Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial

The Indian Polycap Study (TIPS)*

Summary

Background The combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid (the polypill), could reduce cardiovascular events by more than 80% in healthy individuals. We examined the effect of the Polycap on blood pressure, lipids, heart rate, and urinary thromboxane B2, and assessed its tolerability.

Methods In a double-blind trial in 50 centres in India, 2053 individuals without cardiovascular disease, aged 45–80 years, and with one risk factor were randomly assigned, by a central secure website, to the Polycap (n=412) consisting of low doses of thiazide (12·5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg) per day, or to eight other groups, each with about 200 individuals, of aspirin alone, simvastatin alone, hydrochlorthiazide alone, three combinations of the two blood-pressure-lowering drugs, three blood-pressure-lowering drugs alone, or three blood-pressure-lowering drugs plus aspirin. The primary outcomes were LDL for the effect of lipids, blood pressure for antihypertensive drugs, heart rate for the effects of atenolol, urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin, and rates of discontinuation of drugs for safety. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00443794.

Findings Compared with groups not receiving blood-pressure-lowering drugs, the Polycap reduced systolic blood pressure by 7·4 mm Hg (95% CI 6·1–8·1) and diastolic blood pressure by 5·6 mm Hg (4·7–6·4), which was similar when three blood-pressure-lowering drugs were used, with or without aspirin. Reductions in blood pressure increased with the number of drugs used (2·2/1·3 mm Hg with one drug, 4·7/3·6 mm Hg with two drugs, and 6·3/4·5 mm Hg with three drugs). Polycap reduced LDL cholesterol by 0·70 mmol/L (95% CI 0·62–0·78), which was less than that with simvastatin alone (0·83 mmol/L, 0·72–0·93; p=0·04); both reductions were greater than for groups without simvastatin (p<0·0001). The reductions in heart rate with Polycap and other groups using atenolol were similar (7·0 beats per min), and both were significantly greater than that in groups without atenolol (p<0·0001). The reductions in 11-dehydrothromboxane B2 were similar with the Polycap (283·1 ng/mmol creatinine, 95% CI 229·1–337·0) compared with the three blood-pressure-lowering drugs plus aspirin (350·0 ng/mmol creatinine, 294·6–404·0), and aspirin alone (348·8 ng/mmol creatinine, 277·6–419·9) compared with groups without aspirin. Tolerability of the Polycap was similar to that of other treatments, with no evidence of increasing intolerability with increasing number of active components in one pill.

Interpretation This Polycap formulation could be conveniently used to reduce multiple risk factors and cardiovascular risk.

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Introduction

Aspirin,[1] β blockers,[2] angiotensin-converting-enzyme inhibitors,[3] and statins[4] reduce cardiovascular disease. One combination pill including all the above drugs could potentially reduce recurrent vascular events in people with cardiovascular disease by about 75%.[5] Wald and Law extended this hypothesis in several ways.[6–8] First, a combination of three agents to decrease blood pressure at low doses was estimated to reduce blood pressure substantially (11 mm Hg diastolic) in individuals with average blood pressure values, with few adverse effects. Second, they proposed addition of folic acid to reduce homocysteine to reduce cardiovascular disease. Third, they advocated giving this so-called polypill to individuals 55 years and older, irrespective of previous cardiovascular disease or risk factors. Wald and Law estimated that such a polypill would reduce cardiovascular disease by more than 80%. Of the various components they proposed, lowering homocysteine does not reduce cardiovascular disease,[9] whereas all other components have been proven to reduce myocardial infarction and stroke. Therefore, the combination of blood-pressure-lowering drugs (ramipril, atenolol, and hydrochlorthiazide), simvastatin, and aspirin is likely to substantially reduce stroke and myocardial infarction.

Before large trials of a polypill are undertaken to reduce cardiovascular events, we addressed several questions. First, can one pill (or capsule) be formulated that can deliver an effect similar to the additive effect from each component provided separately? Second, what degree of

reduction in blood pressure and LDL cholesterol can be achieved in people with normal levels of risk factors? Third, will a polypill with five components be tolerated? Fourth, do unexpected interactions arise when these drugs are given in a single pill? Fifth, does aspirin reduce the blood-pressure-lowering effects of ramipril, atenolol, and hydrochlorthiazide? We therefore designed The Indian Polycap Study (TIPS) to address the above questions.[10] Additionally, we calculated the potential risk reductions in stroke and cardiovascular heart disease from the Polycap with data for the observed effect on risk factors recorded in TIPS.

Methods

Study design and population

Since we were testing the effects of five active pharmacological components (three agents to lower blood pressure, statin, and aspirin: Polycap [Cadila Pharmaceuticals, Ahmedabad, India]), a full factorial design would require 32 cells. Such a design was not practical. Therefore, we identified five questions (see above) that were most relevant and could be addressed by randomly assigning individuals to one of nine groups (figure 1, table 1). For blood-pressure lowering, we used hydrochlorthiazide 12·5 mg, atenolol 50 mg, and ramipril 5 mg; for lipid lowering we used simvastatin 20 mg and aspirin 100 mg (all once daily). All drugs were generic, and had been shown to be effective and safe.

Between March 5, 2007, and August 5, 2008, we recruited individuals without previous cardiovascular disease, aged between 45 years and 80 years, and with one risk factor (type 2 diabetes; blood pressure >140 mm Hg systolic or

90 mm Hg diastolic, but <160/100 mm Hg; smoker within past 5 years; increased waist to hip ratio [>0·85 for women and >0·90 for men]; or abnormal lipids [LDL cholesterol >3·1 mmol/L or HDL cholesterol <1·04 mmol/L]). Patients were recruited from 50 centres in India, with coordinating centres at St John's Medical College, Bangalore, India, and at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Canada. Individuals were excluded if they were receiving one of the study drugs, taking two or more antihypertensive drugs, had a serum LDL cholesterol greater than 4·5 mmol/L, had creatinine greater than 177 μmol/L (2·0 mg/dL) or potassium greater than 5·5 mmol/L, had abnormal liver function, had asthma, or were pregnant or lactating.

After obtaining written informed consent, individuals entered a 3-week screening phase during which eligibility for the study was confirmed and baseline data were recorded. If the participant was on any study drug and it could be safely withdrawn, the participant could be included after 3 weeks.

The protocol was approved by the respective ethics committees or research ethics boards and regulatory authorities.

