PART I

FUNDAMENTALS OF CARDIOVASCULAR DISEASE

1 Global Burden of Cardiovascular Disease

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Over the past decade, cardiovascular disease (CVD) has emerged as the single most important cause of death worldwide. In 2010, CVD caused an estimated 16 million deaths and led to 293 million disability-adjusted life-years (DALYs) lost[1]—accounting for approximately 30% of all deaths and 11% of all DALYs lost that year. Like many high-income countries (HICs) during the past century, now low- and middle-income countries (LMICs) are seeing an alarming and accelerating increase in CVD rates.

This chapter describes the features of the epidemiologic transition underlying this shift in CVD morbidity and mortality and evaluates the transition in different regions of the world. Also presented is a survey of the current burden of risk factors and behaviors associated with CVD and their regional variations and trends, followed by a review of the economic impact of CVD and the cost-effectiveness of various strategies to reduce it. Concluding the chapter is a discussion of the diverse challenges posed by the increasing burden of CVD for various regions of the world, as well as potential solutions to this global problem.

SHIFTING BURDEN OF CARDIOVASCULAR DISEASE

CVD now causes the most deaths in all low- and middle-income regions, with the exception of sub-Saharan Africa, where it is the leading cause of death among persons older than 45 years of age. Between 1990 and 2010, deaths from CVD increased from 26% to 29.5% of all deaths globally—a reflection of the rapidity of the epidemiologic transition—particularly in low- and middle-income regions (**Fig. 1-1**). Within the six World Bank–defined low-income and middle-income regions, vast differences exist in the CVD burden (**Fig. 1-2**), with CVD death rates as high as 60% in Eastern Europe and as low as 10% in sub-Saharan Africa. The CVD death rate is 36% in HICs.

EPIDEMIOLOGIC TRANSITION IN PREDOMINANT CAUSES OF DEATH

Sequence of Stages

The overall increase in the global burden of CVD and the distinct regional patterns result in part from the epidemiologic transition, which includes four basic stages (**Table 1-1**)[2,3]: pestilence and famine, receding pandemics, degenerative and manmade diseases, and delayed degenerative diseases. Progression through these stages has dramatically shifted the predominant causes of death over the past two centuries, from infectious diseases and malnutrition in the first stage to CVD and cancer in the third and fourth stages. Although the transition through the age of pestilence and famine has occurred much later in LMICs, it also has occurred more rapidly, driven largely by the transfer of low-cost agricultural technologies and public health advances.

Humans evolved during the age of **pestilence and famine** and have lived with these troubles for most of recorded history. Before 1900, infectious disease and malnutrition together constituted the most common cause of death in virtually every part of the world—with tuberculosis, pneumonia, and diarrheal diseases accounting for a majority of deaths. These conditions, along with high infant and child mortality rates, resulted in a mean life expectancy of approximately 30 years. Thanks largely to improved nutrition and public health measures, however, both communicable diseases and malnutrition declined, and life expectancy increased dramatically. Increased longevity and the impact of smoking, diets high in fat and carbohydrates, and other risk factors for chronic diseases, have now combined to make CVD and cancer the leading causes of death in most countries. This transformation in disease burden changes began in higher-income countries, but as they gradually have spread to LMICs, CVD mortality rates have increased globally. In absolute numbers, CVD causes four to five times as many deaths in LMICs as in HICs.

FIGURE 1-1 Changing patterns of mortality, 1990 to 2010. CMNN = communicable, maternal, neonatal, and nutritional diseases; CVD = cardiovascular disease; INJ = injury; ONC = other noncommunicable diseases. *(From Global Burden of Disease Study 2010. Global Burden of Disease Study 2010 mortality results 1970-2010. Seattle, Institute for Health Metrics and Evaluation, 2012.)*

Per capita income and life expectancy increase during the age of **receding pandemics** as the emergence of public health systems, cleaner water supplies, and improved food production and distribution combine to drive down deaths from infectious disease and malnutrition. These advances, in turn, increase the productivity of the average worker, further improving the economic situation with more urban migration as economies move from agrarian to industrially based economies. Improvements in medical education follow, and along with other public health changes, contribute to dramatic declines in infectious disease mortality rates. Rheumatic valvular disease, hypertension, and stroke cause most CVD. Coronary heart disease (CHD) often occurs at a lower prevalence rate than that for stroke, and CVD accounts for 10% to 35% of deaths.

During the stage of **degenerative and manmade diseases**, continued improvements in economic circumstances, combined with urbanization and radical changes in the nature of work-related activities, led to dramatic changes in diet, activity levels, and behaviors such as smoking. For example, in the United States, deaths from infectious diseases decreased to fewer than 50 per 100,000 people per year, and life expectancy was up to almost 70 years. The increased availability of foods high in saturated fat, coupled with decreased physical activity, leads to an increase in atherosclerosis. In this stage, CHD and stroke predominate, and between 35% and 65% of all deaths link to CVD. Typically, the ratio of CHD to stroke is 2:1 to 3:1.

In the age of **delayed degenerative diseases**, CVD and cancer remain the major causes of morbidity and mortality, but CVD age-adjusted mortality rates are nearly cut in half—accounting for 25% to 40% of all deaths. Two significant advances have contributed to the decline in CVD mortality rates: new therapeutic approaches, and prevention measures targeted at people with CVD and people at risk for it.[4]

Treatments once considered advanced—including the establishment of emergency medical systems and coronary care units and the

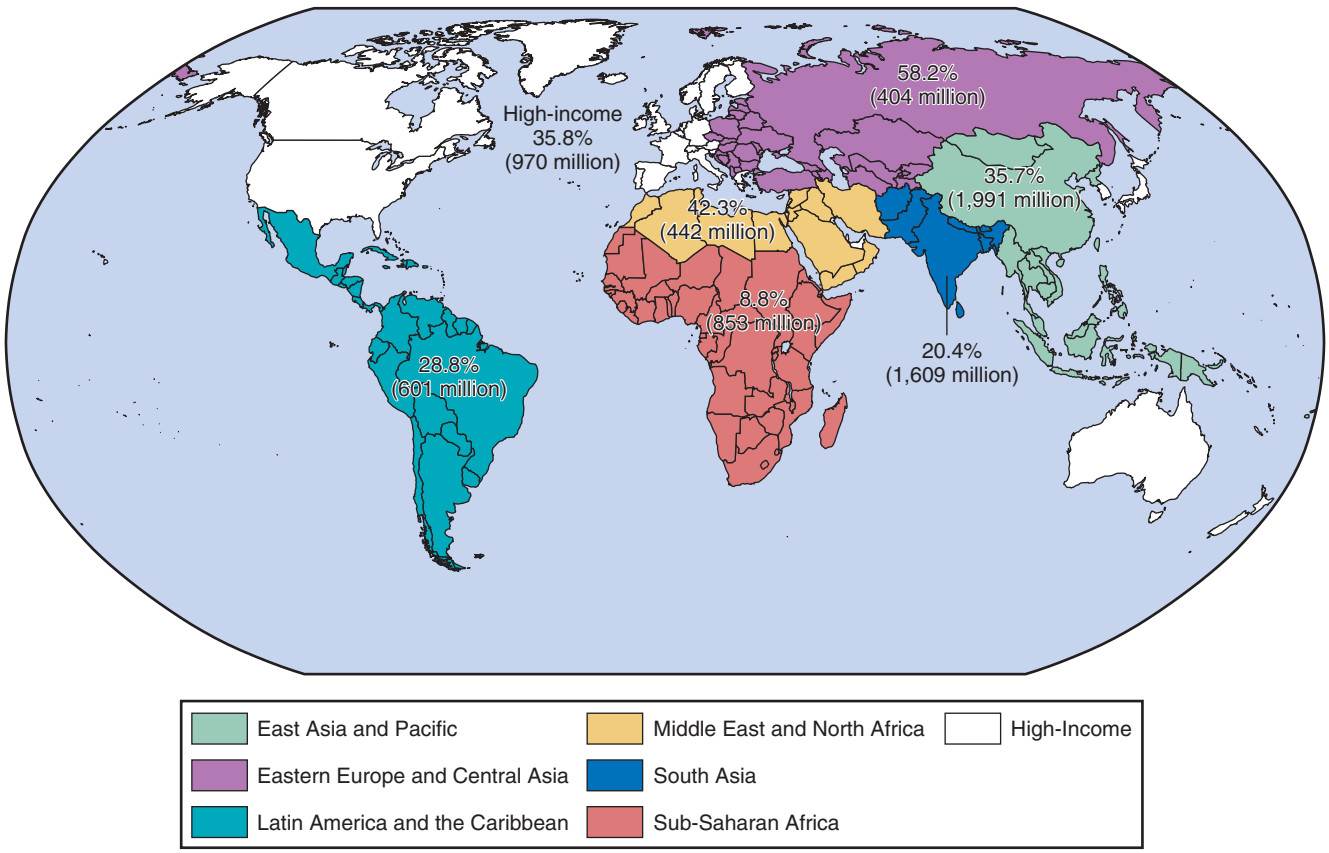

FIGURE 1-2 Cardiovascular disease deaths as a percentage of all deaths in each region and total regional population, 2010. *(From Global Burden of Disease Study 2010. Global Burden of Disease Study 2010 mortality results 1970-2010. Seattle, Institute for Health Metrics and Evaluation, 2012.)*

TABLE 1-1 Five Typical Stages of Epidemiologic Transition in Predominant Causes of Death

STAGE	DESCRIPTION	TYPICAL PROPORTION OF DEATHS CAUSED BY CVD (%)	PREDOMINANT TYPES OF CVD
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths caused by malnutrition and infection; precipitous decline in infant and child mortality rates	10-35	Rheumatic valvular disease, hypertension, CHD, stroke
Degenerative and manmade diseases	Increased fat and caloric intake and decreased physical activity lead to emergence of hypertension and atherosclerosis; with increased life expectancy, mortality rates for chronic, noncommunicable diseases exceed those for malnutrition and infectious diseases	35-65	CHD, stroke
Delayed degenerative diseases	CVDs and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events Age-adjusted CVD mortality declines, with CVD affecting older and older individuals	40-50	CHD, stroke, congestive heart failure
Inactivity and obesity	Increasing obesity and diabetes prevalence rates; some decrease in CVD mortality rates in women	33	

CHD = coronary heart disease; CVD = cardiovascular disease.

Modified from Omran AR: The epidemiologic transition: A theory of the epidemiology of population change. Milbank Mem Fund Q 49: 509, 1981; and from Olshanksy SJ, Ault AB: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. Milbank Q 64:355, 1986.

widespread use of newer diagnostic and therapeutic technologies such as echocardiography, cardiac catheterization, angioplasty, bypass surgery, and implantation of pacemakers and defibrillators—have now become the standard of care. Advances in drug development also have had a major beneficial impact on both acute and chronic outcomes. Efforts to improve the acute management of myocardial infarction (MI) led to the application of lifesaving interventions such as beta-adrenergic blocking agent (beta blocker) therapy, percutaneous coronary intervention (PCI), use of thrombolytics, and angiotensin-converting enzyme (ACE) inhibitor therapy (**see Chapters 52 and 53**). The widespread use of an "old" drug, aspirin, also has reduced the risk of dying of acute or secondary coronary events. Low-cost pharmacologic treatment for hypertension (**see Chapter 44**), and the development of highly effective cholesterol-lowering drugs such as statins, also have made major contributions to both primary and secondary prevention by reducing CVD deaths (**see Chapter 45**).

In concert with these advances, public health campaigns have conveyed that certain behaviors increase the risk of CVD and that lifestyle modifications can reduce risk. In this regard, smoking cessation has been a model of success. In the United States, for example, 57% of men smoked cigarettes in 1955; today, 23% of men smoke. The prevalence of smoking among U.S. women has fallen, from 34% in 1965 to 18.5% today.[5] Campaigns beginning in the 1970s resulted in dramatic improvements in the detection and treatment of hypertension in the United States. This intervention likely had an immediate and profound effect on stroke rates, and a more subtle effect on CHD rates. Public health messages concerning saturated fat and cholesterol had a similar impact on fat consumption and cholesterol levels. Between 1965 and 1995, overall U.S. fat consumption as a percentage of total calories fell from approximately 45% to 34%. Population mean cholesterol levels also declined, from 220 mg/dL in the early 1960s to 197 mg/dL by 2008,[6] with a simultaneous decrease in the prevalence of elevated low-density lipoprotein (LDL) cholesterol.[7]

Is There a Fifth Phase: The Age of Inactivity and Obesity?

Troubling trends in certain risk behaviors and risk factors may foreshadow a new phase of the epidemiologic transition, the **age of inactivity and obesity**[8] (**see also Chapter 42**). In many parts of the industrialized world, physical activity continues to decline while total caloric intake increases at alarming rates, resulting in an epidemic of overweight and obesity. Consequently, rates of type 2 diabetes, hypertension, and lipid abnormalities associated with obesity are rising—trends that are particularly evident in children. These changes are occurring at a time when measurable improvements in other risk behaviors and risk factors, such as smoking, have slowed. If these trends continue, age-adjusted CVD mortality rates, which have declined over the past several decades in HICs, could level out as they have for young women in the United States,[9] or even increase in the coming years. This trend pertains particularly to age-adjusted stroke death rates. Also concerning, even in LMICs, is the uptick in obesity. According to a recent study, one in five people in China are overweight or obese.[10] Other new data indicate that as many as 40% of South African women may be overweight.

Fortunately, recent trends in the first decade of this century suggest there may be a tapering in the increases in obesity among adults, although the rates remain alarmingly high at nearly 34%.[11] Furthermore, continued progress in the development and application of therapeutic advances and other secular changes appear to have offset the effects from the changes in obesity and diabetes—cholesterol levels, for example, continue to decline. Overall, in this decade, the age-adjusted death rate has continued to decline at about 3% per year, from a rate of 341 per 100,000 population in 2000 to 245 per 100,000 in 2008.[12]

Different Patterns of Epidemiologic Transition

Given the large amount of economic, social, demographic, and health data available (**Table 1-2**), the United States serves as a useful reference point for other countries for a classical rise and decline of CVD mortality rates, with CHD rates as high as 600 per 100,000 population at their peak. Several HICs have proceeded through four stages of the epidemiologic transition and are perhaps entering the fifth phase, roughly in the same pattern as for the United States. But many HICs (i.e., Portugal, Spain, Italy, France, Greece, and Japan) never reached the high mortality rates observed in the United States and other countries, with CHD mortality rates of 200 per 100,000 or less. Nor did some countries have the same rapid rate of decline, with slower rates in central European countries (i.e., Austria, Belgium, and

TABLE 1-2 Trends in the United States During the 20th Century

FACTOR/MEASURE	1900	1930	1970	2000	2010
Population (millions)	76	123	203	281	309
Median income (2012 U.S. dollars)	NA	$17,081 (1947)	$23,401	$28,902	$27,635
Age-adjusted cardiovascular disease mortality (*n*/100,000)	352	390	699	341	236.1 (2009)
Age-adjusted coronary heart disease mortality (*n*/100,000)	NA	NA	448	186	116.1 (2009)
Age-adjusted stroke mortality (*n*/100,000)	140	100	148	57	38.9 (2009)
Urbanization (%)	39	56	74	79	80.7
Life expectancy (years)	49.2	59.3	70.8	76.9	78.2
Smoking					
Cigarettes per capita (*n*)	54	1185	3969	1977	NA
Smokers (%)	NA	NA	37.4	23.3	19.3
Total caloric intake (kcal)	3500 (1909)	3300	3300	3800	3900 (2006)
Fat intake (% of total calories)	31.6	37.3	41.2	39.0	40.2 (2006)
Cholesterol level (mg/dL)	NA	NA	216	204	197 (2007-2010)
Overweight or obese (%)	NA	NA	47.7	64.5	68.0 (2007-2010)

NA = not available.

Data from the following sources: Population*: U.S. Census Bureau: Per capita income: US Bureau of the Census. Current population reports, P20-203, measuring 50 years of economic change using the March current population survey. Washington, DC, U.S. Government Printing Office, 1998; and U.S. Bureau of the Census: Historical income tables: people (http://www.census.gov/hhes/www/income/data/historical/people; accessed January 2013).* Cardiovascular disease, coronary heart disease, stroke mortality*: Morbidity & mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. Bethesda, Md, National Heart, Lung and Blood Institute, 2002; and American Heart Association: Heart and stroke statistics—2013 update. Dallas, Lung, and Blood Diseases. Bethesda, Md, National Heart, Lung and Blood Institute, 2002; and American Heart Association, 2013.* Urbanization*: Measuring America: the decennial census, 1790 to 2000: U.S. Bureau of the Census, 2002; and U.S. Census Bureau. Table GCT-P1: Urban/Rural and Inside/Outside Metropolitan and Micropolitan Area (http://factfinder2.census.gov;. accessed January 2013).* Life expectancy*: Arias E: United States life tables, 2000. Natl Vital Stat Rep 51(3):1, 2000.; and Centers for Disease Control and Prevention. Health, United States, 2011: With a special feature on socioeconomic status and health. (http://www.cdc.gov/nchs/data/hus/hus11.pdf; accessed January 2013).* Smoking*: Federal Trade Commission: Cigarette report for 2001 (http://www.ftc.gov/os/2003/06/2001cigreport.pdf; accessed July 1, 2003); Centers for Disease Control and Prevention: Vital signs: current cigarette smoking among adults aged ≥18 years—United States, 2005-2010 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6035a5.htm; accessed January 2013).* Total caloric intake and fat intake*: Nutrient content of the US food supply, 1909-1994: a summary. Washington, DC, U.S. Department of Agriculture, 1998; and U.S. Department of Agriculture: Nutrient content of the US food supply: developments between 2000 and 2006 (http://www.cnpp.usda.gov/Publications/FoodSupply/Final_FoodSupplyReport_2006.pdf; accessed January 2013).* Cholesterol level and obesity*: National Center for Health Statistics: Health, United States, 2002 (http://www.cdc.gov/nchs/data/hus/hus02.pdf; accessed July 15, 2003); Go AS, Mozzafarian D, Roger VL, et al: Heart disease and stroke statistics—2013 update: A report from the American Heart Association. Circulation 127:e6, 2013.*

Germany) compared with northern European countries (i.e., Finland, Sweden, Denmark, and Norway).[13] Furthermore, reliable mortality data for the last 50 years are available for less than a fourth of all countries,[13] with even less information for more than 50 years ago. In some countries, mortality rates appear to continue to rise (particularly, many that were part of the former Soviet Union), whereas others have yet to see any significant increase—such as many countries in sub-Saharan Africa (excluding South Africa). Whether LMICs will follow a "classical" pattern of significant increases followed by rapidly declining rates (as happened in North America, Australia, and northwestern European HICs), a more gradual rise and fall (as in the southern and central European countries), or some other pattern will depend in part on cultural differences, secular trends, and responses at the national level, with regard to both public health and treatment infrastructures.

CURRENT VARIATIONS IN THE GLOBAL BURDEN OF CARDIOVASCULAR DISEASE

Examination of regional trends is helpful in estimating global trends in the burden of disease, particularly CVD. Because 85% of the world's population lives in LMICs, rates in these countries largely drive global CVD rates. Even as rates fall in HICs, CVD rates worldwide are accelerating, because most low- and middle-income regions are entering the second and third phases of the epidemiologic transition, marked by rising CVD rates.

Worldwide, the number of CVD deaths increased by 31% between 1990 and 2010, but age-adjusted death rates decreased by 21.2% in the same period, from 298 per 100,000 population to 235 per 100,000—suggesting significant delays in age at occurrence and/or improvements in case-fatality rates. DALYs lost as a result of CVD decreased as well, from 4540 per 100,000 to 4282 per 100,000.[14] Unfortunately, not all countries appear to share in the reductions. The magnitude of the peak of the CVD epidemic has a great range (**Fig. 1-3**; see also Figs. 1-1 and 1-2), with concomitant variability in whether the peak has been achieved at all. In this section, we describe and highlight trends in the seven regions of the world as defined by the Global Burden of Disease (GBD) project, which includes HICs as one grouping and divides the remaining LMICs into six geographic regions with a variety of subregions, outlined further on.

