Cost-Effectiveness of Treatment and Secondary Prevention of Acute Myocardial Infarction in India

A Modeling Study

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ABSTRACT

Background: Cardiovascular diseases are the single largest cause of death in India, with acute myocardial infarction (AMI) accounting for one-third of all heart disease deaths. Although effective treatment is available for AMI, access to treatment is dictated by cost and ability to pay. With scarce treatment resources, healthcare decisions are guided by local cost-effectiveness, for which country-level data are lacking.

Objectives: We calculate the cost-effectiveness of policies that expand the use of aspirin, injection streptokinase, beta-blockers, angiotensin-converting enzyme inhibitors, and statins for the treatment and secondary prevention of AMI in India. We also estimate the cost-effectiveness of a hypothetical polypill (combining aspirin, beta blockers, angiotensin-converting enzyme inhibitors, and statins) for secondary prevention.

Methods: We conduct cost-effectiveness analyses of AMI treatment and secondary prevention for patients with previous coronary heart disease events in India. We estimate coronary heart disease events using Framingham risk scores and disease prevalence using a cohort ordinary differential model. Other parameter estimates are from the literature. Polypill treatment is assumed to cost less than the additive cost of all 4 oral medications, but it is not assumed to increase adherence. We conduct a Latin hypercube sampling sensitivity analysis on the model parameters.

Results: Increasing coverage of AMI treatment with aspirin and streptokinase would be cost-effective and could avert approximately 335,000 (191,000 to 503,000) disability-adjusted life years among 30- to 69-year-olds in India. Secondary prevention with aspirin and beta-blockers at 80% coverage (and at lower rates) would be highly cost-effective, and the addition of angiotensin-converting enzyme inhibitors would also be cost-effective. Introducing the polypill dominates a strategy of a 4-drug regimen with the aforementioned drugs and statins. The cost-effectiveness ratio of 80% coverage with the polypill would be $1,690 ($1,220 to $2,410) per disability-adjusted life years averted.

Conclusions: Policies expanding both treatment and preventive therapies are cost-effective, based on gross domestic product per capita comparison. Introducing the polypill would be more effective than providing its components separately, even without accounting for the likely increase in treatment adherence.

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality in India [1]. Individuals with previous coronary heart disease (CHD) events are at high risk for AMI. Based on a cohort model of CHD, which uses Framingham risk scores on an Indian population dataset, there are an estimated 19 million CHD patients ages 30 to 69 years in India, and in 2010, there were 2.1 million deaths from cardiovascular and circulatory diseases [2]. Well-established guidelines govern the use of various drugs for the treatment and secondary prevention of AMI [3]. The ISIS-2 (Second International Study of Infarct Survival) finds that treating AMI patients with aspirin (an antiplatelet agent), injection streptokinase (thrombolysis), or a combination of the 2 produces a significant reduction in the 5-week vascular mortality [4].

In addition to primary treatment and management, secondary prevention of AMI remains an important strategy to reduce the burden of CHD and AMI in India. Gaziano et al. [5–7] find secondary prevention with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and statins to be cost-effective for patients in the developing world. These drugs reduce the risk of AMI and lower its case fatality rate.

These 4 drugs—aspirin, beta-blockers, ACEI, and statins—are currently prescribed, albeit at a low rate, in South Asia [8]. The polypill, which would combine these drugs into 1 pill (75 mg aspirin, 50 mg beta-blockers, 5 mg ACEI, and 10 mg statins), has not yet been introduced. Research has shown that the polypill

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potentially increases adherence relative to prescription of all pills [9–11].

In this study, we investigate the cost-effectiveness of AMI treatment and secondary prevention using pharmacological interventions. Specifically, we analyze the cost-effectiveness of interventions with aspirin and injection streptokinase for the primary treatment of AMI, and secondary prevention therapies with aspirin, beta-blockers, ACEI, statins, and the hypothetical polypill for patients with previous CHD events.

Researchers have studied the cost-effectiveness of AMI treatment and secondary prevention in the developing world and in South Asia as a region [5–7] but not specifically in India, which accounts for approximately 60% of heart disease in the world [12]. Disease epidemiology in India is different in several respects: 54% of CHD deaths in India occur before 70 years of age [2], whereas the proportion is 22% in the West [7], 38% in Iran and Sri Lanka, and 34% in China [2]. We follow the World Health Organization (WHO) guidelines for calculating the cost-effectiveness ratio (CER) as the incremental cost per disability-adjusted life year (DALY) averted by an intervention relative to a baseline scenario of current prescription rates in India [13]. We report commonly used thresholds of "cost-effective" and "very cost-effective," which compare the CER with per capita gross domestic product (GDP).