Procedures

We randomly assigned 2053 individuals to one of nine groups with use of a central secure website. To maintain the blinding, participants received a single capsule that looked identical, irrespective of the group that they were randomised to. To avoid hypotension in people with normal blood pressure, the dose of ramipril used for the
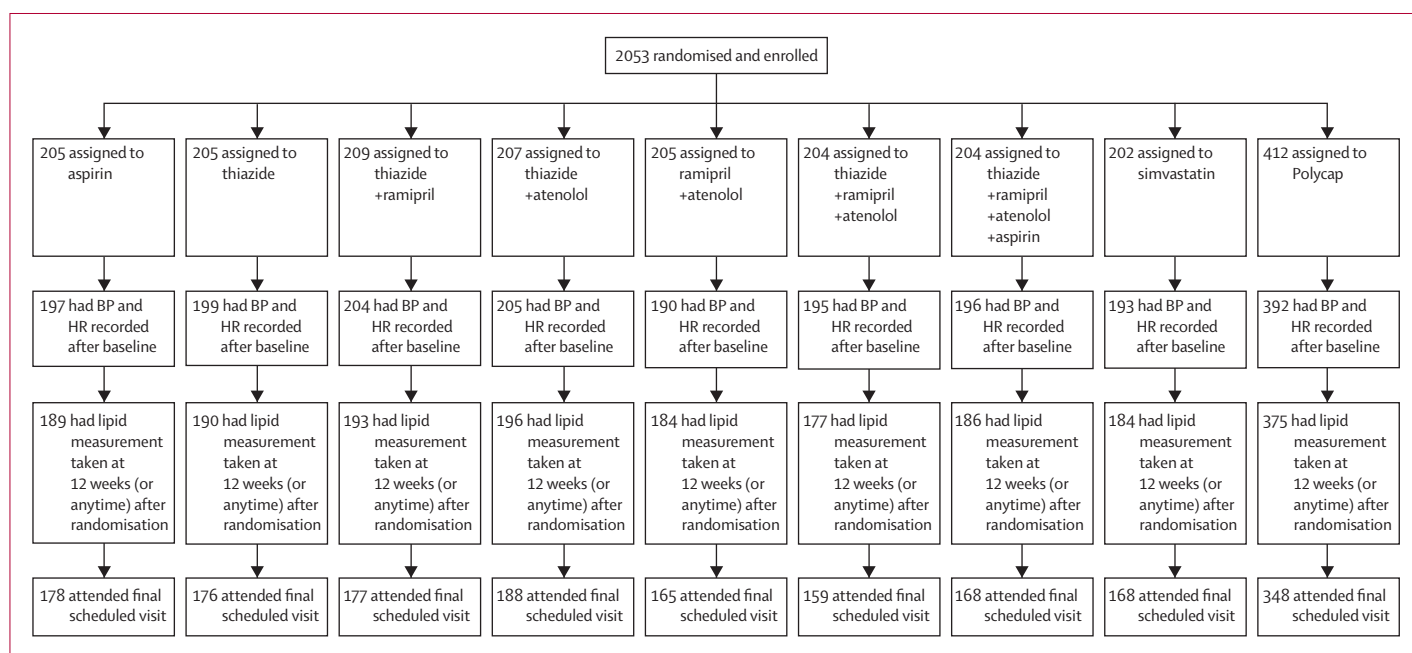

Figure 1: Trial profile
The number of people screened for eligibility was not recorded. BP=blood pressure. HR=heart rate.

	Overall (N=2053)	As (n=205)	T (n=205)	T+R (n=209)	T+At (n=207)	R+At (n=205)	T+R+At (n=204)	T+R+At+As (n=204)	S (n=202)	P (n=412)
Age (years)	54·0 (7·9)	53·4 (7·7)	55·0 (8·5)	54·9 (7·9)	54·1 (8·4)	53·9 (7·5)	54·0 (7·8)	53·6 (7·7)	53·6 (7·9)	53·7 (7·7)
BMI (kg/m²)	26·3 (4·5)	26·5 (4·5)	25·9 (4·4)	26·2 (4·3)	27·1 (4·6)	26·5 (4·0)	26·0 (4·8)	26·7 (4·4)	26·0 (4·4)	26·2 (4·5)
Systolic BP (mm Hg)	134·4 (12·3)	133·0 (12·4)	134·0 (12·2)	134·6 (12·7)	134·5 (12·5)	135·3 (11·4)	133·4 (11·7)	134·9 (13·4)	134·5 (12·4)	134·8 (12·2)
Diastolic BP (mm Hg)	85·0 (8·1)	83·6 (8·2)	84·5 (7·8)	84·6 (7·8)	85·6 (7·9)	86·0 (8·3)	84·8 (8·2)	85·5 (8·6)	84·6 (8·4)	85·6 (7·9)
Heart rate (beats/min)	80·1 (10·7)	79·1 (9·7)	80·2 (10·8)	80·3 (11·3)	80·7 (11·8)	79·6 (10·9)	80·0 (10·4)	80·8 (10·3)	79·4 (10·3)	80·2 (10·5)
Total cholesterol (mmol/L)	4·7 (0·9)	4·7 (0·9)	4·6 (1·0)	4·7 (0·9)	4·7 (0·9)	4·8 (0·9)	4·6 (0·9)	4·7 (0·9)	4·6 (1·0)	4·7 (0·9)
LDL cholesterol (mmol/L)	3·0 (0·8)	3·0 (0·8)	3·0 (0·7)	3·0 (0·8)	3·1 (0·7)	3·1 (0·8)	3·0 (0·7)	3·0 (0·8)	3·0 (0·8)	3·0 (0·7)
HDL cholesterol (mmol/L)	1·1 (0·3)	1·1 (0·3)	1·1 (0·3)	1·1 (0·3)	1·2 (0·3)	1·2 (0·3)	1·1 (0·3)	1·1 (0·3)	1·2 (0·3)	1·1 (0·3)
Triglycerides (mmol/L)	1·9 (1·2)	1·9 (1·1)	2·0 (1·3)	2·0 (1·4)	1·9 (0·9)	1·9 (1·4)	1·9 (1·4)	1·9 (1·0)	1·8 (1·0)	2·0 (1·3)
ApoB	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)
ApoA	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)	1·2 (0·2)
Diabetes	696 (33·9%)	70 (34·1%)	67 (32·7%)	78 (37·3%)	70 (33·8%)	67 (32·7%)	67 (32·8%)	64 (31·4%)	71 (35·1%)	142 (34·5%)
Current smoker	276 (13·4%)	18 (8·8%)	33 (16·1%)	24 (11·5%)	20 (9·7%)	30 (14·6%)	39 (19·1%)	32 (15·7%)	27 (13·4%)	53 (12·9%)
Women	901 (43·9%)	97 (47·3%)	90 (43·9%)	85 (40·7%)	96 (46·4%)	94 (45·9%)	83 (40·7%)	89 (43·6%)	96 (47·5%)	171 (41·5%)
Calcium-channel blockers	445 (21·7%)	43 (21·0%)	52 (25·4%)	43 (20·6%)	41 (19·8%)	50 (24·4%)	47 (23·0%)	37 (18·1%)	38 (18·8%)	94 (22·8%)

Data are mean (SD) or number (%). As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap. BMI=body-mass index. BP=blood pressure. ApoB=apolipoprotein B. ApoA=apolipoprotein A₁.

Table 1: **Baseline characteristics**

first 7 days was 2·5 mg per day, after which 5 mg of ramipril was used in relevant groups, including the Polycap group.

After randomisation, subsequent visits occurred at 10 days, and at 4, 8, 12, and 16 weeks. At 12 weeks, study drug was discontinued and a final visit was scheduled at 16 weeks. All participants received advice about optimum lifestyles.

The duration of the active part of the trial was scheduled for 12 weeks, except for 206 participants who were randomly assigned on or after July 1, 2008, for whom the follow-up on active drug was reduced to 8 weeks, since study drugs were due to expire by September, 2008. The primary outcomes were LDL for the effect of lipids, blood pressure for antihypertensive drugs, heart rate for the effects of atenolol, urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin, and rates of discontinuation of drugs for safety. Before randomisation, all patients underwent a clinical examination. 12-lead electrocardiogram, heart rate, and blood pressure were recorded, and fasting bloods were drawn for glucose, potassium, creatinine, liver function tests, and lipids. Urine was collected for 11-dehydrothromboxane B2 concentrations in 1490 individuals at baseline and in 1185 at study end. All samples were immediately processed, frozen, and shipped in dry ice to a central laboratory (SRL Religare, Mumbai, India). During follow-up, clinical status, concomitant drugs, adverse events, heart rate, and blood pressure were recorded at every visit. We also measured potassium and creatinine at all visits, with all blood tests being repeated at the last scheduled follow-up visit on active drugs. Blood pressure and heart rate were measured after a 5 min rest in a quiet room in the supine position three times, 2 min apart, with an automated sphygmomanometer (Omron,

model IA1B, Kyoto, Japan and Singapore). Two further readings were obtained 30 s and 2 min after standing to check for postural hypotension.

