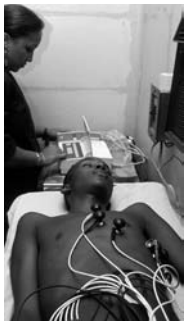
Chapter **33**

Cardiovascular Disease



Thomas A. Gaziano, K. Srinath Reddy, Fred Paccaud, Sue Horton, and Vivek Chaturvedi

Cardiovascular disease (CVD) is the number one cause of death worldwide (Mathers and others 2006; Murray and Lopez 1996; WHO 2002b). CVD covers a wide array of disorders, including diseases of the cardiac muscle and of the vascular system supplying the heart, brain, and other vital organs. This chapter reviews the epidemiological transition that has made CVD the world's leading cause of death, assesses the status of the transition by region, and indicates regional differences in the burden of CVD. It also reviews the cost-effectiveness of various interventions directed at the most relevant causes of CVD morbidity and mortality.

EPIDEMIOLOGY OF CVD

At the beginning of the 20th century, CVD was responsible for less than 10 percent of all deaths worldwide, but by 2001 that figure was 30 percent. About 80 percent of the global burden of CVD death occurs in low- and middle-income countries. Murray and Lopez (1996) predicted that CVD will be the leading cause of death and disability worldwide by 2020 mainly because it will increase in low- and middle-income countries. By 2001, CVD had become the leading cause of death in the developing world, as it has been in the developed world since the mid 1900s (Mathers and others 2006; WHO 2002a). Nearly 50 percent of all deaths in high-income countries and about 28 percent of deaths in low- and middle-income countries are the result of CVD (Mathers and others 2006). Other causes of death, such as injuries, respiratory infections, nutritional deficiencies, and HIV/AIDS, collectively still play a predominant role in certain regions, but even in those areas CVD is now a significant cause of mortality.

Predominant Cardiovascular Diseases

This chapter focuses on the most common causes of CVD morbidity and mortality:

- ischemic heart disease (IHD)
- stroke
- congestive heart failure (CHF).

These diseases account for at least 80 percent of the burden of CVD in all income regions, which share many of the same common risk factors; accordingly, similar interventions are appropriate. A fourth manifestation, rheumatic heart disease (RHD), which accounts for 3 percent of all disability-adjusted life years (DALYs) lost as a result of CVD, does not contribute significantly to the overall global burden of CVD. The burden of RHD will likely continue to diminish, but it is still an important inflammatory cause of heart disease in developing countries and accordingly is addressed in this chapter. We do not address many other forms of CVD because of the scope of this volume; the regional rather than global nature of some inflammatory diseases, such as Chagas disease; or the congenital abnormalities or genetically based cardiomyopathies for which prevention and treatment options remain limited.

Ischemic Heart Disease. IHD is the single largest cause of death in the developed countries and is one of the main contributors to the disease burden in developing countries. The two leading manifestations of IHD are angina and acute myocardial infarction. In 2001, IHD was responsible for 7.3 million deaths and 58 million DALYs lost worldwide (WHO 2002b). Seventy-five percent of global deaths and 82 percent of the total DALYs resulting from IHD occurred in the low- and middle-income countries.

Glossary

ACE inhibitors (angiotensin-converting enzyme inhibitors): a group of antihypertensive drugs that exert their influence through the renin-angiotensin-aldosterone system.

Antiplatelets: drugs that interfere with the blood's ability to clot.

Atheroschlerosis: a chronic disease characterized by thickening and hardening of the arterial walls.

Atrial fibrillation: an abnormal rhythm of the heart that can result in an increased risk of stroke because of the formation of emboli (blood clots) in the heart.

Beta-blockers: a group of drugs that decrease the heart rate and force of contractions and lower blood pressure.

Cardiogenic shock: poor tissue perfusion resulting from failure of the heart to pump an adequate amount of blood.

Cardiomyopathy: a disorder of the muscle limiting the heart's function.

Chagas disease: a tropical American disease caused by a parasitic infection. Chronic symptoms include cardiac problems, such as an enlarged heart, altered heart rate or rhythm, heart failure, or cardiac arrest.

Dyslipidemia: a condition marked by abnormal concentrations of lipids or lipoproteins in the blood.

Embolus: a blood clot that moves through the bloodstream until it lodges in a narrowed vessel and blocks circulation.

Endocarditis: inflammation of the lining of the heart and its valves.

Hypertension: abnormally high arterial blood pressure.

Reperfusion: restoration of the flow of blood to a previously ischemic tissue or organ.

Statins: a group of drugs that inhibit the synthesis of cholesterol and promote the production of low-density lipoprotein (LDL)–binding receptors in the liver, resulting in a decrease in the level of LDL and a smaller increase in the level of high-density lipoprotein (HDL).

Thrombolysis: the breaking up of a blood clot.

Thrombus: a blood clot that forms inside a blood vessel or cavity of the heart.

Transient ischemic attack: transient reduced blood flow to the brain that produces strokelike symptoms but no lasting damage.

Angina is the characteristic pain of IHD. It is caused by atherosclerosis leading to stenosis (partial occlusion) of one or more coronary arteries. Patients with chronic stable angina have an average annual mortality of 2 percent or less. Acute myocardial infarction (AMI) is the total occlusion of a major coronary artery with a complete lack of oxygen and nutrients leading to cardiac muscle necrosis. AMI is usually diagnosed by changes in the electrocardiogram; by elevated serum enzymes, such as creatine phosphokinase and troponin T or I; and by pain similar to that of angina. Thirty-day mortality after an AMI is high: even with best medical therapy it remains at about 33 percent, with half the deaths occurring before the individual reaches the hospital. Even in a hospital with a coronary care unit where advanced care options are available, mortality is still 7 percent. In a hospital without such facilities or therapies, the mortality rate is closer to 30 percent. Even though mortality among patients who have recovered from an AMI has declined in recent decades, approximately 4 percent of patients who survive initial hospitalization die in the first year following the event (Antman and others 2004).

Stroke. Stroke is caused by a disruption in the flow of blood to part of the brain either because of the occlusion of a blood vessel (ischemic stroke) or the rupture of a blood vessel (hemorrhagic stroke). Many of the same risk factors for IHD apply to stroke; in addition, atrial fibrillation is an important risk factor for stroke. The annual risk of stroke in patients with nonvalvular atrial fibrillation is 3 to 5 percent, with 50 percent of thromboembolic stroke being attributable to atrial fibrillation (Wolf, Abbott, and Kannel 1991). Chapter 32 discusses the diagnosis and management of the clinical syndromes in greater detail.

Congestive Heart Failure. CHF is the end stage of many heart diseases. It is characterized by abnormalities in myocardial function and neurohormonal regulation resulting in fatigue, fluid retention, and reduced longevity. CHF is caused by pathological processes that affect the heart; IHD and hypertension-related heart disease are the most common etiologies. The risk of developing CHF is two times more in hypertensive men and three times more in hypertensive women compared with those who are normotensive. CHF is five times more common in those who

have had an AMI than in those who have not. The prognosis for those with established CHF is generally poor and worse than for those with most malignancies (McMurray and Stewart 2000) or AIDS, with a one-year mortality rate as high as 40 percent and a five-year mortality between 26 and 75 percent.

