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Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis

Thomas A Gaziano, Lionel H Opie, and Milton C Weinstein

Division of Cardiovascular Medicine and Division of Social Medicine and Health Inequalities, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02120, USA (T A Gaziano MD); Hatter Institute for Heart Research, Department of Medicine and Hatter Institute, Faculty of Health Sciences, University of Cape Town Observatory, Cape Town, South Africa (Prof L H Opie DPhil); and Department of Health Policy and Management, Harvard School of Public Health, Boston, MA, USA (Prof M C Weinstein PhD)

Summary

Background—Cardiovascular disease is the leading cause of death, with 80% of cases occurring in developing countries. We therefore aimed to establish whether use of evidence-based multidrug regimens for patients at high risk for cardiovascular disease would be cost-effective in low-income and middle-income countries.

Methods—We used a Markov model to do a cost-effectiveness analysis with two combination regimens. For primary prevention, we used aspirin, a calcium-channel blocker, an angiotensin-converting-enzyme inhibitor, and a statin, and assessed them in four groups with different thresholds of absolute risks for cardiovascular disease. For secondary prevention, we assessed the same combination of drugs in one group, but substituted a β blocker for the calcium-channel blocker. To compare strategies, we report incremental cost-effectiveness ratios (ICER), in US\$ per quality-adjusted life-year (QALY).

Findings—We recorded that preventive strategies could result in a 2-year gain in life expectancy. Across six developing World Bank regions, primary prevention yielded ICERs of US\$746–890/QALY gained for patients with a 10-year absolute risk of cardiovascular disease greater than 25%, and \$1039–1221/QALY gained for those with an absolute risk greater than 5%. ICERs for secondary prevention ranged from \$306/QALY to \$388/QALY gained.

Interpretation—Regimens of aspirin, two blood-pressure drugs, and a statin could halve the risk of death from cardiovascular disease in high-risk patients. This approach is cost-effective according to WHO recommendations, and is robust across several estimates of drug efficacy and of treatment cost. Developing countries should encourage the use of these inexpensive drugs that are currently available for both primary and secondary prevention.

Introduction

Cardiovascular disease is responsible for about 30% of all deaths worldwide, with about 80% of total deaths occurring in developing countries.¹ Yet little global attention has been focused

Correspondence to: Dr Thomas A Gaziano, tgaziano@partners.org.

Conflict of interest statement

We declare that we have no conflict of interest.

Contributors

T A Gaziano conceived the idea and design for the study, and drafted the paper. L H Opie helped to assess the primary and secondary regimens and revise the manuscript. T A Gaziano and M C Weinstein analysed and interpreted the cost-effectiveness data and participated in revisions of the paper. T A Gaziano is guarantor of the paper. All three authors give final approval to the manuscript.

on the challenge of reducing this burden in developing countries.^{2,3} This deficit is compounded by the fact that the resources to combat cardiovascular disease in these same countries are typically very scarce. Health-care expenditure per head in developing countries is about 2–3% of the amount spent on health care in developed countries.⁴ Thus, recommendations regarding the prevention of cardiovascular disease should account for the costs of such interventions as well as the best available evidence of efficacy.

Publications^{5–7} have suggested that the combination of several preventive treatments could cut more than half the occurrence of cardiovascular disease. Wald and Law⁵ specifically proposed a polypill, consisting of a statin, aspirin, a β blocker, an angiotensin-converting-enzyme inhibitor (ACEI), a thiazide, and folic acid. Although the notion of one formulation could ultimately prove beneficial, there are several reasons why the polypill as originally proposed would not work nowadays and why we should not delay in recommending a multidrug regimen that is currently known to work. First, trial results with clinical endpoints for the polypill do not yet exist, and could be several years away from validation. Second, randomised trial evidence on folate^{8–11} shows no benefit for cardiovascular disease so far. Third, no data indicate the efficacy of any three added blood-pressure drugs given together. Finally, combination treatment does not require that the different drugs be combined in one pill. Although adherence could be improved if a polypill was used compared with drugs taken separately, this effect has not been proven. While these trials are in progress, individual components of potential multidrug prevention regimens are already available but underused in developing countries, resulting in millions of potential deaths that could be averted. For example, ACEIs and statins are used for secondary prevention by fewer than 20% and 10% of the eligible population, respectively,¹² and even less so for primary prevention. Thus current recommendations, especially for developing countries, should focus on drugs that are proven effective and are also cheap and available.

