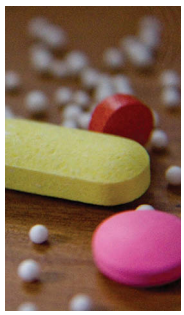

Chapter 8

Ischemic Heart Disease: Cost-Effective Acute Management and Secondary Prevention

Sagar B. Dugani, Andrew E. Moran, Robert O. Bonow, and Thomas A. Gaziano

INTRODUCTION

Cardiovascular disease (CVD) is the single most important cause of death worldwide; in 2010, it resulted in 16 million deaths and the loss of 293 million disability-adjusted life years (DALYs) (Lozano and others 2012; Murray and others 2012). CVD involves conditions that affect the vasculature that supplies the heart, brain, and other vital organs (Roth and others 2015). Of all of the causes of CVD, ischemic heart disease (IHD) remains the major contributor to mortality and morbidity. IHD results from delivery of insufficient oxygen to meet the demands of the heart and largely manifests as angina, acute myocardial infarction, and ischemic heart failure.

Over the past two decades, although age-standardized IHD mortality has decreased in most regions, the global burden of IHD has increased by 29 percent to 29 million DALYs, in part because of a larger aging population and overall population growth (Lozano and others 2012; Moran, Forouzanfar, and others 2014a; Murray and others 2012). IHD is projected to be a major cause of death in 2030, along with unipolar depressive disorders and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) (Mathers and Loncar 2006).

This chapter reviews the global burden of IHD, with a focus on low- and middle-income countries (LMICs). We review the cost-effective management of acute IHD and subsequent secondary prevention; primary prevention is discussed in chapter 22 (Jeemon and others 2017). The chapter concludes with a discussion of the challenges that IHD poses to the global community and of solutions that may help reduce attendant mortality and morbidity.

Data Sources

Data for mortality and DALYs come from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010), which obtained and analyzed mortality data from 187 countries from 1980 to 2010 (Lozano and others 2012; Murray and Lopez 2013; Murray and others 2012). Although the study made extensive efforts to standardize the mortality data, these estimates should be interpreted cautiously; methodologies for coding deaths vary globally and can result in significant misclassification of the cause of death (Pagidipati and Gaziano 2013). The World Bank has divided the world into seven regions: high-income countries (HICs) and six geographic regions of LMICs. Our information on demographic and social indices is obtained from the World Bank's World Development Indicators; data on gross national income (GNI) per capita are obtained from the Atlas method using 2011 U.S. dollar values.

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MANIFESTATIONS OF ISCHEMIC HEART DISEASE

The most common causes of CVD morbidity and mortality are IHD, stroke (chapter 9, Yan and others 2017), and congestive heart failure (chapter 10, Huffman and others 2017); IHD is a major contributor in most world regions. IHD shares several risk factors with peripheral arterial disease, discussed in chapter 14 (Sampson and others 2017).

Two important manifestations of IHD are angina and acute myocardial infarction. Angina is the characteristic chest pain of IHD that develops when atherosclerosis causes partial occlusion of one or more coronary arteries, leading to insufficient oxygen supply to the heart muscle (ischemia). In chronic stable angina, chest pain follows a predictable exertional pattern with the patient aware of activities that trigger it (Kumar and Cannon 2009a, 2009b; Ohman 2016). Those with chronic stable angina have an annual mortality rate of less than 2 percent. Individuals with chronic stable angina or those who were previously asymptomatic may develop acute chest pain of varying intensity either at rest or with minimal activity. Such events are termed *acute coronary syndrome* (ACS) and include unstable angina, non-ST-elevation myocardial infarction (collectively referred to as NSTE-ACS), and ST-elevation myocardial infarction (STEMI). ACS may be diagnosed by symptoms, characteristic electrocardiogram changes, and elevated serum levels of cardiac biomarkers such as troponin T or I and creatine phosphokinase.

Accordingly, unstable angina is defined as the presence of cardiac symptoms in the absence of elevated cardiac biomarkers; non-ST-elevation myocardial infarction is defined as the presence of cardiac symptoms and elevated cardiac biomarkers in the absence of ST-segment elevations on an electrocardiogram; STEMI is defined as the presence of cardiac symptoms and elevated cardiac biomarkers, along with ST-segment elevations in two or more contiguous leads (Anderson and others 2013; Arbab-Zadeh and others 2012; Crea and Liuzzo 2013; Libby 2013; Thygesen and others 2012). A proportion of acute IHD events, including most sudden cardiac deaths, occurs outside of the clinical and diagnostic setting and cannot be classified into ACS categories.

RISK FACTORS FOR ISCHEMIC HEART DISEASE

Traditional Risk Factors

The development of IHD is associated with several traditional risk factors: hypertension (chapter 22, Jeemon and others 2017), hyperlipidemia (chapter 22, Jeemon and others), type 2 diabetes mellitus (chapter 12, Ali and others), obesity (chapter 7, Malik and Hu 2017), suboptimal diet (chapter 6, Afshin and others 2017), physical activity (chapter 5, Bull and others 2017) and lifestyle, and smoking (chapter 4, Roy and others 2017). The GBD assessed the global burden of these risk factors over 20 years (Lim and others 2012). Health care providers and policy makers are working with government- and nongovernment-based stakeholders to develop interventions to curb the rise in these risk factors that impose significant health and economic burdens. Nontraditional risk factors, such as major depression, socioeconomic deprivation, air pollution, and alcohol abuse, are associated with IHD risk and are described in chapter 16 (Magee and others 2017) and in other chapters in this volume. They are also discussed in *Disease Control Priorities*, third edition, volume 4, *Mental, Neurological, and Substance Use Disorder* (Patel and others 2015).

HIV/AIDS and IHD

With improved management of HIV and AIDS, CVD among those receiving antiretroviral medications is a potential risk (Casper and others, forthcoming). In rural South Africa, the number of CVD-related deaths among men older than age 65 years is increasing; however, for men between ages 50 and 64 years, CVD-related deaths have been halved, likely because of the concomitant rise in HIV/AIDS-related mortality (Tollman and others 2008). HIV-seropositive men have a higher prevalence of dyslipidemia, diabetes, peripheral artery disease, and high baseline lipid levels and lipoprotein(a) (Mauss and others 2008; Palacios and others 2008) attributable to smoking, to antiretroviral medications that cause dyslipidemia, and to HIV/AIDS as an independent risk factor for CVD. These trends suggest that closer monitoring is required in HIV/AIDS patients given that their increased life expectancy from improved treatment makes them more likely to have CVDs seen in non-HIV populations.