METHODS

Data sources, assumptions, and calculations

The details of the model parameters are presented in Table 1 [4,5,7,8,12,14–21].

Number of AMI cases and prevalence of CHD. The number of AMI patients in India is currently not known. We estimate the risk of AMI using data on CHD. The estimation process has been described in detail in the Online Appendix.

Death rate. Thirty-day mortality after an AMI, even with effective treatment, is about 33%, with roughly one-half of the deaths occurring before patients reach the hospital [7]. Death rates are 8.6% for hospitalized ST-segment elevation myocardial infarction (STEMI) patients and 3.8% for non–ST-segment elevation myocardial infarction (NSTEMI) patients [12]. For the analysis of the secondary prevention therapies for CHD patients, the annual death rate incorporating the current prescriptions in India is 7.5% [8]. We use a wide range in our sensitivity analysis to incorporate the uncertainty.

Coverage of drugs

Current drug coverage data for AMI treatment are from the results of the CREATE (Treatment and Outcomes of Acute Coronary Syndromes in India) study [12]. We assume the coverage rates of secondary prevention drugs in India are equivalent to the South Asian PURE (Prospective Urban Rural Epidemiology) study estimates [8]. The coverage of the polypill, which is unavailable in India, is set to 0. The assumptions related to coverage of drugs are discussed in the Online Appendix.

Effectiveness of drugs. The INTERHEART study (an international case control study of patients with a first myocardial infarction) confirmed that risk factors for AMI are the same globally, regardless of income levels [13]. Therefore, we assume that interventions have the same effect (relative risk reduction) in developed and developing countries. Effectiveness of aspirin, and aspirin with injection streptokinase, is calculated from the results of the ISIS-2 study. The odds reductions are 23% and 42%, respectively [4].

Effectiveness of the drug combinations used for secondary prevention is calculated from Gaziano et al. [5], and effectiveness of the hypothetical polypill is taken from the Indian Polycap study [19]. Administered to CHD patients, preventive therapy with aspirin alone is estimated to reduce the relative risk of an AMI by 34%. The cumulative risk reduction from the combination of all 4 drugs is approximately 73% [5].

Cost components. Our analysis comprises the summed costs of the interventions for both the health sector and for the patients' expenses in that sector. Primary AMI treatment intervention costs include the cost of drugs, laboratory tests, and inpatient stay at a secondary hospital, whereas secondary prevention costs include outpatient visits, drugs, and the aforementioned costs of AMI. Details of cost components are described in the Online Appendix.

Modeling approach

We assess the cost-effectiveness of AMI treatment and secondary prevention by conducting a cost-effectiveness analysis. We use results from an analysis on Framingham risk scores for a CHD event incidence [20] and estimate the prevalence of CHD in a cohort model. We use the CHD prevalence in a deterministic spreadsheet model programmed in Excel and Visual Basic for Applications (Microsoft, Redmond, WA, USA). Figure 1 describes the structure of the model. Individuals with CHD have a risk of an AMI event (the risk for healthy individuals is lower) and of disease-related death. (*Note*: We do not consider strokes in our cost-effectiveness analysis.) CHD patients (CHD-P) adhere to prescription of secondary prevention drugs (set at the effective coverage rate) that reduce the likelihood of the disease events. In the event of an AMI, individuals either die before reaching the hospital or receive primary care treatment (at the effective coverage rate), reducing their likelihood of death.

Our analysis follows the WHO guidelines for calculating the CER of each intervention as the cost per DALY averted by the intervention relative to the null scenario, in which no effective AMI intervention is administered [22].