Our data for lives lost and DALYs come from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010), which identified and compiled mortality data from 187 countries from 1980 to 2010.[14] Although extensive, data from GBD 2010 have limitations. The availability and reliability of data on cause of death—especially in LMICs without standardized protocols—are uncertain. Data for demographic and social indices are from the World Bank's World Development Indicators (WDI); those for gross national income (GNI) per capita are reported using the Atlas method in 2011 U.S. dollars.

In 2010, CHD accounted for 13.3% of all deaths worldwide. The second largest cause of death was stroke, at 11.1% (equally split between ischemic stroke and hemorrhagic and other nonischemic forms of stroke). An estimated 12.9 million people died from CHD and stroke, which together accounted for nearly a quarter of all deaths worldwide in 2010.[14]

Although still significant, deaths from communicable, neonatal, and maternal diseases are decreasing worldwide[14]—a 17% decrease occurred between 1990 and 2010. Deaths from noncommunicable diseases increased in the same time period. In 2010, CHD accounted for the largest portion of global years of life lost (YLLs) and DALYs. Stroke was the third-largest contributor to global YLLs and DALYs. By contrast, in 1990, communicable diseases accounted for the largest portion of both YLLs and DALYs.

LMICs have a high degree of heterogeneity with respect to the phase of the epidemiologic transition. First, LMIC subregions differ by age-adjusted CVD death rates, as well as by trends over the past 20 years (**Fig. 1-4**; see also Figs. 1-1 to 1-3). CVD mortality rates are increasing in most LMICs but are decreasing in HICs. Next, LMIC subregions are unique, as illustrated by the different CVD disease rates by cause in each region (**Fig. 1-5**). Finally, in the East Asia and Pacific and sub-Saharan regions, stroke still exceeds CHD as a cause of CVD death (**Fig. 1-6**). Countries in the East Asia and Pacific region appear to be following more of a Japanese-like transition, with relatively high stroke rates. Higher stroke rates in Africa, on the other hand, may reflect these countries' positions in an earlier stage of the epidemiologic transition. Hypertensive heart disease is the largest single contributor among remaining causes of CVD morbidity and mortality.

Variability in disease prevalence among various regions probably results from multiple factors. First, the countries are in various phases of the epidemiologic transition described earlier. Second, the regions may have cultural and/or genetic differences that lead to varying levels of CVD risk. For example, per capita consumption of dairy products (and thus consumption of saturated fat) is much higher in India than it is in China, although it is rising in both countries. Third, certain additional competing pressures exist in some regions, such as war or infectious diseases (human immunodeficiency virus infection/acquired immunodeficiency syndrome [HIV/AIDS]) in sub-Saharan Africa.

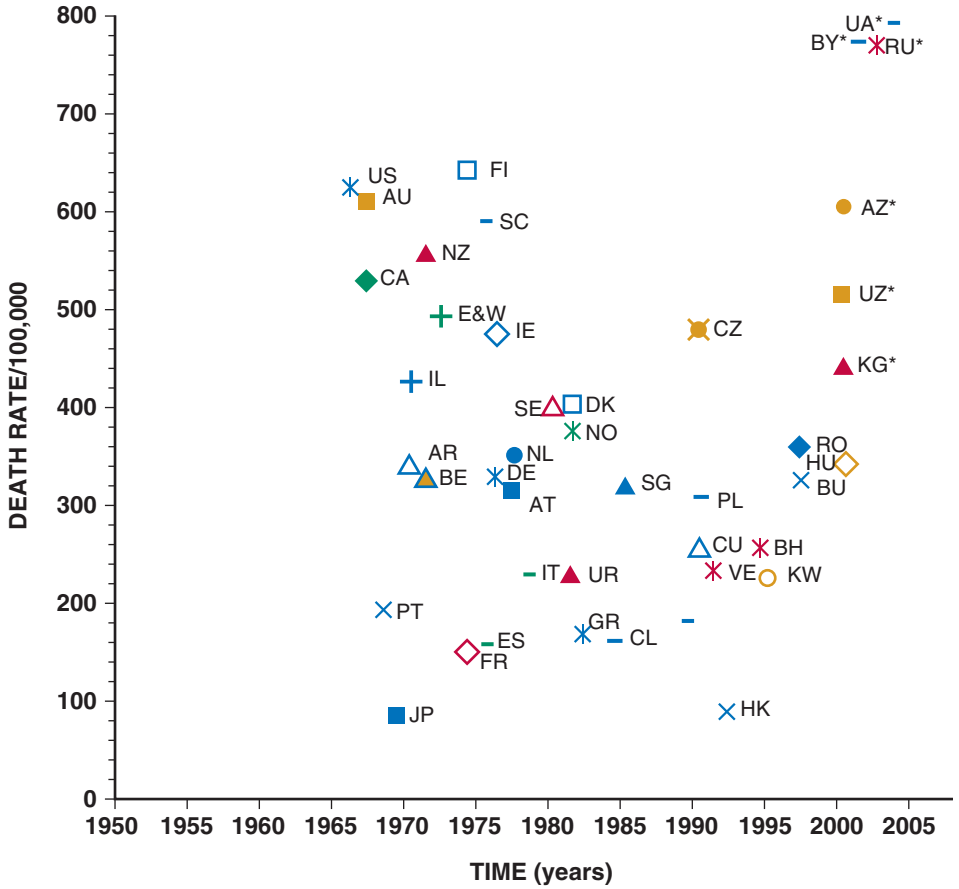

FIGURE 1-3 Coronary heart disease mortality epidemic peaks and maxima in various countries in men 35 to 74 years of age (age-standardized). Symbols reflect exact location of data point. Two-letter country codes are as follows: AR = Argentina; AT = Austria; AU = Australia; AZ = Azerbaijan; BE = Belgium; BH = Bahrain; BR = Brazil; BU = Bulgaria; BY = Belarus; CA = Canada; CL = Chile; CU = Cuba; CZ = Czech Republic; DE = Germany; DK = Denmark; E&W = England and Wales; ES = Spain; FI = Finland; FR = France; GR = Greece; HK = Hong Kong; HU = Hungary; IE = Ireland; IL = Israel; IT = Italy; JP = Japan; KG = Kyrgyzstan; KW = Kuwait; NL = The Netherlands; NO = Norway; NZ = New Zealand; PL = Poland; PT = Portugal; RO = Romania; RU = Russian Federation; SC = Scotland; SE = Sweden; SG = Singapore; UA = Ukraine; UR = Uruguay; US = United States; UZ = Uzbekistan; VE = Venezuela. *Mortality did not reach a discernible peak by 2003. *(From Mirzaei M, Truswell AS, Taylor R, Leeder SR: Coronary heart disease epidemics: not all the same. Heart 95:740, 2009.)*

Because CHD afflicts a younger population in LMICs, an increased number of deaths affect the working population. For some LMICs, the severity of the epidemiologic transition has appeared to follow a reverse social gradient, with members of lower socioeconomic groups suffering the highest rates of CHD and the highest levels of various risk factors.[15] Unfortunately, reductions in risk factors do not follow the same trend. Compared with people in the upper and middle socioeconomic strata, those in the lowest stratum are less likely to acquire and apply information on risk factors and behavior modifications, or to have access to advanced treatments. Consequently, CVD mortality rates decline later among those of lower socioeconomic status.

High-Income Countries

Demographic and Social Indices

Nearly 1 billion people (15% of the world's population) live in HICs, which are divided into four subregions: Asia-Pacific, Australasia, Western Europe, and North America. A majority of the population—close to 80%—is urban. Unlike other GBD regions, HICs are geographically dispersed but economically similar. The United States, the most populous of the HICs, has approximately 312 million people; Brunei Darussalam has the lowest population of 405,900 people.[16] The highest life expectancies in the world occur in HICs, where the average life expectancy is 80 years.[16] The GNI per capita in the region ranges from $18,620 in Malta to $88,890 in Norway. The United States is closer to the middle, with a GNI per capita of $48,450. The region has high health expenditure, accounting for nearly a tenth of the region's gross domestic product (GDP). Brunei Darussalam and Singapore spend only 2.8% and 4.0% of their GDPs, respectively, on health care. The United States, on the other hand, spends nearly 18%, or $8362 per capita. Other HICs—such as Norway, Luxembourg, and Switzerland—have similar per capita expenditures, although these account for much smaller portions of their GDPs.[16]

Burden of Disease

In 2010, CVD was responsible for 35.8% of all deaths in high-income regions, and CHD caused more than half of these deaths (see Fig. 1-6). The movement of most HICs through the epidemiologic transition, with rising levels of risk factors and CVD death rates until the 1970s and then declines in both over the next 40 years, resembles what occurred in the United States. CHD is the dominant form, with rates that tend to be twofold to fivefold higher than stroke rates. Two notable exceptions are Portugal, where stroke rates for both men and women are higher than CHD rates, and Japan, where stroke causes far more fatalities than CHD. In both of these countries, however, the pattern seems to be moving toward that seen in other HICs, with more rapid declines in stroke rates than in CHD rates.

Age-adjusted death rates for CVD declined in almost all high-income regions—with the exception of Asia-Pacific—between 1990 and 2010.[14] This age-adjusted decline results largely from preventive interventions that allow people to avert disease, from treatments to prevent death during an acute manifestation of disease (particularly stroke or MI), and from interventions that prolong survival once CVD

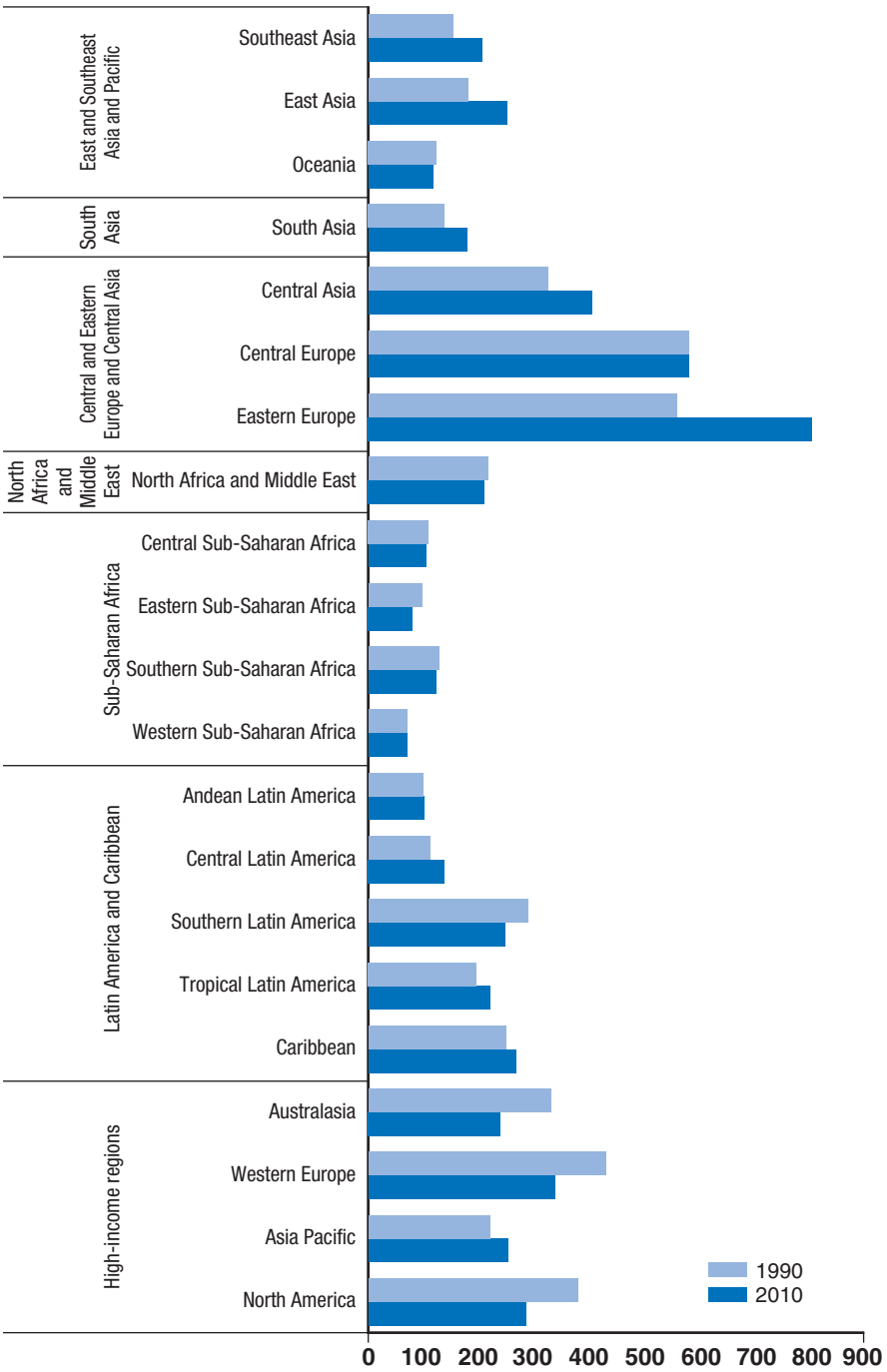

FIGURE 1-4 Age-adjusted death rates per 100,000 for cardiovascular disease, 1990 and 2010. *(From Global Burden of Disease Study 2010. Global Burden of Disease Study 2010 mortality results 1970-2010. Seattle, Institute for Health Metrics and Evaluation, 2012.)*

is manifest. Thus, the average age at death from CVD continues to climb, and as a result, CVD affects a larger retired population.

Western Europe, with a CVD mortality rate of 367 per 100,000 in 2010, had the highest mortality rates, while Australasia had the lowest at 259 per 100,000. As mentioned above, mortality rates for CHD are higher than those for stroke in high-income regions, where CHD also accounts for a larger portion of all CVD deaths. The exception is Asia-Pacific, where death rates for stroke and CHD are 130 per 100,000 and 94 per 100,000, respectively. Mortality rates and number of deaths attributable to stroke and CHD increased in this region between 1990 and 2010; stroke rates increased by approximately 18%, whereas CHD rates increased by nearly 40%.[14] Japan is unique among HICs—as its communicable disease rates fell in the early 20th century, its stroke rates increased dramatically. CHD rates, however, did not rise as sharply as they did in other industrialized nations, and have remained lower than in any other industrialized country. Overall, CVD rates have fallen 60% since the 1960s, largely because of a decrease in age-adjusted stroke rates. Japanese men and women currently have the highest life expectancies in the world: 86.4 years for women and 79.6 years for men. The difference between Japan and other industrialized countries may stem in part from genetic factors, but the Japanese fish- and plant-based, low-fat diet, and resultant low cholesterol levels, probably have played a more important role. Nevertheless, as is true for so many countries, dietary habits in Japan are undergoing substantial changes. Since the late 1950s, cholesterol levels have progressively increased in both urban and rural populations.[17] Although the prevalence of CVD risk factors is increasing in the Japanese population, the incidence of coronary artery disease remains low. This situation could change, however, as there seems to be a long lag phase before dietary changes manifest as CHD events.

East Asia and Pacific

Demographic and Social Indices

The EAP region is the most populated low-income and middle-income region in the world, with nearly 2 billion people; approximately 49% of the region is urban. The GNI per capita is $4243, ranging from $4420 in Thailand to $1130 in Laos. In 2004, total health expenditure was 4.8% of total GDP, or $183 per capita.[16] The region is divided into three distinct subregions: Southeast Asia, East Asia, and Oceania. China is by far the most populated country, representing almost 70% of the region. Life expectancy has risen quickly across the EAP region in past decades, up to an average of 72 years. In China, the increase has been dramatic: from 37 years in the mid-1950s to 73 years in 2010.[16] This increase has been accompanied by a large rural to urban migration pattern, rapid urban modernization, aging of the population, decreased birth rates, major dietary changes, increasing tobacco use, and a transition to work requiring low levels of physical activity.

Burden of Disease

CVD caused more than 4.5 million deaths in the EAP region in 2010, accounting for 35.2% of all deaths in the region. More than half of those deaths resulted from ischemic heart disease, whereas only 31% were due to stroke (see Fig. 1-6). CVD death rates differed significantly between subregions, most notably in Oceania. Mortality rates were highest in East Asia, at 234 per 100,000 in 2010. Death rates in Oceania, on the other hand, were 110 per 100,000, well below the global average. Between 1990 and 2010, death rates for CVD increased in all three subregions, although to various degrees. Rates in East Asia and Southeast Asia increased by approximately 24%, but by only 3% in Oceania. In Southeast Asia and East Asia, CVD accounts for the largest percentage of total DALYs lost in the regions (26 million and 67 million, respectively).[14]

Stroke and CHD are the leading causes of death in the East Asia and Southeast Asia subregions. In Oceania, however, lower respiratory infections and diabetes account for the largest proportion of

deaths. Whereas stroke and CHD rates increased in both East Asia and Southeast Asia, stroke rates decreased slightly in Oceania, from 40 per 100,000 to 36 per 100,000.[14] China appears to be straddling the second and third stages of a Japanese-like epidemiologic transition. Among men in China 35 to 64 years of age, stroke death rates are 217 to 243 per 100,000, versus CHD death rates of 64 to 106 per 100,000.[18]

Even with high stroke rates, CHD is emerging as a large and growing burden in East Asia. Data from the largest death registration and classification study in China showed that CHD accounted for 13% to 22% of overall CVD deaths and 4% to 9% of total deaths, with the higher percentages seen in urban areas.[19] In 2004, the World Health Organization (WHO) estimated that nearly 400,000 people in China died from CHD, and that 652,000 cases of CHD were diagnosed.[19] The rates for age-adjusted mortality from CHD were 80 to 128 per 100,000 for men and 57 to 98 per 100,000 for women.[19] Higher rates were seen in urban areas than in rural areas (by a factor of six), in higher-income areas than in lower-income areas, and in northeastern areas of China than in southern areas.[19]

CHD rates have grown quickly over the past two decades in China. Age-adjusted CHD mortality increased 39% in women and 41% in men, 35 to 74 years of age, between 1984 and 1999. Furthermore, the incidence of CHD increased by 2.7% annually in men and 1.2% annually in women. Although rates are higher, hospitalizations are somewhat low. Acute MI was the diagnosis in 4.1% of all hospital discharges in 2004 in large cities, and in 2.1% of discharges in smaller cities and rural areas.[19]

Central and Eastern Europe and Central Asia

Demographic and Social Indices

Of the three subregions that constitute this region—Central Asia, Central Europe, and Eastern Europe—Eastern Europe is the most populated. Russia alone accounts for more than 30% of the region's 404 million inhabitants. Sixty-five percent of the population in the region is urban, with an average life expectancy of 71 years. The average GNI per capita for the region ranges from $870 in Tajikistan to $23,610 in Slovenia. Russia has a GNI of $10,400. On average, the region spends more than 6% of total GDP on public and private health care. Health expenditure per capita ranges from $49 per capita in Tajikistan to $2154 in Hungary. Russia spends about $525 per capita, or 5.1% of its GDP.[16]

Burden of Disease

The highest rates of CVD mortality occur in this region. CVD mortality rates are 866 per 100,000 in Eastern Europe and 604 per 100,000 in Central Europe. Overall rates resemble those seen in the United States in the 1960s, when CVD was at its peak. CHD is generally more common than stroke, which suggests that the countries that constitute Eastern Europe and Central Asia are largely in the third phase of the epidemiologic transition. As expected in this phase, the average age of people who develop and die of CVD is lower than that in high-income economies. In 2010, CVD accounted for nearly two thirds of all deaths in the region, 58.3% of which were due to CHD and 33.5% due to stroke. In Eastern Europe alone, 29.7 million DALYs were lost as a result of CHD in 2010.[14]