GLOBAL BURDEN OF ISCHEMIC HEART DISEASE

Globally, CVD death rates in HICs are declining. However, the high global burden of CVD is driven by deaths among the 85 percent of the world's population that lives in LMICs. The age-adjusted death rate for CVD has decreased by 21 percent, but the number of deaths has increased by 31 percent. The age-adjusted death rate for IHD fell by 19 percent from 131 deaths per 100,000 population to 106 deaths per 100,000 population; however, the total number of deaths increased by 35 percent. The apparent paradox can be explained in large part by overall population growth and aging, as well as by improvements

in prevention and case-fatality rates. In both 1990 and 2010, IHD was the single most important cause of death (Lozano and others 2012). Although global trends show a larger IHD burden in LMICs compared with HICs, significant variation in the IHD burden occurs across the six LMIC regions and among countries within a given region or World Bank income category (Moran, Forouzanfar, and others 2014a, 2014b) (map 8.1, figures 8.1 and 8.2).

High-Income Countries

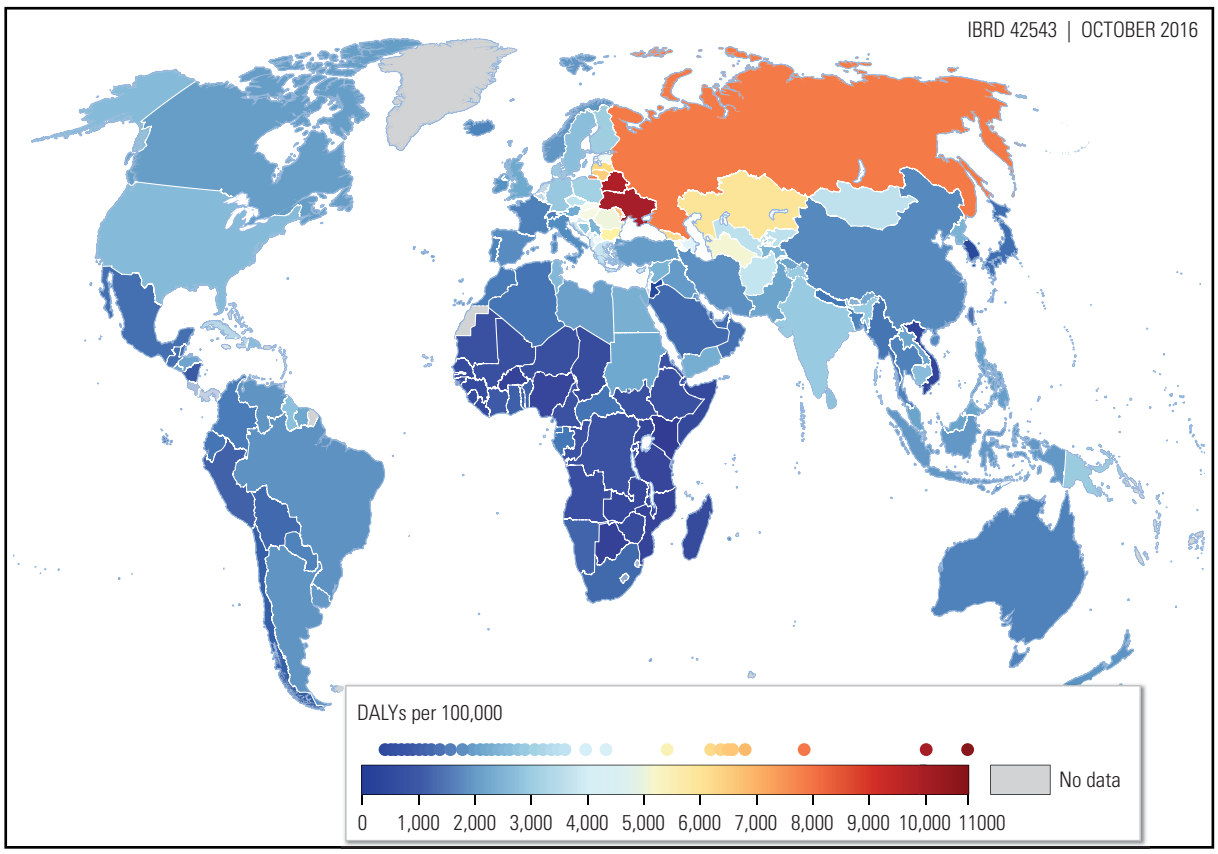
In 2010, CVD was responsible for approximately 36 percent of deaths in HICs; more than 50 percent of these deaths were caused by IHD. The age-standardized loss in DALYs attributed to IHD decreased; France, Japan, and the Republic of Korea reported the lowest DALYs lost among HICs (Moran, Tzong, and others 2014).

East Asia and Pacific

In 1990, IHD was the fourth major cause of death in East Asia and Pacific; in 2010, it was the leading cause. The mortality trends in 2010 from IHD varied among the subregions in East Asia and Pacific. IHD was the second major cause of death in East Asia, the fourth major cause in South-East Asia, and the fifth major cause in Oceania.

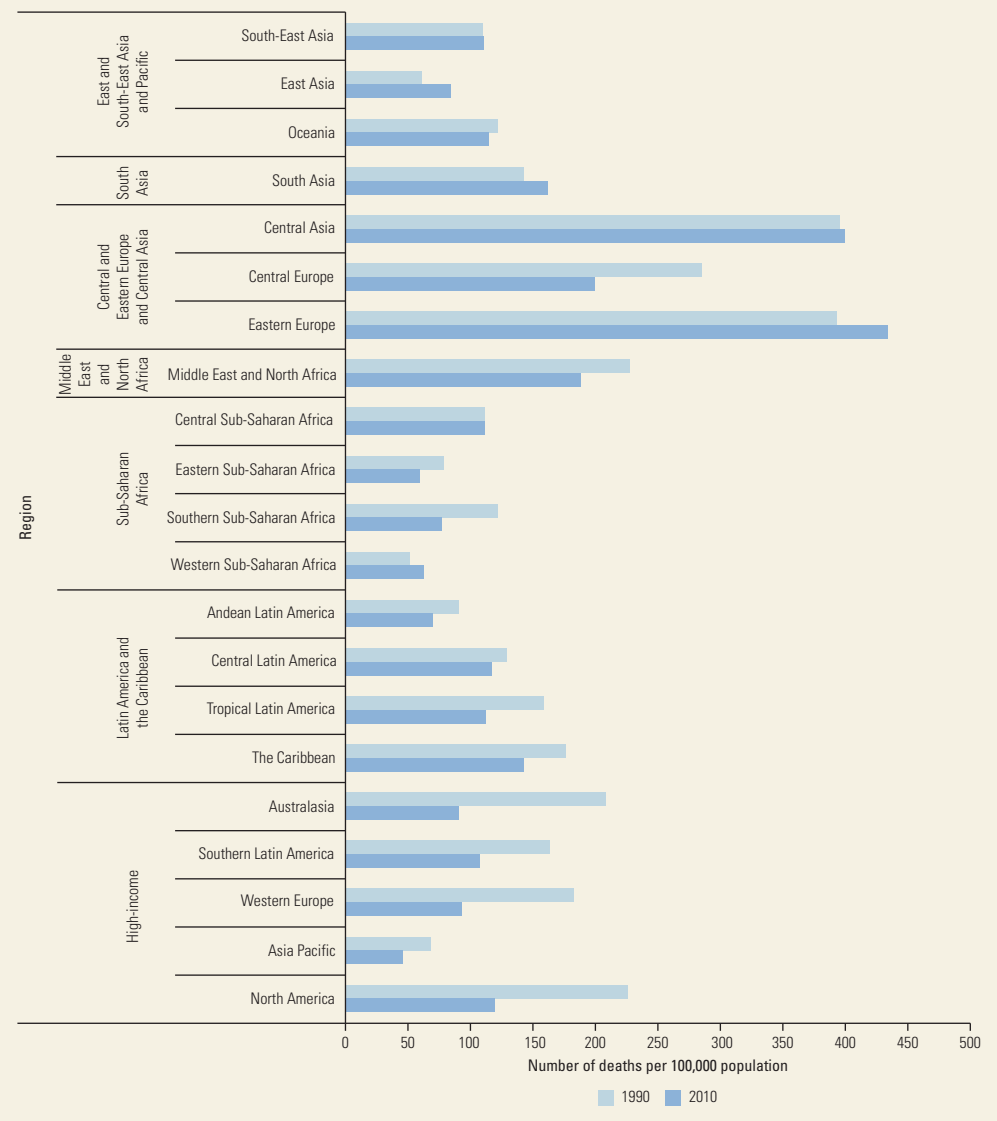
China, which accounts for approximately 70 percent of the region's population, has seen a rapid transition in health in recent decades (Yang and others 2013; Zhang, Lu, and Liu 2008). In 1990, lower respiratory tract infections were the leading cause of death; strokes were the second leading cause of death, accounting for 1.3 million deaths. In 2010, however, stroke-related deaths increased by 35 percent to 1.7 million, making stroke the leading cause of death. IHD, in contrast, was the seventh major cause of death in 1990, accounting for 450,000 deaths; in 2010, it became the second leading cause, claiming approximately 950,000 lives. From 1984 to 1999, the incidence of coronary heart disease (CHD) increased by 2.7 percent annually for men and 1.2 percent annually for women (Zhang, Lu, and Liu 2008).

