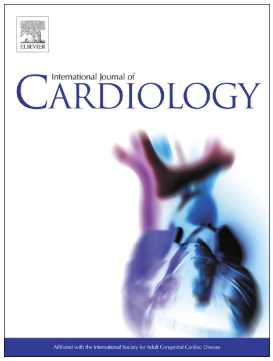

Cost-effectiveness of a fixed dose combination (polypill) in secondary prevention of cardiovascular diseases in India: Within-trial cost-effectiveness analysis of the UMPIRE trial

Kavita Singh, Catriona Crossan, Tracey-Lea Laba, Ambuj Roy, Alison Hayes, Abdul Salam, Stephen Jan, Joanne Lord, Nikhil Tandon, Anthony Rodgers, Anushka Patel, Simon Thom, Dorairaj Prabhakaran

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Title

Cost-effectiveness of a fixed dose combination (polypill) in secondary prevention of cardiovascular diseases in India: Within-trial cost-effectiveness analysis of the UMPIRE trial

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Key words: fixed dose combination (FDC); cardiovascular polypill; cost-effectiveness analysis (CEA); cardiovascular disease (CVD); secondary prevention; India

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ABSTRACT [word count – 244]

Background. The **U**se of **M**ultidrug **P**ill **I**n **R**educing cardiovascular **E**vents (UMPIRE) trial, showed that access to a cardiovascular polypill (aspirin, statin and two blood pressure lowering drugs) significantly improved adherence, lowered systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDLc) in patients with or at high risk of cardiovascular disease (CVD). We aimed to analyze the within-trial cost-effectiveness of the polypill strategy versus usual care in India.

Methods. Relative effectiveness and costs of polypill versus usual care groups in UMPIRE were estimated from the health sector perspective. Only direct medical costs were considered. The effectiveness of the polypill was reported as a percentage increase in adherence and mean reductions in SBP, and LDL-c, over the 15-month trial period. Healthcare resource utilization and costs were collected for each patient during the trial. Polypill price was constructed using a range of scenarios: $0.06 - $0.94/day. The cost-effectiveness of the polypill was measured as the additional cost for 10% increase in adherence, and per unit reduction in SBP and LDL-c.

Results. Overall, the mean cost per patient was significantly lower with the polypill strategy (- $203 per person, (95% CI: -286, -119, p <0.01). In scenario analyses that varied polypill price assumptions, incremental cost-effectiveness ratios for a polypill strategy ranged between cost-saving to $75 per 10% increase in adherence for polypill price of $0.94 per day.

Conclusions. The polypill strategy was cost-saving compared to usual care among patients with or at high risk of CVD in India.

Main article [word count: 3519]

Introduction

The increased prevalence of cardiovascular disease (CVD) in developing countries is placing a huge burden on health care services(1-3). India, in particular, with a large number of individuals with hypertension, dyslipidemia, diabetes and CVD, is facing a significant healthcare delivery challenge(4). Patients with CVD should receive antiplatelet therapy and drugs to lower blood pressure (BP) and low-density lipoprotein cholesterol (LDLc)(5-9). However, the use of preventive cardiovascular medications is disappointingly low(10-12). The cost and complexity of multi-drug regimens impacts adversely on adherence to such treatment and therefore, on its effectiveness(5, 13-17). The use of a cardiovascular polypill has shown to improve adherence to essential cardiovascular drugs and risk factor control (18-20).

The **U**se of **M**ultidrug **P**ill **I**n **R**educing cardiovascular **E**vents (UMPIRE) trial (21) demonstrated that a polypill based strategy improved adherence to prescribed therapy, and reduced BP and LDLc, compared to usual care in patients with or at high risk of CVD. Since the constituent drugs of the polypill used in UMPIRE are off-patent generics, this polypill can be manufactured at low cost. However, pharmaceutical companies are only likely to manufacture the polypill if the scale of prescribing compensates for small profit margins. Robust evidence on the cost-effectiveness of the polypill is therefore required to establish the polypill as part of an Indian CVD preventive strategy and to support the investment case for healthcare funders. India is estimated to have the largest number of prevalent cases of CVD in the world due to a high incidence rate and large population (more than 50% below the age of 25)(4). Further, wide variation in socio-economic status with a substantial proportion of the

population living below the poverty line with a predilection to have CVD at a young-age necessitates affordable and accessible secondary prevention treatment for CVD(22).

