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Reducing The Growing Burden Of Cardiovascular Disease In The Developing World:

Disease burden can be lowered with cost-effective interventions, especially by reducing the use of tobacco around the world.

Thomas A. Gaziano
Thomas Gaziano (tgaziano@partners.org) is an associate physician in the Divisions of Cardiology and Social Medicine, Brigham and Women's Hospital and Harvard Medical School, in Boston, Massachusetts

Abstract

Cardiovascular disease (CVD) has become the number-one cause of death in the developing world. This epidemic has the potential to place a large social and economic burden on developing countries, where CVD tends to strike those in their prime working years. Since resources for managing CVD are limited, it is important that interventions be guided by cost-effectiveness results for low- and middle-income countries. Despite the burden, cost-effective strategies exist at the population and individual levels for reducing CVD. Integral to all personal intervention strategies is an adequate assessment of the underlying risk of disease.

Cardiovascular disease is no longer just a problem of affluent countries.[1] In developing countries, it causes twice as many deaths as HIV, malaria, and tuberculosis combined.[2] Given the nearly $400 billion in direct and indirect annual costs related to cardiovascular disease (CVD) in the Unites States in 2006, the economic implications of this problem are equally important for the sustainability of many developing countries.[3] Therefore, we must make efforts to reduce the CVD burden in developing countries as we have done in developed ones. To do this, we must bring our knowledge of the disease burden and its risk factors together with our understanding of the effectiveness of various interventions and combine them with our successes in developed countries.

The largest effort to date to combine clinical and epidemiological knowledge with policy instruments to address CVD in low- and middle-income countries was made through the recent publication of *Disease Control Priorities in Developing Countries*.[4] This paper briefly reviews those findings and then extends them by detailing the central importance of overall risk assessment in managing the CVD epidemic cost-effectively in developing countries.

Global Burden Of Cardiovascular Disease

Current burden

CVD is the leading cause of death in all World Bank developing regions, with the exception of sub-Saharan Africa.[5] The overall burden continues to grow in both developed and developing countries, but there are distinct differences in patterns of growth between the two.[6]

In developed countries, despite the overall increase in CVD burden, age-adjusted death rates for most causes of CVD are declining. This age-adjusted decline is driven largely by preventive interventions that allow people to avert disease, treatments to prevent death during an acute manifestation of disease (particularly stroke or myocardial infarction [MI]), and interventions

that prolong survival once CVD is manifest. Thus, the average age of death from CVD continues to climb and, as a result, affects a larger population in retirement. Nearly 80 percent of deaths in high-income countries occur among those over age sixty, compared with 42 percent in low- and middle-income countries.

In developing countries, the increase in CVD burden is largely the result of an increase in the prevalence of risk factors and a relative lack of access to the above-mentioned interventions. As a result, age-adjusted death rates from stroke and ischemic heart disease are increasing in some developing regions, and a relatively younger population is afflicted by CVD. This has led to an increased number of deaths in the working-age population.

Epidemiologic transition

The overall increase in global burden and the distinct patterns in various regions can be explained by the epidemiologic transition (Exhibit 1).[7] Movement through its four stages has resulted in a dramatic shift in the cause of death from infectious diseases and malnutrition in the first stage to CVD and cancer in most high-income countries during the past two centuries.[8] Most developing regions appear to be following a similar pattern, but the transition has occurred at a more compressed rate. Between 1990 and 2020, coronary heart disease alone is anticipated to increase 120 percent for women and 137 percent for men in developing countries.[9] However, there remain distinct differences in how severely the burden is affecting various populations.

The World Bank groups low- and middle-income countries (gross national income, or GNI, per capita lower than U.S.$9,200) into six geographic regions: East Asia and the Pacific (EAP), Europe and Central Asia (ECA), Latin America and the Caribbean (LAC), Middle East and North Africa (MNA), South Asia (SAR), and sub-Saharan Africa (SSA). The EAP region appears to be straddling the second and third stages, with higher CVD rates in northern China than in southern China. The ECA region has a rate of 690 CVD deaths per 100,000, more than double the rate of high-income countries. The MNA region appears to be entering the third stage of the epidemiologic transition, with rates just below those of developed nations. As a whole, the LAC region seems to be in the third stage also, but certain parts of South America are still at risk of contracting malaria and dengue fever, and those portions are still in the first or second transitional stage.