The best drugs for secondary prevention in patients with clinical ischaemic heart disease are aspirin, β blockers, ACEIs, and statins. Optimum treatment for primary prevention has had greater debate, especially with respect to antihypertensive drugs. Although the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)¹³ showed that thiazides were as effective as a calcium-channel blocker or ACEI, more than one drug was clearly needed to control blood pressure and the study was not designed to assess which combination was preferable. However, the results of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)¹⁴ showed that a calcium-channel blocker and an ACEI were more effective than the traditionally proposed first-line drugs of thiazide and β blocker. Further, the addition of a statin in the lipid-lowering group of the same trial showed added benefit.¹⁵ The association of β blockers and diuretics with the development of diabetes in hypertension trials^{14,16–18} makes this combination a less attractive choice for primary prevention.

The results of ACEI, CCB, or ACEI over β blockers for primary prevention^{19,20} was assessed by the National Collaborating Centre for Chronic Conditions,²¹ leading to the British Hypertension Society²² to remove β blockers from the first three choices for hypertension. Thus, aspirin, CCB, an ACEI, and a statin should be recommended for primary prevention, which means that two different drug combinations might be needed for primary and secondary prevention. We note that all suitable protective components are now not patented in developing countries and are inexpensive.

Although treatment benefits could be widely applicable, costs and the ability to pay can vary greatly among developing countries. Hence, health-care decisions should be guided by local cost-effectiveness. Therefore, we investigated whether four generic drugs (aspirin, two antihypertensive drugs, and a statin) would be cost-effective in resource-poor settings for three

groups: patients with cardiovascular disease, those without previous disease but with varying 10-year absolute risks of the disease, and those older than 55 years who would not need any additional risk factor assessment.

Methods

Combination regimens and prevention strategies

We developed a Markov model with age-varying probabilities of disease events and mortality to assess the benefits, risks, and costs of two combination regimens of generic drugs on the WHO list of essential drugs to treat and prevent cardiovascular disease. Every regimen assessed in the study included: aspirin, two blood-pressure drugs, and a statin. The Markov model is described in detail elsewhere (webappendix).²³ Cardiovascular disease was defined as myocardial infarction, angina, or ischaemic stroke. The first regimen consisted of 81 mg aspirin, 40 mg lovastatin, 10 mg lisinopril, and 5 mg amlodipine, which used to treat patients without a history of cardiovascular disease (primary prevention). The lower doses of the antihypertensive drugs indicates that the benefits of any individual medication diminishes with increasing dose while the side-effects increase.²⁴ The second combination regimen was modelled for use in patients with a history of cardiovascular disease (secondary prevention). This regimen was the same combination as that used for primary prevention, except that metoprolol was substituted for amlodipine, since data⁶ indicating the benefits of β blockers specifically for patients with postmyocardial infarction warrant their use in that setting. We compared the use of these regimens in one strategy for secondary prevention, five strategies for primary prevention that differed in terms of risk of cardiovascular disease and age, and a comparison strategy of no treatment, for adults aged 35–74 years. No ethics approval was required, because no patients were used for data collection.

For the secondary prevention strategy, patients with cardiovascular were treated with the secondary regimen only and required no additional screening costs. The first primary strategy, treating patients older than 55 years, required the added cost of an outpatient visit. The four remaining strategies for primary prevention included treatment of patients with an absolute risk of a cardiovascular-disease event of 35%, 25%, 15%, and 5% (ie, $AR > 35$, $AR > 25$, $AR > 15$, and $AR > 5$, respectively) over 10 years. These primary prevention strategies had the additional cost of measuring blood pressure and cholesterol concentrations, and checking diabetes status to calculate the 10-year risk. All five primary strategies also included treatment of patients with pre-existing cardiovascular disease undergoing the secondary drug regimen. Further, if an individual had myocardial infarction, unstable angina, or ischaemic stroke, they were switched from the primary regimen to the secondary regimen. We compared the strategies in the six low-income and middle-income regions defined by the World Bank. We assumed a societal perspective for the baseline analysis and adhered to recommendations of the US Panel on Cost-Effectiveness in Health and Medicine.²⁵ The cohort was modelled until death, either from cardiovascular disease or from other causes.