Map 8.1 Ischemic Heart Disease per 100,000 Population, Both Genders, All Ages, 2010



Source: IHME website, http://vizhub.healthdata.org/gbd-compare/.
Note: DALYs = Disability-adjusted life years. Map shows number of DALYs lost per 100,000 population. Each dot in key represents a country and the distribution by each color and number.

Figure 8.1 Global Variation in Mortality from Ischemic Heart Disease in Men, 1990 and 2010



Source: Moran, Forouzanfar, and others 2014b.

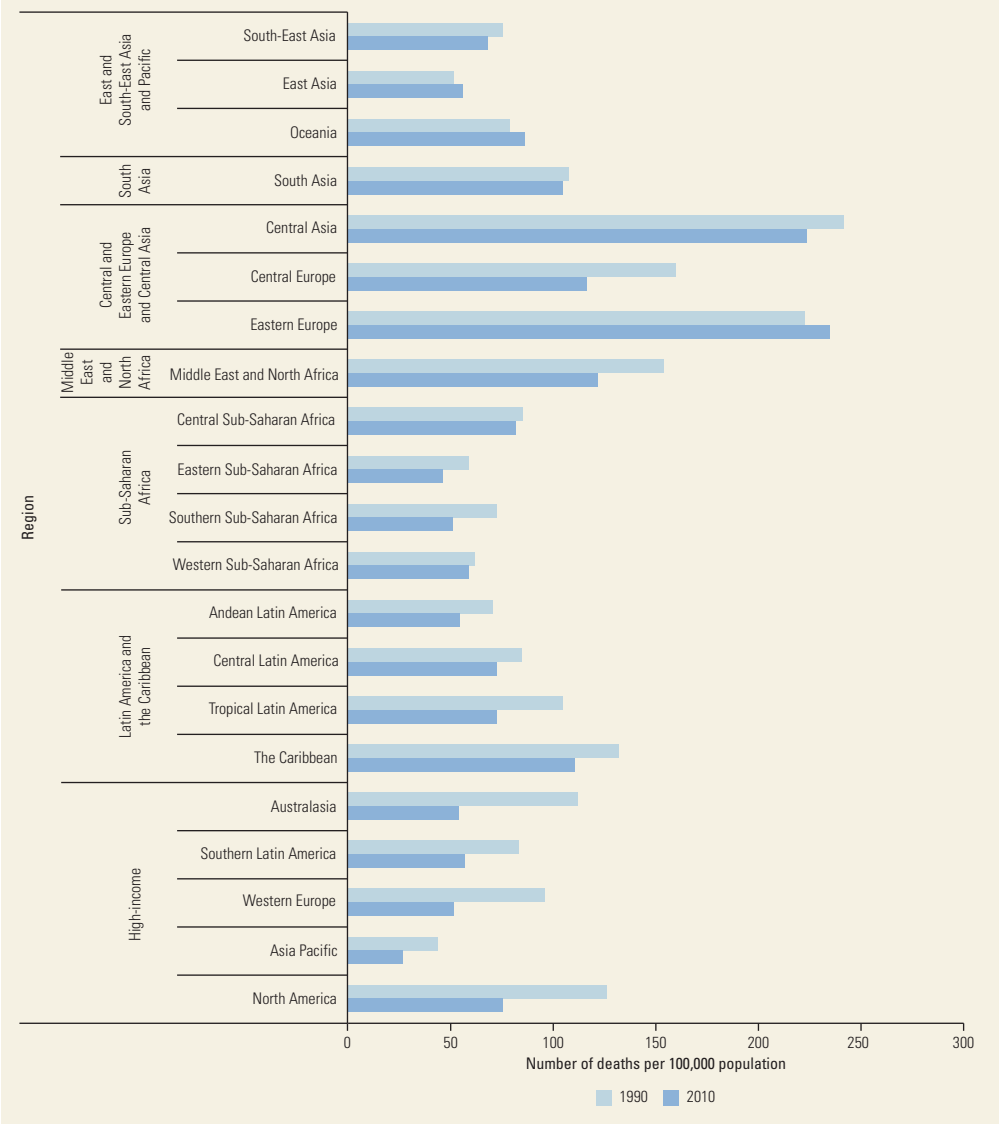
Europe and Central Asia

The rate of CVD mortality is highest in Europe and Central Asia: 866 per 100,000 population in Eastern Europe and 604 per 100,000 population in Central Asia. In 2010, CVD accounted for nearly 66 percent of deaths, most of which were due to IHD. The number of CVD-related deaths varies across countries in this region. In Belarus, Bulgaria, the Russian Federation, and Ukraine, CVD rates have reached an alarming 800 per 100,000 for men (Mirzaei and others 2009).