Although the cost-effectiveness of pharmacological and lifestyle modification interventions to prevent CVD have been evaluated in decision modeling studies [few examples: (23-26)], the cost-effectiveness of a polypill strategy using patient outcomes derived from a randomized controlled trial (RCT) in an Indian context is unknown. The **RUPEE-IND** (**R**esearching **U**MPIRE **P**rocesses, an **E**conomic **E**valuation in **Ind**ia) study was designed to investigate the impact of switching high risk CVD patients from usual care to a polypill strategy. This paper reports the "within-trial" cost-effectiveness of the polypill strategy relative to usual care in India.

Methods

UMPIRE trial

The UMPIRE trial was an open label, RCT of a polypill-based strategy, compared to usual care, in 2004 patients with or at high risk of CVD in India, United Kingdom (UK), Ireland, and Netherlands. The trial was conducted between Feb 2010 and Jan 2013 and ethics approval was obtained at each of the participating trial sites. Full details of the trial protocol and primary outcome results were published previously (21). In India, 1000 individuals aged ≥18 years and of both sexes with or at high risk of CVD (≥15% CVD risk over 10 years), were randomized to receive the polypill or usual care. Two versions of the polypill were used: Red Heart Pill (RHP) version 1: aspirin 75mg, lisinopril 10mg, simvastatin 40mg, atenolol 50mg or RHP version 2: aspirin 75mg, lisinopril 10mg, simvastatin 40mg, hydrochlorothiazide 12.5 mg. The polypill was prescribed to be taken orally, once daily and regarded as 'background treatment' to which other medications could be added to achieve physician recommended BP or

cholesterol targets, and/or to treat comorbidities. The RHPs were manufactured by Dr. Reddy's Laboratories (Hyderabad, India) and were provided without cost to trial participants.

Patient characteristics

The trial population consisted of 501 individuals in the polypill arm and 499 in the usual care arm in India. The baseline characteristics of the two groups were similar [Table 1] and were typical of CVD presentation in India, i.e. occurrence of CVD at a relatively young age, high prevalence of co-morbid conditions (diabetes), and the presence of higher CVD burden in low socio-economic strata.

Resource utilization and costs within trial

Costs per participant were determined from health care utilization and unit costs for these services. Data on treatment or cardiovascular-related use of health services over the study period were extracted from UMPIRE case report forms at 1 month, 6 months, 12 months, 18 months and at the trial end. These data included: medication use, consultations with healthcare professionals, emergency department attendances, and hospitalizations related to prescribed medications. Price estimates of the polypill were derived from five scenarios (Box 1). The cost of Indian rupees 3.3 ($0.06) per day used in **Scenario A** was an aspirational price discussed with Dr. Reddy's Laboratories. This took account of potential bulk purchasing by the government drug procurement agencies and mass prescribing by physicians. Given the large variations in the market price of simvastatin (Indian rupees. 2.3 - 29.3 per pill), we constructed two different scenarios to account for the range of simvastatin price. **Scenario B** used an aggregate sum cost of individual constituents of polypill based on *contemporary drug prices (simvastatin price: Indian rupees 4.0/pill)* applicable to the Indian market i.e. Indian rupees 11.5 ($0.22) per day. **Scenario C** used the market price of Cadila's

Polycap i.e. Indian rupees 15.4 ($0.29) per day. **Scenario D** was constructed using a similar approach as in Scenario B, but with *median market price of simvastatin i.e. Indian rupees 18.6* was used to calculate the aggregate sum cost of polypill constituents, which gave Indian rupees 25.4 ($0.47) per day. Finally, in **Scenario E**, we doubled the price of the polypill as used in Scenario D to understand the maximum threshold at which the polypill is cost-effective i.e. Indian rupees 50 ($0.94) per day. The cost of usual care medications was obtained using the Pharmatrac drug database 2012. More information on the costing of usual care medications is provided in #Appendix 1.

The cost of most events/hospitalizations was limited to a defined acute period, but stroke and renal failure events often require care for months or years after the initial hospitalization. Hence, for strokes we applied a cost that reflects a one-year period and for renal failure we applied a 6-month recurring dialysis cost that continued to the end of the study. A mean cost per unit was applied to resource use by each participant and to the clinical events reported by all study participants. Unit costs for healthcare services was collected from the participating trial sites using a standardized cost survey form (#Appendix 2).