TABLE 1. Description of model parameters

Parameter	Value	Sensitivity Analysis Intervals	Source (Year)
Population distribution			World Bank population projection tables [14]
30–39	177,436,000	(150,820,600–204,051,400)	
40–49	137,941,000	(117,249,850–158,632,150)	
50–59	102,481,000	(87,108,850–117,853,150)	
60–69	56,377,000	(47,920,450–64,833,550)	
CHD incidence per 100,000			Jeemon et al. (2011) [20]
30–39	175	(88–263)	
40–49	590	(295–885)	
50–59	1,018	(509–1,527)	
60–69	1,583	(792–2,375)	
Life expectancy, yrs			WHO life table, World Bank population projection tables [14]
30–39	39.57	(33.64–45.51)	
40–49	30.80	(26.18–35.42)	
50–59	22.56	(19.17–25.94)	
60–69	15.32	(13.03–17.62)	
AMI probability with previous CHD events	0.053	(0.047–0.061)	Prabhakaran et al. (2005) [15]
Percentage of STEMI among AMI patients			Xavier et al. (2008) [12]
30–49	68.0	(57.8–78.2)	
50–69	58.0	(49.3–66.7)	
Percentage of AMI patients dying before hospital	16.5	(14.0–19.0)	Gaziano et al. (2006) [7]
30-day AMI mortality rate			Xavier et al. (2008) [12]
STEMI	0.086	(0.073–0.099)	
NSTEMI	0.038	(0.032–0.044)	
CHD yearly death rate	0.079	(0.039–0.118)	Prabhakaran et al. (2005) [15]
Baseline coverage of drugs, %			
Treatment of AMI			
Aspirin	21.5	(18.3–24.7)	Xavier et al. (2008) [12]
Aspirin + injection streptokinase	58.5	(49.7–67.3)	
Secondary prevention of AMI			
Aspirin	0.0	(0.0–0.1)	Yusuf et al. (2011) [8]
Beta-blocker	0.3	(0.26–0.35)	
Aspirin + beta-blocker	5.3	(4.5–6.1)	
Aspirin + beta-blocker + ACEI	1.6	(1.4–1.8)	
Aspirin + beta-blocker + ACEI + statin	4.8	(4.1–5.5)	
Polypill	0.0		
Drug efficacy (relative risk)			
Treatment of AMI			
Aspirin	0.770	(0.700–0.850)	ISIS-2 (1988) [4]
Aspirin + injection streptokinase	0.580	(0.500–0.660)	
Secondary prevention of AMI (relative risk)			
Aspirin	0.660	(0.600–0.720)	Gaziano et al. (2006) [5]
Aspirin + beta-blocker	0.482	(0.450–0.626)	
Aspirin + beta-blocker + ACEI	0.385	(0.315–0.564)	
Aspirin + beta-blocker + ACEI + statin	0.273	(0.195–0.462)	

(continued)

TABLE 1. Continued

Parameter	Value	Sensitivity Analysis Intervals	Source (Year)
Secondary prevention of death (all-cause mortality relative risk)			
Aspirin	0.850	(0.810—0.890)	Gaziano et al. (2006) [5]
Aspirin + beta-blocker	0.656	(0.559—0.757)	
Aspirin + beta-blocker + ACEI	0.549	(0.419—0.719)	
Aspirin + beta-blocker + ACEI + statin	0.429	(0.252—0.625)	
Polypill prevention of CHD events	0.380	(0.287—0.473)	Yusuf et al. (2009) [19]
Costs, U.S.$			
AMI treatment			
Lab costs	304.92	(259.18—350.66)	Riewpaiboon (2014) [16]
Inpatient costs	118.29	(100.55—136.04)	
Aspirin	0.11	(0.10—0.13)	
Aspirin + injection streptokinase	55.05	(46.79—63.30)	
Secondary prevention (per defined daily dose)			www.cimsasia.com [17]
Aspirin	0.008	(0.007—0.009)	
Beta-blocker	0.071	(0.061—0.082)	
ACEI	0.062	(0.053—0.072)	
Statin	0.179	(0.152—0.206)	
Polypill	0.209	(0.178—0.240)	
Disability weight AMI	0.437	(0.405—0.477)	Mathers et al. (2006) [18]
Discount rate	0.030		
Days of disability for AMI patients	30	(26—35)	NCMH (2005) [21]

Sensitivity analysis ranges are based on ranges provided in published works, where available. Where not available, a range of 85% to 115% of the value was used.
ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; CHD, coronary heart disease; NSTEMI, non—ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; WHO, World Health Organization.