The worldwide burden of CHF is substantial and continues to rise. Throughout the developed world the prevalence is about 2 to 3 percent, with an annual incidence rate of 0.1 to 0.2 percent (McMurray and Stewart 2000). However, the incidence and prevalence of CHF rise dramatically with age. Prevalence is 27 per 1,000 population for those older than 65, compared with 0.7 per 1,000 for those younger than 50 (McKelvie 2003). CHF occurs more frequently in men, and incidence and mortality differ substantially according to gender and socioeconomic status. CHF causes 53,000 deaths in the United States each year and contributes to another 213,000, and the death rate attributed to CHF rose by 155 percent from 1979 to 2001 in the United States (American Heart Association 2002). CHF is the first-listed diagnosis in 1 million hospitalizations.

Rheumatic Heart Disease. RHD is the consequence of an acute rheumatic fever (ARF)—that is, a poorly adapted autoimmune response to group A β-hemolytic streptococci. It affects the connective tissue, mainly the joints and the heart valves. The most serious complications are valvular stenosis, regurgitation following the valvulitis, or both (Ephrem, Abegaz, and Muhe 1990). RHD is also a predisposing factor for infective endocarditis, a disease of younger adults, predominantly males (Koegelenberg and others 2003).

According to 2001 estimates, RHD accounts for 338,000 deaths per year worldwide, two-thirds of them in Southeast Asia and the Western Pacific (WHO 2002b). About 12 million people in developing countries, most of them children, suffer from RHD (WHO 1995). Steer and others' (2002) review of developing countries suggests that RHD prevalence in children is between 0.7 and 14 per 1,000, with the highest rates in Asia. RHD and ARF are the most common causes of cardiac disease among children in developing countries (Ephrem, Abegaz, and Muhe 1990; Schneider and Bezabih 2001; Steer and others 2002) and account for almost 10 percent of sudden cardiac deaths (Kaplan 1985).

Until the 1950s, ARF accounted for a substantial portion of cardiovascular problems among schoolchildren in developed countries, and even though it is now far less common, outbreaks still occur (Carapetis, Currie, and Kaplan 1999), suggesting that neither antibiotics nor other public health measures have been totally effective in controlling ARF.

The Epidemiological Transition

Over the past two centuries, the industrial and technological revolutions have resulted in a dramatic shift in the causes of illness and death. Before 1900, infectious diseases and malnutrition were the most common causes of death; however, primarily because of improved nutrition and public health measures, they have gradually been supplanted in most high-income countries by CVD and cancer. As improvements continue to spread to developing countries, CVD mortality rates are increasing.

Known as the epidemiological transition, this shift is highly correlated with changes in personal and collective wealth (the economic transition), social structure (the social transition), and demographics (the demographic transition). Omran (1971) provides an excellent model of the epidemiological transition that divides it into three basic ages: pestilence and famine, receding pandemics, and degenerative and human-created diseases (table 33.1). Olshansky and Ault (1986) add a fourth stage: delayed degenerative diseases.

The consistent pattern for most high-income countries going through the epidemiological transition has been initially high rates of stroke, mostly hemorrhagic. Only in the third phase, with the presence of increased resources, but coupled with increased diabetes and smoking rates and adverse lipid profiles, do rates of IHD climb. This phase is also accompanied by better control of severe hypertension, reducing the rates of hemorrhagic stroke, which is then replaced by ischemic stroke. Most regions appear to be following this pattern and have a predominance of IHD. The two exceptions are East Asia and the Pacific and Sub-Saharan Africa. The pattern in East Asia and the Pacific is dominated by China and appears to be a result of China's stage in the transition but may also be following a pattern similar to Japan's—that is, dominated by more strokes and fewer IHD deaths—whereas Sub-Saharan Africa is in an earlier phase of the epidemiological transition.

Even though countries tend to enter these stages at different times, the progression from one stage to the next tends to proceed in a predictable manner. The six World Bank regions are at various phases of the epidemiological transition (table 33.1), and where development has occurred, it has often been at a more compressed rate than in the high-income countries. Although rates of IHD and stroke fell 2 to 3 percent per year in the high-income countries during the 1970s and 1980s, the rate of decline has since slowed. Overweight and obesity are escalating at an alarming pace, while rates of type 2 diabetes, hypertension, and lipid abnormalities associated with obesity are on the rise. This trend is not unique to the developed countries, however. According to the World Health Organization, worldwide more than 1 billion adults are overweight and 300 million are clinically obese. Even more disturbing are increases in childhood obesity that have led to large increases in diabetes and hypertension. If these trends continue, age-adjusted CVD mortality rates could increase in the high-income countries in the coming years. These trends are discussed in greater detail in chapter 45.

Table 33.1 Stages of the Epidemiological Transition and Its Global Status, by Region

Stage	Description	Life expectancy (years)	Dominant form of CVD	Percentage of deaths attributable to CVD	Percentage of the world's population in this stage	Regions affected
Pestilence and famine	Predominance of malnutrition and infectious diseases	35	RHD, cardiomyopathy caused by infection and malnutrition	5–10	11	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, IHD, hemorrhagic stroke	15–35	38	South Asia, southern East Asia and the Pacific, parts of Latin America and the Caribbean
Degenerative and human-created diseases	Increased fat and caloric intake, widespread tobacco use, chronic disease deaths exceed mortality from infections and malnutrition	60	IHD, stroke (ischemic and hemorrhagic)	>50	35	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 (especially 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	IHD, stroke (ischemic and hemorrhagic), CHF	<50	15	High-income countries, parts of Latin America and the Caribbean

Source: Adapted from Olshanksy and Ault 1986; Omran 1971; WHO 2003b.

Risk Factors

The risk of developing CVD depends to a large extent on the presence of several risk factors. The major risk factors for CVD include tobacco use, high blood pressure, high blood glucose, lipid abnormalities, obesity, and physical inactivity. The global variations in CVD rates are related to temporal and regional variations in these known risk factors. Discussions of the strength of the associations of the various factors with CVD are found elsewhere (chapters 30, 44, and 45). Although some risk factors, such as age, ethnicity, and gender, obviously cannot be modified, most of the risk is attributable to lifestyle and behavioral patterns, which can be changed.

BURDEN OF DISEASE

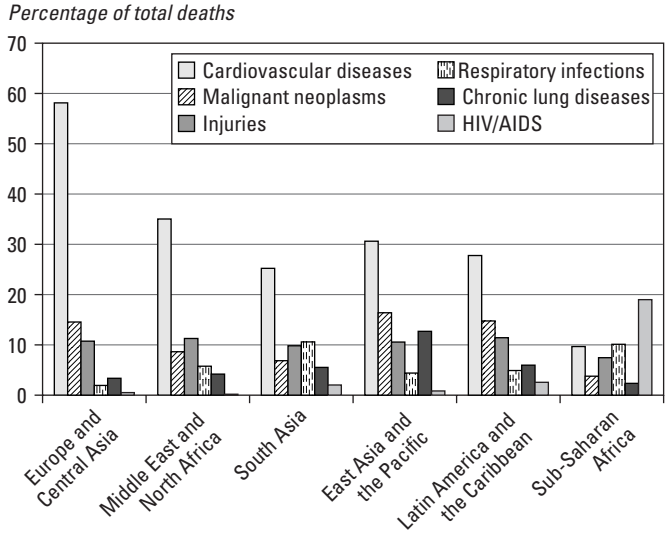
CVD is the leading cause of death in all World Bank regions with the exception of Sub-Saharan Africa (figure 33.1), where HIV/AIDS has emerged as the leading cause of mortality (Mathers and others 2006). Between 1990 and 2020, IHD is anticipated to increase by 120 percent for women and 137 percent for men in developing countries, compared with age-related increases of 30 to 60 percent in developed countries (Leeder and others 2004). Even though 80 percent of CVD deaths occur in low- and middle-income countries, the death rates for most regions are still below the rate for high-income countries, which is 320 per 100,000 population annually. The marked exception is Europe and Central Asia, which has a rate of 690 CVD deaths per 100,000 population.