Within trial Cost-Effectiveness Analysis

The analysis was carried out from a health sector perspective. Consistent with this perspective, we only considered direct medical costs incurred by patients and care providers. Indirect costs (productivity lost) and travel costs incurred by patients and their families/caregivers were not considered. All analyses used the 15-month trial duration and no discount rate was applied. Categorical data were reported as frequencies (percentages) and continuous data as means with standard errors. We performed an intention to treat (ITT) analysis to assess both effects and costs over the trial duration. At the trial end, complete data on effectiveness outcomes (adherence to

therapy, BP and LDLc) were available for 91.1% participants. Adherence to therapy was defined as self-reported use of antiplatelet, statin, and ≥2BP-lowering drugs, for at least 4 days during the week preceding the visit at baseline and at the trial end (21). The EQ5D questionnaire was applied to assess quality of life and we report the Visual Analogue Scale (VAS) results between the two groups because currently there is no value set available to calculate EQ5D utility scores in India. For the base-case ITT analysis, we imputed missing data using the last observation carried forward method. Incremental cost-effectiveness ratios (ICERs) were calculated as the difference in costs divided by the difference in effects between the polypill and usual care group. The ICER is a summary measure indicating the cost-effectiveness of an intervention compared to an alternative. In situations where the intervention costs are higher than usual care, the ICER represents the additional costs per additional unit of benefit. Where an intervention or usual care is dominant (more effective and less expensive than the comparator), the ICER is negative and is not meaningful (27). The cost-effectiveness analysis (CEA) results are reported as incremental cost per 10% increase in adherence and per unit reduction in SBP (mmHg) and LDLc (mg/dl). We report ICERs for the different polypill price scenarios, where appropriate, and do not report negative ICERs. Bootstrap sampling was used to estimate uncertainty around the cost and effectiveness estimates (28, 29). CEA results from bootstrap replications were plotted on a cost-effectiveness plane and using a cost-effectiveness acceptability curve (CEAC) against a range of willingness to pay (WTP) values (30). All statistical analyses were completed using Microsoft Office Excel 2007, and STATA (version 12.0 SE; StataCorp, TX, USA).

Sensitivity analyses

We conducted several deterministic sensitivity analyses to examine uncertainty in the key input variables (e.g. effectiveness, cost of drug), which could

potentially influence the ICER. Further, in a multivariable sensitivity analysis, we simulated the best (and worst) case scenarios using the maximum effectiveness of the polypill, minimum cost of the polypill, minimum cost of healthcare visits and minimum cost of hospitalizations/events. Minimum/maximum cost was defined by lower/upper bound of 95% confidence interval (CI).

Sub-group analyses

Several subgroups were analyzed to explore potential cost differences: established CVD versus high CVD risk patients, age, gender, education strata, income class, employment status, public vs. private health setting, and adherence to prescribed therapy, as defined in the UMPIRE trial (31).

Results

Effectiveness of polypill

At 15 months, compared to usual care, adherence was significantly greater with the polypill strategy compared to usual care (85% vs. 68%, p<0.01), with statistically significant improvement in SBP (3.3 units [mmHg] greater reduction, p=0.004), and LDL-cholesterol (12.3 units [mg/dl] greater reduction, p <0.01). At trial end, the mean EQ5D-VAS score was 75.0 vs. 73.4 in the polypill arm vs. usual care (p=0.08). Total number of people with serious adverse events reported were 26 vs. 15 with polypill strategy vs. usual care (p=0.07) [Table 2].

Medication, healthcare visits and hospitalization costs

Compared to the usual care, the cost of medications per person was significantly lower with the polypill strategy at 15 months (cost difference of $242.8 per person, 95% CI: $-318.7, $-166.7, p<0.01). There was no significant difference in costs associated with out-patient healthcare visits between the two treatment strategies.

However, the costs of hospitalizations were significantly higher with the polypill strategy compared to usual care (cost difference of $39.8 per person, 95% CI: $4.7, $74.7, p=0.03). Overall, the average cost, summing the cost of medications, out-patient healthcare visits and hospitalizations per patient, was significantly lower with the polypill strategy compared to usual care (cost difference of $202.9 per person, 95% CI: $-286.4, $-119.4, p < 0.01) [Table 3].