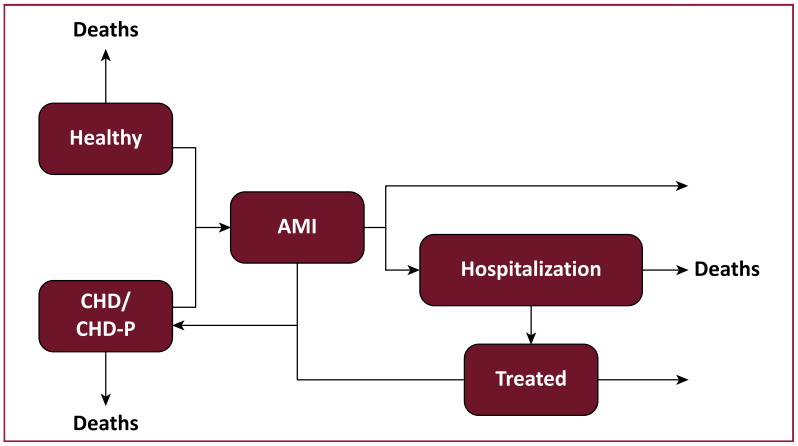

FIGURE 1. Model structure. Healthy individuals have a lower risk of acute myocardial infarction (AMI) than do those with coronary heart disease (CHD). A portion of the population with CHD takes preventative therapy (CHD-P), reducing their likelihood of AMI and of disease-related death. Individuals experiencing AMI may die before reaching a hospital. Primary treatment intervention occurs in the "treated" category and secondary prevention occurs in the CHD/CHD-P category.

We report the commonly used thresholds of "cost-effective" and "very cost-effective," which compare the CER with per capita GDP as described in WHO guidelines [22]. CER are produced for all Indians ages 30 to 69 years. We use uniform age weights that value an extra year of life equally, regardless of the age of the recipient.

Intervention options and strategies

AMI treatment interventions. We separately analyze STEMI and NSTEMI interventions. Treatment of AMI involves medical therapies that restore blood flow (using antiplatelet agents), dissolve the thrombus that is occluding the arterial lumen (thrombolysis), or reduce myocardial oxygen demand and fatal arrhythmias (beta-blockers).

In this study, we present 2 primary treatment scenarios for AMI patients and calculate the CER of each. In intervention scenario 1, patients are treated with aspirin alone (325 mg initial dose and subsequently 75 mg doses once daily); in scenario 2, patients are treated with aspirin and injection streptokinase (1 dose at 1.5 mU); and only STEMI patients are treated with the injection. In both

cases, we assume patients are administered treatment within 24 h of an AMI. We do not consider angioplasty because it is only used in approximately 7.5% of AMI cases in India, and its costs are extremely high for patients, who often (77.3% of the time) pay out of pocket [12]. Even though clopidogrel monotherapy was shown to be modestly superior to aspirin monotherapy in preventing recurrent ischemic events in patients with peripheral vascular disease, ischemic strokes, and recent MI, it did not replace aspirin because of its higher cost; however, clopidogrel monotherapy was promoted as an alternative to aspirin in patients who could not tolerate it [23]. For this reason, we do not consider clopidogrel in our analysis.

Secondary prevention interventions. We calculate the cost-effectiveness analysis for 5 interventions: 1) aspirin (75 mg once daily); 2) aspirin and beta-blockers (75 mg once daily and 50 mg twice daily, respectively); 3) aspirin, beta-blockers, and ACEI (75 mg once daily, 50 mg twice daily, and 5 mg once daily, respectively); 4) aspirin, beta-blockers, ACEI, and statin (75 mg once daily, 50 mg twice daily, 5 mg once daily, and 10 mg once daily, respectively); and 5) a hypothetical polypill to be taken once. Polypill treatment is assumed to cost less than the additive cost of all 4 oral medications taken individually, but conservatively, the polypill is not assumed to increase adherence.

Sensitivity analysis

To assess the uncertainty in the model and the robustness of the results, we conduct a sensitivity analysis using a Latin hypercube sampling technique. The distribution parameters of each variable used in the analysis are listed in Table 1. They are based on the upper and lower limits reported in previously published work, where available. Where limits are not available, we construct intervals at 85% and 115% of the values reported. The exceptions are the CHD incidence and death rates, where the intervals were set to 50% and 150%. Additionally, to conduct sensitivity on lack of adherence, we consider intervention increasing secondary prevention effective coverage to 40% and 60%.

Our analysis satisfies the American College of Cardiology/American Heart Association standards of cost-effectiveness analysis [24]. The American College of Cardiology/American Heart Association checklist for our study is presented in the Online Appendix.

RESULTS

CHD prevalence

Based on the cohort model (using Framingham risk scores), approximately 19 million 30- to 69-year-old individuals in India have CHD. We have wide confidence intervals in our sensitivity analysis (13.4 million to 27.5 million) because of the wide estimates of incidence and CHD death rates (Table 2).