Regional Burdens

The majority of the burden occurs in East Asia and the Pacific, Europe and Central Asia, and South Asia because a large proportion of the world's population lives in East Asia and the Pacific and South Asia and the incidence of IHD is high in Europe and Central Asia.

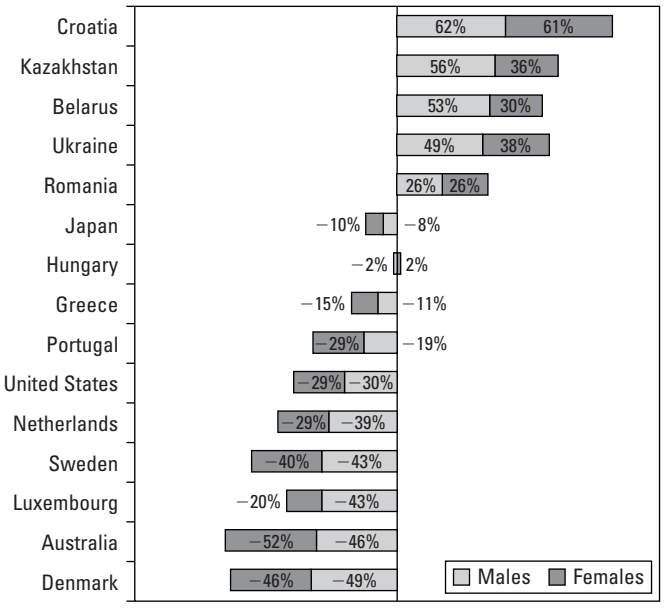
East Asia and the Pacific. The status and character of the epidemiological transition across the region reflects the diversity of economic circumstances in East Asia and the Pacific. Since the 1950s, life expectancy in China has nearly doubled from 37 years to 71 years (WHO 2003b). Approximately 60 percent of the population still lives outside urban centers, and as is the case in most developing countries, rates of IHD, stroke, and hypertension are higher in urban centers. China appears to be straddling the second and third stages of a Japanese-style epidemiological transition, with CVD rates higher than 35 percent, though dominated by stroke, not IHD. However, in urban China, the death rate from IHD rose by 53 percent from 1988 to 1996.

Europe and Central Asia. The emerging market economies, which consist of the former socialist states of Europe, are largely in the third phase of the epidemiological transition. As a group, they have the highest rates of CVD mortality in the world, similar to those seen in the United States in the 1960s when CVD was at its peak. Belarus, Croatia, Kazakhstan, Romania, and Ukraine have seen significant increases in IHD death rates (figure 33.2). In the Russian Federation, life expectancy for men has dropped precipitously since 1986 from 71.6 years to about 59 years in 2004, in large part because of CVD. In the Czech Republic, Hungary, Poland, and Slovenia, age-adjusted CVD rates have been declining. Nevertheless, CVD rates generally remain higher than in Western Europe.



Source: Mathers and others 2006.

Figure 33.1 Major Causes of Death in Persons of All Ages in Low- and Middle-Income Regions



Source: Mackay and Mensah 2004.

Figure 33.2 Percentage Change in Ischemic Heart Disease Death Rates in People Age 35 to 74, 1988–98, Selected Countries

Latin America and the Caribbean. In 2001, CVD accounted for about 31 percent of all deaths in Latin America and the Caribbean, but that figure is expected to rise to 38 percent by 2020 (Murray and Lopez 1996). In recent decades, average life expectancy in Latin America and the Caribbean has risen from 51 to 71 years, and the quality of nutrition has improved steadily. At the same time, the region has seen a switch from vegetables as a source of protein to animal protein and an increase in fat intake as a percentage of energy. As a whole, the region seems to be in the third phase, but in South America, some areas are still in the first phase of the transition.

Middle East and North Africa. Increasing economic wealth in the Middle East and North Africa has been characteristically accompanied by urbanization. The rate of CVD has been increasing rapidly and is now the leading cause of death, accounting for 25 to 45 percent of total deaths. Over the past few decades, daily per capita fat consumption has increased in most countries in the region, ranging from a 13.6 percent increase in Sudan to a 143.3 percent increase in Saudi Arabia (Musaiger 2002). IHD is the predominant cause of CVD, with about three IHD deaths for every stroke death. RHD remains a major cause of morbidity and mortality, but the number of hospitalizations for RHD is declining rapidly.

South Asia. Some regions of India appear to be in the first phase of the transition, whereas others are in the second or even the third phase. Nonetheless, India is experiencing an alarming increase in heart disease, which seems to be linked to changes in lifestyle and diet, rapid urbanization, and possibly an underlying genetic component. Diabetes is also a major health issue. India has 31.6 million diabetics, and the number is expected to reach 57.2 million by 2025 (Ghaffar, Reddy, and Singhi 2004). The World Health Organization estimates that, by 2010, 60 percent of the world's cardiac patients will be in India. About 50 percent of CVD-related deaths occur among people younger than 70, compared with about 22 percent in the West. Between 2000 and 2030, about 35 percent of all CVD deaths in India will occur among those age 35 to 64, compared with only 12 percent in the United States and 22 percent in China (Leeder and others 2004).

Sub-Saharan Africa. In Sub-Saharan Africa, deaths attributable to CVD are projected to more than double in between the years 1990 and 2020. Although HIV/AIDS is the leading overall cause of death in this region, CVD is the second-leading killer and is the first among those over the age of 30. Stroke is the dominant form, in keeping with patterns characteristic of earlier phases of the epidemiological transition. With increasing urbanization, levels of average daily physical activity are falling and smoking rates are increasing. Hypertension has emerged as a major public health concern, and hypertensive disease accounts for the dominance of stroke (Bertrand 1999). RHD and cardiomyopathies, the latter caused mostly by malnutrition, various viral illnesses, and parasitic organisms, are also important causes of CVD mortality and morbidity.

Social and Economic Impact

Leeder and others' (2004) report highlights the economic impact of cardiovascular diseases in developing economies, which arises largely because working-age adults account for a high proportion of the CVD burden. Conservative estimates in Brazil, China, India, Mexico, and South Africa indicate that each year at least 21 million years of future productive life are lost because of CVD. In South Africa, for example, costs for the direct treatment of CVD were equivalent to 2 to 3 percent of gross domestic product, or roughly 25 percent of all health care expenditures (Pestana and others 1996).

Current expenditures in developed countries are indicators of possible future expenditure in developing countries. For example, Hodgson and others (2001) estimated that in 2003 the direct and indirect costs of CVD in the United States would amount to US$350 billion. They also estimated that in 1998 Americans spent US$109 billion on hypertension, equivalent to about 13 percent of the health care budget. Studies are limited but suggest that obesity-related diseases are responsible for 2 to 8 percent of all health care expenditures in developed countries.