Cost effectiveness

In scenarios A-D, we found that the polypill strategy dominated usual care (lower cost and greater benefits with the polypill strategy) [Tables 4a-4c]. Whereas, in scenario E (polypill price: $0.94/day), the ICER for the polypill strategy was: $75.0 per 10% increase in adherence; and $64.7 and $21.0 per unit reduction in SBP and LDLc, respectively (Tables 4a-4c). Using a conservative estimate of CVD prevalence in India (37 million cases) (22, 32, 33), and based on varied polypill price assumptions ($0.06 - $0.94 per day), a polypill-based strategy could potentially result in net saving of $259 - $6096 per million population in India (Tables 4a – 4c).

The bootstrapped CEA results for primary outcomes - adherence, SBP and LDLc - plotted on the cost-effectiveness plane are presented in Online Figure 1 for all five scenarios of cost of polypill. In scenarios A-C, the cost-effectiveness planes demonstrate a high degree of certainty in the dominance of the polypill, as reflected by almost all of the sampled cost-effectiveness point estimates falling in the bottom right (South East) quadrant. This suggests that the polypill strategy is highly likely to be more effective and cheaper than usual care, and therefore, is the treatment of choice for CVD management. Only in scenario E, where we assumed the cost of polypill to be double that of the sum cost of its constituent drugs ($0.94/day), do most of the

cost/effectiveness points fall in top right (North East) quadrant for polypill strategy, indicating a greater benefit at higher cost.

CEACs for the different polypill price assumptions are presented in Online Figure 2. For scenario A - C the polypill remained consistently cost-effective across almost all bootstrapped iterations and at all WTP values. This suggests a very high probability that the polypill would be both cost-effective and cost-saving at prices of up to $0.29 (INR. 15.4) per day. At higher prices (Scenario D and E), as the WTP per unit of effectiveness increases, so does the estimated probability that the polypill is cost-effective. In Scenario D: at $0 WTP for a unit of effect (10% increase in adherence) there is an 80% probability that the polypill would be cost-effective. The probability rises to about 100% for WTP above $800 per 10% increase in adherence. Similarly, for scenario E: at $800 WTP for a 10% increase in adherence, there is an 80% probability that the polypill would be cost-effective. However, the probability rises to 100% at the WTP above $1200 per 10% increase in adherence.

Sensitivity analysis results

Our cost-effectiveness results were robust to several sensitivity analyses. The unit cost of healthcare visits had minimal impact on cost-effectiveness estimates, whereas the ICER was most sensitive to the effectiveness and cost of polypill. In all one-way sensitivity analyses and best-case scenarios usual care therapy was dominated by the polypill strategy, confirming that the polypill is a cost-effective option in the Indian context (Online Table 1). In the worst case-scenario, the ICERs for the 10% increase in adherence, per unit reduction in LDLc and SBP was $373, $504, and $202, respectively.

Subgroup analyses results

Across all major sub-groups, the participants in the polypill group incurred significantly less cost, compared to the usual care group ($p<0.01$). Increased cost

savings were particularly noted in people aged ≥ 55 years, males, and patients at high risk of cardiovascular disease. Individuals with co-morbid conditions such as diabetes and those with high adherence rates had two times greater cost savings with the polypill strategy vs. usual care. [Online Table 2].

Discussion

This trial-based cost effectiveness analysis found the polypill strategy to be cost-effective with greater clinical benefits (improved adherence, lower SBP and LDLc) at lower healthcare cost, compared to usual care in patients with or at high risk of CVD in India. The results were largely driven by the overall net savings in the medication cost with the polypill strategy. The polypill strategy had a very high probability of being cost-saving up to a maximum price of $0.54 per day. At a higher price (>$0.54/pill) the polypill may still be cost-effective depending on decision makers' maximum willingness to pay for a unit of health benefit.

RUPEE is the first study to report the cost-effectiveness of a cardiovascular polypill strategy for secondary prevention of CVD in India. The main strength of this analysis is that it uses patient level data from a well-designed RCT. The trial followed a standardized protocol and measurement tools across 28 participating sites in India to produce strong evidence on the effectiveness of a polypill compared to usual care. Our CEA results are robust to a number of scenario, subgroup and sensitivity analyses.

The CEA has limitations. The analysis is based on the prices of drugs as they stood at the end of the trial in 2012. The results may not hold if there are future price changes in the cost of preventive CVD medicines. However, we have conducted a range of sensitivity analysis around the price of the medication, so this should capture any future changes in the price. The study assumed the market price of a polypill based on

different pricing strategies, which is helpful to understand the threshold at which the polypill is or is not considered cost-effective. The current study could not estimate the likely effect of long-term polypill-based care on cardiovascular events for several reasons – there were relatively few events, follow-up was short considering there is a lag-time of a year or so for the full extent of cardiovascular benefits to appear (e.g., for cholesterol lowering effect (34-36)), and also patients in both groups are generally treated more intensively than average in a clinical trial setting. Furthermore, in an unblinded trial such as this one, it remains possible that differential treatment and/or reporting was provided to the participants in the polypill group.