AMI treatment interventions

Table 3 provides cost-effectiveness analysis results reported in U.S. dollars with 95% confidence intervals (CI) from the Latin hypercube sampling sensitivity analysis. The incremental CER of increasing aspirin AMI treatment coverage at hospitals from the baseline (80%) to the intervention (95%) scenario is only $0.49 ($0.28 to $0.90) per DALY averted. Increasing coverage of injection streptokinase from 22.5% to 80% of STEMI patients (in addition to the aspirin intervention) would avert an additional 38,000 (15,300 to 82,600) DALY in the Indian population and the incremental CER would be $615 ($350 to $1,210) per additional DALY averted.

Secondary prevention interventions

The life expectancy without preventive treatment is approximately 9.7 (95% CI: 8.2 to 11.4 in the sensitivity analysis) years for 30- to 39-year-olds, 9.2 years (95% CI: 7.7 to 10.6) for 40- to 49-year-olds, 8.5 years (95% CI: 7.1 to 9.8) for 50- to 59-year-olds, and 7.4 years (95% CI: 6.3 to 8.5) for 60- to 69-year-olds. Preventive interventions can extend life expectancy by up to 5.2 (95% CI: 1 to 9.6) years, 4.5 (95% CI: 0.8 to 8.3) years, 3.7 (95% CI: 0.5 to 6.8) years, and 2.7 (95% CI: 0 to 5.5) years in the respective age groups.

The incremental cost-effectiveness and DALY averted of the 4 preventive combination therapies would be as follows: 1) aspirin: $265 ($145 to $572) per DALY averted, with almost 1.4 million DALY averted from the baseline; 2) aspirin and beta-blockers: $1,740 ($977 to $4,280) per DALY averted, with more than 2 million additional DALY averted; 3) aspirin, beta-blockers, and ACEI: $2,770 ($1,380 to $10,200) per DALY averted, with almost 1.4 million additional DALY averted; and 4) aspirin, beta-blockers, ACEI, and statins, $6,450 ($3,420 to $18,900) per DALY averted, with approximately 1.8 million additional DALY averted. Provision of the polypill to 80% of CHD patients would avert approximately 7.3 million DALY in the Indian population (from the baseline), with a CER incremental to the baseline of $1,690 ($908 to $4,100) per DALY averted.

The polypill intervention strongly dominates the intervention of the combination of the 4 preventive drugs. (*Note*: Our data source on the efficacy of polypill differs

TABLE 2. CHD cohort model results

Variable	Prevalence (%)	Total
CHD 30–39	0.79 (0.50–1.11)	1,400,000 (814,000–2,130,000)
CHD 40–49	2.97 (1.85–4.44)	4,120,000 (2,420,000–6,250,000)
CHD 50–59	6.68 (3.92–9.69)	6,910,000 (4,280,000–10,300,000)
CHD 60–69	11.50 (6.96–16.86)	6,550,000 (3,820,000–9,550,000)
Total		19,000,0000 (13,400,000–27,500,000)

Results are based on a cohort model using CHD incidence rates and mortality. The 95% confidence intervals from sensitivity analysis are in parentheses.
CHD, coronary heart disease.

TABLE 3. Cost-effectiveness analysis results

Intervention	DALY Averted (From Baseline)	Cost-Effectiveness Ratio ($)	Sequentially Incremental (to Baseline) Cost-Effectiveness Ratio ($)	Cost-Effectiveness
AMI treatment				
Aspirin to baseline	297,000 (149,000–553,000)	98.6 (68.9–157.0)	0.49 (0.28–0.90)	Very cost-effective
Aspirin + injection streptokinase	335,000 (164,000–636,000)	127.0 (89.7–201.0)	615 (350–1,210)	Very cost-effective
AMI prevention				
Aspirin to baseline	1,380,000 (707,000–2,150,000)	1,010 (623–1,955)	265 (145–572)	Very cost-effective
Aspirin + beta-blockers	3,460,000 (1,770,000–5,610,000)	1,380 (844–2,960)	1,740 (976–4,280)	Very cost-effective
Aspirin + beta-blockers + ACEI	4,840,000 (2,167,909–7,986,906)	1,730 (1,060–3,760)	2,770 (1,380–10,200)	Cost-effective
Aspirin + beta-blockers + ACEI + statin	6,700,000 (3,040,000–10,900,000)	2,920 (1,850–6,090)	6,450 (3,420–18,900)	Dominated by polypill intervention
Polypill to baseline	7,320,000 (4,330,000–10,700,000)	1,760 (975–4,120)	1,690 (908–4,100)	Cost-effective