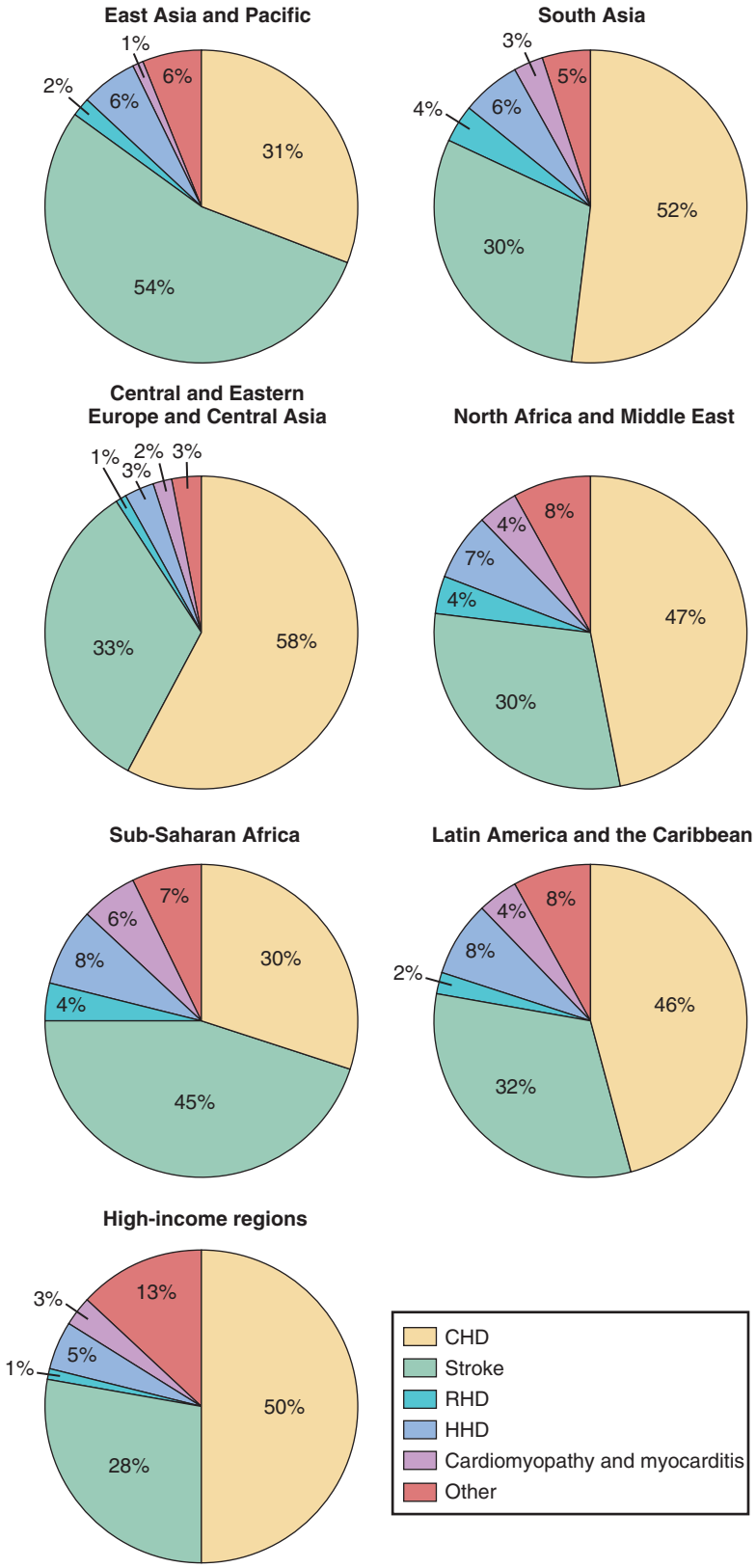

FIGURE 1-5 Cardiovascular disease death by specific cause and region, 2010. CHD = coronary heart disease; HHD = hypertensive heart disease; RHD = rheumatic heart disease. *(From Global Burden of Disease Study 2010. Global Burden of Disease Study 2010 mortality results 1970-2010. Seattle, Institute for Health Metrics and Evaluation, 2012.)*

A country-level analysis reveals important differences in CHD profiles within the region (see Fig. 1-3). Since the dissolution of the Soviet Union, CVD rates have increased surprisingly in some of these countries, with the highest rates (nearly 800 per 100,000 for men) in Ukraine, Bulgaria, Belarus, and Russia.[13] In Russia, increased CVD rates have contributed to falling life expectancy—particularly for men, whose life expectancy dropped steadily from 71.6 years in 1986 to as low as 58 years in 1999. Yet, life expectancy has trended upward in more recent years—67.6 years for men in 2010—even as CVD mortality rates have increased.

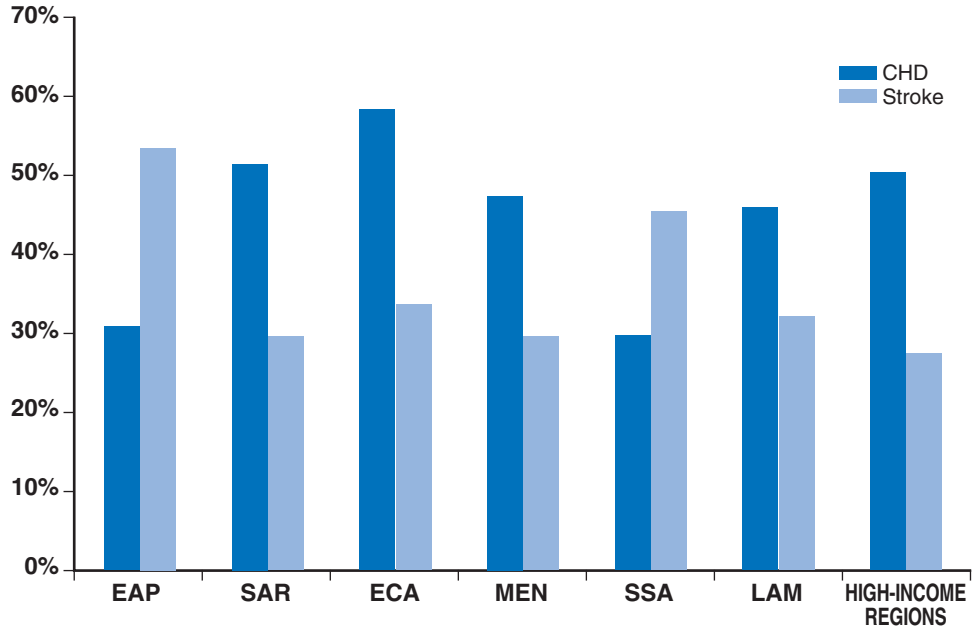

FIGURE 1-6 Comparison of percentages of cardiovascular disease mortality attributable to coronary heart disease (CHD) and stroke by region, 2010. EAP = East Asia and Pacific; ECA = Eastern and Central Europe and Central Asia; LAM = Latin America and the Caribbean; MEN = Middle East and North Africa; SAR = South Asia region; SSA = sub-Saharan Africa. *(From Global Burden of Disease Study 2010. Global Burden of Disease Study 2010 mortality results 1970-2010. Seattle, Institute for Health Metrics and Evaluation, 2012.)*

By 2010, CVD mortality rates in the region were the highest in the world. Importantly, deaths resulting from CHD in these countries are not restricted to older adults. The GBD study estimates that working-age populations (15 to 69 years of age) have a significant CHD burden. Nearly a third of all deaths in persons 45 to 49 years of age, for example, result from CVD. For people 60 to 64 years of age, CVD accounts for half of all deaths, 27% of which are due to CHD.[14]

Latin America and the Caribbean

Demographic and Social Indices

The Latin America and Caribbean (LAM) region comprises Andean Latin America, Central Latin America, Southern Latin America, Tropical Latin America, and the Caribbean. The region has a total population of 589 million, 79% of which is urban.[16] Brazil, the region's most populous country, represents a third of the population, with Argentina, Colombia, Mexico, Peru, and Venezuela making up another third. The Caribbean nations, including the Dominican Republic, Jamaica, and Haiti, account for less than 10% of the population in the region. Life expectancy in the region is approximately 74 years but varies greatly. In 2010, for example, Haiti and Cuba had life expectancies of 64 years and 79 years, respectively. Average GNI per capita in the region is around $8544 (purchasing power parity [PPP] of $11,587). The region spends an average of 7.7% of its GDP on health care. This level of spending translates into health care expenditures that range from $46 per capita in Haiti to $1003 per capita in Barbados.[16]

Burden of Disease

This area bears a substantial CVD burden. In 2010, CVD caused 28.8% of all deaths in the region.[14] Unlike in HICs, where CHD dominates among circulatory diseases, CHD and cerebrovascular disease contribute similarly to mortality in this region (see Fig. 1-6), pointing to relatively higher rates of untreated hypertension.

Mortality rates vary significantly by subregion (see Fig. 1-3). Mortality rates for CHD and stroke are highest in the Caribbean (100 deaths per 100,000 population and 125 per 100,000, respectively); unlike global trends, both mortality rates increased between 1990 and 2010. Death rates also increased in Central Latin America and Andean Latin America; similar increases in mortality rates occurred in Tropical Latin America. Together, CHD (14%), stroke (6.9%), and hypertensive heart disease (2.1%) accounted for nearly a quarter of all deaths in Central Latin America in 2010. Southern Latin America—which includes Argentina, Chile, and Uruguay—was the only subregion to follow global patterns in mortality rates. Overall CVD, CHD, and stroke mortality rates decreased in this subregion between 1990 and 2010, but to a lesser extent than for global changes.[14] The lower reductions in the region are attributed to rapid lifestyle changes—unfavorable dietary changes, increased smoking, increased obesity, and less exercise.

North Africa and the Middle East

Demographic and Social Indices

The 19 countries of the North Africa and Middle East region represent approximately 5% of the world's population (337 million people). Egypt and Iran are the two most populous countries in the region, with Egypt representing 24% of total inhabitants and Iran 22%. Approximately 59% of the population is urban, with an average life expectancy of 72 years. The average GNI per capita for the region is $3869, ranging from $1070 in Yemen to $48,900 in Kuwait. Approximately 5.3% of the GDP, or approximately $203 per capita, is used for health expenditures in the region. The per capita health expenditure ranges from $63 in Yemen to $1450 in the United Arab Emirates.[16]

Burden of Disease

Forty-two percent of all deaths in the region are attributable to CVD, 47% of which are due to CHD and 30% are due to stroke. CVD mortality rates for the region are lower than global averages. In 2010, the death rate per 100,000 for CHD, stroke, and overall CVD were 93, 59, and 199, respectively. Unlike global trends, the mortality rate for CHD increased in the region by approximately 15%. Neither stroke nor CVD mortality rates decreased significantly. In 2010, CVD accounted for 17.2 million DALYs, 14% of all DALYs lost in the region. The DALYs lost were split evenly between CHD and stroke, at 6.8 million and 5.0 million, respectively.[14]

Individual country data show that 12 of the region's countries rank in the top 50 in age-adjusted CHD mortality rates. Somalia, Iraq, and the Sudan are in the top 25 with rates of 219, 214, and 212 per 100,000, respectively.[20] Iran may have a higher prevalence burden than other countries, including Saudi Arabia and Jordan. A study of a random sample of 3723 people in Iran found that 11.3% had coronary symptoms, and an additional 1.4% had an MI; the age-adjusted prevalence was therefore 12.7%.[21] In Jordan, a study showed that 5.9% of 3083 participants had an MI.[22]

South Asia

Demographic and Social Indices

The South Asia region (SAR), one of the world's most densely populated regions, comprises about 24% of the world's population with more than 1.6 billion residents. India, home to nearly 75% of the region's inhabitants, is the largest country in the region. Only 31% of the region is urban, and life expectancy is approximately 65 years.

Average GNI per capita for the region is $1299, ranging from $540 in Nepal to $6530 in Maldives. India's GNI per capita of $1410 sits near the regional average. Countries in the SAR spend an average of 3.9% of the total GDP, or $47 per capita, on health care. Maldives spends the most per capita at $208, and India spends $31, or 5% of its GDP. The lowest expenditures for health care are $22 per capita in Pakistan and $23 in Bangladesh.[16]

Burden of Disease

CVD accounts for 20% of all deaths in the SAR. CHD was the leading cause of mortality in 2010—responsible for 10.6% of total reported fatalities, or 1.8 million deaths, and more than half of CVD mortality. Cerebrovascular disease accounted for 6.8% of all deaths and 30% of CVD deaths. Nearly 60.5 million DALYs are lost due to CVD in the region, accounting for 10% of all DALYs lost. CHD is responsible for 4.6% of the DALYs lost because of CVD, nearly twice as high as for stroke.[14] Mortality rates for CVD are increasing in the region.

Several studies in India and Pakistan suggest substantial morbidity and mortality resulting from CHD in this region. In 1990, 1.18 million people died in India as a consequence of CHD; by 2010, this number increased to an estimated 2.03 million.[23] CVD probably represents 25% of all deaths in India. Studies also show that CHD prevalence is higher in men and in urban residents.[23] Prevalence of CHD in India recently was estimated at more than 10% in urban areas and 4.5% in rural areas.[23] A recent CHD study in Pakistan found a prevalence of approximately 6% in men and 4% in women, but active ischemia was twice as frequent in women. The study authors suggest that one in five adults in urban parts of Pakistan have CHD,[24] and that only a fourth of these adults are aware of their disease and seeking medical care. In contrast with the epidemiologic transition in HICs, recent evidence suggests that residents of the SAR of lower socioeconomic status are developing a higher burden of CHD first.[25] Tobacco use and hypertension, for example, were both significantly more prevalent among cohorts with lower levels of education.[25]

Another demographic trend in the SAR is a considerable increase in urban residents, a shift that usually correlates with increased rates of CHD. Currently, 31% of all inhabitants in the region live in an urban setting, a number that is expected to rise.[16] A review of epidemiologic studies in the country found that between 1965 and 2005, CHD prevalence increased from approximately 4% to 12% in urban populations.[23] Rural populations are experiencing similar increases in CHD prevalence. More recent data from the rural region of Andhra Pradesh in South India suggest an actually higher prevalence in many rural regions.[26] CHD death rates exceeded 15% in this study, meaning that the rural-versus-urban protection factor no longer exists—or that the urban rates, if measured more carefully, could be much higher.

The rise in CHD mortality contributes to the economic burden in the Indian subcontinent. Data indicate that symptoms of CHD arise a full 5 to 10 years earlier in this region than in Western European and Latin American countries.[27] Furthermore, CVD affects a substantial proportion of working-age citizens. A study in rural India, for example, found that 51% of all CVD deaths occurred in individuals younger than 70 years of age.[26]

Sub-Saharan Africa

Demographic and Social Indices

The GBD study divides sub-Saharan Africa into four subregions: Central Africa, East Africa, Southern Africa, and Western Africa. Approximately 875 million people live in these four regions, with Nigeria being the most populous (163 million) and Cape Verde being the least populous (500,600). Only 36% of the population in the region is urban. The average GNI per capita is $1255, ranging from $250 in Burundi to $7480 in Botswana. Overall, the region also has the lowest average life expectancy—54 years.[16]

Average public and private health care expenditures for the region are 6.5% of the total GDP, or $84 per capita. The range of health care expenditures per capita for the region is similar to the GDP range for this region, from $3 in Burundi to $511 in Seychelles. Nigeria spends $23 per capita, or 4.6% of the total GDP.[28]

Burden of Disease

In Western Africa, CVD accounts for 7.5% of all deaths. The highest portion of CVD-caused deaths occurred in Southern Africa, where 13% of all deaths were due to CVD. Mortality rates in the region are lower than global averages, and are decreasing, in line with global trends. The exception is Southern Africa, where rates increased from 129 per 100,000 to 136 per 100,000. Communicable, neonatal, and maternal disorders still dominate causes of death in the sub-Saharan region. Malaria and HIV/AIDS are the leading causes of death, accounting for nearly half of all deaths in the region.[14]

Human Immunodeficiency Virus Infection and Coronary Heart Disease

In view of the large burden of disease attributable to HIV/AIDS, the potential risk of CVD among persons being treated with antiretroviral medications is of growing concern (**see Chapter 70**). As in HICs, CVD death appears to be rising among people older than 65 years of age in rural South Africa.[29] For those between 50 and 64 years of age, however, CVD deaths appear to have halved in South Africa, probably as a consequence of competing HIV/AIDS mortality.[29] HIV-seropositive men older than 50 years of age have a higher prevalence of dyslipidemia, diabetes, and peripheral artery disease (50% of cases were asymptomatic), compared with their noninfected counterparts.[30] Of note, 55% of these HIV-infected men were prior smokers, and they also were more likely to use antihypertensive drugs, lipid-lowering agents, and antidiabetic medications. A recent study of 95 patients initiating antiretroviral drugs indicated that patients who had high baseline lipid levels showed a marked increased in lipoprotein(a).[31] The coupling of HIV infection with expanding uptake of antiretroviral therapy (ART), particularly in South and East Africa,[32-34] adds another layer of complexity. Today, HIV/AIDS can be regarded as a treatable chronic illness, with the expectation that persons with HIV/AIDS will live longer and lead more active lives, consequently increasing their noncommunicable disease risk.[35] HIV infection appears to have an independent cardiovascular effect, and treatment with ART may cause dyslipidemia.[36,37] Further studies suggest that in addition to these mechanisms, HIV seropositive status may serve as a marker to identify a subgroup of persons at high risk for development of CVD.[38] Collectively, these data indicate that the interaction of seropositive HIV status, ART, and risk for acquiring CVD warrants continued attention.

RISK FACTORS

CVD worldwide is largely driven by modifiable risk factors, such as smoking, lack of physical activity, and diets high in fat and salt (**see also Chapters 42 to 45 and 61**). The INTERHEART study showed that smoking, hypertension, abdominal obesity, physical inactivity, and a high-risk diet were responsible for a significant component of MI risk.[39] Elevated levels of blood pressure (BP) and cholesterol remain the leading causes of CHD; tobacco, obesity, and physical inactivity remain important contributors as well.

The GBD project estimated that the population-attributable fraction (PAF) for individual risk factors for CHD in LMICs in 2001 were as follows: high BP, 44%; high cholesterol, 46%; overweight and obesity, 16%; low fruit and vegetable intake, 30%; physical inactivity, 21%; and smoking, 15%. Unique features regarding some CHD risk factors in LMICs are described next.

Tobacco

By many accounts, tobacco use is the most preventable cause of death in the world. Over 1.3 billion people use tobacco worldwide, more than 1 billion of whom smoke[40]; the rest use oral or nasal tobacco. More than 80% of tobacco use occurs in LMICs, and if current trends continue unabated, tobacco will cause more than 1 billion deaths during the 21st century (**Fig. 1-7**).

