No. Events <30 days of stopping drugs for non-medical reasons		No. Events > 30 days		All Events	
	Polypill	Placebo	Polypill	Placebo	Polypill	Placebo
Primary outcome, N (%)	95 (3.3)	126 (4.4)	31 (1.1)	31 (1.1)	126 (4.4)	157 (5.5)
Hazard Ratio	0.74 (0.57-0.97)				0.79 (0.63-1.00)	

Polypill vs Placebo: Safety

	Polypill (N=2,861) N (%)	Placebo (N=2,852) N (%)
SAEs, N (%)	23 (0.8)	33 (1.2)
Discontinuation for AE, N (%)		
Dizziness or Hypotension	77 (2.7)	31 (1.1)
Cough	31 (1.1)	17 (0.6)
Muscle pain or weakness	14 (0.5)	15 (0.5)

Aspirin Alone or in Combination With a Polypill

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Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Aspirin in Primary CVD Prevention

- Clinical trials indicate:
  - 15% RRR in CV events
  - Potential reduction in cancer risk
  - Benefits may be counterbalanced by bleeding
- Limited data in South and East Asian populations
- Unclear whether aspirin should be included with a polypill for primary CVD prevention

Outcomes

Aspirin vs placebo (N= 5713)

Primary: CV death, MI, stroke

Secondary: CV death, MI, stroke, cancer

First and Recurrent Events

Polypill plus aspirin vs *double* placebo (N= 2850)

Primary: CV death, non-fatal stroke, non-fatal MI, HF, cardiac arrest, or arterial revascularization

Secondary:

- CV death, MI, stroke
- Primary + angina

First and Recurrent Events

Aspirin vs Placebo: Clinical Outcomes

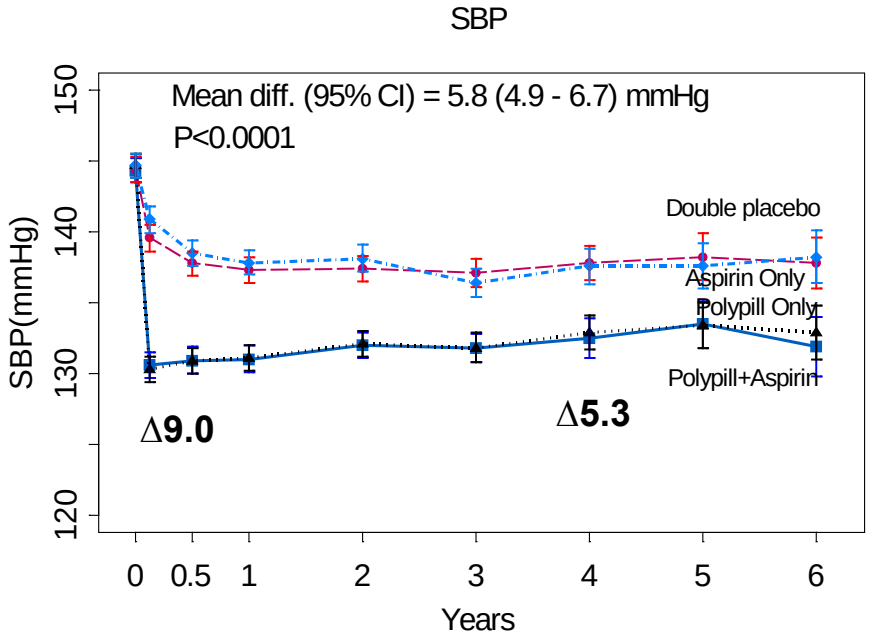
Outcomes	Aspirin (N=2,860) N (%)	Placebo (N=2,853) N (%)	Hazard Ratio (95% CI)	P-value
Primary	116 (4.1)	134 (4.7)	0.86 (0.67-1.10)	0.237
CV Death	85 (3.0)	100 (3.5)	0.85 (0.64-1.14)	0.279
MI	22 (0.8)	21 (0.7)	1.04 (0.57-1.89)	0.903
Stroke	23 (0.8)	39 (1.4)	0.58 (0.35-0.98)	0.041
First + Recurrent Primary Events	124	144	0.86 (0.67-1.11)	0.248
Cancer	38 (1.3)	46 (1.6)	0.83 (0.55-1.27)	0.381
Mortality	145 (5.1)	167 (5.9)	0.87 (0.70-1.89)	0.220