Lipids were measured in fasting blood sample that was collected at screening, randomisation, and the final follow-up visit (weeks 8 or 12). LDL cholesterol was measured with a direct enzymatic photocolourimetric assay (Roche Hitachi 912 analyser with LDL cholesterol second generation kits; Roche Diagnostics, Mannheim, Germany). The coefficient of variation of the assay was less than 4%, with a measurement range of 0·08–14·52 mmol/L (3–560 mg/dL) and an analytic sensitivity of 0·08 mmol/L (3 mg/dL).

We measured urinary concentrations of 11-dehydrothromboxane B2 with a commercially available enzyme immunoassay (Aspirinworks) donated by Corgenix, Broomfield, CO, USA. The assay has interassay and intra-assay coefficients of variation of less than 10%. Control urine samples with assigned values for 11-dehydrothromboxane B2 were run with every batch. We measured urine creatinine with a kinetic colourimetric assay on the basis of a modification of the Jaffe reaction on the Roche Hitachi 917 analyser. Reagents were provided by Roche Diagnostics GmbH (Indianapolis, IN, USA). Control pools at all levels had an interassay precision of less than 2·0% during analysis.

Statistical analysis

We postulated that the Polycap would be non-inferior to the combination of the three drugs to lower blood pressure alone or in conjunction with aspirin. If non-inferiority was confirmed, then all groups with three blood-pressure-lowering drugs would be compared with groups with two drugs, with one drug, and with no blood-pressure-lowering drug to assess the incremental effects of addition of drugs.

	Overall	As	T	T+R	T+At	R+At	T+R+At	T+R+At+As	S	P
Drugs permanently stopped	303 (14·8%)	30 (14·6%)	28 (13·7%)	21 (10·0%)	20 (9·7%)	36 (17·6%)	46 (22·5%)	31 (15·2%)	25 (12·4%)	66 (16·0%)
Reasons for discontinuation										
Drug-specific reasons	77 (3·8%)	8 (3·9%)	9 (4·4%)	6 (2·9%)	4 (1·9%)	11 (5·4%)	8 (3·9%)	12 (5·9%)	5 (2·5%)	14 (3·4%)
Cough	9 (0·4%)	1 (0·5%)	1 (0·5%)	2 (1·0%)	0	1 (0·5%)	1 (0·5%)	2 (1·0%)	0	1 (0·2%)
Dizziness/hypotension	46 (2·2%)	3 (1·5%)	7 (3·4%)	1 (0·5%)	2 (1·0%)	7 (3·4%)	6 (2·9%)	6 (2·9%)	4 (2·0%)	10 (2·4%)
Gastritis/dyspepsia	15 (0·7%)	3 (1·5%)	2 (1·0%)	4 (1·9%)	1 (0·5%)	1 (0·5%)	0	2 (1·0%)	1 (0·5%)	1 (0·2%)
Hyperkalaemia	3 (0·1%)	0	0	0	0	1 (0·5%)	1 (0·5%)	0	0	1 (0·2%)
Bradycardia	4 (0·2%)	0	0	0	1 (0·5%)	1 (0·5%)	0	1 (0·5%)	0	1 (0·2%)
Other reasons	69 (3·4%)	9 (4·4%)	5 (2·4%)	2 (1·0%)	7 (3·4%)	7 (3·4%)	9 (4·4%)	5 (2·5%)	5 (2·5%)	20 (4·9%)
Social reasons/refused treatment	201 (9·8%)	22 (10·7%)	17 (8·3%)	14 (6·7%)	10 (4·8%)	24 (11·7%)	35 (17·2%)	20 (9·8%)	19 (9·4%)	40 (9·7%)

Data are number (%). As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap.

Table 2: Reasons for permanent discontinuation of study drugs

	Overall	As	T	T+R	T+At	R+At	T+R+At	T+R+At+As	S	P
Dizziness or hypotension	92 (4·5%)	10 (4·9%)	8 (3·9%)	4 (1·9%)	6 (2·9%)	11 (5·4%)	11 (5·4%)	11 (5·4%)	5 (2·5%)	26 (6·3%)
Cough	78 (3·8%)	3 (1·5%)	7 (3·4%)	15 (7·2%)	1 (0·5%)	8 (3·9%)	8 (3·9%)	12 (5·9%)	2 (1·0%)	22 (5·3%)
Gastritis/dyspepsia	40 (1·9%)	4 (2·0%)	4 (2·0%)	7 (3·3%)	2 (1·0%)	6 (2·9%)	5 (2·5%)	2 (1·0%)	5 (2·5%)	5 (1·2%)
Fatigue	36 (1·8%)	2 (1·0%)	4 (2·0%)	3 (1·4%)	4 (1·9%)	4 (2·0%)	7 (3·4%)	1 (0·5%)	4 (2·0%)	7 (1·7%)
Bradycardia	5 (0·2%)	0	0	0	2 (1·0%)	0	1 (0·5%)	1 (0·5%)	0	1 (0·2%)
Creatinine increased by >50%*	171 (8·3%)	19 (9·3%)	14 (6·8%)	16 (7·7%)	20 (9·7%)	15 (7·3%)	15 (7·4%)	21 (10·3%)	16 (7·9%)	35 (8·5%)
Potassium >5·5 mmol/L*	108 (5·3%)	12 (5·9%)	9 (4·4%)	11 (5·3%)	10 (4·8%)	12 (5·9%)	15 (7·4%)	14 (6·9%)	7 (3·5%)	18 (4·4%)
SGPT doubled*	75 (3·7%)	9 (4·4%)	7 (3·4%)	14 (6·7%)	10 (4·8%)	6 (2·9%)	1 (0·5%)	6 (2·9%)	10 (5·0%)	12 (2·9%)

Data are number (%). As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap. SGPT=serum glutamic pyruvic transaminase. *On the basis of blood tests.
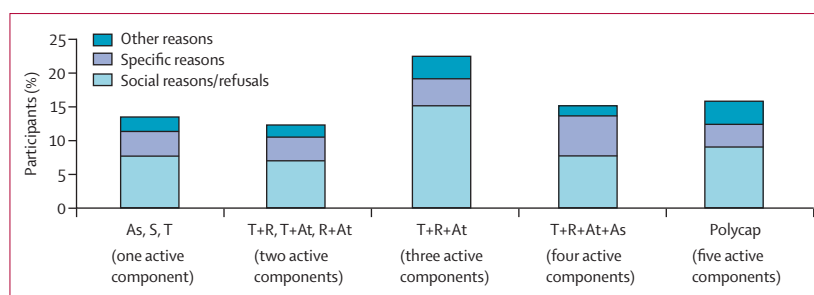
Table 3: Selected adverse effects

Figure 2: Rates of discontinuation of study drug by categories of reasons
Some patients indicated more than one reason for discontinuation of study drugs. In this figure, we use a hierarchical and mutually exclusive approach in which drug-specific reasons are given first priority, other reasons the next priority, and social reasons the last priority. With increasing number of active components in the Polycap, there was no pattern of a progressively increasing rate of discontinuation. Although we noted an apparent higher rate of discontinuation of study drug with three active components, it was accounted for by social reasons, and rates of discontinuation were lower with four and five active components. Rates of discontinuation with four and five active components were similar to those for one or two active components. As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin.