Tobacco use varies greatly across the world (see Fig. 1-7). Although historically greatest in HICs, tobacco consumption has shifted

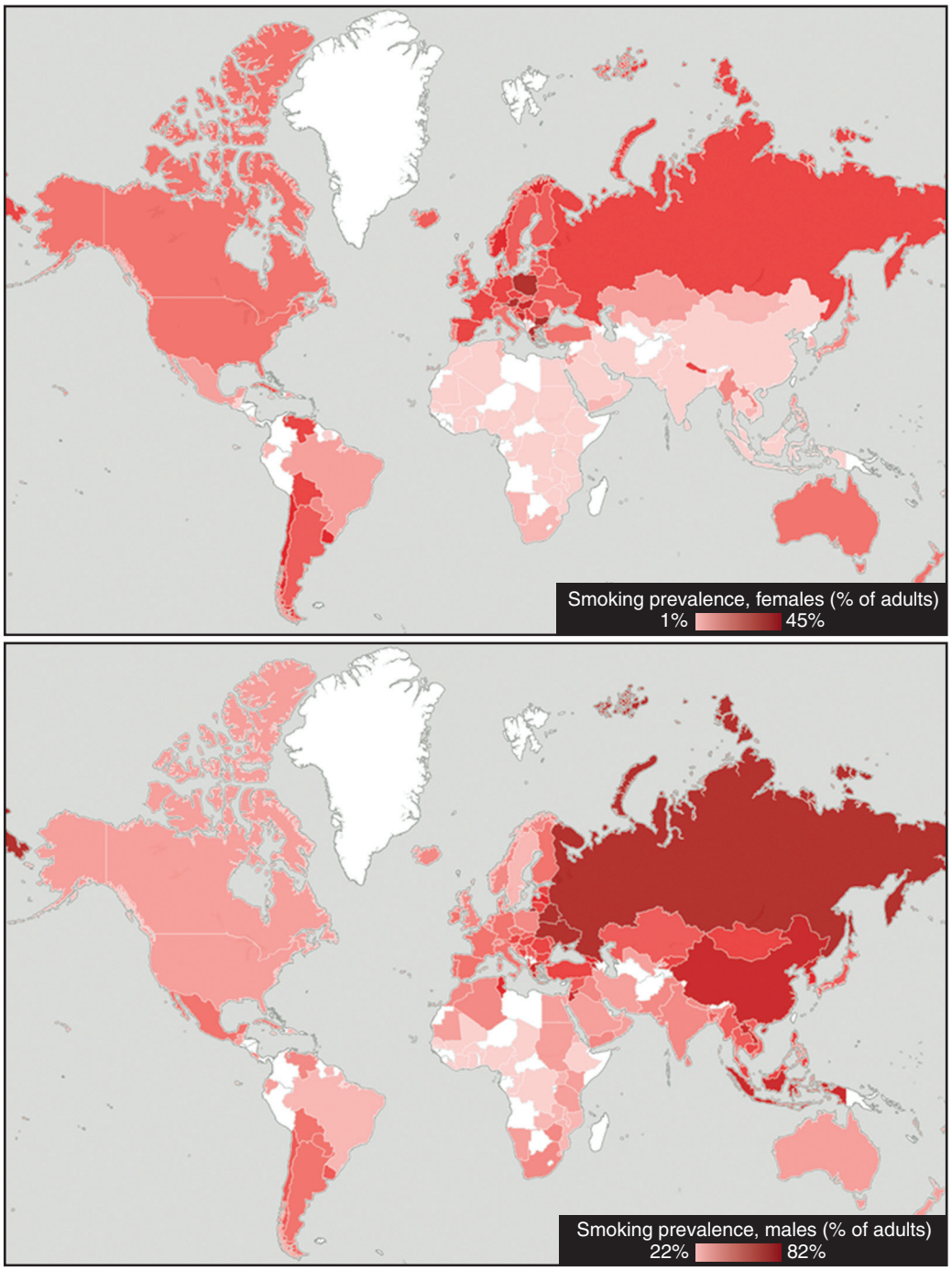

FIGURE 1-7 Smoking prevalence among persons 15 years of age or older, females (*top*) and males (*bottom*), for 2008 to 2012. *(From World Bank. World Development Indicators, 2010 [http://data.worldbank.org/indicator].)*

dramatically to LMICs in recent decades; some of the highest tobacco use now occurs in the EAP region. Kiribati has the highest prevalence of age-adjusted tobacco use in the world—71.0% in men and 42.9% in women. Indonesia has similarly high rates (>60% prevalence in men). China is the largest consumer of tobacco in the world, with an estimated 301 million smokers in 2010 (>50% prevalence in men). Several countries in the Central and Eastern Europe regions also have alarmingly high prevalence rates, including Russia (approximately 60.0% in men and 24.3% in women), Ukraine (>50% prevalence in men), and Albania (60% prevalence in men). Latin America, the Middle East, and North Africa have high rates as well, although smoking is not as common among women in these regions as it is in the Pacific region. Countries in sub-Saharan Africa have some of the lowest prevalence rates; Niger and Ethiopia, for example, have less than 10% and 1% prevalence in men and women, respectively.

High rates of smoking are not limited to men. Smoking prevalence among women is high—and increasing—in several countries in the world, including Kiribati (42.9%), Austria (45.1%), Nauru (50%), and Greece (41.4%). In general, however, considerably more men than women smoke. Exceptions to this pattern include Nauru and Greece, which have comparable tobacco use prevalence in men and in women. Where they do occur, variations by sex can be substantial. In China, for example, tobacco use prevalence is 50% in men but only 2.2% in women. Indonesia has similarly diverging trends: prevalence in men is 61.3%, and only 5.1% in women. Significant variations

also occur in North Africa, the Middle East, and some countries in sub-Saharan Africa. Tobacco use is generally less than 1% in women in these regions, but is much higher in men.

Other forms of tobacco use increase risk for CHD. Bidis (hand-rolled cigarettes common in South Asia), kreteks (clove and tobacco cigarettes), hookah pipes (water pipes used for smoking flavored tobacco), and smokeless tobacco all link to increased CHD risk.[41,42] The combined use of different forms of tobacco is associated with a higher risk of MI than using one type.

Secondhand smoke is another well-established cause of CHD. In 2011, approximately 600,000 nonsmokers died as a consequence of exposure to secondhand smoke. A retrospective analysis of 192 countries found that the largest portion of secondhand smoke–related deaths in 2004 resulted from ischemic heart disease.[43] These observations may explain the large and immediate drop seen in communities such as Helena, Montana, and in Scotland, which implemented smoke-free laws and found 20% to 40% decreases in admissions for MI, controlling for time, locality, and other variables.[44] Smoking bans have both immediate and long-term effects in reducing admissions for acute coronary syndrome (ACS). In Ireland, which implemented a country-wide smoking ban in workplaces, ACS-related hospital admissions promptly decreased by 12%, and 2 years after the implementation of the ban such admissions decreased by an additional 13%.[45]

Hypertension

Elevated BP is an early indicator of epidemiologic transition. Rising mean population BP occurs as populations industrialize and move from rural to urban settings. Worldwide, approximately 62% of strokes and 49% of CHD cases are attributable to suboptimal (above 115 mm Hg systolic) BP, a factor thought to account for more than 7 million deaths annually. A relatively recent study by Lawes and coworkers estimated that 14% of deaths and 6% of DALYs lost globally were due to nonoptimal levels of BP.[46] Although most societies define hypertension as a systolic BP greater than 140 mm Hg, Lawes and colleagues found that just over half of the attributable CVD burden occurs among persons with a systolic BP less than 145 mm Hg. The high rate of undetected, and therefore untreated, hypertension presents a major concern in LMICs. The high prevalence of undetected and untreated hypertension probably drives the elevated rates of hemorrhagic stroke throughout Asia.

The most recent update of the GBD study analyzed mean systolic BP between 1980 and 2008 using multiple published and unpublished health surveys and epidemiologic studies. The analysis—which applied a Bayesian hierarchical model to each sex by age, country, and year—found a global decrease in mean systolic BP between 1980 and 2008 in both men and women.[47] Worldwide, the age-standardized prevalence of uncontrolled hypertension has decreased from 33% to 29% in men, and from 29% to 25% in women, between 1980 and 2008. But the number of people with uncontrolled hypertension (systolic BP of 140 mm Hg or higher) has increased—in 1980, 605 million had uncontrolled hypertension, and by 2008, the number increased to 978 million. The trend results largely from population growth and aging. Globally, mean systolic BP has decreased by 0.8 mm Hg per decade among men; the number is slightly higher among women, at 1.0 mm Hg per decade. In 2008, age-standardized mean systolic BP values worldwide were 128.1 mm Hg in men and 124.4 mm Hg in women.

Regional and sex variations exist in systolic BP (**Fig. 1-8**). The highest mean systolic BP in 2008 occurred in East and West African countries, where both men and women had systolic BP levels that were significantly higher than global averages. In Mozambique and São Tomé and Príncipe, for example, mean systolic BP in women was 135.4 mm Hg and 136.3 mm Hg, respectively. In men, mean systolic BP was as high as 137.5 mm Hg in Mozambique and 139.4 mm Hg in Niger. Men in Eastern Europe had mean systolic BP levels comparable to those in East and West Africa. Mean systolic BP was lowest in high-income regions such as Australasia (systolic BP of 117.4 mm Hg in Australian women) and North America (systolic BP of 123.3 mm Hg in U.S. men).

The most significant decreases occurred in high-income regions, where mean systolic BP decreased by 2.4 mm Hg per decade in men and 3.1 mm Hg per decade in women. The decrease in men ranged from 1.7 mm to 2.8 mm Hg per decade, with the greatest decrease occurring in the North America subregion. The decrease in mean systolic BP in women ranged from 2.3 mm Hg per decade in North America to 3.9 mm Hg per decade in Australasia.

Mean systolic BP increased in several regions. In South Asia, systolic BP increased by 0.8 mm Hg per decade in men and 1.0 mm Hg per decade in women. Southeast Asia saw similar increases: 0.9 mm Hg per decade in men and 1.3 mm Hg per decade in women. In East Africa, mean systolic BP increased by 1.6 mm Hg per decade in men and 2.5 mm Hg per decade in women. The most significant increases in men occurred in East Africa (1.6 mm Hg per decade). In women, mean systolic BP increased the most in Oceania (2.7 mm Hg per decade).

Notable sex differences occurred in Oceania and West Africa. In Oceania, mean systolic BP increased by 2.7 mm Hg per decade, the largest increase in any female cohort in the world. In men in this region, on the other hand, mean systolic BP increased by only 1.2 mm Hg per decade. Data from West Africa show diverging trends in mean systolic BP in men and women. Although mean systolic BP decreased in men in West Africa by 0.4 mm Hg per decade, systolic BP in women in this subregion increased by 2.5 mm Hg per decade.

Lipids

Worldwide, high cholesterol causes some 56% of ischemic heart disease and 18% of strokes amounting to 4.4 million deaths annually. Unfortunately, most LMICs have limited data on cholesterol levels, and often only total cholesterol values are collected. In HICs, mean population cholesterol levels are generally decreasing, but in LMICs, these levels vary widely. As countries move through the epidemiologic transition, mean population plasma cholesterol levels typically rise. Changes accompanying urbanization clearly play a role, as plasma cholesterol levels tend to be higher among urban residents than among rural residents. This shift results largely from greater consumption of dietary fats—primarily from animal products and processed vegetable oils—and decreased physical activity.

Globally, mean serum total cholesterol levels have decreased.[48] The GBD study analyzed data between 1980 and 2008 using a bayesian model to estimate mean total cholesterol by age, country, and year. Age-standardized mean total cholesterol was 4.64 mmol/L (179.6 mg/dL) in men and 4.76 mmol/L in women in 2008 (184.2 mg/dL). Some of the highest levels of cholesterol occurred in high-income regions (**Fig. 1-9**). In 2008, the combined regions of Australasia, North America, and Western Europe had a mean total cholesterol of 5.24 mmol/L in men and 5.23 mmol/L in women. In Greenland, mean total cholesterol was as high as 5.7 mmol/L for both sexes. Sub-Saharan Africa had the lowest levels for both sexes. Some cohorts—largely, men in Southern African countries like Liberia, Nigeria, and Burkina Faso—had levels less than 4.0 mmol/L.

Between 1980 and 2008, mean total cholesterol levels decreased by 0.08 mmol/L per decade in men and by 0.07 mmol/L per decade in women. The most significant decreases in cholesterol levels occurred in the Central Europe, Eastern Europe, and Central Asia regions: 0.23 mmol/L per decade in men, and 0.24 mmol/L per decade in women. The high-income regions of Australasia, North America, and Western Europe had similarly large decreases in cholesterol levels: 0.19 mmol/L per decade in men, and 0.21 mmol/L per decade in women. Countries like Finland and Sweden had notably faster decreases in cholesterol levels than other Western European countries.

Several exceptions to the worldwide downward trend in cholesterol levels occurred. In the EAP region, levels increased by 0.08 mmol/L per decade in men and by 0.09 mmol/L per decade in women. The high-income Asia-Pacific subregion showed a similar trend, but the increase was more moderate (≤0.1 mmol/L per decade). South Korea demonstrated no change in cholesterol levels as a result of maintaining a diet low in saturated fats. Singapore data were also

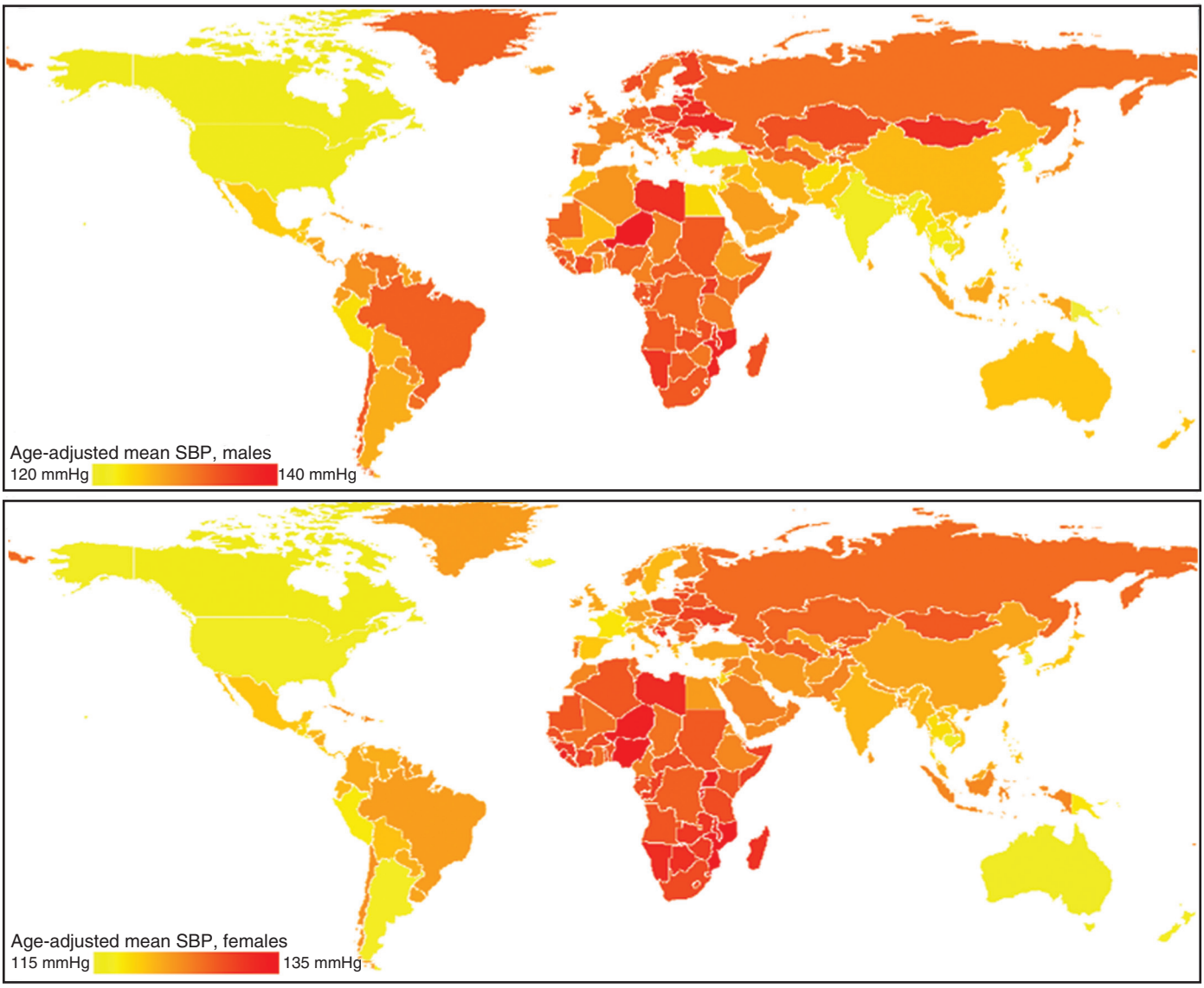

FIGURE 1-8 Age-adjusted mean systolic blood pressure (SBP) for males (*top*) and females (*bottom*), 2008. *(From Goodarz D, Finucane MM, Lin JK, et al: National, regional, and global trends in serum total cholesterol since 1980: Systemic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. Lancet 377:568, 2011.)*

notable: In the 1980s, cholesterol levels decreased for both men and women, but beginning in 2000, the downward trend ended in men. In women, the trend reversed, increasing from 4.7 mmol/L in 2000 to 5.3 mmol/L in 2008. Several regions—including North Africa and Middle East, sub-Saharan Africa, and South Asia—showed no notable change in cholesterol levels, owing in part to a lack of available historical data. In general, women in low-income and middle-income subregions had higher total cholesterol than their counterparts in HICs.

Diabetes

The incidence of diabetes has grown rapidly worldwide in the past 30 years. According to the GBD study, an estimated 346 million people worldwide have diabetes.[49] The more expansive International Diabetes Foundation (IDF) Atlas definition—which, in addition to fasting plasma glucose (FPG) as in the GBD study, includes oral glucose tolerance and HbA_{1c} tests—found that 366 million people had diabetes in 2011. Nearly 50% of these cases were undiagnosed. By 2030, the number of people with diabetes is expected to increase to 522 million. This increase is estimated to occur at 2.7% annually, a higher growth rate than that of the total world adult population.

Eighty percent of people with diabetes live in LMICs (**Fig. 1-10**). The highest regional prevalence for diabetes occurs in the Middle East and North Africa, where an estimated 12.5% of the adult population (20 to 79 years of age) has diabetes. Pacific island and Middle Eastern countries have the highest prevalence, with age-adjusted prevalence ranging from 18.8% to 25.4%. Future growth will be concentrated in LMICs, especially in regions such as sub-Saharan Africa, Middle East and North Africa, and Southeast Asia.[50] In addition, a majority of cases will remain within the 45-to-64-year age group in LMICs, whereas those older than 65 years of age are most affected in HICs.

Rising rates of obesity, and the aging and urbanization of the population, likely link to the diabetes epidemic. Nearly 90% of type 2 diabetes cases relate to obesity, and diabetes and its related complications are the costliest consequence of obesity. Mortality from diabetes is also on the rise, with approximately 4.6 million deaths in 2011.