Heterogeneity is also apparent throughout the rest of the developing world, even within countries. Some regions of India (SAR), for example, appear to be in the first stage of the transition, whereas others are in the second or even the third stage. Sub-Saharan Africa remains largely in the first stage of the epidemiologic transition, with CVD rates half of those in developed countries. Although HIV/AIDS is the leading overall cause of death in this region, CVD is second overall and first among those over age thirty. Hypertension has emerged as a major public health concern; as a result, stroke is the dominant form of CVD.[10] Rheumatic heart disease remains an important cause of CVD mortality and morbidity.

Social And Economic Impact

The social impact has not been quantified to the same extent as the economic impact has been, but it includes loss of employment for the caregiver, relocation due to a loss of a job, or the need to be closer to health care centers where they exist. Adolescents who become caregivers often drop out of the education system. The economic impact comes both in direct costs to the health care system and indirectly in losses to the economy through work loss both to those with disease and their family members who become de facto caregivers or who suffer loss of income because the breadwinner is not in the workforce. In China, annual direct costs of CVD are estimated at more than U.S.$40 billion, or roughly 4 percent of its GNI. In South Africa, 2–3

percent of countries' GNI was devoted to the direct treatment of CVD, or roughly 25 percent of South African health care spending.[11] Indirect costs were estimated as being more than double the direct costs.

This is further compounded by the fact that such a high proportion of CVD burden occurs earlier among working-age adults in developing countries. Under current projections, South Africa will have CVD strike four times more adults ages 35–64 than in the United States (Exhibit 2). Given the large populations in some of these rapidly growing economies, this could have profound economic effects over the next twenty-five years as workers in their prime succumb to CVD.

This can have a large impact on developing countries' economic viability. The 2004 report *A Race against Time* evaluated the potential loss due to early CVD.[12] In the five countries surveyed (Brazil, India, China, South Africa, and Mexico), conservative estimates indicated that at least twenty-one million years of future productive life are lost because of CVD each year. Another large difference between developed and developing countries is the amount spent on CVD care. Although there are limited data to confirm exact amounts for each region, we can assume that it is quite low in developing regions, for a couple of reasons. First, the amount developing countries spend on health care as a percentage of gross domestic product (GDP) is half of that spent on health care in high-income countries. Low- and middle-income countries spend about $74 per capita on health care, compared with $2,700 per capita in high-income countries.[13] In the few countries where data exist, a great disparity is evident in what is spent on CVD. For example, there is about a fiftyfold difference in what the United States and South Africa spend on CVD care.[14]

Cost-Effective Interventions

Cost-effectiveness ratios in context

There is no legal standard or regulation for what is cost-effective. The World Health Organization (WHO) Commission on Macroeconomics and Health recommended choosing interventions that were less than three times a country's GNI per capita.[15] This equates to about $1,300 per quality-adjusted life-year (QALY) in the poorest regions such as South Asia and sub-Saharan African and as much as $11,000 per QALY in wealthier regions such as Latin America. Using this criterion, the strategies reviewed below, with few exceptions, would be acceptable in all developing regions, particularly since many are cost-saving interventions. Furthermore, they are comparable to many commonly accepted interventions for communicable diseases in developing regions.[16] For example, antiretroviral therapy for HIV/AIDS and oral rehydration therapy for diarrheal diseases each cost about $1,000 per disability-adjusted life-year (DALY) averted. Directly observed therapy for tuberculosis is about $102 per DALY. In these studies and those following, ratios are reported in cost in 2001 U.S. dollars per QALY gained or DALY averted.