Multidrug regimens (aspirin, beta-blockers, ACEI, or lipid-lowering drugs) for secondary prevention of CVD have been shown to be cost-effective according to World Health Organization (WHO) standards (37). But, a polypill strategy would be more cost-effective than usual care. Previous studies have modelled CVD reduction on the assumption of aspirin adherence and sustained BP and LDL-c reductions and the established relationships between these risk factor changes and CVD events in past trials (23, 24, 37, 38). A decision modelling study conducted within the Dutch health system found that the polypill would be a cost-effective strategy in individuals with a 10 year cardiovascular (CV) risk of 7.5% (26). Another CEA of the polypill in a high CV risk population (≥15% CV risk over 10 years) in Latin America performed using a Markov model, reported that the provision of a polypill to those with or at high risk of CVD would yield an acceptable ICER: $34–$36 per QALY (38).

A recent study in India evaluated the cost-effectiveness of policies to expand coverage, access and use of CVD prevention drugs including a polypill strategy in patients with acute myocardial infarction for secondary prevention of CVD (39). This study found that a policy to expand access to the polypill is the most cost-effective

option when compared to aspirin, statins and BP lowering drugs prescribed separately [ICER: $1690 per disability-adjusted life years (DALYs) averted]. However, this study did not incorporate the impact of improved adherence to therapy due to the introduction of polypill and did not consider the cost of hospitalizations due to polypill treatment in their analysis (39). More recently, a Markov model based CEA demonstrated the benefits of improved adherence with a cardiovascular polypill versus multiple monotherapy for the secondary prevention of CVD in the UK and Spain (24, 40). The UK study found that an additional 6.7% CVD events can be prevented for 10% increase in adherence and ICERs ranged between cost-saving and £21,430 [$27,319.4] per QALY gained (24). Our study results are consistent with a favorable ICER (across a wide range of willingness to pay threshold) for clinical outcomes such as adherence to medications and improvement in SBP and LDLc. However, as our cost-effectiveness estimates are generated from within the time period of the UMPIRE trial, further long-term studies or modelled evaluations could demonstrate benefits in terms of CVD events averted and quality adjusted life years gained with this polypill based strategy versus usual care. However, such long-term extrapolations from the present study, where we found the polypill strategy to be dominant, is unlikely to alter the existing conclusions that there is a strong investment case for such a strategy.

The disparity in the use of cardio-protective drugs between countries is extremely high (10, 11, 41). Much of the difference in the use of CVD medications is explained by a strong positive correlation with a countries' GDP and health expenditures per capita(42). This is particularly seen in the use of statins, which are more expensive and are used relatively infrequently in South Asia but are the most used drug in high-income countries (10, 42). Apparently, the main barrier to the use of preventive cardiovascular drug is high out-of-pocket health expenditures. However, the

use of aspirin, an inexpensive drug, is also low. Thus, a possible barrier to secondary prevention could be related to adherence to multi-medication therapy. In addition, a sizeable proportion of the Indian population live below the poverty line and treatment for CVD can incur catastrophic health expenditures(43, 44). It is thus, important to advocate for low-cost affordable treatment options for chronic care of CVD. The polypill has the advantage of being one pill instead of four, making it a less complex regimen which could promote more widespread use and greater adherence(45-47). The simplified treatment regimen and lower cost of the polypill relative to usual care further drives the polypill's dominance in our CEA. It is important to note that the polypill was found to be effective and cost-effective, in improving adherence and lowering SBP and LDLc, despite using simvastatin, whereas the usual care strategy used recent and more potent statins [in the Indian pharmaceutical market, simvastatin appears to be more expensive than atorvastatin]. Therefore, the impact of a polypill could be greater with the use of more potent and less expensive statins.

Conclusion

In line with the WHO "25x25" goal and recognizing the urgent need to identify and promote the most cost-effective interventions for CVD prevention, our findings offer a cost-effective option of delivering and improving care for CVD patients in low-resource settings with a polypill strategy. A low-cost polypill would improve the access, availability and affordability of CVD prevention treatment for millions of people living with cardiovascular disease globally.