Asian countries face a relatively larger burden of diabetes, compared with the Europe and Central Asia or Latin America and Caribbean regions. India and China, for example, have the largest numbers of diabetics in the world—61.3 million and 90 million, respectively. Asian populations may have a higher risk for developing diabetes

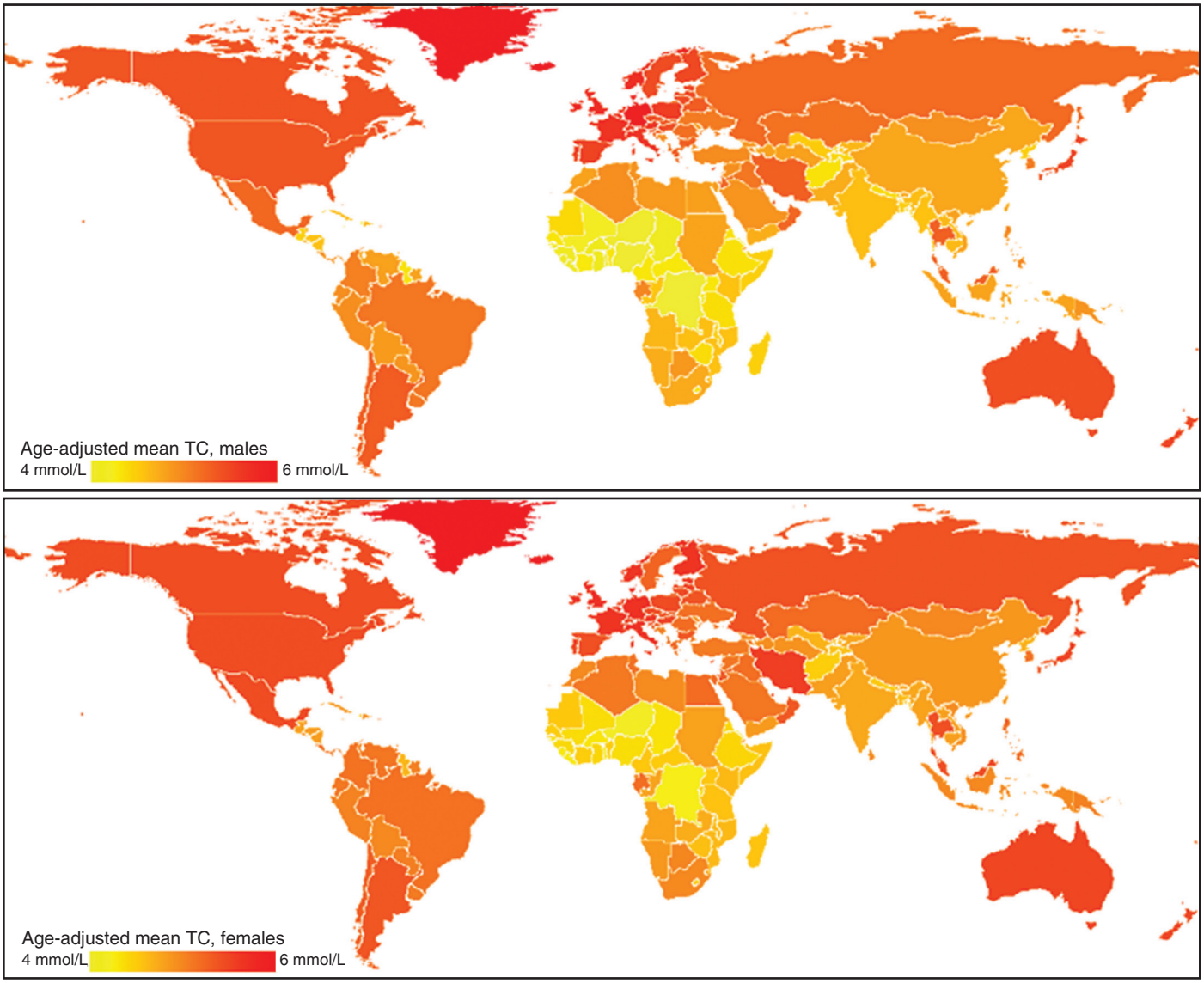

FIGURE 1-9 Age-adjusted mean total cholesterol (TC) for males (*top*) and females (*bottom*), 2008. *(From Farzadfar F, Finucane MM, Danaei G, et al: National, regional, and global trends in serum total cholesterol since 1980: Systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 377:578, 2011.)*

even at a lower BMI, because of a greater tendency toward visceral obesity. In addition, this population may experience both undernutrition (during the perinatal period) and rapid weight gain (during childhood), a combination that increases the risk for insulin resistance.[51]

The most recent GBD study found a global increase in mean FPG. The study analyzed multiple published and unpublished health surveys and epidemiologic studies by applying a bayesian hierarchical model for each sex by age, country, and year. Between 1980 and 2008, mean FPG increased by 0.07 mmol/L (1.26 mg/dL) per decade in men and 0.08 mmol/L (1.44 mg/dL) per decade in women. The upward trend in FPG was nearly universal.[49] In almost every region worldwide, mean FPG increased or remained unchanged; regions that displayed apparent decreases (men in the East Asia and Southeast Asia region, for example) were not statistically different from flat trends (posterior probabilities of 0.80 or less).

Although some regions had unchanging mean FPG levels, other regions—including southern and tropical Latin America, Oceania, and high-income regions—experienced significant increases. The most notable region is Oceania. Between 1980 and 2008, mean FPG increased by 0.22 mmol/L per decade in men and 0.32 mmol/L per decade in women. By 2008, Oceania had the highest mean FPG for both sexes (6.09 mmol/L for men; 6.09 mmol/L for women) and the highest prevalence of diabetes (15.5% in men; 15.9% in women) in the world.

In addition to Oceania, the Caribbean and North Africa and the Middle East have the highest mean FPG levels in the world. Between 21% and 25% of men and between 21% and 32% of women in these countries have diabetes. By contrast, men in sub-Saharan Africa and women in high-income Asia-Pacific countries had the lowest mean FPG in 2008—5.27 mmol/L and 5.17 mmol/L, respectively. The only significant decrease in mean FPG occurred in women in Singapore, where levels fell by 0.21 mmol/L per decade.

Trends in mean FPG also varied by sex. In sub-Saharan Africa, for example, mean FPG increased by 0.05 mmol/L per decade in men, but by 0.13 mmol/L per decade in women. The Central Asia, North Africa and Middle East region had similar differences in sex: mean FPG increased by 0.06 mmol/L per decade in men, and by 0.16 mmol/L per decade in women.

Obesity

Obesity is increasing throughout the world, and particularly in LMICs, where the trajectories are steeper than those in HICs. According to the latest GBD study, nearly 1.46 billion adults were overweight (BMI

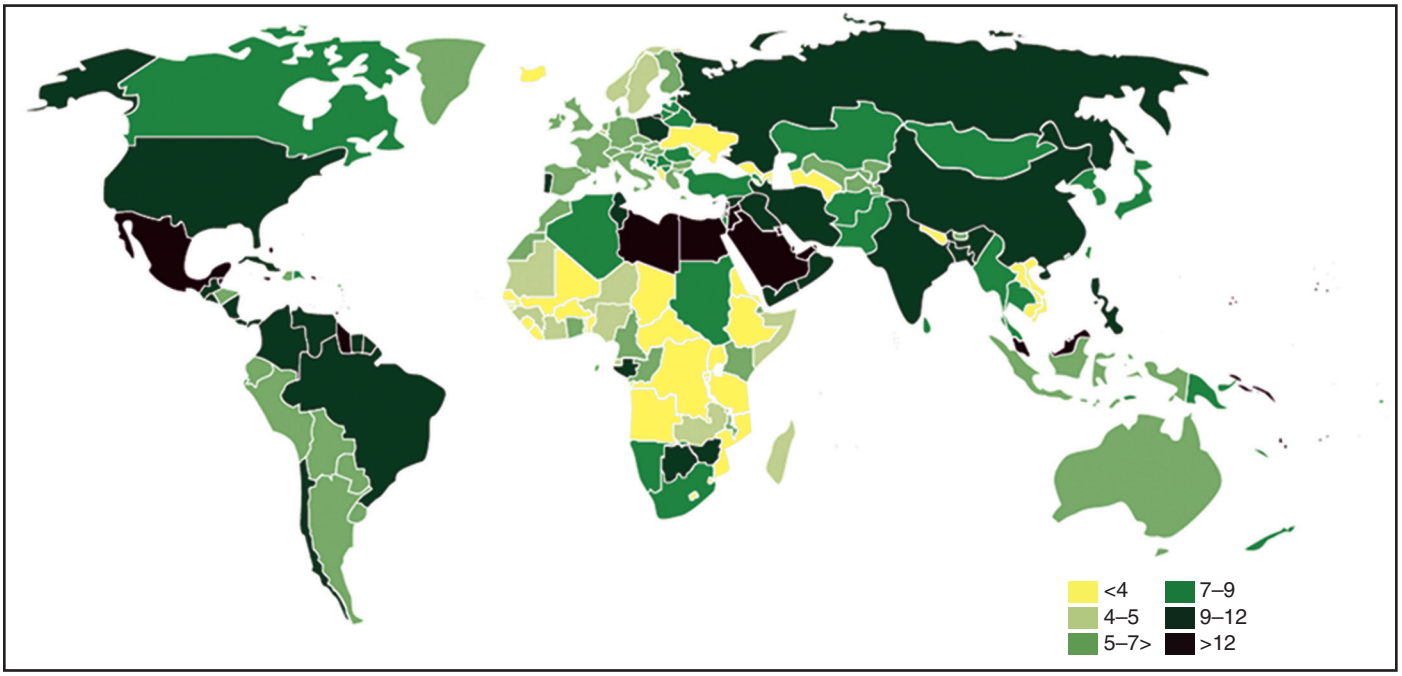

FIGURE 1-10 Prevalence rates (%) for diabetes among individuals 20 to 79 years of age, 2011. *(From International Diabetes Federation: IDF Atlas. 5th ed. Brussels, Belgium, International Diabetes Foundation, 2011 [http://www.idf.org/diabetesatlas].)*

≥25 kg/m^2) in 2008; of these, approximately 502 million were obese (BMI ≥30 kg/m^2).[52]

Explanations for this rapid trajectory are complex and include changes in dietary patterns, physical activity, and urbanization. Popkin and Garden-Larsen report that the use of edible oils, caloric sweeteners, and animal-source foods is increasing.[53] Annual animal food consumption tripled in China from the 1950s to 1990s. Physical activity levels are expected to decline as urbanization leads to increased use of motorized vehicles and a change to more sedentary occupations.

Unlike data from the 1980s, which showed that obesity affected predominantly the higher-income group in LMICs, a recent analysis shows a shift to the poor in the burden of overweight and obesity. Although higher-income groups still have the highest prevalence of overweight and obesity, rates are increasing faster in lower-income groups.[54] The poor have relatively more susceptibility to obesity as a developing country's GNP approaches the middle-income range.[54,55] Higher GDP also is associated with faster rates of increase in the prevalence of overweight and obesity in lower-income groups.[54]

The literature spotlights two groups: Women are more affected than men, with overweight women generally outnumbering underweight women as indicated by data from 36 LMICs.[56] In the same survey, prevalence of overweight women exceeded 20% in more than 90% of surveyed countries. Even rural areas in half of the countries surveyed exhibited such rates. Adolescents are at particular risk, with 1 in 10 children currently estimated to be overweight.[53,57] The number of overweight children is increasing in countries as diverse as China, Brazil, India, Mexico, and Nigeria. According to the most recent WHO estimates, 40 million children younger than 5 years of age are overweight. Brazil saw an alarming rise—from 4% to 14% over a two-decade period. In 1980, the worldwide obesity prevalence rate was 4.8% in men and 7.9% in women. By 2008, prevalence rates had nearly doubled to 9.8% in men and 13.8% in women.

Globally, BMI rose in both men and women. The GBD study analyzed published and unpublished health examination surveys and epidemiologic studies (linear regressions were developed to estimate mean BMI from overweight or obesity prevalence, when available) and found that between 1980 and 2008, global BMI rose by 0.4 kg/m^2 per decade in men and 0.5 kg/m^2 per decade in women.

BMI varied substantially between regions and by sex (**Fig. 1-11**). In 2008, the age-standardized mean BMI in the United States was 28.5 kg/m^2 in men and 28.3 kg/m^2 in women. In contrast with the United States and other HICs with similarly high BMIs, the sub-Saharan Africa and Asia regions have some of the lowest mean BMIs. Men in Ethiopia, for example, have a mean BMI of 20.2 kg/m^2, and women in Bangladesh have a mean BMI of 20.5 kg/m^2.

The largest increase in BMI occurred in Oceania. Between 1980 and 2008, mean BMI rose by 1.3 kg/m^2 per decade in men and 1.8 kg/m^2 per decade in women. Of the islands in the Oceania region, Nauru had the largest BMI increase of more than 2 kg/m^2. BMI trends were similar in the North American high-income region (1.1 kg/m^2 per decade in men and 1.2 kg/m^2 per decade in women). In Latin America and the Caribbean, mean BMI for women increased 0.6 to 1.4 kg/m^2 per decade. By contrast, mean BMI decreased in Central African men by 0.2 kg/m^2 per decade and remained unchanged in South Asian men. In women, mean BMI remained static, with changes less than 0.2 kg/m^2 per decade in central Asia, central Europe, and Eastern Europe.

Although regional trends generally showed concordance between sexes, some exceptions occurred. There was no change in mean BMI in South Asian men, but mean BMI in women increased at a rate close to the global average, 0.4 kg/m^2 per decade. The most significant discrepancy in sex trends occurred in Central Africa. BMI in men in Central Africa decreased by 0.2 kg/m^2 per decade, the only significant decrease in any male population in the world. In women in Central Africa, on the other hand, mean BMI increased by 0.7 kg/m^2 per decade, a rate greater than the world average.

Diet

As humans have evolved, selective pressures have favored the ability to conserve and store fat as a defense against famine. This adaptive mechanism has become unfavorable in light of the larger portion sizes, processed foods, and sugary drinks that many people now regularly consume. Between 1970 and 2010, the average daily per capita calories in the United States increased from 2076 to 2534.[58] As per capita income increases, so does consumption of fats and simple carbohydrates, whereas intake of plant-based foods decreases. A key

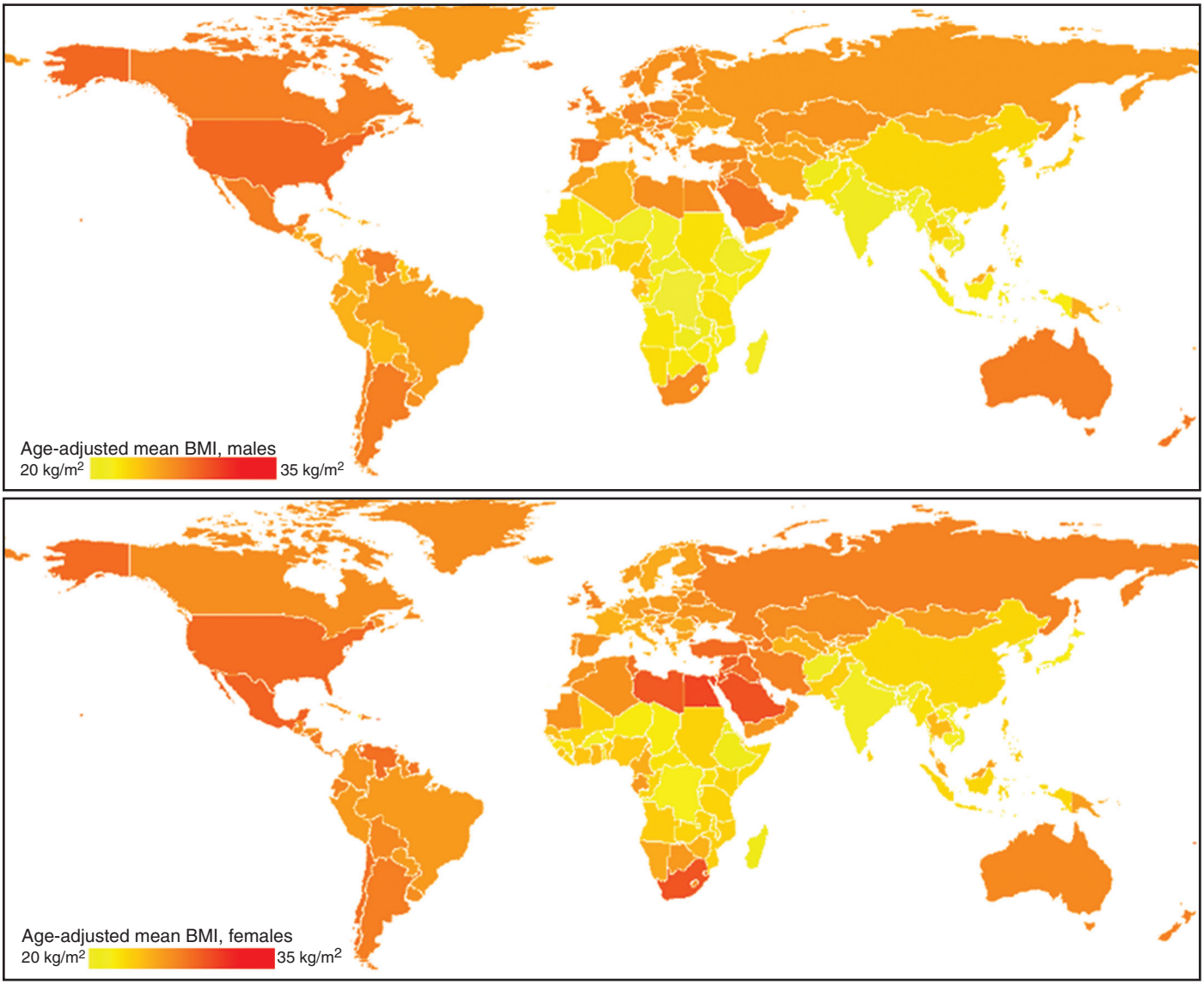

FIGURE 1-11 Age-adjusted mean body mass index (BMI) for males (*top*) and females (*bottom*), 2008. *(From Finucane MM, Stevens GC, Cowan MG, et al: National, regional, and global trends in body-mass index since 1980: Systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 377:557, 2011.)*

element of this dietary change is an increased intake of saturated animal fats and inexpensive hydrogenated vegetable fats, which contain atherogenic trans fatty acids. New evidence suggests that high intake of trans fats may also lead to abdominal obesity, another risk factor for CVD. (**See Chapters 42 and 46** for further discussion of diet and CVD.)

China provides a good example of such a "nutritional transition"—rapid shifts in diet linked to social and economic changes. The China Nationwide Health Survey found that between 1982 and 2002, calories from fat increased from 25% to 35% in urban areas and from 14% to 28% in rural areas, as calories from carbohydrates fell from 70% to 47%. As recently as 1980, the average BMI for Chinese adults was about 20 kg/m^2, and less than 1% had a BMI of 30 kg/m^2 or greater. From 1992 to 2002, the number of overweight adults increased by 41%, while the number of obese adults increased by 97%.

China and other countries in transition have the opportunity to spare their populations from the high levels of trans fats that North Americans and Europeans have consumed over the past 50 years by avoiding government policies that can contribute to the CVD burden. For example, the European Union (EU) Common Agricultural Policy (CAP) program, which subsidizes dairy and meat commodities, has increased the availability and consumption of products containing saturated fats. CAP has contributed to an estimated 9800 additional CHD deaths and 3000 additional stroke deaths in the EU, half of them premature.[59]

Another facet of the nutritional transition for countries adopting a Western diet is the introduction of soft drinks and other high-sugar beverages, which are associated with weight gain and increased risk for development of type 2 diabetes. A recent study of American women shows that these beverages may be linked to CHD. Drinking full-calorie sugar-sweetened beverages on a regular basis was associated with a higher risk of CHD, even after accounting for other unhealthful lifestyle or dietary factors.[60]

Physical Inactivity

In HICs, the widespread prevalence of physical inactivity produces a high population-attributable risk of cardiovascular consequences. Physical inactivity is also increasing in low- and middle-income regions of the world, where a shift from physically demanding, agriculture-based work to largely sedentary service industry–based and office-based work is occurring. A switch from physically demanding transportation to mechanized transportation accompanies this work shift.

Current guidelines call for moderate exercise for at least 30 minutes five or more days a week, or vigorous exercise for 20 minutes three days a week. Gallup's November 2011 Health and Healthcare poll found that 51.6% of adults in the United States say they exercise three or more times a week. These numbers have remained essentially unchanged since 2008. Physical inactivity levels are similarly high in other regions of the world. In the Middle East and North Africa region, for example, physical inactivity is fairly common, with a prevalence ranging from 32.9% in Syria to 56.7% in Iraq. In urban China, the proportion of adults who participate in moderate- and high-level activity has decreased significantly, whereas participation in low-level activity has increased. Between 1986 and 2006, the proportion of adults who participate in low-level activity increased from 44.8% to 66.7%.[61]

Of interest, the Cuban economic crisis that began in 1989 when Cuba lost the Soviet Union as a trading partner, and the resultant hardship for its people, improved their overall cardiovascular health. The crisis worsened for the next 5 years, and complete recovery did not take place until 2000. Sustained food rationing led to a reduction in per capita food intake, and the lack of public transportation resulting from fuel shortages meant that more people were walking and riding bikes. During the crisis period, the proportion of physically active adults increased from 30% to 67%, and a 1.5-unit shift in BMI distribution was observed.[62] From 1997 to 2002, deaths attributed to diabetes, CHD, and stroke decreased by 51%, 35%, and 20%, respectively.

Other Potential Contributing Factors

Aging Demographics

Average life expectancy will reach 73 years by 2025, according to the WHO. This rise relates to a decline in overall infant mortality and fertility rates. Although older adults will constitute a greater percentage of the population in HICs—more than 20% of the U.S. population will be older than 65 years of age by 2025—low- and middle-income regions such as Asia and Latin America will nearly double their relative proportion of elderly people, to 10% of their populations.[63]

The time of transition to an older population is sharply shorter in LMICs. For example, whereas it took the United States and Canada more than 65 years to double their over-65 population, China will do so in 26 years, Tunisia in 24, and Brazil in 21.[64] Currently, 77% of the growth in the older adult population is occurring in low-income and middle-income regions. Such acute changes in the population structure leave less time to expand an already overburdened health infrastructure to address the chronic diseases of older adults, which prominently include cardiovascular conditions.