COST-EFFECTIVENESS OF INTERVENTIONS

CVD remains one of the most studied and written about subjects in medicine. As a result, many interventions exist with strong evidence for significant reductions in morbidity and mortality associated with CVD.

Intervention Effectiveness by Disease

This chapter addresses those interventions believed to have the largest effect because they result in large reductions in CVD events, are inexpensive, or the prevalence or incidence of the diseases to which they are directed is significant. The omission of an intervention does not imply that it is not cost-effective but rather that either it had an effect on a smaller percentage of people or the chapter was unable to encompass all such interventions.

Acute Myocardial Infarction. Treatment of AMI involves medical therapies that reduce myocardial oxygen demand and fatal arrhythmias (beta-blockers), that restore blood flow by inhibiting platelet aggregation (aspirin), or that dissolve the thrombus occluding the arterial lumen (thrombolytics) or an invasive intervention with cardiac catheterization and angioplasty.

Beta-blockers are used both during and after an AMI. Benefits persist for at least 6 years and up to 15 years after the first AMI. The second Thrombolysis in Myocardial Infarction trial showed significant benefits when beta-blockers were used within two hours of symptoms (Roberts and others 1991).

Aspirin, an antiplatelet agent, and thrombolytic agents, the standard treatments for reopening the artery in AMI, have demonstrated an additive effect in reducing mortality (GISSI 1986), with a benefit irrespective of age, sex, blood pressure, heart rate, or previous history of AMI or diabetes (Fibrinolytic Therapy Trialists' Collaborative Group 1994). The benefits are greater the closer the thrombolytics are given to the time of onset, and the risk of bleeding is greater the later they are given. The risk of adverse events following administration of thrombolytics is low during the first 24 hours; trials with thrombolytics show that the benefits are greatest when they are administered less than 12 hours after an AMI and preferably less than 6 hours (Antman and others 2004).

The invasive alternative to immediate medical reperfusion of an occluded coronary artery is angioplasty or percutaneous coronary intervention. Its superiority over thrombolysis in developed countries remains a matter of debate. Issues that remain important in relation to the choice of strategy are overall severity or location of the AMI and the time from symptom onset to initiation of treatment. In patients presenting late or with a high risk of mortality, such as those in cardiogenic shock, percutaneous coronary intervention may be beneficial (Hochman and others 1999). However, as with thrombolytic agents, the benefits of percutaneous coronary intervention diminish significantly with time between the onset of symptoms and the opening of the artery (De Luca and others 2004; D. O. Williams 2004).

The invasive strategy requires a facility and individual physicians who conduct enough of the procedures annually to remain proficient. In the absence of these conditions, the American Heart Association recommends that treatment focus on thrombolytics (Antman and others 2004). Given either a lack of facilities and operators for percutaneous interventions or long distances to such facilities in many developing countries, we did not evaluate this procedure.

Long-Term Management of Existing Vascular Disease. The management of individuals with chronic vascular disease consists of invasive techniques, pharmacotherapy, lifestyle and behavioral changes, and rehabilitative measures. It also involves addressing such issues as adherence to treatment, regular follow-ups to determine compliance and assess risk, and treatment of comorbidities that are likely to have an impact on the progression of vascular disease (for instance, renal disease).

Invasive Interventions The three most common procedures are coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), and PTCA with stents. CABG is the placement of grafts, usually from the saphenous vein or internal mammary artery, to bypass stenosed coronary arteries while maintaining cerebral and peripheral circulation by cardiopulmonary bypass. CABG is a major operative procedure requiring appropriate surgical and anesthetic environments and has a perioperative mortality of 1 to 3 percent, with later complication rates of 15 to 20 percent.

Almost 1 million CABGs per year are performed worldwide, with about 519,000 interventions in the United States alone in 2000 (American Heart Association 2002). The main indication for CABG is for those with left main coronary artery stenosis or those with involvement of multiple coronary arteries with reduced left ventricular function, particularly among diabetics. The prevalence estimates of those with left main coronary artery stenosis or involvement of three coronary arteries has varied over time, but current estimates range from 7 to 20 percent of survivors of myocardial infarction (Kuntz and others 1996; Rogers and others 1991; Topol, Holmes, and Rogers 1991) For these cases, investigators have shown that CABG is more beneficial than medical treatment, both in terms of symptoms and of mortality (Eagle and others 1999).

Both developed and developing countries are increasingly using PTCA (Denbow and others 1997). The main indications for its use are low-risk patients with single- or double-vessel disease and poor response to medical treatment. The success rate of PTCA is more than 95 percent; however, because it has no mortality benefit when compared with medical therapy or CABG, we did not evaluate new analyses of the cost-effectiveness of this intervention, but instead provided information from experience in developed countries. The addition of stents to PTCA has lead to a decrease in restenosis rates and readmissions to hospitals but shows no change in mortality compared with medical therapy.

Pharmacological Interventions The pharmacological interventions either prevent thrombosis, as does aspirin, or target the individual risk factors, as do the antihypertensives (diuretics, beta-blockers, and ACE inhibitors) or statins targeting cholesterol. Furthermore, these agents may possibly have additional properties of reducing the risk of fatal arrhythmias, improving repair after AMI (remodeling), or stabilizing the atherosclerotic plaque.

Overall, the long-term administration of antiplatelet agents in those with vascular disease leads to a 25 percent reduction in the risk of major vascular events: 33 percent for nonfatal AMI, 25 percent for nonfatal stroke, and 16 percent for any vascular death. The use of aspirin has produced similar benefits in individuals with IHD or prior stroke. Antiplatelet treatment in individuals with a previous AMI has been shown to prevent 18 nonfatal myocardial infarctions, 5 nonfatal strokes, and 14 vascular deaths for every 1,000 patients

treated for two years (Antithrombotic Trialists' Collaboration 2002).

The benefits of antiplatelet agents for those with vascular disease far outweigh the risks. The risk of intracranial bleeding increases by nearly 25 percent with the use of antiplatelet agents, but in absolute terms this risk comes to only one or two intracranial bleeds per 1,000 patients treated per year. The risk of major extracranial bleeding, mostly gastrointestinal, also increases by 60 percent, or one or two excess events per 1,000 patients per year.

The most established and commonly used agent is aspirin, although other agents (for example, clopidogrel or ticlopidine) with similar efficacy but much greater cost are available. Low doses of aspirin—75 to 100 milligrams (mg) per day—are as beneficial as higher doses.

Lowering LDL and elevating HDL cholesterol levels is one of the cornerstones of treatment of cardiovascular disease, and investigators have suggested that suboptimal levels of cholesterol contribute to almost two-thirds of the global cardiovascular risk (WHO 2002b). Although the usual target of lipid-lowering therapy has been lowering total or LDL cholesterol, medical experts are increasingly recognizing the importance of increasing HDL cholesterol and lowering triglyceride levels, especially in high-risk individuals, such as those with diabetes or metabolic syndrome, as well as in ethnic populations like Southeast Asians.

Recent evidence has demonstrated that the relationship between cholesterol levels and vascular events is continuous and occurs at much lower cholesterol thresholds than previously believed. The clinical trials have consistently demonstrated a 25 to 30 percent reduction in the risk of cardiovascular morbidity and mortality. Furthermore, the evidence suggests that more aggressive reductions in cholesterol have higher benefits than mild or moderate reductions (Cannon and others 2004; Knatterud and others 2000). No increased risk of cancers appears to exist, as was previously believed, although a small increase exists in the risk of inflammation of noncardiac muscle (myopathy) (Pfeffer and others 2002).