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Tables

Table 1: Baseline characteristics of UMPIRE trial participants (India, N=1000)

Characteristics	Polypill (n=501)	Usual care (n=499)
Age, mean (SD)	57.7 (10.3)	57.3 (10.9)
Males (%)	77.8	78.7
Self-reported medical history (%)		
Established CVD	92	92
Coronary artery disease	83	81
Cerebrovascular disease	13.0	12.6
Diabetes	32.0	34.0
Family history of CVD	11.6	11.4
Ever smoker (%)	32.0	31.0
Current alcohol use (%)	7.6	7.2
Systolic Blood pressure (mmHg), mean (SD)	136.0 (23.3)	136.1 (22.5)
Diastolic Blood pressure (mmHg), mean (SD)	78.5 (13.8)	78.2 (12.6)
Total cholesterol (mg/dl)	153.6 (36.5)	165.3 (43.3)
HDLc (mg/dl), mean (SD)	40.8 (8.6)	40.9 (8.4)
LDLc (mg/dl), mean (SD)	85.4 (30.3)	96.0 (37.9)
Triglycerides (mg/dl), mean (SD)	145.0 (84.4)	149.7 (85.7)
Serum Creatinine, mean (SD)	1.1 (0.3)	1.0 (0.3)
Fasting blood glucose (mg/dl), mean (SD)	115.7 (46.6)	119.1 (47.5)
Education categories (%)		
Post-graduate degree	4.4	5.4
Undergraduate degree	12.2	14.5
Secondary school	36.0	36.0
Primary school	30.7	34.7
None	11.6	12.7
Employment status, (%)		
Full-time	28.0	28.0
Part-time	9.4	9.2
Retired / unemployed	62.5	62.4
Total household income per month (INR), (%)		
<3000	28.0	32.0
3000 - 10,000	41.0	36.0
10,001 - 50,000	14.6	18.5
>50,000	0.8	0.6
Don't know / Didn't respond	15.6	13.5

**Abbreviations: CVD – cardiovascular disease, n – number of participants, mg/dl – milligrams per decilitre, mmHg – millimetre of mercury, SD – standard deviation, HDLc – high density lipoprotein cholesterol, LDLc – low density lipoprotein cholesterol, INR. – Indian rupees*

***Standard deviations reported within parenthesis in the above table.*

Box 1: Indicative price of polypill based on varied pricing strategies (costs, 2012≠)

Scenario	Source of information	Unit price in INR per day	Unit price in $ per day
A	As recommended in the UMPIRE protocol	**3.3**	**0.06**
B	Aggregate sum cost of individual constituents of polypill (based on contemporary drug prices applicable to Indian pharmaceutical market)*		
	RHP1c		
	Simvastatin 40mg (Simvas 40mg)	4.7	0.09
	Aspirin 75 mg	0.3	0.00
	Lisinopril 10mg (Lipril 10mg)	3.4	0.06
	Atenolol 50mg (ATEN 50mg)	3.2	0.06
	Aggregate sum cost	**11.5**	**0.22**
	RHP2c		
	Simvastatin 40mg (Simvas 40mg)	4.7	0.09
	Aspirin 75 mg	0.3	0.00
	Lisinopril 10mg (Lipril 10mg)	3.4	0.06
	Hydrochlorothiazide 12.5mg (Dithiazide 12.5mg)	2.0	0.04
	Aggregate sum cost	**10.4**	**0.19**
C	Equivalent to market price of Cadila's Polycap	**15.4**	**0.29**
D	Aggregate sum cost of individual constituents of polypill (based on median market price for simvastatin) **		
	RHP1c		
	Simvastatin 40mg (Simvas 40mg)	18.6	0.35
	Aspirin 75 mg	0.3	0.00
	Lisinopril 10mg (Lipril 10mg)	3.4	0.06
	Atenolol 50mg (ATEN 50mg)	3.2	0.06
	Aggregate sum cost	**25.4**	**0.48**
	RHP2c		
	Simvastatin 40mg (Simvas 40mg)	18.6	0.35
	Aspirin 75 mg	0.3	0.00
	Lisinopril 10mg (Lipril 10mg)	3.4	0.06
	Hydrochlorothiazide 12.5mg (Dithiazide 12.5mg)	2.0	0.04
	Aggregate sum cost	**24.3**	**0.45**
E	Twice the price of aggregate sum cost of polypill constituents	**50.0**	**0.94**