Fetal Origins

Adverse influences, such as undernutrition during fetal life (fetal "programming") and early postnatal life, appear to affect the prevalence of adult CVD and to contribute to its risk factors. Barker, in his "developmental origins of adult disease" hypothesis, suggested that adverse influences early in development, particularly during intrauterine life, could result in permanent changes in the physiology and metabolism of the pancreas, kidney, muscle, and vascular endothelium, resulting in adult insulin resistance, metabolic syndrome, hypertension, and CHD.[65] Factors such as maternal adiposity, gestational weight gain, maternal nutritional deprivation, fetal exposure to an environment of maternal hyperglycemia, hypercholesterolemia, and exposure to smoking, were identified as the key initiating factors that may lead to CVD later.[66] Recent evidence indicates that the first 2 years of postnatal life are a sensitive or "critical" period of development, and any stimulus or insult during this period appears to have lasting or lifelong significance for adult-onset CVD.[66,67] Several epidemiologic studies have demonstrated these associations, and two randomized trials from Guatemala and India on nutritional supplementation for pregnant mothers demonstrated favorable cardiovascular risk profiles among the children of mothers who received such supplementation.[68,69] The mechanisms of increased risk appear to be both biologic (alterations in fetal tissues and postnatal epigenetic modifications) and social (cognitive impairment, low productivity, and higher prevalence of cardiovascular risk factors among those with lower birth weight and early-life adverse influences), and the risk is further compounded by childhood obesity and sedentary habits. Thus the prevention of adverse fetal exposures and subsequent long-term consequences requires a holistic approach. An understanding of prenatal risk factors and their early childhood modifiers will provide an opportunity for prior to development of risk factors. These include improved maternal nutrition during pregnancy and lactation, emphasis on breastfeeding through early infancy, and assuring adequate balanced nutrition to infants. On the basis of our current understanding, policymakers and health care professionals should design and develop preventive strategies that effectively influence these very early determinants of CVD development.[70]

ECONOMIC BURDEN

Despite some overlap, at least three approaches can measure the economic burden associated with CHD. The first source of financial burden is defined by the costs incurred in the health care system itself and reported in "cost-of-illness" studies. In these studies, the cost of CHD includes the costs of hospitalizations for angina and MI, as well as heart failure attributable to CHD. The costs of specific treatments or procedures related to CVD, such as thrombolytics, catheterization, and PCI, and the costs associated with outpatient management and secondary prevention, including office visits and pharmaceutical costs, are also included. In addition, nursing home, rehabilitation (inpatient and outpatient), and home nursing costs require consideration.

The second economic assessment is based on microeconomic studies that assess the household impact of catastrophic health events such as MI. These studies look at out-of-pocket expenses incurred by the individual patient or family that might have other downstream economic impacts, such as loss of savings or sale of property to cover medical costs. Many LMICs lack an extensive insurance scheme, and health care costs are almost entirely borne by individuals,[71] so microeconomic studies to date have not considered CHD exclusively, instead looking more generally at chronic diseases overall. Furthermore, the limited data do not confirm the causality between chronic disease and individual or household poverty. Expenditures for coronary disease or its addictive risk factors such as tobacco, however, could lead to substantial and even impoverishing costs.

The third method of determining financial burden from CHD is based on a macroeconomic analysis. These assessments look at lost worker productivity, or economic growth lost by adults with CHD or their caregivers being partially or completely out of the work force because of illness. The data for the impact of chronic diseases on labor supply and productivity are more robust. An additional cost not often accounted for is the intangible loss of welfare associated with pain, disability, or suffering by the affected person. These indirect costs are often accounted for by "willingness-to-pay" analyses, asking generally how much would an individual pay to avert suffering or dying prematurely from CHD. The gains are not merely improved work performance, but also enjoying activities beyond production. Studies in the United States suggest that as much as 1% to 3% of GDP is attributable to the cost of care for CVD, with almost half of that related to CHD.[72] In China, annual direct costs of CVD are estimated at more than $40 billion (U.S.), or roughly 4% of GNI. In South Africa, 2% to 3% of GNI is devoted to the direct treatment of CVD, which equates to roughly 25% of South African health care expenditures. The indirect costs are estimated at more than double that of the direct costs. Although few cost-of-illness studies for CHD have been performed in other regions, such studies have reported on the financial burdens attributed to risk factors for CHD. For example, the direct costs caused by diabetes in the Latin American and Caribbean countries were estimated at $10 billion (U.S.). Indirect costs were estimated at more than $50 billion in 2000. The limited studies available

suggest that obesity-related diseases account for 2% to 8% of all health care expenditures in HICs. In India and China, the costs for obesity are about 1.1% and 2.1% of GDP, respectively.

Recently, the costs attributable to nonoptimal BP levels as mediated through stroke and MI were evaluated for all regions of the world.[73] Globally, the health care costs of elevated BP were estimated at $370 billion (U.S.) for 2001; this amount represented approximately 10% of all global health care expenditures for that year. Regional variations do exist, with hypertension being responsible for up to 25% of health care costs in the Eastern European region (**Fig. 1-12**). Over a 10-year period, BP-related health care costs could equal $1 trillion (U.S.) globally, and indirect health care costs attributed to BP could be nearly four times as much.

That a high proportion of CVD burden occurs earlier among adults of working age augments its macroeconomic impact in LMICs. Under current projections, in LMICs such as South Africa, CVD will strike 40% of adults between 35 and 64 years of age, compared with 10% in the United States. India and China will have death rates in the same age group that are two and three times that for most HICs. In view of the large populations in these two rapidly growing economies, this trend could have profound economic effects over the next 25 years, as workers in their prime succumb to CVD.

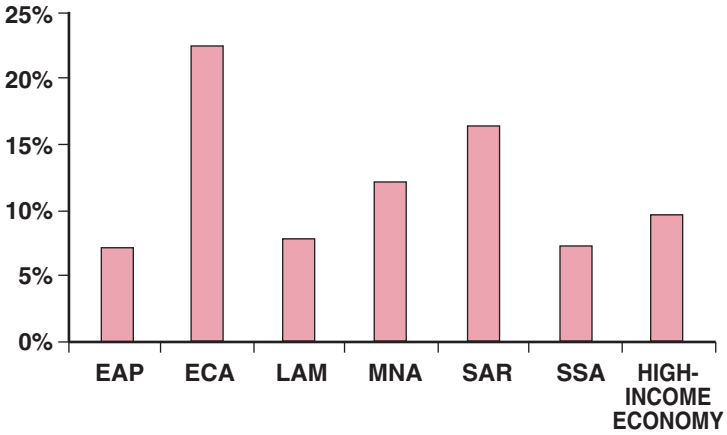

FIGURE 1-12 Percentage of health care expenditures attributed to high blood pressure. EAP = East Asia and Pacific; ECA = Europe and Central Asia; LAM = Latin America and the Caribbean; MNA = Middle East and North Africa; SAR = South Asia region; SSA = sub-Saharan Africa.

COST-EFFECTIVE SOLUTIONS

The large reductions in age-adjusted CVD mortality rates that have occurred in HICs result from three complementary types of interventions. One strategy targets those with acute or established CVD. A second entails risk assessment and targeting persons at high risk because of multiple risk factors for intervention before their first CVD event. The third strategy uses mass education or policy interventions directed at the entire population to reduce the overall level of risk factors. This section reviews various cost-effective interventions (**see also Chapter 42**). Much work remains undone in LMICs to determine the best strategies given limited resources, but if implemented, these interventions could go a long way toward reducing the burden. **Table 1-3** lists the cost-effectiveness ratios for many high-yield interventions that could be or have been adopted in low- and middle-income regions.

Established Cardiovascular Disease Management

People at highest risk are those suffering an MI or stroke; as many as half die before they ever receive medical attention. For those who do make it to a hospital, standard medical therapies were examined in a cost-effectiveness analysis in the Disease Control Priorities Project in Developing Countries.[74]

Four incremental strategies were evaluated for the treatment of MI and compared with a strategy of no treatment as a control for the six World Bank low- and middle-income regions. The four strategies compared were (1) aspirin; (2) aspirin and atenolol; (3) aspirin, atenolol, and streptokinase; and (4) aspirin, atenolol, and tissue plasminogen activator (t-PA). The incremental cost per quality-adjusted life-year (QALY) gained for both the aspirin and beta blocker interventions was less than $25 for all six regions. Costs per QALY gained for streptokinase were between $630 and $730 across the regions. Incremental cost-effectiveness ratios for t-PA were around $16,000/QALY gained, compared with streptokinase. Minor variations occurred between regions as a result of small differences in follow-up care based on regional costs.

Secondary prevention strategies are equally cost effective in LMICs. Studies show that a combination of aspirin, an ACE inhibitor, a beta blocker, and a statin for secondary prevention can lead to acceptable cost-effectiveness ratios in all low- and middle-income regions. Use of currently available generic agents, even in the absence of the so-called "polypill," could be highly cost-effective, on the order of $300 to $400 per person per QALY gained.

TABLE 1-3 Cost-Effectiveness for a Selection of CHD Interventions in Developing Regions

INTERVENTION	COST-EFFECTIVENESS RATIO ($ U.S./DALY)
Drug Treatments	
Acute myocardial infarction	
ASA, BB (global)	11-22
ASA, BB, SK (global)	634-734
ASA, BB, tPA (global)	15,860-18,893
Prehospital thrombolysis (Brazil)	457/LY
Secondary Treatment (CHD)	
Multidrug regimen (ASA, BB, ACEI, statin) (global)	1686-2026
Coronary artery bypass graft (global)	24,040-72,345
Primary prevention	
Cholesterol-lowering (Brazil)	441/LY
Multidrug regimen (AR >20%-25%) (global)	771-1195
Policy Interventions	
Tobacco	
Price increase of 33%	2-85
Non-Policy Interventions	**33-1432**
Salt reduction†	
2- to 8-mm Hg reduction	Cost saving—250
Fat-related interventions‡	
Reduced saturated fat intake	Cost saving—2900
Trans fat replacement—7% reduction in CHD	50-1500
Devices	
Cardioverter-defibrillators—primary prevention (Brazil)	50,345 (US$PPP/QALY)

ACEI = angiotensin-converting enzyme inhibitor; AR = absolute risk; ASA = aspirin; BB = beta blocker; CHD = coronary heart disease; SK = streptokinase; tPA = tissue plasminogen activator.

*Across six World Bank regions.

†Range includes different estimates of cost of interventions, as well as blood pressure reduction (<$0.50-$1.00).

‡Range includes estimates of cost of interventions (<$0.50-$6.00).

Data from Gaziano TA: Cardiovascular disease in the developing world and its cost-effective management. Circulation 112:3547, 2005; and from Gaziano TA, Galea G, Reddy KS: Chronic diseases 2—scaling up interventions for chronic disease prevention: The evidence. Lancet 370:1939, 2007.

Risk Assessment

Primary prevention is paramount for the large number of people who are at high risk for acquiring CVD. In view of limited resources, finding low-cost prevention strategies is a top priority. Using prediction rules or risk scores to identify persons at higher risk in order to target specific behavioral or drug interventions is a well-established primary prevention strategy and has proved to be cost-effective in LMICs.[75] Most such scoring systems include age, sex, hypertension, smoking status, diabetes mellitus, and lipid values; some also include family history.[76,77] Recently, many investigators have examined whether additional laboratory-based risk factors can add to predictive discrimination of the risk factors used in the Framingham Heart Study risk score. The recent analyses in the Atherosclerosis Risk in Communities (ARIC) Study[78] and the Framingham Offspring Study[79,80] suggested that little additional information was gained when other blood-based novel risk factors were added to the traditional risk factors. Although the Reynolds risk score[81] for women—which added family history, C-reactive protein (hsCRP), and hemoglobin A_{1c} levels—had only a marginally higher C-statistic (0.808) than the Framingham covariates (0.791), it correctly reclassified many persons at intermediate risk (**see also Chapters 10 and 42** in this regard). Some women deemed to be at low risk by the Framingham risk score were reclassified as being in the intermediate or high risk category according to the Reynolds risk score, and thus would have been eligible for more aggressive management. Conversely, some women who were initially at high risk according to the Framingham criteria were reclassified as being at lower risk, and thus would not have needed treatment. Coronary artery calcium scoring may add the most in terms of changes in C-statistic or the net reclassification improvement (NRI) in intermediate-risk populations, but it has limitations as a screening strategy (**see Chapter 42**).[82]

More attention is now focused on developing risk scores that would be easier to use in clinical practice, without loss of predictive discrimination in resource-poor countries. In HICs, a prediction rule that requires a laboratory test is an inconvenience; in LMICs with limited testing facilities, it may be too expensive for widespread screening, or the cost may preclude its use altogether. In response to this concern, the WHO recently released risk prediction charts for the different regions of the world, with and without cholesterol data.[83,84] A study based on the U.S. National Health and Nutrition Examination Survey (NHANES) follow-up cohort demonstrated that a non–lab-based risk tool that uses information obtained in a single encounter (age, systolic BP, BMI, diabetes status, and smoking status) can predict CVD outcomes as well as one that requires lab testing, with C-statistics of 0.79 for men and 0.83 for women that were no different from those obtained using the Framingham-based risk tool.[85] Furthermore, the results of goodness-of-fit tests suggest that the non–laboratory-based model is well calibrated across a wide range of absolute risk levels and without changes in risk classification. The ankle-brachial index (ABI) also appears to add to risk discrimination and improve the NRI as an alternative noninvasive tool.[82]

Policy and Community Interventions

Education and public policy interventions that have reduced smoking rates, lowered mean BP levels, and improved lipid profiles are recognized to contribute to reduction in CHD rates.[4] Education and policy efforts directed at tobacco consumption have contributed substantially to the reductions in CVD. In addition, salt and cholesterol reduction has been evaluated as a cost-effective strategy to reduce stroke and MI in LMICs by WHO investigators.[86] Community interventions have reduced levels of multiple risk factors and, in some cases, CHD mortality (**see also Chapter 42**).

Tobacco Use

Tobacco control can be conceptualized in terms of strategies that reduce the supply of, or demand for, tobacco. Most public health and clinical strategies to date focus on reducing demand through economic disincentives (taxes), health promotion (media and packaging efforts), restricted access (to advertising and tobacco), or clinical assistance for cessation. The WHO effort to catalyze the creation of a global treaty against tobacco use was a key milestone. In May 2003, the WHO World Health Assembly unanimously adopted the WHO Framework Convention in Tobacco Control (FCTC), the first global tobacco treaty.[41] The FCTC had been ratified by 168 countries as of April 2009, making it one of the most widely embraced treaties in the United Nations.[41] The FCTC has spurred efforts for tobacco control across the globe by providing both rich and poor nations with a common framework of evidence-based legislation and implementation strategies known to reduce tobacco use.

Jha and colleagues presented a landmark analysis of tobacco control cost-effectiveness in 2006.[87] They calculated the reductions in future tobacco deaths as a result of a range of tax, treatment, and non-price interventions among smokers alive in 2000. They found that a 33% price increase would result in a reduction of between 19.7 million and 56.8 million (5.4% to 15.9% of total) deaths in smokers from the developing world who were alive in 2000.[87] Calculations show that nicotine replacement therapy (NRT) could reduce the number of deaths by between 2.9 million and 14.3 million (0.8% to 4.0% of total) in the 2000 cohort.[87] A range of nonprice interventions such as advertising bans, health warnings, and smoke-free laws would reduce deaths by between 5.7 million and 28.6 million (1.6% to 7.9% of total) in that cohort.[87] These reductions would translate into developing world cost-effectiveness values of between $3 and $42/QALY saved for tax increases (not including tax revenue), $55 to $761/QALY for NRT, and $54 to $674/QALY for nonprice measures.[87]

Critically important for patients who have had a coronary event, smoking cessation saves lives at a greater rate than any individual medical treatment. Mohiuddin and associates conducted a randomized controlled trial of a behavioral and medication smoking cessation program for smokers who were hospitalized with a coronary event in the critical care unit.[88] These investigators observed nearly threefold higher quit rates and a decrease in all-cause mortality at 1 year by an absolute risk of 9% (77% reduction in relative risk). This reduction corresponded with a number needed to treat (NNT) of 11 for smoking cessation to prevent 1 death in the year after a major coronary cardiac event.[88] This NNT for secondary prevention is more favorable than that for statins, beta blockers, or even aspirin.[89]

Salt and Lipid Reductions

The cost-effectiveness analyses on salt reduction achieved as a result of public education are quite favorable.[90,91] The intervention ranges from being cost-saving to $200/DALY averted. The results of a campaign for reducing saturated fat and replacing it with polyunsaturated fat was also likely cost-effective. In the base case, a 3% decline in cholesterol and a $6 per capita education cost were assumed. Findings included a cost as low as $1800/DALY averted in the South Asia region, and up to $4000/DALY averted in the Middle East and North Africa region. If the cost for the education plan were halved, however, the ratio is approximately $900/DALY, which would be cost-saving if the reduction could be achieved for under $0.50 per capita—a possibility in areas with less expensive access to media.

Community Interventions

In the 1970s and 1980s, a series of population-based community intervention studies were conducted to reduce risk factors for chronic disease, and are reviewed elsewhere.[92] These studies focused on changes in health behaviors or risk factors such as tobacco use, body weight, cholesterol, and BP, as well as a reduction in CVD morbidity and mortality. In general, they included a combination of community-wide actions and those focused on persons identified as being at high risk for CVD-related health problems.

One of the earliest and most often-cited community interventions is the North Karelia project in Finland, begun in 1972. The community-based interventions included health education, screening, a hypertension control program, and treatment. Over the first 5 years of the study, reductions in risk factors occurred, along with a decline in CHD mortality by 2.9% per year—versus a 1% per year decline in the rest of Finland. During the next 10 years, declines were greater in the

rest of Finland. Over a follow-up period of 25 years, a large decline in CHD occurred in both the North Karelia region (73%) and the rest of Finland (63%). Although the overall difference in the decline in CHD deaths was not significantly greater in the study area of North Karelia, the reduction in tobacco-related cancers in men was significant. A similar study in the Stanford, California, area showed reductions in risk factors—cholesterol (2%), BP (4%), and smoking rates (13%)—compared with sites without the intervention, but no impact on disease endpoints.

Later, community interventions in HICs showed mixed results, with some showing improvements in risk factors beyond the secular decline that was occurring throughout most HICs and others exhibiting no additional decline. A meta-analysis of the randomized multiple risk factor interventions, however, showed net significant decreases in systolic BP (4.2 mm Hg), smoking prevalence (4.2%), and cholesterol (0.14 mmol/L).[93] The declines in total and CHD mortality of 3% and 4% were not significant. All of these projects are limited by the challenge of detecting small changes that, on a population level, may be significant—a 10% reduction in mortality could have been missed.[93]

Several community intervention studies have been conducted in LMICs, including China, Mauritius, and South Africa. The Tianjin project showed reductions in hypertension and obesity. The Mauritius project, among other interventions, resulted in a government-led program that changed the prime cooking oil from a predominantly saturated fat palm oil to a soybean oil high in unsaturated fatty acids. Overall total cholesterol levels fell 14% during the 5-year study period from 1987 to 1992. Changes in other risk factors were mixed with declines in BP and smoking rates and increases in obesity and diabetes. The Coronary Risk Factor Study in South Africa compared a control community with two communities receiving interventions at two different levels of intensity. The interventions included mass media messages, group sponsored educational sessions, and BP screening and follow-up with the health sector when appropriate. Both high-intensity and low-intensity interventions resulted in improvements in BP, smoking rates, and HDL–to–total cholesterol ratio over the control community, but with little difference between the two intervention communities.