The 95% confidence intervals from sensitivity analysis are in parentheses. The thresholds of "cost-effective" and "very cost-effective" compare the CER with per capita GDP. A very cost-effective intervention is assumed to have a CER less than per capita GDP per DALY averted, and a cost-effective intervention has a CER of $<3\times$ per capita GDP per DALY averted.
CER, cost-effectiveness ratio; DALY, disability-adjusted life year; GDP, gross domestic product; other abbreviations as in Table 1.

from the data on combination therapy with all 4 drugs. However, even if their efficacy is equal, the polypill intervention still dominates because its cost is lower than that of the combination therapy.) Results from the Latin hypercube sampling sensitivity analysis provide a similar outcome, maintaining the same CER rank; in a few (parameter combination) scenarios, the DALY averted from the 4 combination-therapy interventions would be higher than for the polypill intervention, though the CER rank remains the same. If we increase coverage to 40% or 60% (instead of 80%) the number of DALY averted (in each intervention) decreases by roughly 28% and 56%, respectively. For example, intervention 1 averts almost 1 million DALY at 60% coverage and almost 600,000 DALY at 40%. The interventions would remain cost-effective with the lower increase in coverage, though at 40% coverage, intervention 1 is no longer very cost-effective.

DISCUSSION

We model policy interventions to alleviate the burden of heart disease in India. We find that expanding treatment for AMI and for secondary prevention for CHD patients would be cost-effective.

CHD prevalence

Our estimated disease prevalence using Framingham risk scores fits well with the values in Basu et al. [25] but is lower than those in the National Commission on Macroeconomics and Health background papers [21]. Increasing CHD prevalence in the model increases the DALY averted and the cost of intervention by the same factor. Therefore, the CER remain unchanged.

AMI treatment

Treatment in hospital with aspirin is already relatively high in India, and thrombolysis (injection streptokinase) is more common there than in other developing countries [26]. AMI management with thrombolysis is also higher in India than in developed countries, where there is a higher prevalence of primary angioplasty [12]. In India, the costs of angioplasty are extremely high for patients, who often (77.3% of the time) pay out of pocket [12]. Our analyses have shown that the AMI treatment interventions, expanding provision of both aspirin and streptokinase, would be highly cost-effective. The case remains so when conducting a sensitivity analysis on the parameters used in the model.

Secondary prevention

The variation in the use of AMI drugs across the globe is extremely high. CHD patients in South Asia use secondary prevention therapy, such as antiplatelet drugs (11.6%) and ACEI (6.4%), at a slightly lower rate than in China (15.5% and 7.8%, respectively) and Malaysia (14.9% and 12.8%, respectively). Beta-blockers and statins are used at a lower rate in China (6.8% and 2%, respectively) than in South Asia (11.9% and 4.8%, respectively) but at a higher rate in Malaysia (12.5% and 15.9%, respectively). Prescription use is much higher in North America and Europe (range: 45.4% to 56.7% for the 4 drugs), South America (19% to 40.2%), and the Middle East (26.2% to 52.7%) [8].

Much of the variation in drug use is explained by a strong correlation with countries' health expenditures per head and with GDP. The discrepancy is clearest in the case of statins, which are more expensive and are used relatively infrequently in South Asia and China but are the most-used

drug in high-income countries (70.9%) [8]. The culprit for the low rates in India may again be the high percentage of out-of-pocket expenditure in the healthcare system. However, even use of aspirin, an inexpensive drug, is low.

Preventive therapy interventions have a higher cost because of the need to target a far greater population than the population for AMI in the hospital. In India, where the onset of cardiovascular diseases is 5 to 10 years earlier in life than in Western populations [27], that population is especially large. However, for the same reasons, the number of DALY averted and burden alleviated by interventions with preventive strategies is very high. Interventions 1 (aspirin) and 2 (aspirin and beta-blockers), assuming 80% coverage in both, would be very cost-effective according to the GDP per capita threshold. If the prevalence of CHD is extremely high, intervention 2 would no longer be very cost-effective but would remain cost-effective. Intervention 3 (aspirin, beta-blockers, and ACEI), also at 80% coverage, would remain cost-effective and alleviate the burden further. Gaziano et al. [5–7] similarly find secondary prevention combination therapies to be cost-effective; their dollars-per-quality-adjusted life year ratios are slightly lower than our dollars-per-DALY averted, though they include the benefits from reductions of strokes. Additionally, WHO finds that use of aspirin for secondary prevention in India and comparable countries is cost-saving per life year gained [28].