Effectiveness data

For patients taking the multidrug regimen for primary prevention, we derived our estimates for relative risk reduction from blood-pressure reduction, aspirin, and a statin from meta-analyses (table 1, webappendix).^{5,24,26–28} For secondary prevention, some of the benefits from atenolol, enalapril, and statins might not be due to their effects on blood pressure and cholesterol. Therefore, we modelled the risk reductions directly from the secondary prevention trials using these drugs and aspirin (webappendix), which also had the advantage of incorporating separate effects on fatal and non-fatal events of ischaemic heart disease. In both regimens, the intervention effects for the drugs were assumed to be independent and therefore we calculated the overall effect by multiplying the individual relative risks associated with

every drug. We did not include any additional benefit that might have been derived from improved compliance with any one pill form over the individual drugs, for either primary or secondary prevention.²⁹

Outcome measures and costs

Outcomes in the analyses were measured in quality-adjusted life years (QALYs) gained and net health-care costs. Total life years and QALYs were accumulated for the cohort for each guideline. QALYs were obtained by use of the weighted disease-state values from the Disability Weights of the WHO Global Burden of Disease project,³⁰ as used in the 2nd edition of the Disease Control Priorities Project (DCPP; webappendix),³¹ DCPP was a combined effort of more than 350 scientists worldwide to investigate various interventions to reduce the burden of disease in developing countries. The project involved collaboration from the World Bank, WHO, and the US National Institutes of Health, with support from the Gates Foundation. Table 2 shows costs related to the intervention itself, cardiovascular disease events, and their sequelae included in the model. Health-care delivery costs included personnel salaries, health-care visits, diagnostic tests, and hospital stays, and are recorded according to DCPP Working Paper number 9³² that provides cost estimates (US\$) for the six World Bank regions (table 2)^{32,33} in 2001, which we maintained for consistency with other analyses in the DCPP. For the base analysis, we excluded costs of hospital care for acute events cardiovascular disease based on the assumption of limited availability for admission in most of the developing world; we then tested this assumption in a secondary analysis that assumed access to hospitals in the few middle-income countries where these facilities are more widely available.

We obtained combination drug costs from the International Drug Price Indicator Guide.³³ Non-health-care costs, such as work loss or family assistance, were not included in the analysis. Both future costs and health outcomes were discounted at 3% per year, which was consistent with other guidelines.^{25,34} Incremental cost-effectiveness ratios were calculated as the difference in costs between competing strategies divided by the increase in QALYs. To compare one strategy with the next more expensive alternative, we used incremental cost-effectiveness ratio (ICER), which is the difference in costs divided by the difference in QALYs. We eliminated strategies that had higher costs and were less effective (ie, with fewer QALYs) than at least one other strategy (ie, that were strongly dominated), or those that had higher ICERs than a more costly strategy (ie, that were weakly dominated).