Another significant reduction in CHD came not through a concerted community intervention but through changes in fiscal policy. In Poland, reductions in subsidies for animal products such as butter and lard led to a switch from saturated to polyunsaturated fats, mainly rapeseed-based and soybean-based oils. The decrease in CHD mortality by more than 25% between 1991 and 2002 could not be explained by increased fruit consumption or decline in smoking rates. Success stories such as in Poland and Mauritius are rare, however, suggesting the challenges to achieving meaningful changes targeting single risk factors at a national level.

SUMMARY AND CONCLUSIONS

CVD remains a significant global problem. The swift pace of economic and social transformation in a postindustrial world with rapid globalization presents a greater challenge for low- and middle-income economies than for high-income economies. Although CVD rates have declined in HICs, they are increasing in virtually every other region of the world. From a worldwide perspective, the rate of change in the global burden of CVD is accelerating, reflecting the changes in the low- and middle-income economies, which represent 85% of the world's population. This preventable epidemic will have substantial consequences on many levels: individual mortality and morbidity, family suffering, and staggering economic costs—both the direct costs of diagnosis and treatment and the indirect costs of lost productivity.

Different regions of the world face different stages of the epidemic. In HICs, managing an ever-older population with chronic manifestations of CVD such as heart failure will strain health care budgets. Currently, the Eastern European countries and members of the former Soviet Union face enormous burdens, with more than half of all deaths attributed to CVD. Meanwhile, countries in sub-Saharan Africa are just beginning to see increases in these chronic illnesses while still grappling with HIV/AIDS. No single global solution to the rising burden of CVD exists, in view of the vast differences in social, cultural, and economic circumstances. HICs must minimize disparities, reverse unfavorable trends in CVD risk factors and behaviors, and deal with the increasing prevalence of CVD in an aging population. The most complex challenges face LMICs—with increasing access to low-cost tobacco products and ready access to less than favorable dietary options. Preventing the poverty-inducing effects of catastrophic CVD events will require efforts to improve access to low-cost prevention strategies at both the societal and the individual level.

A reduction in the disease burden would similarly require both policy and personal changes. In the long run, the allocation of resources to lower-cost strategies will likely prove more cost-effective than dedicating resources to high-cost management of CVD. From a societal perspective, efforts to strengthen tobacco control strategies, improve dietary choices, and increase physical activity will be paramount. At the personal level, risk assessment strategies and treatment modalities require simplification. Furthermore, alternative deployments of allied health workers such as community health workers will need evaluation, in view of the limited human resources in most LMICs. HICs must share with leading and emerging middle-income countries the burden of research and development into every aspect of prevention and treatment. Through further expansion of the knowledge base, particularly regarding the economic consequences of various treatment and prevention strategies, the efficient transfer of low-cost preventive and therapeutic strategies may alter the natural course of the epidemiologic transition in every part of the world, thereby reducing the excess global burden of preventable CVD.

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2 Heart Disease in Varied Populations

Anne L. Taylor, Jackson T. Wright, and Ileana L. Piña

CHANGING DEMOGRAPHICS OF THE U.S. POPULATION

Cardiovascular disease (CVD) and stroke remain the leading causes of death and disability in the United States. These illnesses afflict the entire U.S. population. In the past, data extracted from large epidemiologic studies and major clinical trials with racially homogeneous cohorts were used to assess risk and describe the natural history of CVD, but the generalizability of these risks and disease traits to a more heterogeneous populace (i.e., varied populations) has been confirmed in contemporary population surveys that are racially and ethnically diverse. The risk for heart disease and stroke is ubiquitous and affects all populations. However, current data suggest that the racial or ethnic attributes of CVD may vary significantly among populations. Given the consequences of heart disease, it is imperative that the practice of cardiovascular medicine address the nuanced risk profiles and different manifestations of disease within varied populations. The emerging importance of these varied populations is directly related to the changing U.S. demographics. Currently, 14% of the U.S. population is black and 16% is Hispanic, and the Asian cohort is growing rapidly.[1] When added to the Native American population, the aggregate representation of these varied populations now approaches 40%, and a majority population in the United States will probably no longer exist by 2050 (**Fig. 2-1**). Accordingly, cardiovascular physicians and scientists must be aware of the epidemiology, pathophysiology, and treatment of heart disease in varied U.S. populations.

DISTRIBUTION OF KNOWN RISK FACTORS FOR HEART DISEASE

The incidence of known risk factors for CVD varies considerably by race and ethnicity (**see Chapters 42, 43, and 60**). The Third National Health and Nutrition Examination Survey (NHANES III) contains data on the distribution of hypertension in non-Hispanic white, non-Hispanic black, and Hispanic groups. Hypertension affects at least 33 million whites, almost 6 million blacks, and 1.3 million Hispanics. The rate of hypertension in blacks is approximately 40% (among the highest in the world); in whites, 25.6% in men and 23.8% in women; and in Hispanics, 14.6% in men and 14% in women. Worse disease severity accompanies a higher prevalence of hypertension in blacks. The prevalence of stage 3 hypertension (>180/110 mm Hg) is 8.5% in blacks versus 1% in whites. Mean systolic and diastolic blood pressure (BP) in blacks is 125/75 mm Hg and 122/74 mm Hg in whites. For hypertensive blacks, the difference in BP versus that in normotensive blacks is 30/20 mm Hg, whereas for hypertensive whites, the difference in BP is 23/15 mm Hg.[2]

Diabetes, a deadly risk factor for CVD, currently affects 17 million Americans. The incidence of the disease has increased 49% in the last decade, probably because of the increased incidence of obesity. Blacks have the highest prevalence of hemoglobin A1c: 7% or greater. In individuals 40 to 74 years of age, the prevalence of diabetes is 11.2% in whites, 18.2% in blacks, and 20.3% in Hispanics. Despite the higher incidence of diabetes in Hispanics, mortality rates from diabetes are highest in blacks—28.4/100,000 for men and 39.1/100,000 for women. This compares with 23.4/100,000 and 25.7/100,000 for white men and white women, respectively.[3] Hypertension occurs concomitantly in 75.4% of blacks with diabetes, 70.7% of Hispanics with diabetes, and 64.5% of whites with diabetes. Insulin resistance, along with obesity, hypertension, and dyslipidemia, constitutes the metabolic syndrome, which is associated with excessive CVD. Applying the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria to the NHANES III database, the incidence of metabolic syndrome might exceed 30% in the U.S. population older than 20 years but increases to greater than 40% in older adults and is highest in the varied populations.[4-6]

Hispanics have the highest incidence of metabolic syndrome—31.9% overall and 35% in Hispanic women. Despite the high incidence of insulin resistance and metabolic syndrome, Hispanics have a lower prevalence of hypertension than blacks do. When the influence of obesity, body fat distribution, and insulin concentration is followed prospectively in whites and Hispanics, each factor is independently associated with the development of hypertension—with the greatest risk in subjects with the highest body mass index (BMI; >30 kg/m^2) and the highest insulin concentration (>95 pmol/L). There appears to be no additional risk for CVD in Hispanics as compared with whites.[7]

The incidence of overweight or obesity (BMI >25 kg/m^2 being defined as overweight, >30 kg/m^2 as obese, and >40 kg/m^2 as morbidly obese) is growing in the U.S. population, and the varied populations are affected disproportionately. The prevalence of overweight and obesity is probably 60% or higher in the United States, and a third of all children and adolescents are overweight or obese.[2] The prevalence of both overweight and obesity is higher in blacks than in whites and higher in Hispanics than in whites. The mean BMI is 29.2 kg/m^2 in blacks, 28.6 kg/m^2 in Hispanics, and 26.3 kg/m^2 in whites. Black women are on average 17 lb heavier than white women of comparable age and socioeconomic status. Six of the 15 states with the highest prevalence of hypertension are located in the southeastern part of the United States (corresponding to the "stroke belt"), and half of all blacks live in this region. The highest prevalence of obesity, 44%, is found in black women, and in the southeastern United States a striking 71% of black women are obese.[8,9] Although Asians have lesser rates of overweight and obesity, standard BMI weight class definitions may be inappropriate for this population. Dyslipidemia is an important modifiable risk factor for heart disease in the United

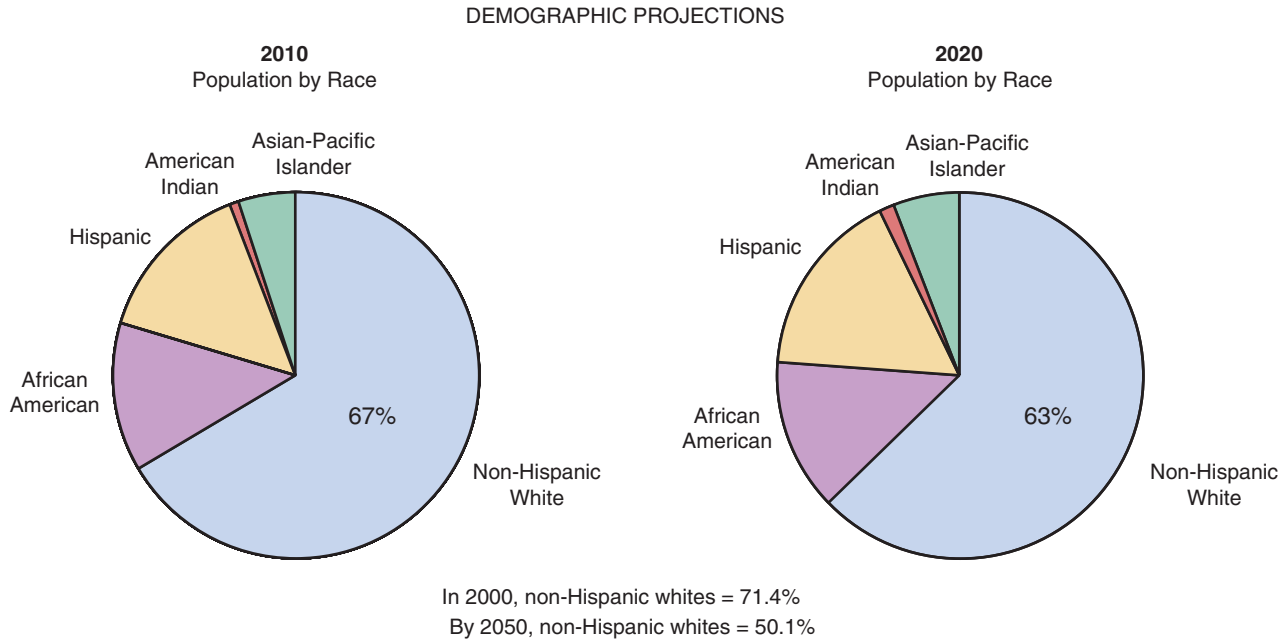

FIGURE 2-1 U.S. population estimates from the U.S. Census Bureau. (http://www.census.gov/population/www/projections/usinterimproj/natprojtab01a.pdf).

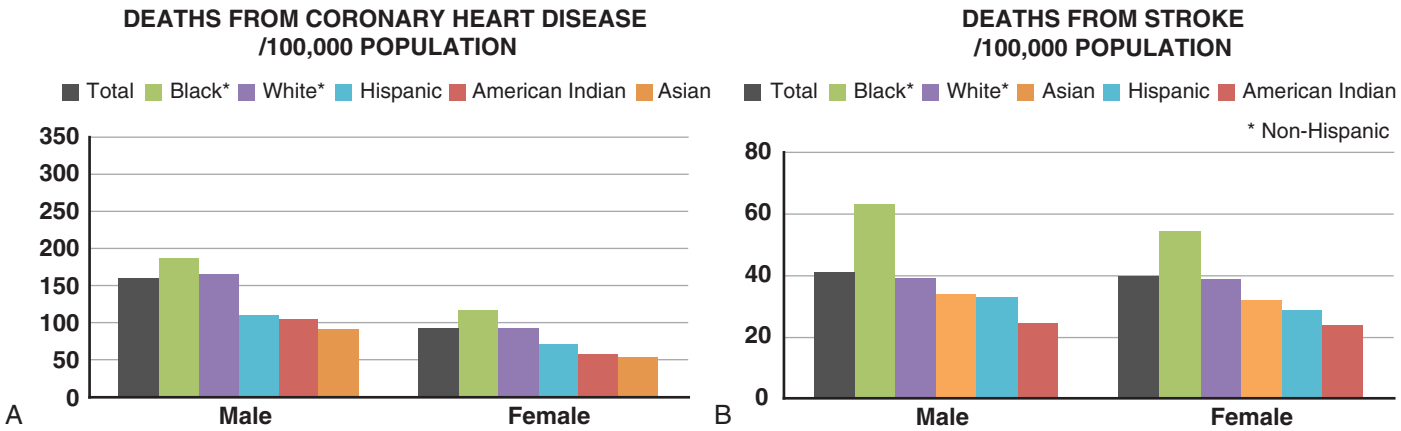

FIGURE 2-2 **A,** Age-adjusted death rates for coronary heart disease by race/ethnicity and sex in the United States (2008). **B,** Age-adjusted death rates for stroke by race/ethnicity and sex in the United States. *(From National Heart, Lung and Blood Institute. Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases. Bethesda, Md, NHLBI, 2012.)*

States, and treatment of lipid disorders decreases the incidence of heart disease. Several reports have suggested that blacks have lower low-density lipoprotein (LDL) cholesterol concentrations and less hypercholesterolemia than whites do. The CARDIA (Coronary Artery Risk Development in Young Adults) study identified the prevalence of high LDL cholesterol levels in young adults; LDL cholesterol exceeded 160 mg/dL in 10% and 5% of young black men and women, respectively, as opposed to 9% and 4% of young white men and women. High-density lipoprotein cholesterol levels were higher in black men than in white men.[8] Levels of lipoprotein(a), a known risk factor for coronary heart disease (CHD) (**see Chapter 45**), are twofold to threefold higher in blacks.

CORONARY HEART DISEASE

The United States is among the high-income countries that have experienced steep declines in CHD-related mortality since 1968.[10,11] The decline in mortality is attributed both to improved management of risk profiles and to treatment strategies. Rosamond and colleagues[12] found that over a period of 22 years (1987 to 2009), CHD mortality and incident myocardial infarction (MI) declined significantly in four U.S. communities, with the steepest declines occurring in the second decade. Declines were significant in both black and white Americans in the cohort; however, the magnitude of decline was less in black Americans. Similar findings were noted by Chen and coworkers[13] in a Medicare cohort. Comparing U.S. mortality data from 1980 and 2000, Ford and associates[5] estimated that 47% of the decrease in mortality was attributable to treatments whereas 44% was attributable to improved risk factor control, including reduced total cholesterol, decreased systolic BP, decreased smoking, and increased physical activity. In this same period, however, the authors estimated that the increasing prevalence of obesity and diabetes resulted in a small increase in the number of deaths (8% and 10%, respectively).[3]

Even though risk factors and mortality from CHD have been declining in the United States, both still vary considerably by U.S. racial and ethnic groups (**Fig. 2-2**). These groups are classified by race (white, black American, Native American/Alaskan Native, and Asian) and by Spanish language grouping (Hispanic). In the United States there are significant admixtures of populations by racial groups, as well as racial heterogeneity among Spanish language groups. Although these broad categories are used to examine population-based

cardiovascular risk profiles, disease patterns, and outcomes, they are not independent of socioeconomic, psychosocial, genetic, epigenetic, and other determinants of CHD. Nonetheless, there are population-associated differences in CHD risk profiles, disease patterns, and outcomes that can and should be used to better understand the pathophysiology of CHD, to assist in targeted disease reduction strategies, and to improve outcomes across all U.S. population groups.

Risk for Coronary Heart Disease and Mortality in U.S. Hispanics. In the United States, Hispanic groups are the minority group with the most rapid increase in population; they originate from various countries, including Mexico (the largest number of U.S. Hispanics), the Caribbean Islands (Puerto Rico, Cuba, and the Dominican Republic), and Central and South America. Contemporary U.S. Hispanic populations have varying proportions of ancestral admixture of European, black, and Native American descent, depending on their country of origin.[14-18] Even though population health data are often collected by Spanish language group, it is important that studies addressing risk and outcomes in Hispanics take into consideration the heterogeneity in this population.[19] In MESA (Multi-ethnic Study of Atherosclerosis)[15] and in the Hispanic Community Health Study,[19] those of Hispanic origin were further subdivided by geographic locus of family origin into Mexican American, Dominican American, Puerto Rican American, and other. The prevalence of risk factors differed significantly in the four groups, and the association between risk factors and measures of subclinical CHD also varied significantly. Mexican Americans had the highest levels of subclinical measures of CHD, with Puerto Rican Americans having the next highest levels despite distinctly different risk profiles between the groups.[15] Consistent with other immigrant populations, lower socioeconomic status and greater acculturation were associated with greater risk for CHD. Overall, however, the prevalence of CHD and stroke by self-report was low (4.2% and 2.0% for men, 2.4% and 1.2% for women).

Coronary Heart Disease in Black Americans. As shown in Figure 2-2, black American men and women have the highest age-adjusted mortality from CHD of all the racial/ethnic groups in the United States.[20] Rosamond and colleagues[12] found that between 1987 and 2008, CHD-related mortality in four U.S. communities declined significantly, with the steepest declines occurring in the second decade. Declines in CHD mortality were significant in both black and white Americans; however, the magnitude of the decline was less in blacks. Similar findings were reported by Chen and coauthors[13] in a Medicare cohort. Ford[21] examined trends in risk for CHD in 7800 participants in NHANES between 1999 and 2010 and found that risk for CHD declined significantly in men and whites, declined nonsignificantly in Mexican Americans, and increased nonsignificantly in black Americans. Although black and white men have been found to have a similar incidence of total CHD, black men had a greater incidence of fatal CHD. Black women had a higher incidence of both total CHD and fatal CHD than white women did. Importantly, although BP, total cholesterol, and smoking status improved in the cohort overall, no significant improvement in BP or total cholesterol occurred in black Americans and an increased prevalence of diabetes was noted in this group. Of interest, even though mortality from CHD is higher in black than in white Americans, at coronary angiography blacks have been found to have less obstructive coronary disease[22,23] and differences in the anatomic distribution of coronary lesions. Significant differences have been identified in the number and type of risk factors for CHD between black and white Americans.[24] In 2010, 58% of blacks had at least one risk factor versus 47% of whites and 45% of Mexican Americans. Lifetime risk for CVD across all population groups has been found to be dependent on the number of risk factors present in each age and race group and thus may in part explain the greater mortality in blacks.

Even though the burden of risk factors for CHD is substantially greater in black Americans, when risk factors are controlled, outcomes are improved irrespective of race. Yang and coworkers[25] studied the impact of achievement of ideal measurements of seven CVD health metrics in 45,000 U.S. subjects over a 22-year period. Across all racial groups, the more of these CVD risk metrics that were at ideal measurement, the lower the risk for mortality from CHD. Elevated BP, a risk factor notably more prevalent in black Americans at younger ages, was associated with the highest risk for mortality from CVD.

Coronary Heart Disease in Asian Americans. Asian Americans account for a smaller percentage of U.S. minority populations but are analogous to Hispanics with respect to heterogeneity in national origin and parameters such as U.S. or foreign born, duration of U.S. residence, English language fluency, level of education, and income. Included in this group are individuals of Asian Indian, Chinese, Filipino, Korean, Japanese, Vietnamese, and other Asian backgrounds. Health statistics often group Asians as a single group; however, this practice obscures distinctive CVD risk profiles, as well as differences in outcomes.[26] U.S. data comparing the CHD risk profiles of Asians grouped together found that overall risk for CHD is lower than that for other racial/ethnic groups but that risk factors varied by the specific Asian subgroup and that the pattern of vascular disease associated with risk also differed.[26] Although less likely than U.S. whites to smoke or have increased BMI, the prevalence of metabolic syndrome has been found to be higher in Asian Americans than in non-Hispanic whites and is identified at a lower BMI.[26] This has been noted particularly in Asian Indians, who have been found to have higher rates of insulin resistance, diabetes, and dyslipidemia; greater waist circumference; and higher plasma concentrations of procoagulants[26] than whites do. Rates of hospitalization for CHD have been reported to be higher in Asian Indians than in whites and lower in Chinese Americans than in whites. By contrast, the incidence of hemorrhagic stroke is higher than that of MI in Japanese and Chinese Americans. Stroke prevalence in these two groups has been reported to decrease with longer duration of U.S. residency.