Risk assessment

Global risk assessment is the most essential solution to making cost-effective treatment decisions at the personal level. The following examples of treatment with the same cholesterol-lowering agent for three different patients illustrate this point.[17] Treatment with lovastatin for someone with a history of MI is a cost-saving intervention: It not only saves lives but also reduces overall health care costs by reducing future hospitalizations and revascularizations. However, the same dose of this medication for a fifty-year-old man without a history of heart disease but with an elevated total cholesterol level and three other CVD risk factors costs $20,000 per life-year saved. In contrast, treatment with the same medication for a thirty-five-year-old woman with the same cholesterol level but no other risk factors costs $2 million per

life-year saved. The large difference in the global risk attributed to the presence of prior disease or the other risk factors results in cost-effectiveness ratios that differ by more than two orders of magnitude. Thus, targeting treatments at people with the highest risk for CVD will lead to the greatest absolute reduction in disease and will likely be the most cost-effective. Population-based interventions, in contrast, will have smaller individual risk reductions but a great reduction overall because of the large numbers concerned. All interventions discussed in the text below are summarized in Exhibit 3.

Population-based strategies

Because of major difficulties in design and cost, most population-based interventions have not been evaluated in randomized controlled trials. However, several epidemiological studies—in particular, the North Karelia project—confirm that several lifestyle interventions should play a role in the management of the CVD burden.[18] These include avoiding tobacco use (discussed below), maintaining a healthy weight, continuing daily physical activity, and eating a healthy diet. Reductions in these risk factors will also lead to reductions in other chronic causes of morbidity and mortality, such as kidney and respiratory diseases and cancer. The only studies evaluating the cost-effectiveness of these interventions (excluding tobacco) in developing countries focus on dietary interventions. A public awareness campaign to reduce saturated fat content in the diet would cost $1,900–$4,000 per DALY averted in developing countries. An intervention that substituted 2 percent of energy from trans fat with polyunsaturated fat would be anywhere from $2,000 per DALY averted to cost saving. The range in the cost-effectiveness results depends on the assumptions of how much of a reduction in coronary artery disease would result and how much it would cost to achieve such a change. The wide range of estimates reflects the uncertainty around both of these estimates because few trials have evaluated the intervention. Likewise, the best estimates for the intervention to reduce salt content in manufactured foods through legislative efforts ranges from $1,320 to $3,100 per DALY averted across all of the regions. However, in the South Asian region specifically, the range could be anywhere from being cost-saving to as much as $2,800 per DALY averted under various assumptions about the cost and the expected reduction in blood pressure from the intervention.[19]

Tobacco control

There are more than one billion smokers worldwide, and 80 percent of them reside in developing countries.[20] Nearly one-third of all tobacco users in the developing world die from CVD.[21] One of the major differences between developed and developing countries is quit rates. More than 30 percent of men in the United Kingdom are ex-smokers, compared with 5 percent in China and 2 percent in India.[22] Strategies should include interventions to both quit smoking and prevent its initiation. Interventions that focus on current adult smokers will lead to most of the near-term benefits, given that the health risk associated with smoking diminishes to nearly normal three years after having quit. Strategies to prevent the uptake of tobacco among adolescents will yield results over a fifty-year period.

As with the other CVD risk factors, efforts to control tobacco use are both population and individual based. The prime population-based strategy is centered on taxation policy. Most developed countries' tax rates are more than 65 percent of the total price of the tobacco product, compared with less than 50 percent in developing countries.[23] Elasticity studies suggest that a 10 percent increase in price leads to about a 2.5–5 percent decline in smoking.[24] The affect appears to be even stronger among current smokers, those of lower socioeconomic status, and youth.[25] Prabhat Jha reports that a 33 percent price increase would cost about $3–$42 per DALY averted.[26] Other public measures that are non-price-related, such as restrictions on smoking in public places, public health education, and advertising bans, would cost $200–$3,000 per DALY averted, depending on the estimate of effectiveness. The individual-based

interventions such as nicotine replacement therapies would cost $56–$761 per DALY averted in developing countries.[27]