A possible barrier to secondary prevention is adherence. The polypill has the advantage of being 1 pill instead of 4, which could contribute to more widespread use and greater adherence [9–11]—not taken into account in this analysis. Except for rare (parameter combination) cases, provision of the polypill to 80% of previous CHD event cases dominated intervention 4 (aspirin, beta-blockers, ACEI, and statins) and it remains cost-effective when CHD prevalence is extremely high. The lower cost of the polypill relative to the combination therapy drives the polypill's dominance in our model, and if we were to consider possible increased adherence, it would amplify the result. It should be noted that the only polypill trial carried out in India (TIPS [The Indian Polycap Study]) focused on middle-aged individuals without cardiovascular diseases; it was used as a primary prevention intervention [19].

Secondary prevention for CHD patients saves lives and increases the life expectancy of patients, and it could be cost-effective. However, the barriers to increased secondary prevention are not immediately clear. There is a paucity of national data in India. Most developed countries have established registries documenting AMI intervention. In the developing world, most of the data come from small studies. Nationally representative data are important for research, for formulating guidelines, and for devising strategies of adherence to those guidelines.

Medical expenditure in India is predominantly private and borne out of pocket and therefore may affect adherence rates. Increasing the availability of interventions through the public health system for free or at highly subsidized prices could increase compliance and avert a substantial amount of burden from the disease and related out-of-pocket medical expenditure. However, there are no reliable data to estimate the possible health systems costs (including infrastructure, human resources, administrative overhead) of a national policy of increasing secondary prevention. In particular, the marginal cost of increasing compliance may not be constant, because it will be susceptible to economies and diseconomies of scale at various levels of coverage. Therefore, only a rigorous costing exercise can help estimate the health systems' cost of the national policy, which is unfortunately beyond the scope of this paper.

The following limitations of the present study merit comment. First, as the number of AMI patients for India is not available, we used the number of CHD patients to estimate the number of AMI patients, which might be an overestimation. Second, our calculation did not take into account the travel cost and missed work cost; hence, cost is underestimated. Third, the unit cost data for laboratory tests were not available for India; hence, we used the cost data for Thailand (adjusted to Indian currencies). Finally, there are some risks involved for using AMI treatment and secondary prevention medications. In our cost-effectiveness analysis, we did not consider these risks.

CONCLUSIONS

Current prescription rates for secondary prevention drugs of patients with previous CHD events in India are very low. Given the favorable cost-effectiveness of their incremental use, policymakers should concentrate on increasing the availability of preventive drugs, their prescription, and patients' adherence to them. Increasing primary treatment can further alleviate the burden. Although there are some risks involved in using AMI treatment and secondary prevention medications that we did not consider, the benefits of these drugs far outweigh the risks.

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APPENDIX

NUMBER OF AMI CASES AND PREVALENCE OF CHD

The number of acute myocardial infarction (AMI) patients in India is currently not known. We estimate the risk of AMI from existing data in a 2-step process. First, we calculate the prevalence of coronary heart disease (CHD). Existing measures of CHD prevalence differ substantially. National Commission on Macroeconomics and Health (NCMH) background papers predict 42.5 million CHD patients ages 30 to 69 years [1]. Based on that, in a rough approximation of the death rate of CHD patients who die from their heart disease, the 2010 Global Burden of Disease Study predicts the percentage of deaths to be 1.4%

Quality of Health Economic Studies Instrument (American College of Cardiology/American Heart Association)

	Questions	Points	Yes	No
1.	Was the study objective presented in a clear, specific and measurable manner?	7	√	
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	√	
3.	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial — best, expert opinion — worst)?	8	√	
4.	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1	√	
5.	Was uncertainty handled by 1) statistical analysis to address random events, or 2) sensitivity analysis to cover a range of assumptions?	9	√	
6.	Was incremental analysis performed between alternatives for resources and costs?	6	√	
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	√	
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	√	
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	√	
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term, and negative outcomes included?	6	√	
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	√	
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	√	
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	√	
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	√	
15.	Were the conclusions/recommendations of the study justified and based on study results?	8	√	
16.	Was there a statement disclosing the source of funding for the study?	3	√	

[2]. (The approximation is a simple division of deaths by prevalence. Because the death rate affects prevalence, the result is a slight underestimation.) Based on a meta-analysis of Indian district surveys updated to 2013, Basu et al. 2013 [3] assume that approximately 21.9 million Indians ages 30 to 69 years have CHD. Given the number of deaths they predict, the approximate death rate is 3.3%.