For non-inferiority comparisons, with a margin of 2 mm Hg diastolic, an SD of 6, and a type-1 error of 0·025, there would be 94% power with 400 individuals randomly assigned to the Polycap group and 200 to each comparator group. For superiority comparisons, of the Polycap versus each of the other individual groups, there would be more than 90% power to detect differences of 2 mm Hg in diastolic blood pressure.

The Polycap group would be compared with the simvastatin alone group for non-inferiority related to changes in LDL cholesterol. With δ=0·155 mmol/L in LDL cholesterol, an SD of 0·46, and a one-sided type-1 error of 0·025, the comparison of the Polycap group with simvastatin alone would have 97% power for non-inferiority. Additional analyses for changes in apolipoprotein B, HDL cholesterol, and apolipoprotein A, would also be undertaken. The combined groups with simvastatin versus other groups without statins would provide an estimate of the effect of statins. This analysis had high power to detect very small differences, and was therefore used for subgroup analysis.

Reduction in heart rate was taken as a measure of β blockade of the groups containing atenolol. The Polycap was compared with other groups containing atenolol for non-inferiority.

We compared the Polycap group with aspirin alone by use of changes in urinary 11-dehydrothromboxane B2 concentrations. For non-inferiority comparisons, a δ of 60 with an SD of 181 and a one-sided type-1 error of 0·025 would provide 96% power.

We used a repeated measures modelling strategy to analyse outcomes recorded at four timepoints after randomisation. The mean of the two sitting blood pressure and heart rate measurements from every

timepoint was included in the analysis. The analysis included all measurements after randomisation that were available for a participant, even if study drugs had been discontinued (ie, we used an intention-to-treat analysis). Mixed model procedures were used in statistical analysis software (version 9.1) with the specification of appropriate correlation structure between different timepoints and with adjustment for the corresponding baseline measure. One-way analysis of covariance was used for biochemical measures obtained at baseline and at week 12 only. All participants with at least one measure available after baseline were included in the analysis. 388 (19%) individuals did not have a measurement for fasting blood lipid at study end. To keep any biases to a minimum, we analysed lipids in participants with bloods drawn at earlier visits for safety. This method increased the proportion available for lipid analysis from 81% to 91%. Data for outcomes are presented as mean (SD).

This study is registered with ClinicalTrials.gov, number NCT00443794.

Role of the funding source

The sponsor of the study was part of the steering committee that designed the trial, but had no role in data collection, data analysis, data interpretation, or writing of the report. S Yusuf, R Afzal, and P Pais had full access to the data, and S Yusuf takes responsibility for the manuscript and the decision to submit for publication.

Results

Figure 1 shows the trial profile. 412 individuals were randomly assigned to the Polycap group and about 200 to each of the other eight groups. Table 1 shows the baseline characteristics.

The final scheduled follow-up was not available in 326 individuals, mainly because some participants perceived little benefit by participating in the trial. However, at least one recording of blood pressure after randomisation was available in 1971 (96%) patients. We obtained fasting blood samples at the last scheduled visit on treatment for 1665 (81%) patients. 1874 (91%) patients had at least one blood sample available after randomisation for analysis of lipids.

The rates of discontinuing drugs were similar across study groups (table 2). The number of individuals with dizziness, increased creatinine (an increase by >50%), raised potassium (>5·5 mmol/L), or increased liver enzymes (doubling of serum glutamic pyruvic trans-aminase) did not differ significantly between study groups (table 3). The main social reason for discontinuation of study drug was refusal of treatment by patient (9·8% of 14·8% overall) followed by other reasons (3·4%), whereas drug-specific side-effects were noted in 77 (3·8%) of participants (figure 2). Reasons for discontinuing drugs did not differ significantly between the groups (table 2). We detected this pattern both for drug-specific reasons and for non-specific reasons for
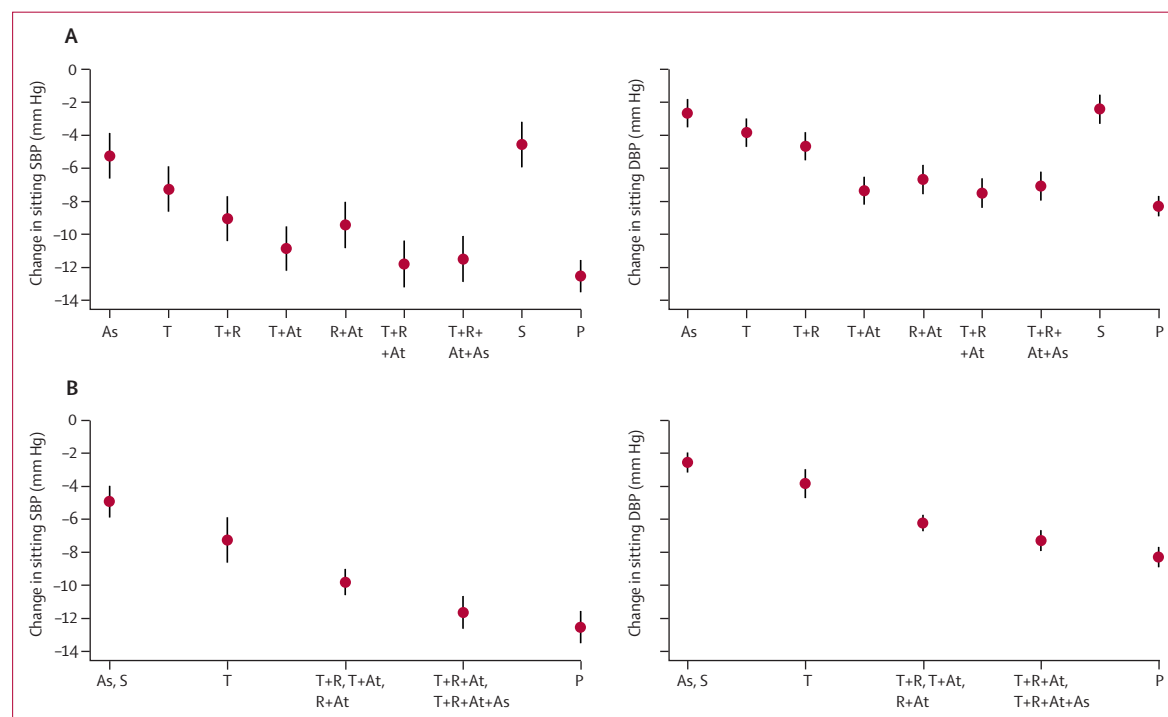