Statistical analysis

Sensitivity analyses on the effectiveness of the various interventions relied on the upper and lower limits reported previously in published work. Analyses of health-care delivery costs used the range reported in the DCPP working paper (table 2).^{32,33} We assessed analyses of medication costs over a range of half to double the reported costs in table 2. Because of the concerns of bleeding and the results of the Women's Health Study,³⁵ which showed no benefit of the 100 mg dose of aspirin taken every other day by very low-risk women, we did one analysis with no aspirin in the primary prevention strategy. For statin use in primary prevention, we used CIs listed in table 1. In years 6 and beyond, we therefore used 0.55 and 0.74 as the range tested for the relative risk. To achieve the same efficacy in developing countries in practice as that in trial conditions in developed country trials, we also assessed a reduction in drugs efficacy of the regimens of up to 50%. Finally, we examined different assumptions for the possible overestimation of up to 20% of the Framingham risk function. We also did a probabilistic, multivariate sensitivity analysis with the Monte Carlo simulation³⁶ of 1000 randomly selected sets of variables, in which we simultaneously sampled values from the logistic-normal distributions with corresponding logit-means and logit-SDs of the relative risks of drug efficacies (table 1).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Lifetime risk of death from cardiovascular disease at baseline in patients aged 35–74 years was 22–40% across the regions (table 3) without treatment of either regimen. Use of the secondary prevention regimen reduced the lifetime risk of death from cardiovascular disease by 10–15%. The primary prevention strategy of also treating patients with a 10-year absolute risk of cardiovascular disease of more than 5% resulted in the greatest reductions of 42–57% in lifetime risk of death from cardiovascular disease compared with baseline (table 3). The figure shows the lifetime costs and QALYs of every strategy in the six World Bank regions. The efficiency frontier or curve in every panel of the figure represents the strategies that dominate those strategies to the left of it.

The ICER for the secondary regimen was \$306–388/QALY gained across the regions, compared with no treatment (table 4). The incremental cost per QALY gained increased for patients with absolute disease risks greater than 25%, 15%, and 5%, respectively (table 4). In areas with access to hospitals, ICERs for all strategies were about 20% less than areas without access, and hence savings could be made by reduced admissions from events prevented. Compared with the secondary strategy, the ICER for the primary strategy treating patients with a 10-year absolute risk of cardiovascular disease greater than 35% was greater than the ICER of the next more costly strategy for patients with an absolute risk of 25% or more (ie, weakly dominated), and thus was eliminated in all regions. The strategy for patients older than 55 years also had a higher ICER than the next more expensive strategy, and was eliminated by weak dominance in all the regions.

The sensitivity analysis on statin use over the full range of relative risk reductions made no difference on the ranking of the strategies. Furthermore, ICERs for the primary regimens did not change by more than \$40/QALY, and results did not differ between regions. However, the strategies were more sensitive to changes in the efficacy assumptions. A reduction in efficacy by 20% led to an increase of about \$100/QALY gained for the secondary strategies across the regions and about \$200/QALY in the primary strategies for absolute risk greater than 5%. With a 50% reduction in treatment efficacy, the secondary strategy nearly quadrupled to about \$1300/QALY across regions. The effect on the other strategies was less pronounced, and the ICERs rose to about \$1500/QALY, \$1600/QALY, and \$2000/QALY gained for the primary strategies for absolute risk greater than 25%, 15%, and 5%, respectively.

We also examined the effect of a change in the cost of multidrug regimens from a half to two times our base analysis estimate. The rankings of the strategies remained the same, as did the elimination of the strategies for age greater than 55 years and absolute risk greater than 35%. However, the ICERs nearly doubled at the higher estimate of costs with little change at the lower estimate. For example, in the east Asia and Pacific region, the ICERs for secondary prevention, and primary prevention for absolute risk greater than 25%, 15%, and 5% were \$390, \$1700, \$1950, and \$2350, respectively. These ratios were similar in the other regions. When we doubled or halved the cost to screen for cholesterol and diabetes, we recorded no significant change from the original analysis. In a further analysis, we set the screening cost as high as \$1000 and the strategy for age over 55 years would still be eliminated. When we removed aspirin costs and effects in a three-drug regimen of ACEI, calcium-channel blockers, and statin, the ICERs for the primary strategies at every risk threshold increased by about \$200/QALY gained or by 20% in all regions. We did a probabilistic sensitivity analysis in the east

Asia and Pacific region using distributions from all the relative risk distributions. As in the base analysis, the strategies for age greater than 55 years and absolute risk greater than 35% were eliminated by extended dominance in all 1000 replicates. The mean ICER for the secondary strategy was \$265/QALY (mean incremental cost divided by mean incremental QALY gain), with minimum and maximum values of \$225/QALY and \$330/QALY, and with 95% of the values falling between \$235/QALY and \$300/QALY. The ICERs of the primary strategies for absolute risk greater than 25%, 15%, and 5% were \$630 (95% CI 580–690), \$750 (695–815), and \$1110 (1030–1200), respectively. These results were similar for the other regions.