As with cholesterol, the relationship between blood pressure and vascular events is continuous and is discussed further in chapter 45. Even patients with presumed "normal" blood pressure and prior vascular disease benefit from lowering blood pressure (Nissen and others 2004), confirming earlier evidence that individuals with a history of AMI who have lower blood pressure are less likely to have future vascular events. Furthermore, investigators have established mortality and morbidity benefits for several specific classes of drugs to reduce blood pressure in patients with vascular disease, namely, beta-blockers, calcium-channel blockers, and ACE inhibitors (Fox 2003).

In patients with a prior history of stroke or transient ischemic attack (transient occlusion of artery supplying the brain), the long-term benefits of lowering blood pressure have been clearly established. Lowering blood pressure reduces the overall risk of future stroke by 28 percent and of other vascular events and CHF by 26 percent in patients with a history of stroke disease, irrespective of their hypertension status. The benefits are even more pronounced for individuals with a history of hemorrhagic stroke. Larger reductions in blood pressure confer greater benefits, and benefits are present across different age groups, genders, and ethnicities and with varying comorbid status.

Beta-blockers are one of the cornerstones of long-term treatment of individuals with IHD, especially those with a history of AMI. Long-term use of beta-blockers has been associated with 23 percent relative risk reduction in mortality (Freemantle and others 1999), 25 percent relative risk reduction in nonfatal myocardial infarction, and 30 percent relative risk reduction in sudden cardiac death (Yusuf and others 1985). The benefits are larger for those at highest risk of sustaining a vascular event in the future and are present across all age groups and sexes. Furthermore, beta-blockers provide clear benefits in patients with chronic stable angina, where they provide symptom relief as well as reductions in vascular events (Heidenreich and others 1999).

ACE inhibitors have proved invaluable in preventing cardiovascular events and CHF in those with IHD. The extent to which the benefits conferred by their use are caused by their ability to lower blood pressure or by their other properties, such as cardiac remodeling and neurohormonal modulation, is not clear. Long-term use of ACE inhibitors in those with a history of myocardial infarction and in other individuals at high risk of vascular disease reduces vascular mortality by 25 percent and other nonfatal events, such as recurrent myocardial infarction, revascularization, hospitalization, progression or new onset of CHF, and stroke (Teo and others 2002). In those with asymptomatic or symptomatic left ventricular dysfunction after myocardial infarction, ACE inhibitors reduce the risk of a variety of vascular endpoints by 20 to 26 percent. Similarly, the use of ACE inhibitors even in those with no evident left ventricular dysfunction confers a 21 percent reduction in risk for major coronary events (Dagenais and others 2001), 32 percent for stroke (Bosch and others 2002), and 20 to 22 percent for composite vascular outcomes (Fox 2003).

Nonpharmacological Interventions Cessation of smoking and dietary modifications are important goals of secondary prevention of CVD. Cardiac rehabilitation, including exercise, is useful for a wide range of patients with IHD and reduces future vascular events by about 15 percent. Exercise alone reduces vascular mortality by 24 percent and vascular endpoints by 15 percent (Jolliffe and others 2000). Results of trials for psychological interventions targeted at stress, depression, low social support, and so on have been conflicting.

Congestive Heart Failure. Diuretics are standard therapy for CHF, with the loop and thiazide diuretics most commonly used. Diuretics provide relief of symptoms more rapidly than any other CHF medication because they are the only drugs that can adequately control the fluid retention associated with CHF. Using spironolactone, a neurohormonal antagonist, together with a diuretic decreased the risk of mortality by 30 percent and of hospitalization by 35 percent, compared with a placebo in patients with severely advanced heart failure (Pitt and others 1999); however, this combination requires intensive monitoring of electrolytes and testing to follow patients and thus was not included in our cost-effectiveness analyses.

Investigators have shown that ACE inhibitors reduce risks related to a variety of endpoints, including mortality, hospitalization, major coronary events, deterioration of symptoms, and progression from asymptomatic to symptomatic left ventricular dysfunction, by 25 to 33 percent. The benefit is conferred irrespective of the etiology of systolic failure; begins soon after the start of treatment; persists over the long term; and is independent of age, sex, and baseline use of other medications. Furthermore, the use of ACE inhibitors has proved to be highly cost-effective in developed countries.

Beta-blockers improve symptoms, decrease hospitalization and deterioration of heart function, and improve mortality. They should be used even when the patient becomes asymptomatic. Beta-blockers are beneficial at all stages of CHF, reducing the morbidity and mortality associated with CHF by 25 to 33 percent. Because most patients with CHF die of sudden cardiac death, the protective effects of beta-blockers are probably related to their antiarrhythmic properties.

Digitalis decreases hospitalization rates in individuals with CHF but has no effect on vascular or total mortality (Digitalis Investigation Group 1997). Given that it also has a narrow therapeutic-toxic window and requires careful monitoring, its role in standard treatment for CHF has diminished and has not been included in our cost-effectiveness analyses.

Rheumatic Heart Disease. The management of patients with ARF includes providing antistreptococcal treatment, managing clinical manifestations, and screening children. In the acute stage, all patients with ARF should be treated as if they have a group A streptococcal infection—that is, with a 10-day course of penicillin. Anti-inflammatory agents provide symptomatic relief during ARF but do not prevent RHD. Secondary prophylaxis prevents colonization of the upper respiratory tract and consists of penicillin or sulfadiazine for the first five years (and for life for patients with valvular heart disease). Noncompliance is frequent, reaching rates as high as one-third of patients (Bassili and others 2000). Tertiary treatment entails surgery for valve replacement or valvuloplasty.

Linking Costs and Effectiveness in Developing Countries

Few intervention trials have been carried out solely in developing countries, but investigators have extrapolated estimates of cost-effectiveness ratios for the developing world in general based on changes in key input prices (Goldman and others 1991); however, this process is limited by the fact that both the underlying epidemiology and the costs can differ significantly across and within countries and regions. Thus, our results reflect models that used prices and epidemiological data for World Bank regions where applicable. Intervention effects were, however, based on systematic reviews of randomized trials or meta-analyses in developed countries. Until intervention trials are conducted in developing countries, this option remains the best for evaluating the cost-effectiveness of various interventions in the developing regions. In cases in which models for diseases in selected regions were not developed, we present results of cost-effectiveness analyses from high-income countries.

We used estimates of life expectancy for the model from data supplied by the volume editors. The model includes only the costs related to the intervention itself and to CVD events and their sequelae. Costs include personnel salaries, health care visits, diagnostic tests, and hospital stays as provided by the volume editors. Our analysis does not include indirect costs, such as those arising from lost work time or family assistance. Drug costs are from McFayden (2003). All are in U.S. dollars unless otherwise specified. Disability weights were taken from Mathers and others (2006).

Ischemic Heart Disease.