Latin America and the Caribbean

Latin America and the Caribbean has a high CVD burden (Glassman and others 2010). In 2010, IHD was the region's leading cause of DALYs, increasing 36 percent from 1990 (IHME 2013). IHD accounted for 100 deaths per 100,000 population in the Caribbean and for approximately 14 percent of all deaths in Central Latin America. Mortality rates in these regions have increased over the past two decades. It is interesting to note that southern Latin America experienced a decrease in IHD mortality rates

Figure 8.2 Global Variation in Mortality from Ischemic Heart Disease in Women, 1990 and 2010



Source: Moran, Forouzanfar, and others 2014b.

from 1990 to 2010. In a nationwide comparative observational study examining five regions in Brazil from 2000 to 2010, 627,786 men and 452,690 women died because of IHD, absolute increases of 19 percent and 17 percent for men and women, respectively (Baena and others 2013).

Middle East and North Africa

In 2010, CVD was responsible for 199 deaths per 100,000 population in the Middle East and North Africa. Of these, IHD claimed 93 deaths per 100,000 population, representing a 15 percent increase in IHD mortality rates since 1990. In addition to increased mortality, CVD was responsible for 17.2 million DALYs lost, of which 6.8 million were attributed to IHD. A study of the 22 Arab League countries (comprising 5 low-income countries, 11 middle-income countries, and 6 HICs) showed that IHD was responsible for 14.3 percent of deaths in 2010, making it the leading cause of death. Furthermore, IHD was the leading cause of DALYs lost in men (and accounted for 6 percent of DALYs lost) and was the third leading cause of DALYs lost for women (Mokdad and others 2014).

South Asia

CVD accounted for 20 percent of all deaths in South Asia, and IHD was responsible for more than 50 percent of these deaths. In 2010, IHD was responsible for 1.8 million, or 10.6 percent of all deaths. CVD was responsible for 60.5 million DALYs lost in 2010. India, with a population of 1.2 billion, has an extremely high burden of IHD. In 1990, 1.18 million people died because of IHD; in 2010, this number increased to 2.03 million (Gupta and others 2008). A large cross-sectional study showed that CVD causes an estimated 25 percent of deaths in India, and 51 percent of CVD deaths occur in those younger than age 70 years (Reddy and others 2007). In Pakistan, the burden is equally high: approximately 20 percent of adults have IHD (Jafar, Qadri, and Chaturvedi 2008). By 2025, an estimated 3.87 million premature deaths in Pakistan will be due to CVD, cancers, and chronic respiratory diseases in people ages 30–69 years (Jafar and others 2013). These trends threaten significant economic consequences if they are not reversed.

Sub-Saharan Africa

Overall, Africa has a high CVD burden (Gaziano 2008). Of all subregions in Sub-Saharan Africa, southern Africa has the highest number of CVD deaths at 13.0 percent; in western Africa, CVD accounts for 7.5 percent of deaths. Overall across Sub-Saharan Africa, the mortality rates are lower than global averages, with the exception of southern Africa, where the rates have increased from 129 per 100,000 to 136 per 100,000 population.

ECONOMIC BURDEN OF ISCHEMIC HEART DISEASE

The economic burden of IHD is significant and can be measured in at least three ways:

- By financial costs that are incurred in the health care system and described in cost-of-illness studies
- By microeconomic studies that assess the household impact of health events, such as myocardial infarctions
- By macroeconomic analyses that assess worker productivity or loss of economic growth caused by individuals or their caregivers being partially or completely out of work because of illness.

The literature on the first and second measures in LMICs is sparse, and no microeconomic studies focus exclusively on IHD (Huffman and others 2011; Murphy and others 2013; Schieber and others 2007). Many LMICs lack extensive insurance plans, and government-funded programs may be inadequate, forcing individuals to pay out of pocket for health services in the acute setting and for medications and outpatient follow-up (Kruk, Goldmann, and Galea 2009; Leive and Xu 2008; Xu and others 2003).

Relatively more information is available on the economic burden from a macroeconomic perspective (Gaziano and others 2010). In China, the annual direct costs of CVD are estimated to be more than US$40 billion, or 4 percent of GNI. In South Africa, 25 percent of health care expenditure is devoted to CVD. There are relatively few cost-of-illness studies in other regions, but information on the costs associated with risk factors for IHD is available. Globally, health care costs related to hypertension are an estimated US$370 billion and are expected to rise to US$1 trillion in direct costs and up to US$4 trillion in indirect costs (Gaziano and others 2009). In HICs, 2 percent to 4 percent of health care expenses are devoted to the management of obesity-related illnesses. Although data are not available for all six LMIC regions, estimates from Latin America and the Caribbean indicate that diabetes-related costs are US$10 billion. The cost of long-term management of IHD is equally high. Heart failure, the most common sequela of IHD, costs an estimated US$108 billion annually worldwide (Cook and others 2014; Miller and others 2009; Safraj, Ajay, and Prabhakaran 2013) and is discussed in chapter 10 in this volume (Huffman and others 2017).

INTERVENTIONS

Success in improving CVD mortality rates depends on improved primary and secondary prevention strategies. Accordingly, 25 percent to 50 percent of the reduction in mortality is related to treatments; the remainder is due to changes in risk factors (Ford and Capewell 2011). Improvements in acute care reduce case fatality, but they also increase the size of the chronic IHD population in need of secondary prevention. Strategies to improve primary prevention are described in chapter 22 (Jeemon and others 2017). This chapter discusses individual-level interventions for management of IHD (table 8.1) and population-level interventions for tobacco cessation (table 8.2).

Acute Management

Several factors contribute to the acute management of ACS, starting with the quality of prehospital care available to those experiencing cardiac symptoms. The literature on this topic is sparse, but a survey of emergency medicine leaders in 13 LMICs in Asia, Latin America and the Caribbean, and Sub-Saharan Africa showed that the availability and use of emergency medical transport in LMICs is low, particularly in rural areas,

Table 8.1 Cost-Effectiveness of Interventions for IHD at the Individual Level

		Low-Income Countries		Middle-Income Countries	
	Country or World Bank regions studied	Very cost-effective (up to 1 times GNI per QALY, US$)	Cost-effective (up to 3 times GNI per QALY; that is, up to $3,135, US$)	Very cost-effective (up to 1 times GNI per QALY, US$)	Cost-effective (up to 3 times GNI per QALY; that is, up to $38,238, US$)
Acute management of IHD					
Intervention					
Aspirin + beta-blocker	All non-high-income regions	$11–$22			
Aspirin + beta-blocker + SK	All non-high-income regions	$634–$734			
Aspirin + beta blocker + tPA	All non-high-income regions				$15,860–$18,900
Clopidogrel[a]	China				$17,600
Primary PCI[a]	China				$9,000–$23,000
Coronary artery bypass graft surgery	South Asia, Sub-Saharan Africa, and East Asia and Pacific				$24,000–$33,800 (ICER compared with four medications: aspirin, beta-blocker, statin, and ACE inhibitor)
Secondary prevention of IHD					
Aspirin + beta-blocker + statin + ACE inhibitor	All non-high-income regions	$300–$400			
Aspirin + beta- blocker + statin + ACE inhibitor[a]	China		$3,100	$3,100	
Aspirin + beta- blocker + statin + ACE inhibitor	India			$2,920	
Polypill (aspirin + beta-blocker + statin + ACE inhibitor) to baseline	India			$1,760	
Nicotine-replacement therapy	All non-high-income regions	$55–$761			
Community pharmacist–based smoking cessation program	Thailand	$500 with 0.18 QALY gained (men); $614 with 0.24 QALY gained (women)			
Nicotine-based gum	Seychelles	$599			
Bupropion	Seychelles	$227			
ICD	United States				$17,000
CRT in heart failure	Brazil				$15,700
CRT	Argentina	$34 (ICER compared with medical therapy)			

Note: ACE = angiotensin-converting enzyme; CRT = cardiac resynchronization therapy; GNI = gross national income; ICD = implantable cardioverter defibrillator; ICER = incremental cost-effectiveness ratio; IHD = ischemic heart disease; PCI = percutaneous coronary intervention; QALY = quality-adjusted life year; SK = streptokinase; tPA = tissue plasminogen activator.
a. ICER compared with current treatment.