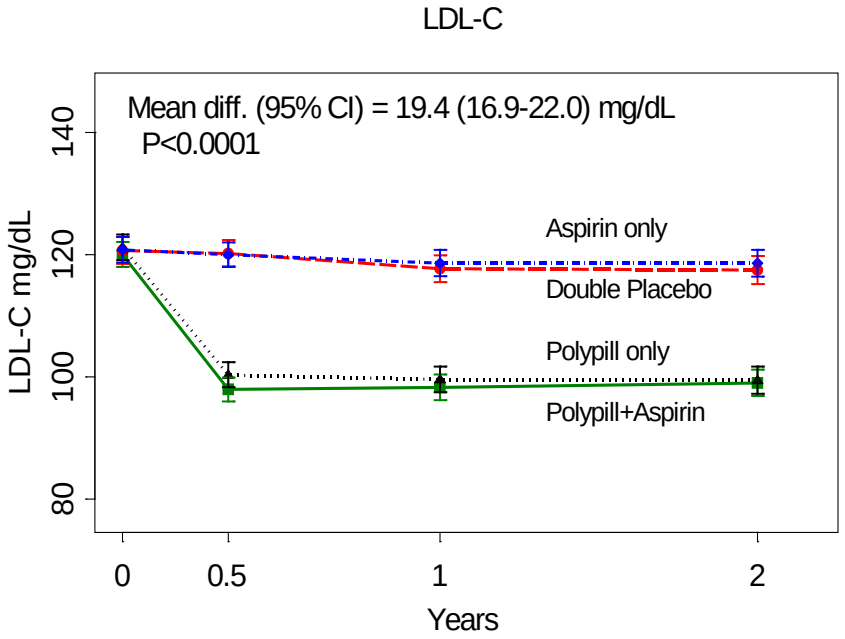
Aspirin vs Placebo: Safety

Outcome	Aspirin (N=2,860) N (%)	Placebo (N=2,853) N (%)
Bleeding:		
Major*	20 (0.7)	19 (0.7)
Minor	17 (0.6)	14 (0.5)
GI Bleed	12 (0.4)	10 (0.4)
Dyspepsia/peptic ulcer with discontinuation	8 (0.3)	6 (0.2)

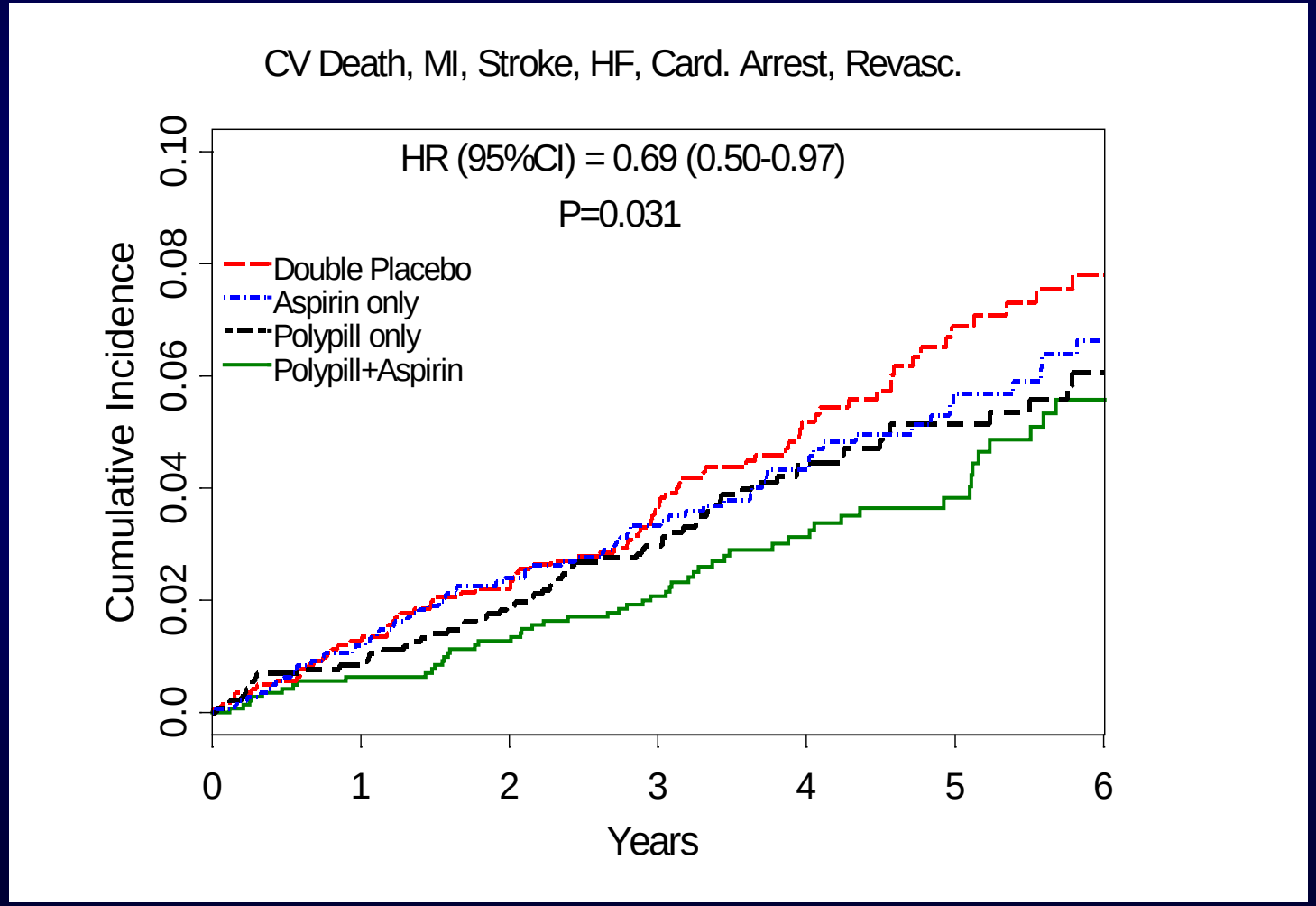
*International Society on Thrombosis and Haemostasis criteria for major bleeding