Figure 3: **Mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP)**
Error bars indicate 95% CI. Mean changes from baseline in the nine groups (A), and the effects of no blood-pressure-lowering drugs (As, S), one blood-pressure-lowering drug (T), two blood-pressure-lowering drugs (T+R, T+At, or R+At), or three blood-pressure-lowering drugs (T+R+At, T+R+At+S), or the Polycap (B). As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap.
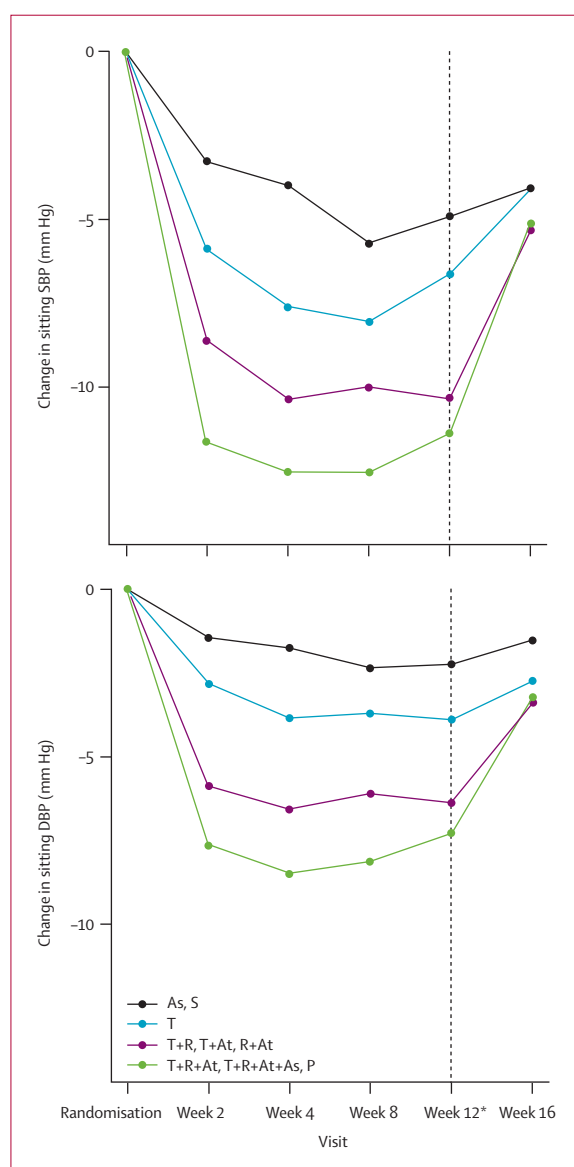
Figure 4: **Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) after randomisation over time**

Most of the reduction in blood pressure was detected early and was sustained until the end of active treatment. As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap. *End of treatment.

drug discontinuation. Further analysis of the rates of drug discontinuation in groups with one drug or more did not show an increasing rate of study drug discontinuation with increasing number of active components (figure 2).

Compared with the two groups with no drugs to lower blood pressure (aspirin alone or simvastatin alone), thiazide alone reduced systolic blood pressure by 2·2 mm Hg (95% CI 0·6–3·8; p=0·008) and diastolic blood pressure by 1·3 mm Hg (0·2–2·3; p=0·017), two drugs reduced blood pressure by 4·7 mm Hg (3·5–5·9) systolic (p=0·001) and 3·6 mm Hg (2·8–4·4) diastolic

(p<0·0001), and three drugs by 6·9 mm Hg (5·8–8·0) systolic (p=0·0001) and 5·0 mm Hg (4·3–5·8) diastolic (p<0·0001; figures 3 and 4). Combinations containing three blood-pressure drugs lowered blood pressure to a similar extent, irrespective of the presence or absence of aspirin (with aspirin: 6·1/4·2 mm Hg [95% CI 4·4/3·2–4·7/5·2], no aspirin: 6·6/4·8 mm Hg [4·9/3·7–8·2/5·8], and Polycap: 7·4/5·6 mm Hg [6·1/4·7–8·7/6·4]; p<0·0001 for non-inferiority).

Figure 5 shows the changes in lipids in each of the nine groups. The reduction in LDL cholesterol was 0·83 mmol/L (95% CI 0·72–0·93, 27·7%) with simvastatin alone compared with 0·70 mmol/L (0·62–0·78, 23·3%) with the Polycap (difference simvastatin *vs* Polycap −0·13, 95% CI −0·25 to −0·01; p=0·041; difference of 4·4%). We noted similar effects for total cholesterol (reduction of 0·83 mmol/L, 95% CI 0·75–0·92; p<0·0001 with the two simvastatin groups *vs* all other groups without simvastatin) and triglycerides (difference of 0·24 mmol/L, [95% CI 0·14–0·33] between simvastatin and non-simvastatin groups; p<0·0001). The reduction in total cholesterol did not differ significantly between simvastatin alone and Polycap (0·13 mmol/L, 95% CI −0·02 to 0·28; p=0·097 for superiority). However, we detected a significantly greater reduction in triglycerides with simvastatin alone compared with the Polycap (0·20 mmol/L, −0·03 to 0·36, p=0·02). Simvastatin had no effect on concentrations of HDL cholesterol or apolipoprotein A_1. The two simvastatin groups reduced apolipoprotein B compared with the non-statin groups (0·19 mmol/L, 95% CI 0·17–0·21; p<0·0001). The effect of the Polycap in reducing apolipoprotein B was slightly less than with simvastatin alone (0·18 mmol/L *vs* 0·21 mmol/L) (adjusted difference of 0·03 mmol/L, 95% CI −0·01 to 0·07; p=0·06).

Heart rate was reduced by 7 beats per min (95% CI 6–8) with the Polycap, which was identical to that with the other groups that included atenolol (7·0 beats per min *vs* non-atenolol groups; difference of 0·0, 95% CI −0·85 to 0·84; figure 6).

The mean reductions in 11-dehydrothromboxane B2 with aspirin alone (348·8 ng/mmol of creatinine [95% CI 277·6–419·9]) or the group with three blood-pressure-lowering drugs plus aspirin (350·0 ng/mmol creatinine [294·6–404·0]) were similar to the reductions noted with the Polycap (283·1 ng/mmol creatinine [229·1–337·0]). However, the difference between Polycap and other groups with aspirin was 66 ng/mmol creatinine (95% CI −0·4 to 132·9; non-inferiority p=0·57), with the upper confidence limits crossing the prespecified non-inferiority margin of 60 ng/mmol creatinine. However, the reductions in 11-dehydrothromboxane B2 in each of the three groups compared with baseline or with non-aspirin groups was significant (p<0·0001). We detected a non-significant increase in 11-dehydro-thromboxane B2 with thiazides (39·7 ng/mmol creatinine, 95% CI −26·5 to 105·8; p=0·24), which was
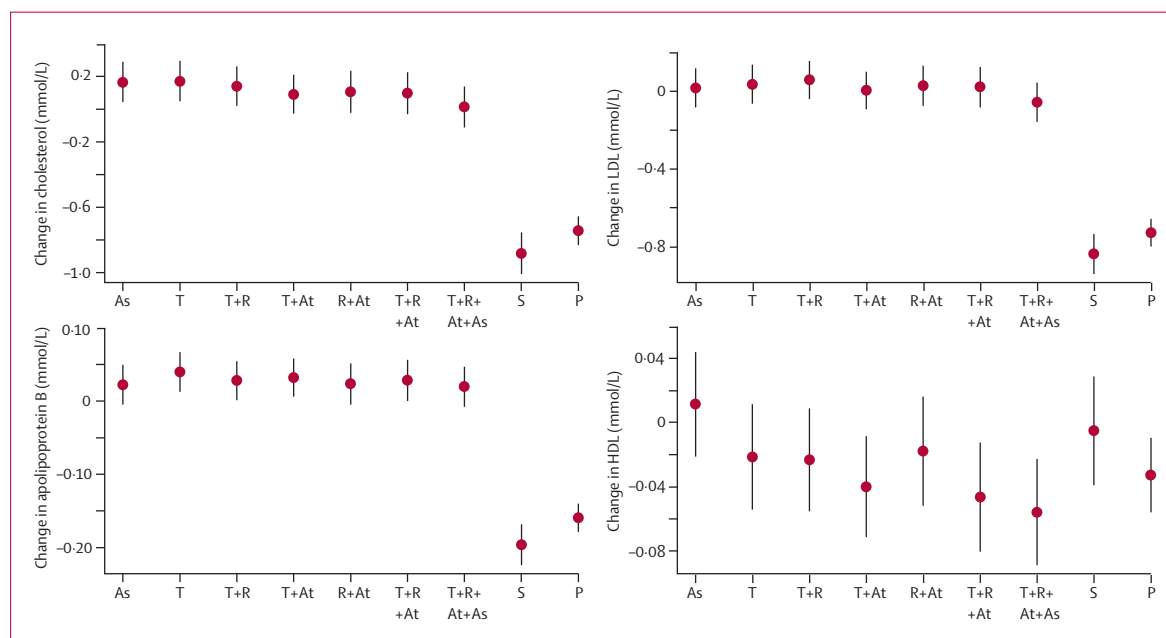
Figure 5: Changes in lipids in each of the nine groups
Error bars indicate 95% CI. As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap.