Table 8.2 Cost-Effectiveness of Interventions for IHD at the Population or Health Systems Level

		Low-Income Countries		Middle-Income Countries	
	Countries or World Bank regions studied	Very cost-effective (up to 1 times GNI per QALY, US$)	Cost-effective (up to 3 times GNI per QALY; that is, up to US$3,135, US$)	Very cost-effective (up to 1 times GNI per QALY, US$)	Cost-effective (up to 3 times GNI per QALY; that is, up to US$38,238)
Secondary prevention of IHD					
Tax increase on tobacco	All non-high-income regions	$3–$42			
Nonprice measure	All non-high-income regions	$54–$674			
Tobacco tax strategy	South Africa	$31			
Tobacco indoor air strategy	South Africa	$410			

Sources: Bitton and Gaziano 2011; Jha and others 2006.
Note: GNI = gross national income; IHD = ischemic heart disease; QALY = quality-adjusted life year.

which is largely attributed to deficiencies in funding and administrative leadership (Nielsen and others 2012). Additional studies are required to understand the availability and barriers to use of formal emergency medical transport systems in these settings. Given the high proportion of patients with ACS who die before coming to the hospital, a modeling study from China estimated that even optimal use of standard hospital-based treatments would have a limited impact on approximately 50 percent of acute IHD mortality (Wang and others 2014).

Where infrastructure exists, the medical management of ACS is well established through clinical trials; it may involve the use of aspirin, beta-blockers, statins, angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACE-Is), additional antiplatelet agents, thrombolytics, and anticoagulants.

The availability of and adherence to clinical guidelines vary significantly. A retrospective analysis of studies involving 50,310 STEMI patients from 63 countries showed that the use of aspirin and beta-blockers varies from 75 percent to 95 percent in middle-income countries (Orlandini and others 2006). These findings are consistent with data from the Gulf Registry of Acute Coronary Events (Gulf RACE; 8,176 adults, 6 countries); Acute Coronary Events—A Multinational Survey of Current Management Strategies (ACCESS; 11,731 adults, 19 countries in Africa, Latin America, and the Middle East); and Zyban as an Effective Smoking Cessation Aid (ZESCA; 127 adults, 4 countries) studies that showed that 68 percent to 96 percent of patients received aspirin, beta-blockers, ACE-Is, or statins (ACCESS Investigators 2011; Shimony and others 2014; Zubaid and others 2009). Several countries have increased the use of evidence-based medications, as seen in the expanded Global Registry of Acute Coronary Events (GRACE2) trial of 31,982 adults in 25 countries (Goodman and others 2009), and in the study of 1,025 patients with ACS managed at a third-level hospital in Lebanon (Abdallah and others 2010). This expansion may be due to effective government-based health care reform, as in Chile (Nazzal and others 2008), or quality improvement measures as in the Brazilian Intervention to Increase Evidence Usage in Acute Coronary Syndromes (BRIDGE-ACS) study of 1,150 patients in Brazil (Berwanger and others 2012).

Despite the availability and use of these medications, certain groups are less likely to receive appropriate therapy. This limited access, which resulted in higher mortality rates, was seen among individuals of lower socioeconomic status in the Treatment and Outcomes of Acute Coronary Syndromes in India (CREATE) prospective registry study (Xavier and others 2008) and among women in a study of six countries in the Middle East and North Africa (El-Menyar and others 2009).

The cost-effectiveness of four incremental strategies for the treatment of ACS has been evaluated:

- Aspirin
- Aspirin + beta-blocker (atenolol)
- Aspirin + beta-blocker (atenolol) + thrombolytic (streptokinase)
- Aspirin + beta-blocker (atenolol) + thrombolytic (tissue plasminogen activator).

The incremental cost per quality-adjusted life year (QALY) gained for aspirin + beta-blocker was less than US$25 for all six LMIC regions; the cost per QALY gained for streptokinase varied from US$630 to US$730; and the incremental cost-effectiveness ratio (ICER) for tissue plasminogen activator was approximately US$16,000 per QALY gained compared with streptokinase. Furthermore, recent Markov modeling of optimal medical management of in-hospital ACS showed that optimal use of aspirin, beta-blockers, ACE-Is, and statins had an ICER of less than US$3,100 (Megiddo and others 2014; Wang and others 2014).

In addition to these medications, management of ACS may require percutaneous coronary intervention (PCI). PCI is a nonsurgical procedure that uses a stent to open occluded coronary arteries. The use of PCI varies by region because thrombolytics, unlike PCI, do not require a dedicated catheterization laboratory onsite with a specialized team. In LMICs, although thrombolytics are more commonly used than PCI, the time to initiation of thrombolytic therapy is longer than in their higher-GNI counterparts: 4.3 hours versus 2.8 hours (Orlandini and others 2006). Delay adversely affects outcomes; the ideal is within 90 minutes and preferably less than six hours from onset of symptoms, because effectiveness declines to near zero at 12 hours from onset of symptoms.

The rates of PCI are higher in the United States than in Eastern Europe (Giugliano and others 2001; Kramer and others 2003). In a study of 13,591 patients enrolled in Ministry of Health hospitals in the National Cardiovascular Disease Database Registry in Malaysia, the use of streptokinase was higher for minorities (Chinese and Indians) than for local Malaysians, who were more likely to get PCI (Lu and Bin Nordin 2013). In India, the overall use of PCI was low, and even lower for those with lower socioeconomic status, reflecting inequity in care even within a country (Xavier and others 2008). In the Thai Registry in Acute Coronary Syndrome (TRACS), the Kerala ACS Registry based in India, and the Gulf RACE study, approximately 40 percent to 80 percent of patients with STEMI received thrombolytic therapy (Mohanan and others 2013; Srimahachota and others 2012; Zubaid and others 2009). Remarkably, in the ACCESS study of 11,731 adults from 19 countries in Africa, Latin America, and the Middle East, approximately 40 percent of adults with confirmed ACS did not receive PCI or thrombolytics, resulting in a higher mortality rate (ACCESS Investigators 2011). In Europe, PCI is emerging as the preferred choice in most countries, with improvements in both time to implant a coronary stent and rates of in-hospital mortality (Kristensen and others 2014; Mandelzweig and others 2006; Schiele and others 2010).