We calculate the prevalence of CHD using 10-year Framingham risk scores of CHD event incidence based on data from Jeemon et al. [4]. We then estimate the prevalence for 4 age groups between 30 and 69 years using a cohort ordinary differential equation model. Because of the large variance in prevalence estimates across studies and because Framingham risk scores may underestimate CHD in this age group in particular (CHD events occur earlier in life in India), we use a wide range for CHD incidence in our sensitivity analysis.

At the second step, the risk of AMI [5] is back-calculated to incorporate current secondary prevention prescriptions in India [6].

Coverage of drugs

The drug coverage data for AMI treatment are from the results of the CREATE (Treatment and Outcomes of Acute Coronary Syndromes in India) study [7] and for the secondary prevention these are equivalent to the South Asian PURE (Prospective Urban Rural Epidemiology) study estimates [6]. We also assume that the drugs are prescribed in combination therapies as follows: because statins have the lowest prevalence, the 4.8% of patients who take them also take all other drugs; next come angiotensin-converting enzyme inhibitors, with a prevalence of 6.4%, and therefore, 1.6% take all drugs but statins; and similarly with aspirin and beta-blockers. Compared with the above-mentioned baseline rates, we analyze new health policy scenarios that would lead to a 95% coverage for AMI treatment with aspirin, and 80% intervention coverage for all other scenarios.

Cost components

Our analysis comprises the summed costs of the interventions for both the health sector and the patients' expenses in that sector. Primary AMI treatment intervention costs include the cost of drugs, laboratory tests, and inpatient stay at a secondary hospital. Drug costs are from the Current Index of Medical Specialties India website [8]. The laboratory tests required to diagnose and treat AMI patients were identified in the NCMH background papers [1]. Laboratory tests needed during a hospital stay include 1 lipid profile, 1 chest x-ray, 5 electrocardiographies, 2 echocardiographies, a liver function test, a renal function test, a hemogram, 3 tests for cardiac enzymes, and 1 test for blood glucose. Unit cost data for these tests are not available for India; we therefore use the "standard unit cost" (at 2009 Thai baht) calculated by Riewpaiboon [9] for Thailand's Health Intervention and Technology Assessment Program. The unit cost of inpatient stay is from World Health Organization (WHO) estimates for district hospitals in India (at 2005 prices) [10]. This cost, specific to public district hospitals with an occupancy rate of 80%, includes personnel, capital, and food costs but excludes the costs of drugs and diagnostic tests. All costs are adjusted using the consumer price index, and the final estimate is presented in 2010 U.S. dollars.

Secondary prevention costs include outpatient visits, drugs, and the aforementioned costs of AMI. WHO's estimate is used for the unit cost per outpatient visit [10]. The number of times that patients need to visit the hospital per year and the number of laboratory tests they receive per year are taken from the NCMH background papers [1]. The costs of both treatment and secondary prevention interventions exclude travel and missed days of work to obtain treatment.

Disability-adjusted life years calculation

The disease burden in the baseline scenario is calculated by accounting for the effectiveness of the current treatment and prevention therapy prescription regimens [11]. We incorporate morbidity reductions (years of life lost to disability, or YLD) and mortality reductions (years of life lost, or YLL) from the intervention drugs relative to the baseline. The cost-effectiveness ratio is the ratio of the total cost of the intervention, both to the health sector and to the patient, and the sum of YLL and YLD averted by the intervention.

YLL is calculated based on the age at death, remaining life expectancy, and a 3% discount rate. Life expectancy for CHD patients is estimated based on WHO life tables, the mortality rate from the disease, and the secondary prevention regimen offered. Higher levels of preventive therapy prescription increase the life expectancy of the patients. Averted YLL are based on the deaths that would occur in the baseline scenario, the level of intervention coverage, and the effectiveness of the treatment. Averted YLD are the product of the disease duration, disability weight, incidence of the condition, and coverage and effectiveness of the intervention. For secondary prevention, we assume that patients are on the treatment regimen for the rest of their lives (remaining life expectancy). The disability weight for AMI is 0.437 (range 0.405 to 0.477) based on risk factors and the global burden of disease [12].

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