UMPIRE = Use of Multidrug Pill in Reducing cardiovascular Events trial, INR = India Rupee, USD = United States Dollar

**Scenario B - Source, Pharmatrac database, 2012: Lupin - starstat (simvastatin 40mg) - INR 4.71 (or $0.09) per pill*

***Scenario D - Source, Pharmatrac database, 2012: Median market price of simvastatin 40mg was used few examples: Zocor (MSD) INR. 20.32 (or $ 0.38)/pill, SIMVOTIN (Ranbaxy) INR. 32.25 (or $0.60) / pill, ZOSTA (USV) - INR. 17.15 (or $ 0.32)/pill*

≠conversion rate used: 1US$ = 53.4 INR. https://data.oecd.org/conversion/exchange-rates.htm#indicator-chart conversion rate (2012)

Table 2: Summary of UMPIRE Trial results at the end of study: India

Outcomes (Primary end points)	Polypill (N = 501)	Usual care (N = 499)	Treatment effect (relative risk for adherence, mean difference for SBP & LDLc), (95% CI)	P value
Self-reported use of antiplatelet, statin and combination (>=2) blood pressure lowering therapy at the end of study	387/457(0.85)	310/454(0.68)	1.24 (1.15, 1.34)	<.001
Systolic blood pressure (mmHg), SD	123.6 (19.2)	126.9 (18.1)	-3.3 (-8.5, -1.9)	0.004
LDL cholesterol (mg/dl), SD	81.4 (27.9)	93.74 (36)	-12.3 (-21.2, -3.49)	<0.01
Secondary end point				
Health related quality of life (EQ-VAS), SD	75 (13.7)	73.4 (13.9)	1.6 (-0.19 ; 3.4)	0.08
Serious adverse events (total = 41)	26	15		0.07

Abbreviations: N-number of participants, SBP – systolic blood pressure, LDLc – low density lipoprotein cholesterol, QALYs – quality adjusted life years, EQ-VAS – European quality of life – Visual Analogue Scale, mmHg- millimetre per mercury, mg/dl – milligram per decilitre, CI – Confidence Interval, SD- Standard Deviation

Table 3: Summary of mean resource use and cost per patient [Within-trial cost analysis] - US$, 2012

Item	**Polypill**		**Usual care**		**Difference**		
	Cost[mean]	S.E	Cost[mean]	S.E	Cost [mean]	95% CI	p-value
Medication cost (total)	213.6	20.9	456.3	32.7	-242.8	(-318.7, -166.7)	<0.01
CVD medicines cost	70.2	3.2	240.8	5.0	-170.6	(-182.3, -159.0)	<0.01
Other medicines cost	143.7	20.6	214.1	31.4	-70.3	(-144.0, 3.2)	0.06
Healthcare visits cost (total)	9.8	1.1	10.1	1.1	-0.3	(-3.3, 2.8)	0.8
Hospitalizations cost (total)	55.7	16.6	16.0	6.5	39.8	(4.7, 74.7)	0.03
CVD events cost	53.6	16.6	12.7	6.3	40.9	(6.1, 75.7)	0.02
Other events cost	2.1	1.0	3.3	1.6	-1.2	(-4.8, 2.4)	0.5
Overall mean cost per patient	279.5	26.6	482.4	33.3	-202.9	(-286.4, -119.4)	<0.01

*SE: standard error, CVD – cardiovascular disease, CI – Confidence Interval, US$ - united states dollar

Table 4.a. Within trial costs, effects and cost-effectiveness of polypill strategy versus usual care (**10% increase in adherence**), US$, 2012

Adherence outcome	Cost ($)	Incr. cost ($)	Effect (% Increase in adherence)	Incr. effect	ICER - 10% increase in adherence	Total cost per million popn ($) (India)	Cost-saving per million popn ($) (India)
Scenario A (PP = $0.062 (INR.3.3)/day)							
Polypill	279.1	-203.3	25.3	20.7	dominant	408.2	3472.0
Usual care	482.4		4.6			3880.1	
Scenario B (PP = $0.22 (INR.11.55)/day)							
Polypill	343.9	-138.5	25.3	20.7	dominant	502.9	3377.2
Usual care	482.4		4.6			3880.1	
Scenario C (PP = $0.29 (INR.15.4)/day)							
Polypill	372.0	-110.4	25.3	20.7	dominant	544.0	3336.1
Usual care	482.4		4.6			3880.1	
Scenario D (PP = $0.47 (INR. 25)/day)							
Polypill	445.7	-36.7	25.3	20.7	dominant	651.8	3228.3
Usual care	482.4		4.6			3880.1	
Scenario E (PP = $0.94 (INR.50)/day)							
Polypill	637.6	155.2	25.3	20.7	75.0	932.5	2947.7
Usual care	482.4		4.6			3880.1	