Overall, thrombolysis with streptokinase continues to be a cost-effective strategy in LMICs (Ford and Capewell 2011; Gaziano 2005; Megiddo and others 2014; Sikri and Bardia 2007; Wang and others 2014). From these studies and the GRACE Trial (Fox and others 2003; Goodman and others 2009), it is evident that the use of thrombolytics and PCI varies significantly. In the appropriate ACS setting, PCI can be as cost-effective as medical management (Kuntz and others 1996; Wang and others 2014); however, additional studies are required. In some LMICs, the use and quality of PCI care are improving despite barriers (Ranasinghe and others 2014); in several other countries, including, for example, India, treatment will continue to rely on thrombolytics until PCI-based infrastructure, access to services, and quality of cardiac care improve (Dalal and others 2013). Individuals in several LMICs may live in areas without timely access to PCI facilities; simulation analysis of a hypothetical nonurban population in Canada shows that building a new PCI facility would cost US$7,478 per QALY gained in comparison with ambulance transport (Potter, Weinstein, and Gaziano 2013). Future studies in LMICs are required to estimate costs associated with building new PCI facilities.

In comparison with thrombolytics and PCI, data on the number of coronary artery bypass graft (CABG) operations performed and their outcomes are sparse (Ribeiro and others 2006). The GRACE study based in 14 countries showed that CABG was performed in fewer than 10 percent of patients with ACS (Steg and others 2002). Although CABG is a cost-effective intervention in HICs, its ICER (compared with a combination of aspirin + beta-blocker + ACE-I + statin) may be attractive in middle-income countries (US$24,040–US$72,345 per QALY gained) but may be available only to a smaller proportion of the population (Ford and Capewell 2011; Gaziano 2005).

Regardless of the intervention used, patients may require management in a coronary care unit (CCU) where they can be monitored closely. When appropriately triaged, CCU-level management is cost-effective despite increased staffing and facilities (Kupersmith and others 1995; Weinstein and Stason 1985), but it may not be as widely available in LMICs.

Secondary Prevention

Strategies for the secondary prevention of CVD include population-based and individual-level interventions.

- Population-based interventions are often directed to cessation of tobacco use, reduction in the consumption of dietary salt and trans fatty acids

(chapter 6, Afshin and others, increased physical activity (chapter 10, Bull and others 2017), and revision of regional or national government and health policies to improve chronic care services.
- Individual-level interventions are typically seen where access and adherence to essential medications, availability of cardiac resynchronization and defibrillation therapy, and access to and the use of cardiac rehabilitation are all increasing.

Other strategies for the secondary prevention of CVD involve the management of diabetes (chapter 12, Ali and others 2017), obesity (chapter 7, Malik and Hu 2017), and hypertension (chapter 10, Huffman and others 2017).

Smoking

Although tobacco products are a major risk factor for CVD, a significant proportion of the global population continues to smoke (Giovino and others 2012; Jha and Peto 2014; Ng and others 2014). Worldwide, approximately 1.1 billion people smoke; 82 percent of smokers reside in LMICs (Jha and others 2002). Forms of tobacco include bidis, kreteks, hookah pipes, smokeless tobacco, and secondhand smoke, all of which are associated with an increase in CVD (Balbinotto Neto and da Silva 2008; Cronin and others 2012; Gupta, Gupta, and Khedar 2013; Oberg and others 2011; Pell and others 2008; Piano and others 2010). The mortality rate for cigarette smokers is two to three times higher than for similarly aged nonsmokers (Jha and Peto 2014); by 2030, approximately 10 million deaths annually will be attributable to smoking (Jha and Chaloupka 2000). To address the significant mortality and morbidity associated with smoking, the WHO World Health Assembly adopted the Framework Convention on Tobacco Control (FCTC) in 2003, which was the first global tobacco treaty to regulate smoking. Several countries have implemented FCTC measures to curb the use of tobacco and the effects of smoking.

Population-level interventions. The price of tobacco products is a major determinant in smoking uptake and cessation (Jha and Peto 2014). The International Agency for Research on Cancer has shown that a 50 percent increase in inflation-adjusted tobacco prices reduces consumption by 20 percent in LMICs (Jha and Peto 2014). In LMICs, the low specific excise tax is the main reason that cigarettes cost 70 percent less than in HICs (Jha and Peto 2014); it is estimated that a 33 percent price increase worldwide would avert 22 million to 65 million smoking-attributable deaths; 90 percent of these prevented deaths would be in LMICs (Jha and Chaloupka 2000; John 2008; Kerry and Lee 2007). Some countries, such as Uruguay, have implemented several FCTC measures, for example, banning advertisements, raising taxes, and banning smoking in public places. Over a six-year period, these countries have been able to decrease per-person consumption by 4.3 percent and prevalence of tobacco use by 3.3 percent per year (Abascal and others 2012). Simulation modeling of the effects of tobacco control measures in India shows that increased tobacco taxation and smoke-free laws could potentially avert 25 percent of myocardial infarctions and strokes in that country (Basu and others 2013). Tobacco taxation is the most cost-effective anti-smoking intervention (Ruger and Lazar 2012); however, strong political opposition in many countries remains a major barrier to wider implementation of higher tobacco taxes (Jha and others 2006).

Several other strategies have been implemented to limit the use of tobacco products. One approach is to regulate advertisements and smoking in public spaces. Advertising bans can result in a significant decline in smoking (Blecher 2008; Higashi and others 2011), and legislation-based smoking bans can reduce hospital admissions for cardiac events (Callinan and others 2010). Plain packaging of tobacco products and pictorial warnings can increase smoking cessation, as seen in Australia, Canada, India, and Thailand (Hammond 2010; Wakefield and others 2013). Furthermore, a 15 percent to 30 percent long-term cumulative decline in smoking rates has been seen as a result of effective public health efforts, as has a 6 percent reduction in the demand for tobacco (Jha and Chaloupka 2000; Saffer and Chaloupka 2000; Townsend 1993). In LMICs, mass media campaigns may decrease overall consumption, as was seen in the United States (Bala and others 2013).

Individual-level interventions. Individual-level interventions, including nicotine replacement therapy (NRT) and non-nicotine-based products and behavioral modification, have been implemented (Jha and Chaloupka 2000). A study of 484 smokers in Northern Ireland and London, England, showed that adults randomly assigned to a community-based cessation program had higher abstinence rates at 12 months compared with usual care, 14.3 percent and 2.7 percent, respectively (Maguire, McElnay, and Drummond 2001). Similarly, community-based interventions in Mauritius and South Africa resulted in a 3 percent to 11 percent decrease in smoking (Hodge and others 1996; Rossouw and others 1993; Uusitalo and others 1996). Systematic reviews of studies in HICs and LMICs show that NRT can increase the rate of tobacco-use cessation by 50 percent to 70 percent and is effective in sustaining smoking abstinence (Moore and others 2009; Stead and others 2008).