Primary prevention

Prevention strategies have also been put in place to target those without CVD but with risk factors for the disease. These strategies target the major risk factors for which interventions exist: tobacco consumption, hypertension, cholesterol abnormalities, obesity, physical inactivity, and diabetes mellitus. Some interventions are directed at those already with high levels of the risk factor (individual based); others are directed at the entire population (population based), to prevent the presence of risk factors among individuals, as discussed above. Individual-based strategies traditionally include screening for risk factors and introducing treatment for people above a certain threshold, such as the U.S. hypertension guidelines that recommend treatment for those with a blood pressure over 140/90 mm Hg. Population-based approaches attempt to reduce the level or presence of a risk factor across an entire population. An example is food-labeling requirements for fat content in an effort to reduce populationwide cholesterol levels.

Historically, individual-based strategies have used two approaches. The initial approach has been to develop guidelines for each CVD risk factor. However, the linear associations between blood pressure, cholesterol, and body weight and CVD in both developed and developing countries demonstrate the lack of biological justification for current threshold levels.[28] Indeed, most of the disease burden resulting from these three risk factors occurs in the large majority of the population with nonoptimal levels but without hypertension, abnormal lipids, or obesity as defined by the arbitrary cut-offs in multiple guidelines.

Guidelines that focus on arbitrary levels of a single risk factor can be quite inefficient. For example, a patient with mildly elevated blood pressure of 142/80 mm Hg but no other risk factors might be treated according to blood pressure guidelines despite having an overall risk of CVD of 2 percent over ten years. Meanwhile, another patient with a blood pressure of 138/78 mm Hg and multiple other risk factors would not get treated despite having a 20 percent or tenfold risk of CVD in comparison. This can lead to overtreatment of some relatively low-risk patients and undertreatment of some relatively high-risk patients.

An advance in the individual-based approach has been to recognize this multi-factorial involvement of CVD risk factors and screen for those at high risk for CVD on the basis of multiple risk factors. New Zealand and the countries addressed by the British Hypertension Society have adopted this “absolute risk” approach in their CVD guidelines.[29] This approach was also found to be cost-effective in a model of hypertension treatment in South Africa.[30] In that analysis, it was projected that the current South African guidelines cost an additional $30 million annually compared with an approach of treating those with a ten-year absolute risk of CVD of 15 percent or greater. Further, the current approach would result in 5,000 fewer QALYs for the adult population over ten years. A similar result was seen in the WHO assessment of multiple interventions for the prevention of CVD in developing countries using absolute risk criteria in comparison to individual risk-factor thresholds for initiation of treatment in all developing regions.[31]

For those at highest risk for CVD, it has been proposed that treatment with a multidrug regimen might be cost-effective. In the WHO proposal, a three-drug regimen was proposed; in fact, the “polypill” paper suggested that six medications combined into a single pill be given to everyone over age fifty-five.[32] More recent data suggest that these regimens and the one-pill-fits-all approach might not be grounded in the best evidence. First, it appears that beta-blockers are not the best agents for primary prevention.[33] As a result, the U.K. National Health Service has removed beta-blockers from the first three options for treating hypertension. Further, folate

has not been proved to reduce CVD in randomized trials. In a recent analysis, it was shown that two different combinations of four medications are needed.[34] The two regimens include one for primary prevention (aspirin, amlodipine, lisinopril, and a statin) and the other for secondary prevention, substituting a beta-blocker for the amlodipine. Under these strategies, treatment with aspirin, two antihypertensive agents, and a statin could reduce CVD death by up to 50 percent and extend life by two years; it was deemed cost-effective according to WHO standards. Use of these regimens would range between $310 and $1,220 per QALY gained across the developing regions, depending on the risk level of those taking them for primary prevention. Furthermore, even when it was assumed that the regimen would only be half as effective in developing as in developed countries, the cost-effectiveness ratios were still acceptable. These strategies assumed that the cost of the drug regimen would cost no more than twice the current combined cost of the generic components. No additive benefit was modeled from gains that might be made from improved adherence with an easier formulation.