Discussion

Our analyses have shown that two multidrug regimens of four highly effective drugs could lead to cost-effective prevention and treatment for patients with cardiovascular disease in all developing regions. Even with our conservative estimate and without aspirin in primary prevention, the ICERs remain at \$300–\$1300/QALY gained in all the regions. The lower the risk of the population targeted, the higher the ICER recorded, because more individuals need to be treated to prevent an event. We estimate that a 50–60% reduction in cardiovascular disease would occur if all patients with a 10-year risk greater than 5% were treated with the regimens of four drugs, which are currently available and widely assessed in clinical trials with event reductions.

WHO considers interventions to be cost-effective if they have ICERs that are less than three times the gross national income (GNI) per head.³⁷ The ICERs in this study are below this threshold in all the regions (table 4). The ICERs for all the primary prevention strategies were under \$1300/QALY gained. These values make these strategies acceptable in all the developing regions of the world under this criterion.

An alternative perspective is to assess what the effect these strategies would have on the health-care budgets of developing countries. The regimens could be implemented for less than \$32 per year, and potentially less so in India, where generic drugs are being produced at very low costs. This price is quite reasonable compared with the yearly cost of a triple course of antiretroviral drugs (\$180–380)³³ approved for treatment in many developing countries.

In the south Asia region, less than 2% of the population would be eligible for the secondary regimen. About 6% of the population would be eligible to be given the primary regimen for patients with a 10-year risk of cardiovascular disease greater than 25%, along with secondary prevention. In India, which represents 70% of this region, these two strategies would increase yearly health-care expenditure per head by 1.8% (\$0.47) or 5.4% (\$1.41), respectively. However, for that expenditure, corresponding cardiovascular death rates would be reduced by 13% or 26%. By comparison, a middle-income country such as South Africa has less than 1% of the population eligible for the secondary strategy and 3.6% eligible for the primary strategy for risk greater than 25%. Thus, yearly health-care expenditure per head would increase by less than \$0.10 and \$1, respectively, to implement. But since health expenditures in South Africa are ten times that in India, the percentage increase in expenditure per head would be much less than 1% in both strategies, yet would yield reductions in lifetime risk of cardiovascular death by 10% and 30%, respectively.

Because the health-care workforce is severely depleted in many parts of the developing world,³⁸ the aggressive strategies might not be feasible enough to adopt in the near future. For example, 20–30% of the population in the various regions would be eligible for treatment at the 10-year risk threshold of greater than 5%, which could be difficult to implement in some countries because of few health personnel or facilities. However, where resources do exist, this

strategy would result in an increase in life expectancy of at least 2 years for patients older than 35 years, in all regions if all other causes of death remained constant.

Proponents of multidrug regimens recommend its wide use to reduce the burden of disease. However, the primary strategy of treating all patients older than 55 years was not an efficient strategy. Instead, our findings suggest that the improved risk estimate achieved by measuring cholesterol concentrations and blood pressure, and assessing smoking and diabetes status is worth the additional costs. As long as the screening costs remain below \$1000, the additional risk factor information beyond age is worth obtaining.

We should now focus on increasing the proportion of eligible patients who benefit from the multidrug regimens. Improvements in the scarce human resources³⁸ available in developing countries will be needed to increase the probability of appropriate medication use. Advances in simplified medication regimens, such as fixed-dose combinations or unit-of-use packaging, will probably improve adherence for both communicable and non-communicable diseases.²⁹ However, recommendations for appropriate medication use also should be supported by clinical trial data, if a large portion of the cardiovascular disease burden is to be averted and substantially constrained resources is to be used cost-effectively. For these reasons, the notion of an evidence-based polypill remains a possibility, but the individual constituents of such a pill should be more thoroughly assessed than originally proposed, in view of the little evidence of benefit from folate or three antihypertensive drugs given at the same time. The choice of aspirin, ACEI, calcium-channel blocker, and statin in primary prevention and the substitution of a β blocker for the calcium-channel blocker in secondary prevention accords with the best trial data for reductions in events so far;^{6,8–11,13–15} although other blood-pressure combinations could be as efficacious in primary prevention. If two polypills, consisting of the same drug combinations as the primary and secondary prevention strategies, would also improve adherence, the results would be even more favourable.