blunted by the addition of ramipril (−33·7 ng/mmol creatinine, −96·2 to 28·9) or atenolol (−32·8 ng/mmol creatinine, −94·7 to 29·1). The group with ramipril and atenolol (−123 ng/mmol creatinine, −192·1 to 55·0; p=0·01) and the group with simvastatin (−85·1 ng/mmol creatinine, −150·2 to −20·0; p<0·0001) significantly reduced urinary 11-dehydrothromboxane B2 (figure 7).

Wald and Law claimed that the reductions in risk factors were independent of initial levels. Moreover, people with initial low blood pressure or heart rates might have excessive reductions in blood pressure or heart rate. We, therefore, undertook subgroup analyses to estimate whether the baseline level of a risk factor affected its response to treatment. Furthermore, we explored the effects in people with diabetes (an indicator of risk) and those on a calcium-channel blocker (providing an assessment of the added effect of four blood-pressure drugs together). Figure 8 shows that the extent of blood-pressure lowering does not differ significantly with three drugs compared with no such drugs in people with a blood pressure greater than 140 mm Hg versus less than that value (reductions in systolic blood pressure of 8·3 mm Hg [95% CI 6·3–10·1] vs 6·1 mm Hg [4·7–7·5], p=0·08; reductions in diastolic blood pressure of 5·9 mm Hg [4·6–7·1] vs 4·6 mm Hg [3·7–5·5], p=0·09) or in those with diabetes versus those without diabetes (reductions in systolic blood pressure of 8·3 mm Hg [6·4–10·3] vs 6·1 mm Hg [4·7–7·6], p for interaction=0·07; reductions in diastolic blood pressure of 5·3 mm Hg [4·0–6·5] vs 4·9 mm Hg [4·0–5·8], p=0·68).

Compared with the groups without statins, the proportionate reductions in LDL cholesterol in the two
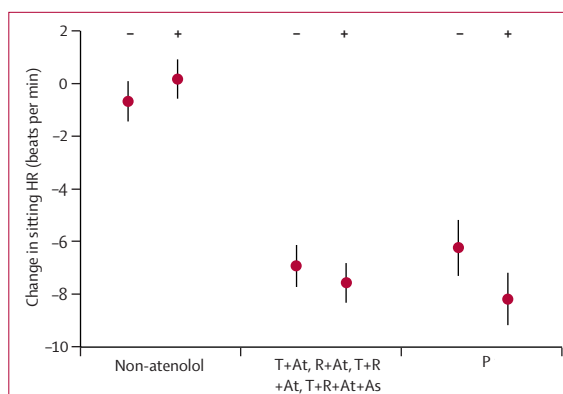

Figure 6: Changes in heart rate compared with baseline
Error bars indicate 95% CI. −=less than 81 beats per min at baseline. +=81 beats per min or more at baseline. As=aspirin. T=thiazide. R=ramipril. At=atenolol. P=Polycap.

groups with simvastatin were similar in those above (24%, 95% CI 21–28) and below (25%, 19–29) the median (figure 9). Consequently, the absolute reductions in LDL cholesterol with simvastatin were greater in participants with concentrations above the median (0·94 [95% CI 0·82–1·06] in those with LDL ≥3·3 mmol/L) than in those at lower levels (0·65 mmol/L [0·56–0·73] in those with LDL <3·3 mmol/L). The degree of LDL cholesterol reduction, both absolute and proportionate, was significantly greater in participants with diabetes (0·92 mmol/L [0·8–1·04], 29%; p<0·0001) compared with those without diabetes (0·65 mmol/L [0·56–0·73], 22%; p=0·022). In individuals already receiving calcium-channel blockers, the addition of the Polycap or three
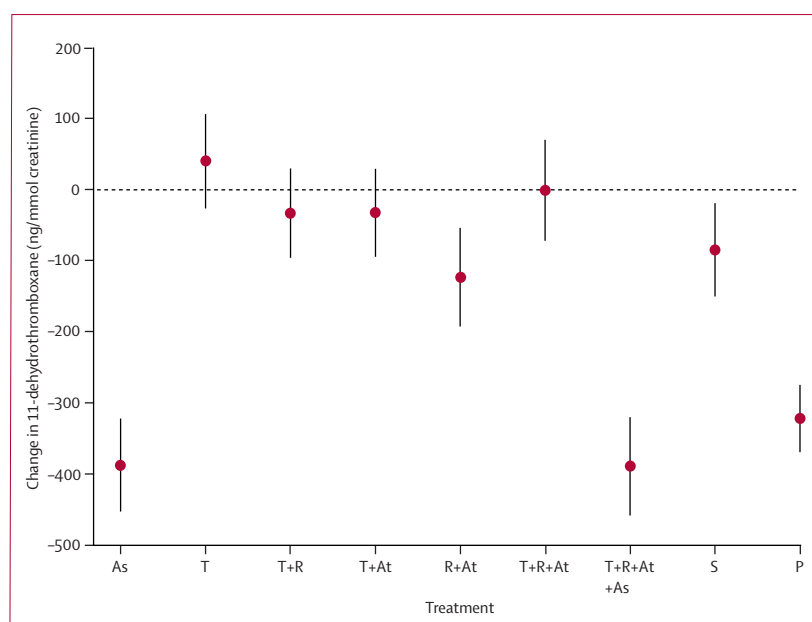
***Figure 7*: Changes in urinary 11-dehydrothromboxane B2 concentrations**
Error bars indicate 95% CI. As=aspirin. T=thiazide. R=ramipril. At=atenolol. S=simvastatin. P=Polycap.

blood-pressure-lowering drugs reduced blood pressure by 6·6 mm Hg (95% CI 4·1–9·1) systolic and 5·8 mm Hg (4·2–7·4) diastolic, which was similar to those not receiving calcium-channel blockers (7·0 mm Hg [5·7–8·3] systolic and 4·9 mm Hg [4·0–5·7] diastolic). The rates of permanent discontinuation of the Polycap (19·4%) and three drugs to lower blood pressure (14·5%) in those receiving calcium-channel blockers was not higher than in those not receiving calcium-channel blockers at baseline (15·1% and 20·3%, respectively).