Acute Myocardial Infarction We evaluated four incremental strategies for the treatment of AMI and compared them with a strategy of no treatment as a base case. The four treatment strategies were aspirin (162.5 mg per day for 30 days); aspirin and atenolol (100 mg per day for 30 days); aspirin, atenolol, and streptokinase (1.5 million units); and aspirin, atenolol, and tissue plasminogen activator (100 mg accelerated regimen). Doses for the aspirin and streptokinase were those used by the Second International Study of Infarct Survival Collaborative Group (ISIS-2 Collaborative Group 1988), the atenolol regimen was that of the First International Study of Infarct Survival (ISIS-1 Collaborative Group 1986), and the tissue plasminogen activator dosing was that used in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)–I trial (GUSTO Investigators 1993). The relative risk of dying from AMI was reduced for all patients receiving the medications. Patients receiving the thrombolytics faced increased risks of major bleeds and hemorrhagic strokes. Because the effectiveness of streptokinase diminishes over time, we carried out two further sensitivity analyses to compare its use for patients over and under the age of 75 and for patients who receive the intervention sooner or later than six hours after the onset of symptoms.

Table 33.2 presents incremental cost-effectiveness ratios (ICERs) for each therapy by region. The incremental cost per DALY averted was less than US$25 for all six regions for the aspirin and aspirin plus atenolol interventions; US$634 to US$734 for aspirin, atenolol, and streptokinase; and slightly less than US$16,000 for aspirin, atenolol, and tissue plasminogen activator. Minor variations occurred between regions because of small differences in follow-up care costs. The results for an analysis that evaluated ICERs as cost per life year saved showed no significant differences.

Table 33.3 displays the results of the secondary analysis for streptokinase and tissue plasminogen activator. Giving the streptokinase sooner than six hours following onset reduces the incremental cost per DALY to less than US$440 compared with more than US$1,300 if given after six hours. Similar effects are seen when streptokinase is given to those under 75 compared with those 75 years or older.

According to meta-analyses, nitroglycerin has a modest effect on mortality in AMI: a 3 percent reduction. However, given that it can have profound effects on blood pressure that could limit the use of beta-blockers that confer more significant benefits, its use should be limited to patients with ongoing ischemic pain and systolic blood pressures greater than 90 millimeters of mercury who do not have ongoing right ventricular infarction. When modeled, it had a reasonable cost-effectiveness ratio of US$70 per life year saved, but we did not include the analysis in the incremental analysis because of the blood pressure effects of the multiple agents.

Secondary Prevention Four medical therapies—aspirin, beta-blockers, statins, and ACE inhibitors—have been the mainstay of treatment for those with IHD in the developed world. To evaluate the best medical intervention, we used incremental cost-effectiveness analysis to examine the 15 different possible combinations of the four standard medical therapies. The four therapies were 75 to 100 mg per day of aspirin, 100 mg per day of atenolol, 10 mg per day of enalapril, and 40 mg per day of lovastatin. In addition, CABG surgery provides an invasive option that gives added mortality benefit when compared with conventional medical therapy in patients with certain anatomical obstructions in coronary circulation. Thus, we evaluated CABG in addition to all four medications for those with left main coronary artery disease or with three-vessel coronary artery disease and reduced left ventricular function. Because these therapies also have significant effects on the incidence of stroke, we included the effect on DALYs and costs for stroke in the analyses.

In addition to the mortality benefits demonstrated by trials of the individual medications or surgery, they also resulted in significant reductions in hospitalizations in developed countries. The cost savings from these reduced hospitalizations make the cost-effectiveness of such interventions quite favorable in developed countries; however, given that hospital facilities may not be available to most patients in many developing regions, we undertook two separate analyses, one with hospital costs and one without.

In a setting where hospitals are available, a combination of aspirin and atenolol dominated no therapy and was cost saving in all regions (table 33.2). The ICERs for the addition of enalapril ranged from US$660 per DALY in Sub-Saharan Africa to US$866 per DALY in Europe and Central Asia. The combination of all four medications ranged from US$1,720 per DALY to US$2,026 per DALY. For CABG the costs per DALY ranged from about US$24,000 to more than US$72,000. Despite having similar benefits as aspirin and atenolol in relation to mortality, enalapril and lovastatin demonstrated higher per DALY costs because of the added costs of monitoring renal and liver function, respectively, as is required for these two medications.

When we assumed that hospitals were not readily available (table 33.2), no therapy combination was cost saving compared with no therapy. The combination of aspirin and atenolol was the next best strategy, with ICERs ranging from US$386 per DALY in South Asia to US$545 per DALY in Latin America and the Caribbean. The addition of enalapril increased the range of ICERs to US$783 per DALY to US$1,111 per DALY, and the addition of lovastatin increased them still further. CABG was not evaluated because of the underlying assumption that hospitals were not available.

Table 33.4 shows the number of events prevented with the four-drug combination medical therapy compared with no therapy and the additional number of events averted with CABG compared with the four-drug combination. The medical regimen alone would prevent some 2,000 CVD deaths, about 4,000 myocardial infarctions, and approximately 200 strokes per million persons treated in each region. The use of CABG in addition to the medical regimen would prevent an additional 65–70 deaths, nearly 300 myocardial infarctions, and up to 30 strokes per million population.

Congestive Heart Failure. The interventions examined for CHF were the addition of the ACE inhibitor enalapril, the beta-blocker metoprolol, or both to a baseline of diuretic treatment. As for the IHD interventions, we performed separate analyses for each assumption of whether or not hospital facilities would be available. For the model of treatment for CHF assuming hospitalization (table 33.2), the addition of enalapril is cost saving and the ICER for the addition of metoprolol ranges from US$124 to US$219 per DALY depending on the region. When the availability of hospitals is limited (table 33.2), the enalapril plus diuretics strategy is no longer cost saving, but it costs only US$31 per DALY or less, and the ICER for enalapril, metoprolol, and diuretics increases only to about US$275 per DALY. These figures are probably underestimates of the cost per

Table 33.2 ICERs for Treatment Compared with No Treatment, by Region
US$/DALY

	Medical therapy for AMI compared with baseline of no treatment				Medical therapy and CABG for IHD compared with baseline of no treatment, hospital access				Medical therapy and CABG for IHD compared with baseline of no treatment, limited hospital access			ACE inhibitors and beta-blockers for CHF compared with baseline of diuretics, hospital access		ACE inhibitors and beta-blockers for CHF compared with baseline of diuretics, limited hospital access	
Region	**ASA**	**ASA, BB**	**ASA BB, SK**	**ASA, BB, TPA**	**ASA, BB**	**ASA, BB, ACEI**	**ASA, BB, ACEI, Statin**	**CABG**	**ASA, BB**	**ASA, BB, ACEI**	**ASA, BB, Statin**	**ACEI**	**ACEI, MET**	**ACEI**	**ACEI, MET**
East Asia and the Pacific	13	15	672	15,867	Cost saving	781	1,914	33,846	461	942	2,220	Cost saving	189	27	274
Europe and Central Asia	19	21	722	15,878	Cost saving	866	2,026	47,942	530	1,097	2,470	Cost saving	144	30	275
Latin America and the Caribbean	20	22	734	15,887	Cost saving	821	1,942	62,426	545	1,111	2,497	Cost saving	124	31	275
Middle East and North Africa	17	20	715	15,893	Cost saving	672	1,686	72,345	527	996	2,305	Cost saving	128	29	275
South Asia	9	11	638	15,860	Cost saving	715	1,819	24,040	386	828	2,034	Cost saving	219	25	273
Sub-Saharan Africa	9	11	634	15,862	Cost saving	660	1,720	26,813	389	783	1,955	Cost saving	218	25	273

Source: Authors' calculations.
ASA = aspirin, BB = atenolol, SK = streptokinase, TPA = tissue plasminogen activator, ACEI = enalapril, Statin = lovastatin, MET = metoprolol.
Note: The intervention in the first column of each set of strategies is compared with the baseline; each successive intervention for each set of strategies is compared with the intervention immediately to its left.