A reservation of our results is that our model uses the Framingham risk function. The Framingham risk function has overestimated risk by as much as 7% in Europe and 17% in China. We therefore did a sensitivity analysis in which we assumed that the risk function overestimated risk by as much as 20%. These analyses were done only in the primary strategies with absolute risk thresholds, because they relied on the risk score. In the east Asia and Pacific region, which includes China, an overestimation of risk of 20% resulted in an increase of almost 20% in the ICER for every strategy. At the highest extreme, the strategy for absolute risk greater than 5% in this region rose to \$1400/QALY gained, which is still much lower than three times the GNI per head. As a further check, we also ran the model in every region to check its ability to predict yearly mortality rates, and compared them with the actual yearly rates for 2001. We could not measure the actual level of primary and secondary treatment given in every region, but in five of the six regions, the actual death rate is between those predicted by the no treatment strategy, and those predicted by secondary prevention. Thus our estimates are consistent with the actual death rates because of the incomplete secondary prevention and low levels of primary prevention in many regions.¹²

Moreover, does the combination of drugs used in developed countries have the same efficacy if used in developing countries? The INTERHEART³⁹ study confirmed that the same risk factors are applicable in developing countries as they are in developed countries. Because the risk factors are the same, we can assume the same reductions in relative risk in developing countries. The proportion of people receiving treatment for hypertension that target blood-pressure goals in South Africa⁴⁰ is similar to that of developed countries, suggesting that equivalent efficacy can be achieved. Further, a 20% reduction in efficacy would not bring any of the strategies to more than the WHO threshold of three times GNI per head. At a 50% reduction in efficacy, all the strategies fall under the threshold apart from those implemented

in the regions of south Asia and the sub-Saharan Africa. In these two regions, the secondary prevention and the strategy for absolute risk of greater than 25% still remain acceptable under this criterion.

Finally, some reservations have been made regarding the use of generic preparations versus patented drugs. However, use of generic drugs has been shown to be as efficacious as the patented formulations across many cardiovascular drug classes.^{41,42} Industry standards in developing countries that produce these low-cost drugs must ensure that good-quality generic treatments are produced.

Cardiovascular disease remains the most common cause of death in all developing countries (excluding sub-Saharan Africa, where it is the second).¹ Effective and inexpensive treatments are underused¹² in developing countries, even in secondary prevention, despite the proven benefits. This problem is partly due to a belief that the treatments are too expensive. Yet we have shown that both the primary and secondary prevention regimens are cost-effective in developed countries. Until data for a multidrug regimen in a single formulation becomes available, we recommend that these combinations of effective drugs should be used widely in developing countries. This treatment could have the profound effect of halving the risk of death from cardiovascular disease and increasing life expectancy by up to 2 years.

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References

1. Mathers, CD.; Lopez, A.; Stein, C., et al. Working paper 18. Bethesda, MD: Disease Control Priorities Project; 2005. Deaths and disease burden by cause: global burden of disease estimates for 2001 by World Bank Country Groups.
2. Fuster V, Voûte J. MDGs: chronic diseases are not on the agenda. *Lancet* 2005;366:1512–14. [PubMed: 16257330]
3. Horton R. The neglected epidemic of chronic disease. *Lancet* 2005;366:1514. [PubMed: 16257331]
4. World Bank. World development indicators. Washington, DC: World Bank; 2002.
5. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419. [PubMed: 12829553]
6. Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 2002;360:2–3. [PubMed: 12114031]
7. Murray CJL, Lauer JA, Hutubessy RC, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;361:717–25. [PubMed: 12620735]
8. Davey Smith G, Ebrahim S. Folate supplementation and cardiovascular disease. *Lancet* 2005;366:1679–81. [PubMed: 16291049]
9. Loscalzo J. Homocysteine trials—clear outcomes for complex reasons. *N Engl J Med* 2006;354:1629–32. [PubMed: 16531615]
10. Lonn E, Yusuf S, Arnold MJ, et al. 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. [PubMed: 16531613]
11. Bona KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578–88. [PubMed: 16531614]
12. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention and REcurrences of Myocardial Infarction and Stroke (WHO-PREMISE). *Bull World Health Organ* 2005;83:820–28. [PubMed: 16302038]