Table 4 summarises the potential reduction in cardio-vascular heart disease and strokes on the basis of the observed reductions in blood pressure and heart rate in our trial with use of the Wald and Law estimates and their approach as a basis.[6] We used the same risk reductions ascribed to aspirin by Wald and Law, but did not assume any benefit from homocysteine lowering. We used a simple multiplication of risk ratios estimated for the individual effects of aspirin, blood-pressure lowering with three drugs, and simvastatin (the latter two based on the effect that we noted in this study). Our findings suggest that the Polycap could potentially reduce cardiovascular heart disease by 62% and stroke by 48%.
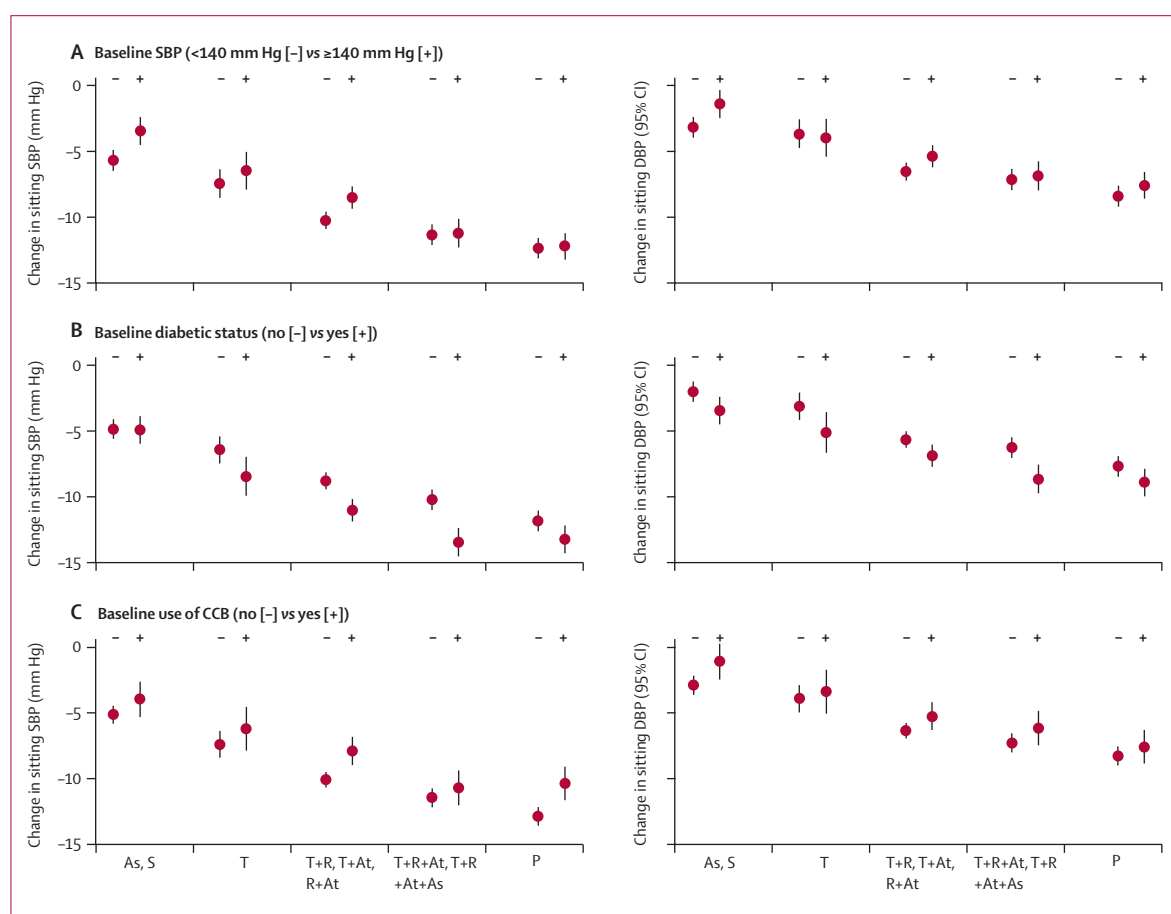
***Figure 8*: Changes in blood pressure in subgroups based on baseline systolic blood pressure (A), diabetes (B), and use of calcium-channel blockers (C)**
Error bars indicate 95% CI. As=aspirin. T=thiazide. R=ramipril. At=atenolol. P=Polycap. SBP=systolic blood pressure. CCB=calcium-channel blocker.
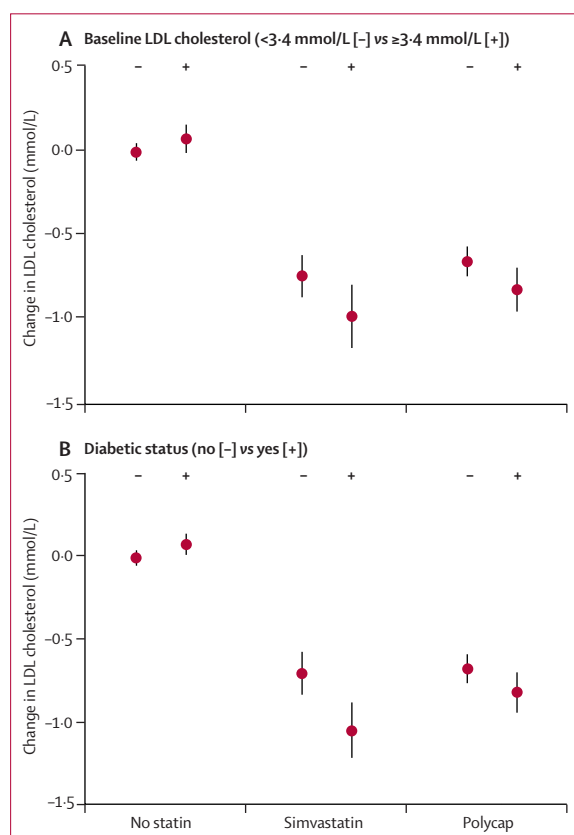
Figure 9: Changes in LDL cholesterol in subgroups on the basis of baseline concentrations and diabetes

Agent		Reductions in risk factors	Reduction in risk (%)	
			CHD event	Stroke
LDL cholesterol				
Wald and Law	Simvastatin (40 mg per day)	1·74 mmol/L	61%	17%
Polycap	Simvastatin (20 mg per day)	0·80 mmol/L	27%	8%
Diastolic blood pressure				
Wald and Law	Three classes of drugs at half standard doses	−11 mm Hg	46%	63%
Polycap	Three classes of drugs at half standard doses	−5·7 mm Hg	24%	33%
Serum homocysteine				
Wald and Law	Folic acid	3 μmol/L	16%	24%
Polycap	Not assessed*	..	..	..
Platelet function				
Wald and Law	Aspirin 75 mg per day	Not quantified	32%	16%
Polycap	Aspirin 100 mg per day	Assumed to be similar between the Polycap and aspirin alone on urinary 11-dehydrothromboxane B2	32%†	16%†
Combined effects				
Wald and Law	All above	..	88%	80%
Polycap	All above	..	62%‡	48%‡

The methods used by Wald and Law to estimate treatment benefits have been used as the reference to compare their claims for a potential to reduce cardiovascular disease by more than 80% versus estimates derived from actual data. We recognise that the estimates from clinical trials of a few years of intervention (eg, 5 years, in which the mean time to event is generally half the mean duration of the trials—ie, 2·5 years) are lower than the projections that Wald and Law have used, on the basis of differences in risk factor levels. Our analyses with the actual data for changes in risk factor level, but with the approach taken by Wald and Law, suggest that the potential benefit from the Polycap is substantially smaller than their projections. These projections are a useful basis on which to consider the maximum benefit that can be expected in long-term trials (≥5 years) and suggest that in trials of a few years duration, it would be prudent to expect no more than a halving of cardiovascular disease events. *Folic acid was not assessed since several large trials have shown no benefit. †These estimates used are the same as Wald and Law. ‡Derived from a simple multiplication of the risk ratios of the individual estimates. CHD=coronary heart disease.