Polypill + *Aspirin* vs *Double Placebo*: Risk Factors





Polypill + Aspirin vs Double Placebo: Primary Outcome



Polypill + Aspirin vs Double Placebo: Pre-specified Outcomes

	Polypill + Aspirin N=1,429 (%)	Double Placebo N=1,421 (%)	Hazard Ratio (95% CI)	P-value
Primary	59 (4.1)	83 (5.8)	0.69 (0.50-0.97)	**0.031**
Secondary				
CV death, MI, Stroke	52 (3.6)	75 (5.3)	0.68 (0.47-0.96)	**0.030**
Primary + angina	61 (4.3)	86 (6.1)	0.69 (0.50-0.96)	**0.028**
First + Recurrent Primary Events	64	93	0.68 (0.48-0.96)	**0.027**
Other				
CVD + Cancer	76 (5.3)	106 (7.5)	0.70 (0.52-0.94)	**0.016**
Cancer	19 (1.3)	24 (1.7)	0.78 (0.43-1.42)	0.414
Mortality	75 (5.2)	93 (6.5)	0.80 (0.59-1.08)	0.145

Polypill + Aspirin vs Double Placebo: Clinical Outcomes

	Polypill + Aspirin N=1,429 (%)	Double Placebo N=1,421 (%)	Hazard Ratio (95% CI)
Component CVD events			
CV death	38 (2.7)	54 (3.8)	0.69 (0.46-1.05)
MI	10 (0.7)	14 (1.0)	0.69 (0.31-1.56)
Stroke	10 (0.7)	23 (1.6)	0.42 (0.20-0.89)
HF	7 (0.5)	3 (0.2)	2.30 (0.60-8.90)
Revascularization	5 (0.3)	12 (0.8)	0.40 (0.14-1.14)
Angina	6 (0.4)	10 (0.7)	0.59 (0.22-1.63)

Sensitivity analysis for non-adherence

	No. Events <30 days of stopping drugs for non-medical reasons		No. Events > 30 days		All Events	
	Polypill + Aspirin	Double Placebo	Polypill + Aspirin	Double Placebo	Polypill + Aspirin	Double Placebo
Primary outcome (%)	40 (2.8)	64 (4.5)	19 (1.3)	19 (1.3)	59 (4.1)	83 (5.8)
Hazard Ratio	0.61 (0.41-0.91)				0.69 (0.50- 0.97)	

Conclusions

- In an intermediate risk population without CVD over 4.6 years:
  - Polypill: 21%* reduction in CVD
  - Aspirin: 14%* reduction in CV death, MI, or stroke
  - Polypill + Aspirin: 31%* reduction in CVD
- Benefits larger (about 40% with polypill + aspirin) in those without discontinuation for non-medical reasons
- Aspirin contributes importantly to benefits

**ITT estimates*

Implications

- 30-40% CVD risk reduction with polypill + aspirin is lower than original hypothesized benefits, but nevertheless is important
- If half of eligible people use a polypill with aspirin: 3 to 5 million CVD events avoided each year globally
- Likely a cost effective strategy to meet global targets of reducing CVD by 30% by 2030.
- Future polypills which reduce LDL-C and BP to greater extent might lead to larger benefits

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Polypill with or without Aspirin in Persons without Cardiovascular Disease

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