Table 33.3 Sensitivity Analyses: Effect of Time to Treatment and Age on Use of Thrombolytics in AMI (All Regions Combined)

	SK[a] (US$/DALY)	TPA[a] (US$/DALY)
Time to thrombolysis		
<6 hours	374–437	15,800
6–12 hours	1,300–1,440	15,700
Age at treatment		
<75	559–650	14,800
75 or older	1,260–1,350	21,000

Source: Authors' calculations.
SK = streptokinase; TPA = tissue plasminogen activator.
a. In addition to aspirin and atenolol.

DALY, given some loss in the mortality benefit for the hospitalization that the model does not capture.

Rheumatic Heart Disease. For RHD, except in epidemics, secondary prevention is more effective than primary prevention. Primary prevention by means of antibiotic treatment of streptococcus infections of the pharynx is not highly cost-effective in endemic situations, given that only 10 to 20 percent of such infections are from streptococcus, less than 3 percent of these will evolve into rheumatic fever, and only a proportion of these continue on to RHD (Strasser 1985). The development of a rapid antigen test for diagnosing group A streptococcal pharyngitis may make primary prevention more cost-effective (Majeed and others 1993). Similarly, in an epidemic in which the proportion of infections from streptococcus is higher or the rate of progression to rheumatic fever is higher, primary prevention may be cost-effective. Secondary prevention using benzathine penicillin injections is cost-saving according to Strasser (1985) and should be considered for all developing countries with the infrastructure to perform the required follow-up.

Cost-Effectiveness Analyses in High-Income Countries

Table 33.5 summarizes the results of cost-effectiveness analyses for CVD interventions in high-income countries. These results include analyses that are similar to ours. The differences are that they reflect costs and treatment patterns in the high-income countries studied, mostly the United States. Costs in developing countries are roughly one-fifth of those in developed countries (but closer to one-third in Latin America and approaching one-half in South Africa). However, where patented drugs are involved and patent laws are enforced, the costs may be much closer to U.S. levels.

Because the cost-effectiveness studies have been undertaken largely in the United States, the results do not always readily transfer to developing countries. In some U.S. studies, the alternative procedure considered is medical management; such facilities simply may not exist in developing countries. Similarly, interventions that are cost saving in the United States may not be cost saving in developing countries but may well be cost-effective in terms of cost per DALY saved. Furthermore, the cost-effectiveness analyses reflect morbidity and mortality rates in developed countries.

Interventions that Kupersmith and others (1995) classify as highly cost-effective in the United States (less than US$20,000 per life year saved or quality-adjusted life year saved) may be cost-effective in many developing countries. Interventions that

Table 33.4 Number of Deaths and CVD Events Prevented by the Use of a Four-Component Medical Regimen and CABG per 100,000 Myocardial Infarction Survivors over 10 Years, by Region

	Number of events prevented with four-component medical regimen compared with no therapy[a]				Number of incremental events prevented with CABG compared with medical therapy			
Region	IHD deaths averted	Stroke deaths averted	Myocardial infarctions prevented	Strokes prevented	IHD deaths averted	Stroke deaths averted	Myocardial infarctions prevented	Strokes prevented
East Asia and the Pacific	1,900	104	4,077	209	79	11	248	22
Europe and Central Asia	1,990	89	3,964	179	83	1	294	7
Latin America and the Caribbean	1,913	83	4,040	118	62	4	258	18
Middle East and North Africa	1,908	95	4,294	118	62	1	296	22
South Asia	1,930	97	4,043	122	34	2	275	30
Sub-Saharan Africa	1,909	91	4,233	173	69	12	254	1

Source: Authors' calculations.
a. Aspirin, atenolol, enalapril, and lovastatin.

Table 33.5 Cost-Effectiveness Analyses for CVD Interventions in High-Income Countries

Intervention	Alternative	Cost-effectiveness	Source
IHD			
Lovastatin, 20 mg/day	Diet	Cost saving (males age 45–54); US$4,700/life year saved (females age 45–54)	Goldman and others 1991[a]
Defibrillators in emergency vehicles	No defibrillators	US$47 to US$551/life year saved; up to US$2,600 in rural areas	Jermyn 2000; Ornato and others 1988; Rowley, Garner, and Hampton 1990[b]
Propranolol for postmyocardial infarction (beta-blocker)	No beta-blockers	US$2,400 for high-risk patients; US$23,400 for low-risk patients	Goldman and others 1988[a]
CABG for left main disease	Medical management	US$2,700 to US$6,700/life year saved	Weinstein and Stason 1982;[b] A. Williams 1985[a]
PTCA (men age 55 with severe angina)	Medical management	US$6,400 to US$8,800/life year saved (US$28,000 to US$132,000 for mild angina)	Wong and others 1990[b]
Primary angioplasty	No intervention after AMI	US$12,000/quality-adjusted life year	Parmley 1999
Three-vessel CABG	Medical management	US$14,000/life year saved	Weinstein and Stason 1982
Streptokinase (reperfusion), with PTCA available	No intervention after AMI	US$15,000/quality-adjusted life year	Parmley 1999
Tissue plasminogen activator (AMI)	Steptokinase	US$33,500/life year saved	Lorenzoni and others 1998
Primary stenting, one-vessel, men over age 55	PTCA	US$32,000/life year saved	Cohen and others 1993
Three-vessel CABG for severe angina	PTCA	US$41,000/life year saved	Wong and others 1990[b]
Two-vessel CABG	Medical management	US$33,000 to US$90,000/life year saved	Weinstein and Stason 1982; A. Williams 1985
Angiography for coronary artery disease	CABG	US$45,000/quality-adjusted life year	Doubilet, McNeil, and Weinstein 1985[a]
Stroke			
Anticoagulants (warfarin) for chronic nonvascular atrial fibrillation	Aspirin	Warfarin dominates for high-risk patients; US$10,000/quality-adjusted life year for medium-risk patients; US$462,000/quality-adjusted life year for low-risk patients	Gage, Cardinalli, and Owens 1998[c]
Anticoagulants for mitral stenosis and atrial fibrillation	No anticoagulants	US$5,500/quality-adjusted life year	Eckman, Levine, and Pauker 1992[c]
Carotid endarterectomy (symptomatic patients)	Aspirin	US$5,100 to US$51,000/life year saved	Kuntz and Kent 1996; Matchar, Pauk, and Lipscomb 1996[c]
Cardiac transplant	No transplant	US$54,000/life year saved	Evans 1986[a]
Arrhythmias			
Implantable cardioverter-defibrillator for cardiac arrest (long term)	Medical management	US$28,000/life year saved	King, Aubert, and Herman 1998; Kuppermann and others 1990
RHD			
Benzathine penicillin injections	No injections	Cost saving	Strasser 1985

Source: Authors.
Note: All costs have been converted to 2001 U.S. dollars.
a. Surveyed in Kupersmith and others 1995.
b. Surveyed in Tengs and others 1995.
c. Surveyed in Holloway and others 1999.

Kupersmith and others (1995) classify as cost-effective in the United States (US$20,000 to US$40,000 per life year saved or quality-adjusted life year saved) are probably borderline cost-effective for developing countries. Interventions that Kupersmith and others (1995) classify as borderline, expensive, or very expensive in the United States are unlikely to merit public funding in developing countries.