Acute management

Those at highest risk are those suffering an acute myocardial infarction (AMI) or stroke, with as many as half dying before they ever reach medical attention. For those who do make it to a hospital, standard medical therapies were analyzed in the Disease Control Priorities Project in Developing Countries (DCP2) (Exhibit 3).[35] The incremental cost per DALY averted for the generic agents ranged from $9 to $734 for MI. Based on a large trial in China, the beta-blocker in these strategies probably should not be given immediately to those presenting in cardiogenic shock. The one nongeneric agent, tissue-plasminogen activator (t-PA), cost $16,000 per DALY averted in comparison. For acute stroke treatment, it ranged from $100 to $5,400 per DALY averted.[36]

Secondary prevention

The highest groups at risk for death among initial survivors of AMI are those with congestive heart failure (CHF). The prognosis for those with established CHF is generally poor and worse than for most malignancies or AIDS, with a five-year mortality of 26–75 percent overall and a one-year mortality rate as high as 40 percent for those at the most advanced stage.[37] The interventions examined for CHF were the addition of an angiontensin-converting enzyme (ACE) inhibitor, enalapril or metoprolol (or both), to a baseline of diuretic treatment. In this intervention, enalapril is cost saving, and the incremental cost-effectiveness ratio (ICER) for the addition of metoprolol is in the range of $124–$219 per DALY averted, depending on the region.

The next-highest group at risk is those who have survived the first thirty days after AMI and are without CHF. There is a 10 percent risk of dying in the first year and a 5 percent risk of dying in subsequent years.[38] Four generic medicines—aspirin, beta-blockers, cholesterol reducers (in particular, statins), and ACE inhibitors —have been the mainstay of treatment for those with coronary heart disease in the developed world. The first four agents were evaluated in a stepwise fashion along with and compared to coronary artery bypass graft (CABG).[39] A combination of aspirin and atenolol was cost saving when compared to no therapy in all developing regions (Exhibit 3). The ICERs for the combination of aspirin, atenolol, and enalapril ranged from $660 per DALY averted in sub-Saharan Africa to $866 in the ECA region. The combination of all four drugs taken separately ranged from $1,720 to $2,026 per DALY averted across the regions when compared with three drugs. CABG compared with the four-drug combination had ICERs ranging from $24,000 (SAR region) to $72,000 (MNA region) per DALY averted.

The cost-effectiveness ratio of the four-drug regimen would likely be acceptable in most developing regions. Unfortunately, individual components of potential multidrug prevention

regimens are available there but underused (Exhibit 4), resulting in millions of potential deaths that could be averted. For example, ACE inhibitors and statins are used for secondary prevention by fewer than 20 percent and 10 percent of those eligible, respectively, and even less for primary prevention.[40] Although there have been no long-term trials of a "polypill," it has been shown in an analysis with a developing country CVD model that using a multidrug regimen of aspirin, lisinopril, metoprolol, and a statin could produce a cost-effectiveness ratio of $310–$390 per QALY gained, compared to no treatment in secondary prevention in developing countries.[41]

Concluding Comments

A global CVD epidemic is rapidly evolving, and the burden of disease is shifting. Three times as many deaths from CVD now occur in developing countries as compared with developed countries.[42] The economic and social costs of this burden will be great, particularly because many developing nations are still grappling with poverty-related diseases such as malnutrition, infectious diseases, and poor health care facilities. However, a broad range of individual- and population-based strategies exists at affordable prices and, if implemented, could reduce the burden of CVD disease by more than half. Reductions in tobacco use should be the cornerstone of these interventions. Simultaneously, efforts can be adopted to prevent the further development of CVD risk factors. These interventions are often less expensive per capita but often do not yield the benefits until much later. The interventions that are most cost-effective target those who are at highest risk for death, such as those with advanced disease or overall high risk for CVD.