In addition to NRT, bupropion is a non-nicotine-based medication with similar efficacy to NRT (Hughes and others 2014); however, this medication is not on the WHO's Model List of Essential Medications, and additional studies are required to determine the potential availability of this medication to large populations in LMICs.

Cost-effectiveness. Of the interventions discussed, tobacco taxation is the most cost-effective option to reduce smoking (Gaziano and Pagidipati 2013; Ruger and Lazar 2012), although NRTs are also cost-effective, depending on their price and availability. Jha and others (2006) analyzed the cost-effectiveness of tobacco control using a cohort of smokers in 2000. They calculated that NRT could reduce the number of deaths by 2.9 million to 14.3 million and that a range of nonprice interventions, such as advertising bans, health warnings, and smoke-free laws, could reduce the number of deaths by 5.7 million to 28.6 million. The cost-effectiveness value associated with this reduction is US$3–US$42 per QALY saved for tax increases, not including tax revenue; US$55–US$761 per QALY saved for NRT; and US$54–$674 per QALY saved for other nonprice measures.

Although data on cost-effective interventions in LMICs are limited, a few country-specific studies have been conducted. In South Africa, the tobacco tax and indoor air policies are highly cost-effective, with an ICER of US$31 per DALY averted for the tobacco tax strategy and US$410 per DALY averted for the indoor air strategy (Bitton and Gaziano 2011; Gaziano and Pagidipati 2013). In Thailand, a community pharmacist–based smoking cessation program was cost-effective, resulting in cost savings of US$500 per life-year gained, with an average of 0.18 life-year gained in men, and of US$614 per life-year gained, with an average of 0.24 life-year gained in women (Thavorn and Chaiyakunapruk 2008). In the Seychelles, a cohort study showed that the incremental cost per life-year saved was US$599 for nicotine-based gum and US$227 for bupropion.

These studies show that the effectiveness of a strategy may vary across regions and that additional studies are required to identify cost-effective interventions. The financial investment needed for NRT may be prohibitive on a population scale in some LMICs, but it may be more cost-effective and feasible to treat the smaller, higher-risk population of IHD patients.

Access to Essential Medications for Secondary Prevention

Several evidence-based medication regimens are effective in the secondary prevention of CVD. These include aspirin, beta-blockers, ACEi and ARBs, statins, and more recently, a multidrug combination pill regimen.

Several studies have shown that the use of medications for secondary prevention varies significantly across LMIC regions, despite the inclusion of these agents in the WHO's Model List of Essential Medications (WHO 2013). The WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE) in 10 LMICs showed that among those with IHD, only 81.2 percent were prescribed aspirin, 48.1 percent a beta-blocker, 39.8 percent an ACE-I, and 29.8 percent a statin (Mendis and others 2005). A survey of nine European countries (EUROASPIRE III study) showed that among patients with IHD, only 71 percent and 78 percent were on a statin and ACEi or ARB, respectively (Kotseva and others 2009). The most recent Prospective Urban and Rural Epidemiological (PURE) study, which enrolled 153,996 adults in 3 HICs and 14 LMICs, showed that only 25.3 percent were on an antiplatelet medication, 17.4 percent on a beta-blocker, 19.5 percent on ACEi or ARBs, and 14.6 percent on a statin (Yusuf and others 2011). The results are less encouraging in India, where a survey of 53 villages observed that 14 percent of those with IHD were on aspirin, 41 percent on blood-pressure-lowering medication, and 5 percent on cholesterol-lowering medication (Joshi and others 2009). Supporting this finding was an observational study of statin use in India, which showed that although the use of statins had increased from 2006 to 2010, only 8 percent of CHD patients were on a statin (Choudhry, Dugani, and others 2014).

Several factors are responsible for the low use of medications, including inadequate availability of and access to affordable medications, low numbers of health care providers, and complicated medication regimens. In many LMICs, the cost of a month's supply of generic secondary prevention medications ranges from 1.5 to 18.4 days' wages of government workers (Mendis and others 2007); the availability of cardiovascular medications, measured by the percentage of facilities in which a medicine is available ranges from 25 percent in the public sector to 60 percent in the private sector (Cameron and others 2011; van Mourik and others 2010). The availability of generic medications had been influenced by the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement of 1995, which obliged World Trade Organization members to protect pharmaceutical patents for 20 years from the date they were filed (Smith, Lee, and Drager 2009). The subsequent Doha Declaration of 2003 granted nations compulsory licenses to domestically manufacture essential medications without permission of patent holders (Beall and Kuhn 2012; Correa 2006; Lybecker and Fowler 2009). Canada was the only country to issue a compulsory

license to export generic medications to poorer nations (Lybecker and Fowler 2009), which has helped increase the availability of generic medications in LMICs. More recent studies have shown that from 2001 to 2011, generic medications in the private sectors of 19 LMICs (10 in Latin America and the Caribbean, 8 in the Middle East and North Africa, plus South Africa) represented approximately 70 percent to 80 percent of the market share (Kaplan, Wirtz, and Stephens 2013).

Most patients with CVD require several medications, and a polypill was developed to increase the availability of these medications in LMICs. Polypills have fixed-dose combinations of different cardiac medications; they have the potential to reduce IHD and to become more widely available (Bautista and others 2013; Lonn and others 2010; Wald and Law 2003; Yusuf and others 2009). This development is encouraging, but analysis of studies shows that improved access to pharmaceuticals; improved use of insurance policies; and alignment of incentives for physicians, consumers, and pharmaceutical sellers may be needed to increase the uptake of generic medications (Faden and others 2011; Kaplan and others 2012). Greater availability of trained professionals may help improve patients' access to medications.

Medications are cost-effective in the treatment of myocardial infarction and in the secondary prevention of IHD. Combination therapy consisting of aspirin, ACE-I, a beta-blocker, and a statin is cost-effective in LMICs; combination therapy is associated with a cost of US$350 (range US$300–US$400) per QALY gained, even in the absence of a polypill (Gaziano, Opie, and Weinstein 2006; Gaziano and Pagidipati 2013).

Medication Adherence

Medication adherence refers to whether patients take medications at the required frequency and for the required duration; patients who take the prescribed medications more than 80 percent of the time are considered to be adherent (Ho, Bryson, and Rumsfeld 2009). In addition to having reduced access to affordable medications, approximately 60 percent of people in different regions who are prescribed medications are adherent to the prescribed therapy (Bowry and others 2011; Chowdhury and others 2013). The PURE study observed the lowest medication use in low-income countries, which may be due to several reasons ranging from availability of medications to adherence (Yusuf and others 2011). Medication adherence is associated with a cost reduction of 10.1 percent to 17.8 percent between high- and low- adherence groups (Bitton and others 2013). Adherence is associated with lower mortality rates, as was seen in the international REduction of Atherothrombosis for Continued Health (REACH) Registry (Kumbhani and others 2013). Overall, medication adherence remains a major challenge, likely further complicated by the complexity of different regimens.