Table 4: Projected and estimated effects of a polypill, comparing estimates from Wald and Law[6-8] versus that obtained in the Polycap study

Discussion

Our study has shown that the Polycap is non-inferior to its individual components in lowering blood pressure and heart rate (an indicator of β blockade). It lowers LDL cholesterol and urinary 11-dehydrothromboxane B2 substantially, but to a degree that is slightly less than that with simvastatin or aspirin alone. The differences in effect of the Polycap on lipids compared with simvastatin is of borderline significance, but is consistent with unpublished pharmacokinetic data (Khamar B, Cadila, Ahmedebad, India, personal communication) in a parallel study undertaken by the sponsors, indicating that the drug concentration of simvastatin with the Polycap was 20% lower than with simvastatin alone. By contrast, its active metabolite was higher with the Polycap. We are unable to clarify why the lowering of LDL cholesterol of the Polycap was less than when simvastatin alone was used. The reductions in urinary 11-dehydrothromboxane B2 did not differ significantly between the Polycap and aspirin, but the comparison did not meet our prespecified non-inferiority margin, possibly because urine samples were obtained in only about three-fifths of patients randomised (with loss of study power) and because some components of the Polycap (eg, thiazides) raised 11-dehydrothromboxane B2. Nonetheless, the extent of 11-dehydrothromboxane B2 suppression with the Polycap was substantial.

Our findings emphasise that the effects of the polypill cannot be assumed to equal the combined effects of its individual components. Every preparation of a combination pill needs to be tested to assess its pharmacokinetic and pharmacodynamic effects, before it is used in larger studies examining clinical outcomes. The substantial preservation of the lowering of blood pressure, heart rate, LDL cholesterol, and 11-dehydrothromboxane B2 with the Polycap suggests that it has the potential to greatly reduce cardiovascular disease.

Reductions in blood pressure and LDL cholesterol were lower than projected by Wald and Law. The reasons for this are unclear, but might include baseline differences, non-adherence, or drug interactions. A per-protocol analysis confined to participants who continued the Polycap (or three drugs to lower blood pressure) until 12 weeks and had an initial systolic blood pressure of 140 mm Hg or more (ie, hypertension) suggests a slightly larger reduction in blood pressure (by 8·7 mm Hg systolic and 6·1 mm Hg diastolic). We noted no interaction on blood-pressure lowering by addition of aspirin to the group with three drugs when given alone or in the Polycap. Conversely, studies investigating

urinary concentrations of thromboxane metabolites indicated a similar effect on 11-dehydrothromboxane B2 with the Polycap compared with the other groups with aspirin. The reductions in blood pressure that we recorded in this non-hypertensive population with the Polycap could theoretically lead to about a 24% risk reduction in cardiovascular heart disease and 33% risk reduction in strokes in individuals with average blood pressure levels. Alternatively, future preparations of a polypill might consider higher doses of antihypertensive drugs or even four-drug combinations to lower blood pressure (eg, addition of a calcium-channel blocker) at low doses (note that tolerability was similar in those receiving and not receiving calcium-channel blocker at baseline).

Reductions in LDL cholesterol, triglycerides, or total cholesterol seem to be slightly lower with simvastatin together with three drugs to lower blood pressure and aspirin, than with simvastatin alone. On the basis of the more modest lowering of LDL cholesterol that we noted, a 27% relative risk reduction in cardiovascular heart disease and an 8% risk reduction in stroke can be projected. Larger reductions in LDL cholesterol can be safely achieved with higher doses of simvastatin (40 mg per day), atorvastatin (20 mg per day), or rosuvastatin (10 mg per day),[7] and so a combination pill containing these alternative statins or doses could potentially increase the projected benefits. The projected benefits on reduction of cardiovascular heart disease and stroke based on our data with the Polycap are significantly less than that expected from Wald and Law's analysis. Nevertheless, a 50–60% risk reduction in events of cardiovascular disease in apparently healthy individuals or in high-risk people with average levels of risk factors would be important.

The effect of the Polycap on LDL cholesterol was greater in participants with diabetes. These findings suggest that the potential relative and absolute benefits of the Polycap on clinical outcomes are likely to be larger in high-risk than in low-risk subgroups, but are still important in the latter group. The tolerability and safety of the Polycap were similar to that of the other groups with single drugs, suggesting no increase in drug-specific adverse events or side-effects with the Polycap. We noted no increase in discontinuations of the Polycap from side-effects, specific to each component, and the major reason for discontinuation of study drug was social reasons. Furthermore, an analysis by one or more active components in the pill suggests similar rates of drug discontinuation, allaying concerns that the Polycap would have increased rates of side-effects and intolerability as the number of active components increased.

Our study has some limitations. First, in about 4% of individuals we could not obtain follow-up blood pressure or heart rate, and follow-up lipid values were unavailable in 9%, mainly because participants perceived no benefit by taking study drugs when they were told that they had normal risk factor levels and therefore refused further participation. Our experience suggests that large and long-term trials of the Polycap (or any other combination pill) assessing the effect on clinical outcomes in individuals with average risk factor levels need to pay careful attention to retention and adherence. Alternatively, the initial trials of the combination pill should select individuals with at least moderate increases in risk of cardiovascular disease to ensure good long-term adherence and retention, as well as increased efficacy. Second, we used a lower dose of simvastatin (20 mg) than that suggested by Wald and Law (40 mg). A 40 mg dose of simvastatin would have lowered LDL cholesterol by an additional 5–6%, which would increase the projected benefits. Third, our study was undertaken in India, and whether the effects of the drugs studied would be similar in other ethnic groups is not known. Large studies assessing prevention strategies with adequate numbers of individuals from each of the major regions of the world are needed.

Our study has several strengths. By including nine groups and a large number of patients, we have been able to assess the effects of various combinations of drugs on a range of outcomes and on safety and tolerability. Our data for a lack of substantial interactions between the effects of the various components of the Polycap on risk factors are supported by parallel pharmacokinetic data for blood levels of the drugs (or its active components) (Khamar B, personal communication). This finding indicates that the formulation of the Polycap used in this study can be conveniently used to reduce multiple risk factors and cardiovascular risk. It is also a suitable preparation for trials examining major vascular events in large and long-term studies.

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References
1 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86.
2 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985; **27:** 335–71.
3 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342:** 145–53.
4 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005; **366:** 1267–78.
5 Yusuf S. Two decades of progress in preventing cardiovascular disease. *Lancet* 2002; **360:** 2–3.
6 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; **326:** 1419–24.
7 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; **326:** 1423.
8 Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; **326:** 1427.
9 Lonn E, Yusuf S, Arnold MJ, et al for the Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006; **354:** 1567–77.
10 Xavier D, Pais P, Sigamani A, Pogue J, Afzal R, Yusuf S. The need to test the theories behind the Polypill: rationale behind the Indian Polycap Study. *Nat Clin Pract Cardiovasc Med* 2009; **6:** 96–97.