Thus, medical interventions that are likely to be cost-effective in developing countries include benzathine penicillin injections as secondary prevention for those who have had rheumatic fever (usually for five years); ACE inhibitors for CHF; and various drugs (beta-blockers, off-patent statins) for long-term care following a myocardial infarction, confirming our earlier analyses. Other therapies that are probably cost-effective but that we did not analyze include antithrombotic agents (aspirin, heparin) to prevent venous thromboembolism; anticoagulants for medium- and high-risk nonvalvular atrial fibrillation (stroke); and anticoagulants for mitral stenosis and atrial fibrillation (stroke).

Selected invasive interventions that might possibly be cost-effective for CVD in certain developing countries include pacemaker implants for atrioventricular heart block, primary angioplasty for acute myocardial infarction, and reperfusion with streptokinase. Of course, the ability to undertake these interventions assumes a cost-effective infrastructure for diagnosis and referral and an adequate volume of cases. For example, the American Heart Association recommends acute angioplasty in centers where the physician conducts at least 75 such procedures each year and the hospital conducts at least 200 per year. For stroke, carotid endarterectomy is potentially cost-effective for symptomatic patients compared with aspirin alone, again in an environment with an adequate volume of cases. Cost-effectiveness is much lower for asymptomatic cases.

Interventions that rank as cost-effective for heart disease in the U.S. context and that are borderline cost-effective in developing countries include implantable cardioverter-defibrillator for cardiac arrest, primary stenting for single-vessel disease (the study was for men over age 55), CABG for two-vessel disease, and angiography for patients with a high probability of coronary artery disease.

RESEARCH AND DEVELOPMENT

Even though most of the interventions currently available appear to be expensive and complex for developing countries, the demand for effective care for cardiovascular diseases will exert major pressure on health systems in coming decades. Increased use of these procedures is already documented in China and India (Murray and Lopez 1994, 1997; Unger 1999). In this context, cardiovascular research should be concentrated in the fields of primary prevention, health services, clinical guidelines, clinical research, and epidemiology.

Primary Prevention

Because the control of many cardiovascular risk factors is strongly related to the legislative environment—for example, that pertaining to tobacco use or nutrition—the design and implementation of appropriate laws and regulations is likely to increase in developing countries. However, any such initiatives need to be monitored and systematically evaluated, especially to estimate the magnitude of the reduction achieved.

Another area of research is the assessment of chemoprophylaxis in primary prevention. Multidrug combinations such as the hypothetical "polypill" are likely to be the first practical initiative of a long list of important innovations. Both the efficacy and the effectiveness of new interventions in primary prevention should be evaluated as a matter of urgency, because no results of large-scale clinical trials in developing countries are as yet available.

Health Services

Capacity building—more specifically, education and training—of health care workers in developing countries, is a major issue for the future, along with critical evaluations of the performance of health workers. Such evaluations should compare various capacity-building strategies; for instance, they could compare the delivery of simplified regimens of care by community health workers versus delivery of care by trained health professionals.

The dissemination of innovations deserves special attention in a context of scarce resources (Berwick 2003). The transfer of technologies to developing countries should be made on cost-effectiveness criteria, which implies analysis conducted in the specific situation of developing countries—for example, cost-effectiveness for thrombolytics in a developing country might be much worse than in the United States if getting to a hospital on time is a problem. Sensitivity analysis of the cost-effectiveness of surgical and medical interventions in developing countries is also needed.

Furthermore, the appropriate incentives for technological changes in health care should be investigated (McClellan and Kessler 1999). This line of research includes analyses of the pricing of technologies (including drugs) or of new designs for services, such as point-of-care devices for use by community health workers.

The long period of incubation of CVD opens up opportunities for extensive screening based on preclinical signs and biomarkers. However, strong lines of research are needed to secure effective and safe screening programs and should include opportunistic screening for places where visits to health centers are limited.

Finally, all assessments made in relation to health services research should take into account the costs related to scaling up any procedure evaluated.

Clinical Guidelines

The diffusion of health technologies usually leads to a widening of the clinical indication beyond the evidence-based scope of the intervention (PTCA is a classic example) (Dravik 1998), corresponding to a decrease not only in the procedure's efficacy, but also in its effectiveness (Anderson and Lomas 1988; Blustein 1993). Several studies suggest that overuse and underuse tend to coexist in the same community and that even severe scarcity of resources does not protect against overuse of cardiological interventions, at least among certain segments of the population (Joorabchi 1979; Soumerai and others 1997).

The consequences of such trends are more dramatic in developing than developed countries. Therefore, the introduction of costly care should be accompanied by a corresponding effort in relation to the provision of formal education to providers and prescribers, complemented by the development of clinical guidelines aimed at avoiding both the overuse and the underuse of procedures.

Clinical guidelines are already numerous, but all have been established in affluent countries. A new, specific effort should be made in developing countries to address local issues, such as problems related to the availability of procedures or drugs or to accessibility of services, and the development and maintenance of these guidelines should follow best available standards.

Clinical Research

In most situations, health care innovations should be introduced as experimental interventions to permit proper monitoring and evaluation. These experiments do not have to address the efficacy of the procedure (many innovations will already have been tested), but rather issues pertaining to their effectiveness and efficiency in the specific context of developing countries.

Another reason for the experimental approach is the rapidity with which the field of CVD is evolving. It is not reasonable, at the local level, to wait until the publication of trial results and meta-analyses, which often takes place years after changes have occurred in everyday practice. For this reason, a new culture of clinical research should be developed in which every innovation should be taken as an opportunity for systematic experimental evaluation.

Among various topics in clinical research, adherence deserves special mention. On average, 50 percent of patients in developed countries do not take their prescribed medicines after one year, despite having full access to medicines. In developing countries, this poor adherence is made worse by poor access to health services and drugs, to lack of education, and to other factors (Bovet and others 2002; WHO 2003a). Options for improving adherence should be designed and experimented with.

Epidemiological Research

A basic task of epidemiological research is to assess geographic and secular trends in the distribution of risk factors. Of special relevance is the movement from regional to country levels and the trend within a country. The impact of poor health status in early life should be assessed from the impact of poor fetal health to the consequence of multiple childhood infections on the risk for CVD. Because of the scarce availability of resources, the development and maintenance of health care should be supported by a comprehensive information system. Simple, affordable health information systems are preferable along the lines of the framework developed by the World Health Organization.

CONCLUSIONS: PITFALLS AND PROMISES

A global CVD epidemic is rapidly evolving, and the burden of disease is shifting. Twice as many deaths from CVD now occur in developing as in developed countries. The vast majority of CVD can be attributed to conventional risk factors. Even in Sub-Saharan Africa, high blood pressure, high cholesterol, extensive tobacco and alcohol use, and low vegetable and fruit consumption are already among the top risk factors for disease. Because of the time lag associated with CVD risk factors, especially in children, the full effect of exposure to these factors will be seen only in the future. Information from more than 100 countries shows that more 13- to 15-year-olds smoke than ever before, and studies show that obesity levels in children are increasing markedly in countries as diverse as Brazil, China, India, and almost all island states (Leeder and others 2004). Populationwide efforts now to reduce risk factors through multiple economic and educational policies and programs will reap savings later in medical and other direct costs as well as indirectly in terms of improved quality of life and economic productivity.

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