The literature on interventions to improve medication adherence is evolving rapidly. Investigators found that a simple change in prescription length from a 30- to a 60- or 90-day supply could save 1,700–2,500 premature CVD deaths per million patients treated, in addition to up to US$200 per patient over his or her lifetime in reduced costs. In particular, significant savings accrue to patients from reduced time and transportation costs (Gaziano and others 2015). Recent reports of interventions to improve medication adherence suggest that reduced out-of-pocket expenses, better case management, improved patient education with behavioral support, expanded mobile phone messaging—supported by broader practice guidelines as well as regulatory and communication-based policies—may improve medication adherence (de Jongh and others 2012; Laba and others 2013; Tajouri, Driver, and Holmes 2014; Viswanathan and others 2012). In this context, the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial in the United States has shown that elimination of copayments for drugs after a myocardial infarction improved medication adherence to 49.0 percent from 35.9 percent (Choudhry and others 2011), although adherence remained suboptimal. Furthermore, insurance plans that were generous, targeted high-risk patients, offered wellness programs, did not offer disease management programs, and made the benefit available only for medication ordered by mail were associated with significantly higher adherence rates, as much as 4 percentage points to 5 percentage points higher (Choudhry, Fischer, and others 2014). Although these studies are promising, future research will reveal if these models can be successfully replicated in LMICs.

The polypill is a promising intervention for improving adherence. A randomized clinical trial of 2,004 participants in India and Europe showed that use of a polypill containing aspirin, a statin, and two blood-pressure-lowering agents was associated with improved medication adherence compared with usual care, at 86 percent and 65 percent, respectively, resulting in concurrent reduction in systolic blood pressure (by 2.6 millimeters of mercury, a measure of pressure) and LDL cholesterol (4.2 milligrams per deciliter) (Thom and others 2013). Several other secondary prevention trials are underway, including the Indian Polycap-K Trial, the Kanyini Guidelines Adherence with the Polypill Study of indigenous and nonindigenous people in Australia, and the Trial in Secondary Prevention in Spain and Latin American countries (Lonn and others 2010; Sanz and Fuster 2009). These and other studies will provide information on the effectiveness of polypills for

the secondary prevention of CVD and may support the suggestion that polypills be included in the WHO's Model List of Essential Medications (Huffman and Yusuf 2014).

Cardiac Rehabilitation

Cardiac rehabilitation programs are professionally supervised programs that provide education and counseling on diet, lifestyle, and physical fitness to patients recovering from myocardial infarctions, PCI, and cardiac surgery, with the goal of reducing the likelihood of future cardiac events. Data on the effectiveness of rehabilitation programs come from studies largely conducted in HICs. Two systematic analyses show that exercise-based rehabilitation programs can reduce hospital readmission rates (Davies and others 2010; Heran and others 2011). A randomized study showed that patients who received cardiac rehabilitation had shorter lengths of hospital stay and reduced cardiac risk factors (Zwisler and others 2008). Recent studies have shown that cardiac rehabilitation programs are offered in LMICs, particularly in Latin America and the Caribbean and in India, and show positive outcomes. Despite these findings, there is a general dearth of rehabilitation programs (Boriani and others 2014; Grace and others 2013; Madan and others 2014; Shanmugasegaram and others 2014) and studies on their cost-effectiveness in different countries, prompting the International Charter on Cardiovascular Prevention and Rehabilitation to call for increased implementation and expansion of programs worldwide (Grace and others 2013).

Cardiac Resynchronization Therapy and Implantable Cardioverter Defibrillators

Cardiac resynchronization therapy (CRT) seeks to improve symptoms in patients with symptomatic heart failure due to systolic dysfunction and a delay between repolarization of the left and right ventricles of the heart. CRT synchronizes the timing of right- and left-ventricular depolarization, and improves contractility and backflow of the blood through leaky mitral valves (known as *mitral regurgitation*) (Strickberger and others 2005). Implantable cardioverter defibrillators (ICDs) are devices to rectify life-threatening abnormal heart rhythms, namely, ventricular tachycardia and ventricular fibrillation. ICDs constantly monitor heart rate and rhythm and deliver electrical pulses to restore normal heart rhythm.

Some of the earliest articles on CRT in the United States showed that ICDs are cost-effective and cost approximately US$17,000 per life-year saved in selected patients (Kuppermann and others 1990). Markov analysis of heart failure patients in Argentina showed that management with optimal medical therapy and CRT is cost-effective compared with optimal medical therapy alone. In the analysis, the ICER was I$38 (international dollars) per year of life gained and US$34 per QALY gained (Poggio and others 2012). In Brazil, Markov analysis of heart failure patients showed that management with ICD is cost-effective (Bertoldi and others 2013; Ribeiro and others 2010) where the ICER of CRT over medical therapy was US$15,723; however, upgrading to CRT in combination with ICD was associated with an ICER of US$84,345, which is well above the WHO willingness-to-pay threshold of Brazil's GDP per capita of US$31,689 (Bertoldi and others 2013). Similar cost-effectiveness was seen in Markov modeling of a European cohort of patients with reduced systolic function; placement of an ICD was associated with an ICER of US$50,161 per QALY gained, suggesting that this is a cost-effective intervention (Smith and others 2013). Additional studies are required to assess whether these interventions are cost-effective in LMICs.

CONCLUSIONS

Several cost-effective interventions are available for acute and chronic management of ACS and for long-term management of IHD risk factors. Most of the data on cost-effectiveness come from studies in HICs; however, emerging literature is directed toward estimating cost-effectiveness at regional and country levels in LMICs (Gaziano and Pagidipati 2013; Huffman and others 2013; Myers and Mendis 2014; Suhrcke, Boluarte, and Niessen 2012).

Acute Care

In acute settings, the medical management of ACS is cost-effective; emerging literature shows that PCI may also be cost-effective, but facilities providing this type of care may not be available in all regions. Furthermore, when appropriately triaged, intensive monitoring with CCU-level care is cost-effective; however, such monitoring requires significant infrastructure and qualified health professionals and is not widely available. Comparative effectiveness and cost-effectiveness information needs to be developed to guide the implementation of ACS care components so that they are widely accessible and equitably distributed.

Long-Term Management

Once patients have been managed in acute settings, subsequent mortality and morbidity can be lowered through a combination of reducing risk factors, increasing access

and adherence to medications, and using the placement of CRT and ICDs in areas where advanced care and subspecialists are available. Smoking is a major risk factor for IHD, and several cost-effective interventions have been identified, including increased tobacco taxes, use of NRT and non-nicotine-based medications, and policies to restrict smoking in public spaces; the combination of these interventions could help reduce IHD-related mortality and morbidity. Combination therapy of aspirin, beta-blockers, ACE-Is, and statins is cost-effective in the chronic management of IHD. However, IHD patients in LMICs have inadequate access to affordable medications and show low adherence to medications even when they can afford them. Interventions are being developed to support patients by increasing medication availability and encouraging adherence.

Finally, when used in the appropriate patients, CRT and ICDs can be cost-effective; however, these interventions are not widely available. The implementation of cost-effective interventions may depend on country- or region-specific factors, and additional studies on interventions and their cost-effectiveness are urgently required to tackle the significant mortality and morbidity associated with IHD.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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