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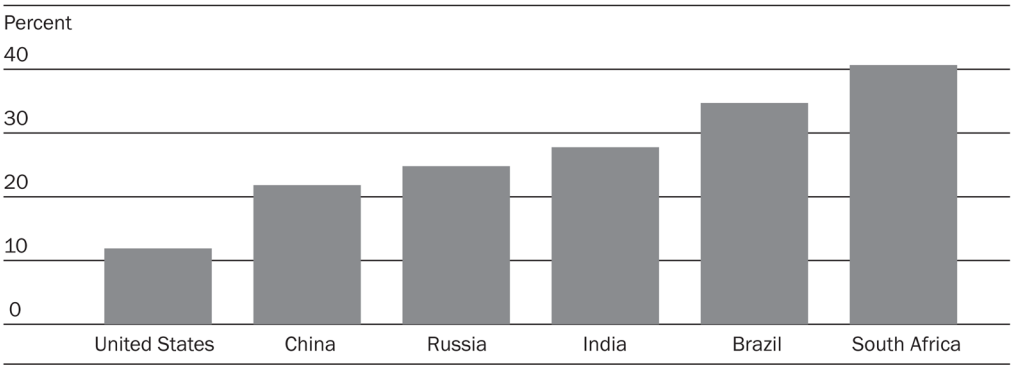
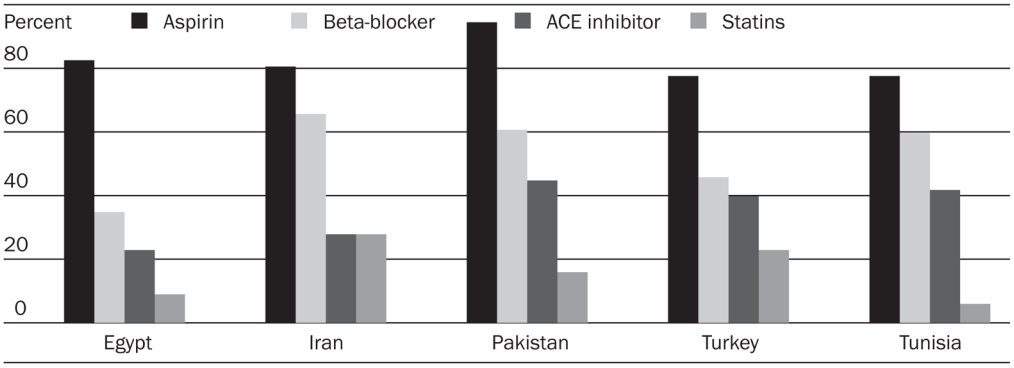


SOURCE: S. Leeder et al., *A Race against Time: The Challenge of Cardiovascular Disease in Developing Countries* (New York: Trustees of Columbia University, 2004).

EXHIBIT 2.
Proportion Of Deaths In Six Countries Attributable To Cardiovascular Disease (CVD) Among People Ages 35–64, 2000–2030



SOURCE: S. Mendis et al., "WHO Study on Prevevention and Recurrences of Myocardial Infarction and Stroke (WHO-PREMISE)," *Bulletin of the World Health Organization* 83, no. 11 (2005): 820–828.
NOTE: ACE is angiotensin-converting enzyme.

EXHIBIT 4.
Rate Of Use Of Indicated Prescriptions For Cardiovascular Disease (CVD) In Selected Developing Countries, In Primary, Secondary, And Tertiary Care Centers, 2002–03