13. the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA* 2002;288:2981–97. [PubMed: 12479763]
14. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895–906. [PubMed: 16154016]
15. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–58. [PubMed: 12686036]
16. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. the Atherosclerosis Risk in Communities Study. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000;342:905–12. [PubMed: 10738048]
17. Jandeleit-Dahm KA, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J Hypertension* 2005;23:463–73.
18. Opie LH, Schall R. Old antihypertensives and new diabetes. *J Hypertension* 2004;22:1453–58.
19. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004;364:1684–89. [PubMed: 15530629]
20. Lindholm LH, Carlberg B, Samuelsson O. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005;366:1545–53. [PubMed: 16257341]
21. National Institute for Health and Clinical Excellence/British Hypertension Society. Clinical guideline 34. Hypertension: management of hypertension in adults in primary care: partial update. [accessed July 8, 2006]. <http://www.nice.org.uk/CG034guidance>
22. Williams B. Evolution of hypertensive disease: a revolution in guidelines. *Lancet* 2006;368:6–8. [PubMed: 16815359]
23. Gaziano TA, Steyn K, Cohen DJ, Weinstein MC, Opie LH. Cost-effectiveness analysis of hypertension guidelines in South Africa: absolute risk versus blood pressure level. *Circulation* 2005;112:3569–76. [PubMed: 16330698]
24. 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. [PubMed: 12829555]
25. Gold, M.; Siegel, J.; Russell, L.; Weinstein, M., editors. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
26. 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. [PubMed: 12829554]
27. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827–38. [PubMed: 1969567]
28. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765–74. [PubMed: 1969518]
29. Connor J, Rafter N, Rodgers A. Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review. *Bull World Health Organ* 2004;82:935–39. [PubMed: 15654408]
30. Murray, CJ.; Lopez, AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge: Harvard University; 1996.
31. Jamison, D.; Breman, J.; Measham, A., et al. Disease control priorities in developing Countries. 2. New York: Oxford University Press and the World Bank; 2006.
32. Mulligan, J.; Fox-Rushby, J.; Taghreed, A. Unit costs of health care inputs in low and middle income regions. Bethesda, MD: Disease Control Priorities Project Working Paper 9; 2004.

33. McFayden, JE., editor. International drug price indicator guide. Boston: Management Sciences for Health; 2005.
34. DCCP Secretariat. Disease Control Priorities Project: guidelines for authors. Bethesda, MD: National Institutes of Health; 2004.
35. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293–304. [PubMed: 15753114]
36. Doubilet P, McNeil BJ, Weinstein MC. The decision concerning coronary angiography in patients with chest pain. A cost-effectiveness analysis. *Med Decis Making* 1985;5:293–309. [PubMed: 3939247]
37. Batussen, RM.; Adam, T.; Tan Torres, T., et al. Generalized cost-effectiveness analysis: a guide. Global Programme on Evidence for Health Policy. Geneva: WHO; 2002.
38. World Health Organization. World Health Report 2006: working together for health. Geneva: WHO; 2006.
39. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52. [PubMed: 15364185]
40. Steyn K, Levitt NS, Hoffman M, et al. The global cardiovascular diseases risk pattern in a peri-urban working-class community in South Africa. The Mamre study. *Ethn Dis* 2004;14:233–42. [PubMed: 15132209]
41. Amit G, Rosen A, Wagshal AB, et al. Efficacy of substituting innovator propafenone for its generic formulation in patients with atrial fibrillation. *Am J Cardiol* 2004;93:1558–60. [PubMed: 15194037]
42. Pereira JA, Holbrook AM, Dolovich L, et al. Are brand-name and generic warfarin interchangeable? Multiple n-of-1 randomized, crossover trials. *Ann Pharmacother* 2005;39:1188–93. [PubMed: 15914517]

Figure.
Lifetime costs and QALYs of strategies assessed in six World Bank regions