**Total cost per million population was calculated based on a conservative estimate of prevalence of CVD in India i.e. 35 million CHD and 2 million stroke cases (source: Circulation, 2016, and National Commission on Macroeconomics, 2005); Abbreviation – PP – Polypill; SBP – systolic blood pressure, CHD – Coronary heart disease, CVD – cardiovascular disease, $ - United States dollar, INR. – Indian rupees, Incr. - Incremental, popn. – population, ICER – incremental cost-effectiveness ratio*

Table 4.b. Within trial costs, effects and cost-effectiveness of polypill strategy versus usual care (**Systolic blood pressure (SBP) outcome measure**), US$, 2012

SBP outcome	Cost ($)	Incr. cost ($)	Effect (SBP reduction)	Incr. effect	ICER	Total cost ($) per million popn (India)	Cost-saving ($) per million popn (India)
Scenario A (PP = $0.062 (INR.3.3)/day)							
Polypill	279.1	-203.3	7.9	2.4	dominant	1307	1938
Usual care	482.4		5.5			3245	
Scenario B (PP = $0.22 (INR.11.55)/day)							
Polypill	343.9	-138.5	7.9	2.4	dominant	1611	1634
Usual care	482.4		5.5			3245	
Scenario C (PP = $0.29 (INR.15.4)/day)							
Polypill	372.0	-110.4	7.9	2.4	dominant	1742	1503
Usual care	482.4		5.5			3245	
Scenario D (PP = $0.47 (INR. 25)/day)							
Polypill	445.7	-36.7	7.9	2.4	dominant	2087	1158
Usual care	482.4		5.5			3245	
Scenario E (PP = $0.94 (INR.50)/day)							
Polypill	637.6	155.2	7.9	2.4	64.7	2986	259
Usual care	482.4		5.5			3245	

**Total cost per million population was calculated based on a conservative estimate of prevalence of CVD in India i.e. 35 million CHD and 2 million stroke cases (source: Circulation, 2016, and National Commission on Macroeconomics, 2005); Abbreviation – PP – Polypill; SBP – systolic blood pressure, CHD – Coronary heart disease, CVD – cardiovascular disease, $ - United States dollar, INR. Indian rupees, Incr. - Incremental, popn. – Population, ICER – incremental cost-effectiveness ratio*

Table 4.c. Within trial costs, effects and cost-effectiveness of polypill strategy versus usual care (**Low density lipoprotein cholesterol (LDLc) outcome measure**), US$, 2012

LDLc outcome	Cost ($)	Incr. cost ($)	Effect (LDLc reduction)	Incr. effect	ICER	Total cost per million popn ($) (India)	Cost-saving per million popn ($) (India)
Scenario A (PP = $0.06 (INR. 3.3)/day)							
Polypill	279.1	-203.3	9.9	7.4	dominant	1043	6096
Usual care	482.4		2.5			7139	
Scenario B (PP = $0.22 (INR. 11.5)/day)							
Polypill	343.9	-138.5	9.9	7.4	dominant	1285	5854
Usual care	482.4		2.5			7139	
Scenario C (PP = $0.29 (INR. 15.4)/day)							
Polypill	372.0	-110.4	9.9	7.4	dominant	1390	5749
Usual care	482.4		2.5			7139	
Scenario D (PP = $0.47 (INR. 25)/day)							
Polypill	445.7	-36.7	9.9	7.4	dominant	1666	5474
Usual care	482.4		2.5			7139	
Scenario E (PP = $0.94 (INR.50)/day)							
Polypill	637.6	155.2	9.9	7.4	21.0	2383	4756
Usual care	482.4		2.5			7139	

**Total cost per million population was calculated based on a conservative estimate of prevalence of CVD in India i.e. 35 million CHD and 2 million stroke cases (source: Circulation, 2016, and National Commission on Macroeconomics, 2005); Abbreviation – PP – Polypill; SBP – systolic blood pressure, CHD – Coronary heart disease, CVD – cardiovascular disease, $ - United States dollar, INR. Indian rupees, Incr. - Incremental, popn. – population, ICER – incremental cost-effectiveness ratio*