EXHIBIT 1

Stages Of The Epidemiological Transition And Its Status By Region

Stage	Description	Life expectancy (years)	Dominant form of CVD	Percent of deaths due to CVD	Regions affected
Pestilence and famine	Predominance of malnutrition and infectious diseases	35	RHD, cardiomyopathy due to infection and malnutrition	5–10	Sub-Saharan Africa, parts of all regions excluding high-income regions
Receding pandemics	Improved nutrition and public health leads to increase in chronic diseases, hypertension	50	Rheumatic valvular disease, CHD, hemorrhagic stroke	15–35	South Asia, southern East Asia and the Pacific, parts of Latin America and the Caribbean
Degenerative and man-made diseases	Increased fat and caloric intake, widespread tobacco use, chronic disease deaths exceed mortality from infections and malnutrition	60	CHD, stroke (ischemic and hemorrhagic)	> 50	Europe and Central Asia, northern East Asia and the Pacific Latin America and the Caribbean, Middle East and North Africa, and urban parts of most low-income regions (esp. India)
Delayed degenerative diseases	CVD and cancer are leading causes of morbidity and mortality; prevention and treatment avoids death and delays onset; age-adjusted CVD declines	> 70	CHD, stroke (ischemic and hemorrhagic), CHF	< 50	High-income countries, parts of Latin America and the Caribbean

SOURCES: Adapted from A.R. Omran, “The Epidemiologic Transition: A Theory of the Epidemiology of Population Change,” *Milbank Quarterly* 49, no. 4 (1971): 509; and S.J. Olshansky and A.B. Ault, “The Fourth Stage of the Epidemiologic Transition: The Age of Delayed Degenerative Diseases,” *Milbank Quarterly* 64, no. 3 (1986): 355–391.

NOTES: CVD is cardiovascular disease. RHD is rheumatic heart disease. CHD is coronary (ischemic) heart disease. CHF is congestive heart failure.

EXHIBIT 3

Incremental Cost-Effectiveness Ratios For Multiple Cardiovascular Disease (CVD) Interventions

Intervention	Cost-effectiveness ($U.S. per DALY averted)
Population-based strategies[a]	
Substituting polyunsaturated for trans fat	25–2,300
Salt reduction (population level)	1,320–3,100
Public education to reduce saturated fat	1,900–4,000
Tobacco control[a]	
Tobacco price increase of 33%	3–42
Nicotine replacement therapies	56–761
Tobacco education and advertising ban	200–3,000
Primary prevention[a]	
Multidrug regimen for all with AR > 25%	750–890
Multidrug regimen for all with AR > 15%	790–930
Multidrug regimen for all with AR > 5%	1,040–1,220
Target blood pressure of 160/95 mm Hg	Dominated[b]
Target blood pressure of 140/90 mm Hg	Dominated[b]
Acute myocardial infarction[a]	
ASA	9–20
ASA/BB	11–22
Streptokinase	634–734
t-PA	15,900–16,000
Acute stroke	
ASA	100–700
t-PA	600–2,500
Heparin	1,300–5,400
Congestive heart failure[a]	
ACE inhibitor	Cost-saving
ACE inhibitor/BB	124–219
Secondary prevention[a]	
ASA/BB	Cost-saving
ASA/BB/ACE inhibitor	660–866
ASA/BB/ACE inhibitor/lovastatin	1,720–2,026
Multidrug regimen compared to no treatment	310–390
CABG+ASA/BB/ACE inhibitor/lovastatin	24,000–72,000

SOURCES: D. Jamison et al., eds., *Disease Control Priorities in Developing Countries*, 2d ed. (New York: Oxford University Press and World Bank, 2006); and T.A. Gaziano, L.H. Opie, and M.C. Weinstein, "Cardiovascular Disease Prevention with a Multidrug Regimen in the Developing World: A Cost-Effectiveness Analysis," *Lancet* 368, no. 9536 (2006): 679–686.

NOTES: DALY is disability-adjusted life-year. AR is absolute risk for CVD over ten years. ASA is aspirin. BB is beta-blocker. t-PA is tissue plasminogen activator. ACE is angiotensin-converting enzyme (in this case, enalapril). CABG is coronary artery bypass graft. Multidrug regimen: (1) primary prevention is ASA, amlodipine, ACE inhibitor, and lovastatin; (2) secondary prevention is ASA, BB, ACE inhibitor, and lovastatin.

[a] Within each category, initial strategies are listed as incremental ratios compared to no treatment, with each successive intervention incremental to the one above. However, each of the population-based and tobacco-control strategies is compared to a strategy of no intervention and is not incremental to each other.

[b] More expensive and less effective than a strategy based on absolute risk.