Table 1

Relative risks of clinical events for primary and secondary prevention with selected drugs

	Death	Ischaemic heart disease (95% CI)	Stroke
Primary prevention			
Aspirin	..	0.68 (0.60–0.77)	0.84 (0.75–0.93)
ACEI and calcium-channel blocker	..	0.66 (0.60–0.71)	0.51 (0.45–0.58)
Statin	..	0.64 (0.55–0.74) [†]	0.94 (0.78–1.14)
Secondary prevention			
Aspirin	0.85 (0.81–0.89)	0.66 (0.6–0.72)	0.78 (0.72–0.84)
β blocker	0.77 [‡] (0.69–0.85)	0.73 (0.75–0.87) [‡]	0.71 (0.68–0.74)
ACEI	0.84 (0.75–0.95)	0.80 (0.70–0.90)	0.68 (0.56–0.84)
Statin	0.78 (0.69–0.87)	0.71 (0.62–0.82)	0.81 (0.66–1.00)

Relative risk reduction in deaths for primary prevention was modelled with ischaemic heart disease and stroke, of which a proportion is fatal.

[†] Risk is graduated by 0.89 at 1 year, 0.76 at 2 years, 0.67 at 3–5 years, and 0.64 in subsequent years.

[‡] β blockers modelled with decreasing benefit over time: relative risk in first 3 years is 0.77 for death and 0.73 for ischaemic heart disease, and 0.93 at 4–6 years for each disease, and 0.99 in subsequent years for each disease.

Table 2**Region-based costs of cardiovascular disease interventions**

Event or yearly care *	Cost (US\$ in 2001)
Myocardial infarction	\$270–690
Stroke	\$404–910
Re-infarction [†]	\$32–125
Yearly care after myocardial infarction	\$54–64
Yearly care after stroke	\$408–775
Yearly drug costs [‡]	
Aspirin	\$2
Metoprolol	\$43
Amlodipine	\$9
Enalapril	\$7
Lovastatin	\$14
Screening	\$6–12
Monitoring	\$6–12

* Unit costs consisting of different costs for events or yearly care (low and high estimates in parentheses):³² hospital bed day, \$16.15 (8.07–49.88); health-centre visit, \$2.36 (1.61–4.81); laboratory cost, \$6.22 (no range provided); outpatient visit (hospital), \$2.97 (1.35–4.96); operation room (per min), \$3.12 (no range provided); specialist daily salary, \$41.64 (29.36–105.3); family practitioner daily salary, \$26.37 (19.73–63.60); nurse daily salary, \$15.66 (11.84–38.27); health worker daily salary, \$10.86 (8.12–26.14).

[†] Event took place during first admission.

[‡] Range for sensitivity analysis was a half to two times more than stated value.

Table 3
Lifetime risk of death from cardiovascular disease according to regimen strategies* for World Bank regions

	No treatment	Secondary regimen	Primary regimen	AR>25	AR>15	AR>5
East Asia and Pacific	28%	26%		20%	16%	13%
Eastern Europe and central Asia	40%	34%		28%	25%	23%
Latin America and Caribbean	34%	30%		23%	19%	16%
Middle East and north Africa	34%	29%		24%	20%	17%
South Asia	30%	26%		22%	18%	15%
Sub-Saharan Africa	22%	20%		15%	12%	9%

* AR>35% and age>55 years not shown, because they were eliminated by extended dominance.

Table 4
Incremental cost-effectiveness ratios (\$/QALY) for treatment regimens compared with no treatment

	Secondary regimen		Primary regimen		GNI ×3 [*]
			AR>25	AR>15	
East Asia and Pacific		\$336	\$890	\$923	\$3180
East Europe and central Asia		\$362	\$858	\$905	\$6030
Latin America and Caribbean		\$388	\$881	\$930	\$11010
Middle East and north Africa		\$341	\$872	\$930	\$6270
South Asia		\$306	\$746	\$790	\$1320
Sub-Saharan Africa		\$312	\$771	\$846	\$1410

* GNI=gross national income per head by region. WHO recommends that interventions less than three times the GNI per head is cost-effective for that country.