Coronary Heart Disease in American Indians and Alaskan Natives. Despite being the smallest population subgroup in the United States (1.5%), the prevalence of risk factors for CHD in American Indians/Alaskan Natives has risen dramatically since the 1970s. Diabetes, elevated cholesterol, and smoking are now more prevalent in Native Americans than in whites, black Americans, and Hispanics. Rates of CHD and CHD mortality have also risen and now exceed rates in the general population. Declines in heart disease and stroke mortality have also been nonsignificant in this population in comparison to non-Hispanic whites. Of importance, mortality from heart disease and stroke is much more likely to occur at 65 years or younger in this population. Reasons for the increase in the incidence of CVD, as well as mortality, are multifactorial and include decreases in deaths from infectious diseases; an increased prevalence of diabetes, hyperlipidemia, tobacco abuse, and obesity; geographic isolation; poor access to health care; high psychosocial stress; and a poorly functioning health system.

Racial/Ethnic Differences in Health Care for Coronary Heart Disease

In addition to differences in CHD risk burden and patterns of vascular disease, significant differences in care, including risk assessment, risk management, and treatment of acute CHD, exist when blacks, Hispanics, and American Indians are compared with non-Hispanic whites.[27] Asians with acute coronary syndromes undergo diagnostic and therapeutic procedures at equivalent rates as non-Hispanic whites and have equivalent in-hospital mortality and reinfarction rates.[26] Blacks are less likely to be referred for cardiovascular specialty consultations, are less likely to undergo revascularization after acute MI, even with adjustment for severity of illness, and continue to experience higher long-term mortality.[27-30] Racial and ethnic minority patients are more likely to be hospitalized at institutions with worse outcomes, are less likely to survive in-hospital cardiac arrest,[29,30] and are more likely to undergo coronary artery bypass grafting procedures by surgeons with higher risk-adjusted mortality rates.[31] Socioeconomic disadvantage explains some, but not all of the ongoing disparity in care.[32] Cromwell and colleagues[33] examined the use of cardiovascular technologies and outcomes in Medicare beneficiaries and found that blacks and Native Americans were much less likely to undergo invasive diagnostic and therapeutic procedures despite similar insurance benefits. Although disparities in CVD outcomes are multifactorial in origin and require multidisciplinary interventions, it is clear that organizational quality improvement initiatives have a significant impact on chronic disease measures in all patients and can result in diminution in disparities between groups.[34] Treatment of acute MI in hospitals participating in the Get with the Guidelines—Coronary Artery Disease Program was improved across all racial/ethnic groups. A meta-analysis[35] of studies linking use of guideline-recommended therapies with CVD outcomes demonstrated a strong relationship between adherence to guidelines/performance measures and improved patient outcomes.

TABLE 2-1 Hypertension Awareness, Treatment, and Control by Race/Ethnicity and Sex: NHANES 1999-2004 and 2005-2010

	AWARENESS (%)		TREATMENT (%)		CONTROL (%)	
	1999-2004	2005-2010	1999-2004	2005-2010	1999-2004	2005-2010
NH white males	71.2	77.5	61.2	69.4	41.0	50.1
NH white females	74.4	84.0	65.3	78.2	37.2	53.9
NH black male	69.1	77.5	58.1	66.9	32.3	39.7
NH black female	83.5	88.5	73.9	81.5	40.4	52.8
Mexican American males	57.0	64.8	41.8	54.0	23.3	35.1
Mexican American females	67.9	75.5	56.3	68.1	29.6	41.6

NH = non-Hispanic.
Sources: NHANES (1999-2004, 2005-2010) and National Heart, Lung and Blood Institute.

HYPERTENSION

Epidemiology

Race and ethnicity substantially influence the prevalence, impact, and control of hypertension in the U.S. population. In the United States, hypertension is more common, is more severe, develops at an earlier age, and leads to more clinical sequelae in blacks than in age-matched non-Hispanic whites.[36] Prevalence rates in Mexican Americans are lower than those in black Americans and comparable to those in non-Hispanic whites, but BP control rates in Mexican Americans and Native Americans are lower than in both non-Hispanic whites and black Americans (**Table 2-1**). Among Hispanics, higher hypertension prevalence rates have been reported in Hispanics of Puerto Rican background.[36,37]

The increased prevalence and severity of hypertension in black Americans and other ethnic minority groups are also associated with higher rates of morbid and mortal cardiovascular and renal disease events.[37] Hypertension-related mortality is approximately three times higher in black than in white Americans. Age-adjusted stroke mortality is approximately 50% higher in black Americans than in other U.S. ethnic groups (Fig. 2-2B). Other ethnic minorities, such as Native Americans and Hispanics, also have a twofold to fourfold higher prevalence of end-stage renal disease (ESRD) than whites do.[38] In 2010, black Americans accounted for almost 37% of the entire ESRD population, a rate 3.4 times higher than that in whites. Although hypertension has dropped to the second leading cause of ESRD after diabetes in black Americans, adjusted incident ESRD rates per million population secondary to hypertension were six times greater in black Americans (46/million) than in whites (7.6/million). Rates were 15.1/million in Hispanics, 6.3/million in Native Americans, and 10.8/million in Asians. The excess ESRD rate in black Americans may be linked to a specific genetic haplotype not found in other subgroups.

Racial/Ethnic Differences in the Pathophysiology of Hypertension

The cause of essential hypertension remains elusive, as does the explanation for population differences in hypertension. Many mechanisms have been proposed to account for the earlier onset, greater severity, and increased morbidity of hypertension in black Americans (see **Table 2-2**)[37-39]; however, no single mechanism is fully explanatory, and it is likely that the ethnic differences in hypertension are multifactorial.

Genetic Versus Socioeconomic Status. The contribution of genetics to hypertension in black Americans, as in the general population, is a subject of intense investigation. Hypertension appears to be highly heritable with a multigenetic pattern of heritability, and BP heritability is estimated to be approximately 30% to 40%. However, in studies of populations of European descent, in which 16 functional genetic variants have been identified, genetics has been shown to account for only a small fraction of phenotypic BP variability (<5 mm Hg).[39] As in other racial/ethnic groups, no major gene or gene family has been identified that is directly linked to hypertension in black Americans. However, genetic variants in the chromosome 22q region (*APOL1* gene) have been shown to contribute significantly to black Americans' excess risk for ESRD, which has been attributed to hypertensive, diabetic, focal segmental glomerulosclerosis and human immunodeficiency virus–associated nephropathy.[40,41] Socioeconomic status has received considerable attention, and studies controlling for (or minimizing) differences in socioeconomic status report reduced racial/ethnic differences in the epidemiology of hypertension and its morbidity/mortality. The effect of socioeconomic status on health outcomes is complex, and the gross estimates provided by current markers (e.g., income, education, employment, insurance status, place of residence) probably oversimplify its significance.

TABLE 2-2 Proposed Mechanisms for the Increased Incidence of Hypertension in Blacks

Genetic susceptibility
Socioeconomic status
Renal and cellular salt handling
Dietary Na/K
Alterations in renin-angiotensin-aldosterone system
Vasodilator deficiency
Increased sleep apnea
Low birth weight

Salt Metabolism. Racial differences in renal salt handling have also been proposed as a potential explanation for the increased incidence and severity of hypertension in black Americans versus nonblack American populations, as well as the favorable responses of hypertensive black Americans to diuretic therapy. Although salt sensitivity is more common in hypertensive black Americans, it is also very common (>50%) in other populations, and the increased salt sensitivity in black Americans may be explained at least in part by differences in disease onset, severity, concomitant diseases, or dietary patterns. A major limitation of many studies reporting racial differences in salt sensitivity is failure to adequately control for differences in age, severity of hypertension, renal function, BMI, and BP variability because these characteristics may alter rates of salt sensitivity. In a study in which groups were closely matched for sex, age, renal function, hypertension status, and weight, no racial difference in the prevalence of salt sensitivity was seen.[42] However, the magnitude of increase in BP in response to salt loading in this study was found to be greater in black than in white American hypertensive individuals, although not in normotensive subjects, thus suggesting that the increased salt sensitivity may be a consequence rather than a cause of the hypertension. Another suggested defect in salt handling related to altered Na^+ transport has been proposed. Higher intracellular Na^+ has consistently been reported in black Americans more than in whites, as well as up to a 30% depression in Na^+,K^+-adenosine triphosphatase pump activity. Elevated intracellular Na^+ can trigger a cascade of compensatory events leading to elevated intracellular Ca^{2+}, increased vascular reactivity, and eventual BP elevation.[40]

Neurohormonal Activation. Differences in the expression and activity of a variety of neurohumoral factors, particularly of the renin-angiotensin system (RAS), have been described in black versus white Americans to explain the higher incidence and severity of hypertension. Many studies have reported suppressed activity of the

renin-angiotensin-aldosterone system (RAAS) in black Americans as opposed to whites in response to changes in intravascular volume or BP. Thus hypertension in black Americans is usually classified as low renin and is generally associated with a diminished response to antihypertensive drugs that inhibit the RAAS. Increased levels of the pressor peptide endothelin-1 have been reported in hypertensive black Americans, with circulating endothelin-1 levels being almost eightfold higher than in normotensive black Americans and almost fourfold higher than in white hypertensives.[38] Furthermore, increased cardiovascular reactivity and higher circulating levels of endothelin-1 in response to acute physical or mental stress have been reported in adolescent males with a family history of hypertension. In contrast, lower levels of endogenous vasodilators such as kallikrein, atrial natriuretic peptide, prostacyclin, and nitric oxide have been reported in hypertensive black Americans.[36,43,44] Regardless of BP, black Americans have been found to excrete less urinary kallikrein than whites do. Markedly reduced levels of atrial natriuretic peptide during salt loading have been reported in children of hypertensive versus normotensive parents, and salt-sensitive black Americans have been found to exhibit a paradoxical decrease in atrial natriuretic peptide in response to increased dietary salt intake. Rigorous assessment of the relative roles of these systems in the pathogenesis of hypertension in individuals of African ancestry remains to be carried out.

Low Birth Weight. Epidemiologic studies have raised the possibility that low birth weight (LBW) may influence disease later in life, and the increased prevalence of hypertension in blacks has been attributed to a higher incidence of LBW with an associated nephron deficit acquired in utero that does not recover after birth and leads to glomerular sclerosis, increased salt sensitivity, and subsequent hypertension.[36,45] In a study of almost 5000 persons, a statistically significant inverse relationship was found between systolic BP and birth weight at all ages beyond birth. By the age of 64 to 71 there was a 5.2–mm Hg increase in systolic BP for every 1-kg decrease in birth weight. Although the LBW-hypertension hypothesis has been questioned by many and has yet to be rigorously evaluated in populations of African ancestry, it provides a unifying explanation for the increased salt sensitivity, severity of hypertension, and proclivity for the development of ESRD seen in this population.

Asians, Pacific Islanders, and Native Americans

Asians/Pacific Islanders are reported to have a similar or slightly higher level of BP and prevalence of hypertension.[46] Salt reduction in Asians/Pacific Islanders produces similar BP reduction as in black populations.[47] Although the data are extremely limited, the prevalence of hypertension in Native Americans appears to be similar to that in the general population. As in other populations, a higher incidence of hypertension is associated with obesity, older age, and diabetes.

Evaluation of Hypertension (see also Chapter 43)

True population-based surveys of the epidemiology of secondary causes of hypertension are not available. Despite the reported higher rates of salt sensitivity and responsiveness to BP reduction with diuretic therapy suggesting a volume overload–associated form of hypertension, particularly in black American cohorts, a racial difference in the prevalence of hyperaldosteronism has not been shown.[48,49] Sleep-disordered breathing has been reported to be more common in black Americans, and the difference appears to be greatest at early ages (see Chapter 75).[50,51] However, except for hypertension associated with renal disease and a higher incidence of sleep apnea, there is currently little evidence of significant racial or ethnic differences in the incidence or prevalence of secondary hypertension. Because the major factors (i.e., early age at onset, severity of hypertension, and resistance to therapy) triggering a search for secondary hypertension occur more commonly in black Americans with essential hypertension, evaluations for secondary hypertension based on these triggers are more likely to confirm essential hypertension in this subgroup. However, this should not discourage evaluation for secondary causes.

Racial/Ethnic Differences in the Treatment of Hypertension (see also Chapters 44 and 44G)

Goal Blood Pressure

The optimal BP for achieving maximal reduction in hypertensive complications has not been established, even in nonminority hypertensive populations. Randomized controlled clinical outcome trials in older (mostly nonminority) populations have documented the benefit of treatment to a systolic BP lower than 150 mm Hg versus a higher target.[52-54] Several clinical outcome trials have also documented the lack of significant benefit of treatment to systolic BP targets lower than 120 mm Hg versus targets lower than 140 mm Hg in diabetic hypertensive patients or mean arterial pressure equivalent to 125/75 versus 140/90 in patients with chronic kidney disease (CKD).[55-57] Only two small and underpowered randomized controlled outcome trials in older (age >60) Japanese hypertensive patients that compared systolic BP targets between 140 and 160 mm Hg are available.[58,59] Thus recommendations for BP targets lower than 140/90 mm Hg remain based on expert opinion level of evidence. The higher risk for complications in black American hypertensive patients led the consensus panel established by the International Society of Hypertension in Blacks to recommend a lower BP goal (<135/85 mm Hg) in black Americans with uncomplicated hypertension and a goal of lower than 130/80 mm Hg in those with other risk factors for CVD or with clinical or subclinical target organ damage. However, there is little evidence that the lower BP targets in black Americans or other racial/ethnic subgroups result in better outcomes.[60] Studies such as the original Veterans Administration Cooperative Trials and the Hypertension Detection and Follow-up Program contained ample numbers of black hypertensive Americans and make a goal of lower than 140/90 mm Hg a very reasonable target in this population.

Treatment Strategies in Minorities (see also Chapter 44)

Lifestyle Strategies

As in the general population, lifestyle modification is recommended for all members of ethnic minority groups who have elevated BP. Calorie reduction is especially important in the black American, many Hispanic, and other minority populations with a high prevalence of obesity. Physical inactivity is also a particular problem in minorities; approximately half of black American adults (44% of men, 55% of women) report no participation in any leisure-time activity.[36] Reductions in dietary salt and improvements in diet quality (i.e., the DASH [Dietary Approaches to Stop Hypertension] diet) are also important in these populations. Recent guidelines from the U.S. Food and Drug Administration and the American Heart Association recommend more aggressive salt restriction (<1500 mEq/day), especially in black hypertensive individuals.

Drug Therapy (see also Chapter 44)

In most cases, drug selection for the treatment of hypertension in ethnic minorities is similar to that in the general population of hypertensives. The best evidence from clinical trials is that in the absence of specific indications (i.e., heart failure [HF], CKD, or CHD), it is the ability of the regimen to lower BP that is the major factor determining the effect of these agents on BP-related clinical outcomes in all racial/ethnic groups. In addition, most patients will require multiple agents to achieve their BP target. Almost all national guidelines, including those from the countries of origin for most minorities, have recommended initiating antihypertensive drug therapy with either a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker (CCB) based on clinical outcome trial data documenting a reduction in clinical outcomes. In addition to ALLHAT (Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial) and INVEST (INternational VErapamil SR Trandolapril Study), which contained a considerable number of Hispanics, significant numbers of Asians/Pacific

Islanders were included in several trials evaluating CCBs and RAS inhibitors.[61-63] Although surveys of Hispanics report lower rates of BP control, this group appeared to achieve higher rates of BP control than did non-Hispanic cohorts in both ALLHAT and INVEST.[47,64]

There are several important racial/ethnic differences in response to some classes of antihypertensive drugs, and for this reason race/ethnicity should play a role in the selection of antihypertensive drugs. A variety of studies have shown that although BP-lowering efficacy is similar across population subgroups for most antihypertensive classes, black American patients respond better to diuretics and CCBs than to drugs that block the RAS (i.e., ACE inhibitors, ARBs, renin inhibitors, and beta blockers).[36] This racial difference is eliminated when these agents are combined with diuretics or CCBs, thus suggesting that the latter two classes should be preferred initial agents in this population. Abundant outcome data from randomized controlled trials with significant numbers of hypertensive black American subjects have demonstrated benefit of multidrug regimens that include a diuretic. ALLHAT enrolled more than 15,100 blacks (36%) and 8300 Hispanics (19%).[65] It compared treatment initiated with the ACE inhibitor lisinopril, the alpha blocker doxazosin, and the CCB amlodipine with treatment initiated with the thiazide-type diuretic chlorthalidone in black, Afro-Caribbean, and Hispanic populations. Neither of the newer classes were more effective than the diuretic arm in reducing any prespecified cardiovascular, renal, or stroke outcome in either population subgroup in ALLHAT.

Even though the primary coronary outcome in ALLHAT did not differ with respect to treatment assignment, there were significant differences in major secondary outcome rates by treatment group that were exaggerated in ALLHAT participants of African ancestry. Among those of African ancestry in ALLHAT, both ACE inhibitor and alpha blocker treatment assignment was associated with a significant increase in stroke, HF, and the combined CVD outcome when compared with assignment to diuretic treatment.[66] Adjustment for BP achieved failed to account for the racial differences in response to treatment. ACE inhibitor–based treatment was shown to be more effective in slowing the progression of kidney disease (mean rate of decline in the glomerular filtration rate [GFR] and the composite of ESRD, death, or 50% decline in GFR) than was amlodipine- and metoprolol-based treatment.[66] Diuretics are usually necessary for BP control in hypertensive patients with CKD; the ACE inhibitor was not more effective than the diuretic chlorthalidone in preventing negative renal outcomes in black Americans in ALLHAT.[66] In addition to racial/ethnic differences in BP-lowering and CVD outcomes, there are also clinically important differences in the adverse effects of antihypertensive drugs. ALLHAT and other studies,[65] as well as some surveys of Asians, report a threefold to fourfold higher risk for angioedema and cough attributed to ACE inhibitors in black and Asian Americans than in white Americans.[65,66] However, the LIFE (Losartan Intervention for Endpoint Reduction) trial provided no evidence that treatment with ARBs provides an advantage in black American hypertensive patients over diuretics, CCBs, or ARBs.

HEART FAILURE

Heart Failure in Black Americans

Epidemiology, Cause, and Clinical Features

The burden of HF is higher in black Americans than in any other U.S. ethnic or racial group, both in incidence and in prevalence.[67] The relative incidence of HF in black Americans is 50% higher than that in the general population, and the rate of hospitalization for HF in black Americans is also higher. When hospitalized for HF, black American patients have more risk factors such as diabetes and hypertension, which may be poorly controlled. The registry of the SOLVD (Studies on Left Ventricular Dysfunction) trial demonstrated that the cause of HF in black Americans was more commonly hypertension, in contrast to whites, in whom the strongest risk factor was coronary artery disease.[68] Recent data from the CARDIA investigations[69] have highlighted the magnitude of the dissimilarity between blacks and whites in the onset of HF. Young black adults are much more likely to be hypertensive, with a baseline incidence rate of almost 33%; more than 60% of those affected are either untreated or not treated to goal BP reductions. Even after enrollment in the CARDIA study for 10 years, the number untreated or not treated to goal remained at almost 50%, a prominent portrayal of disparate care. In this group of at-risk individuals, the subsequent development of HF at an early age is almost 20-fold greater than in whites (**Fig. 2-3**).[69] From a public health perspective these findings are extremely important and suggest the need for early detection and treatment to goal BP in young black adults as a strategy to prevent HF. As a case in point, rates of HF-related hospitalization in Medicare beneficiaries dropped substantially between the years 1998 to 2008. However, black American men had the smallest drop in rates when compared with white beneficiaries.[70] Although black Americans are hospitalized more frequently for HF, several studies have shown that in-hospital mortality, as well as 1-year mortality, is lower.[71-73] In Medicare beneficiaries, blacks have slightly better 1-year mortality.[74] Other studies have identified a higher 5-year case fatality rate in black than in white Americans.

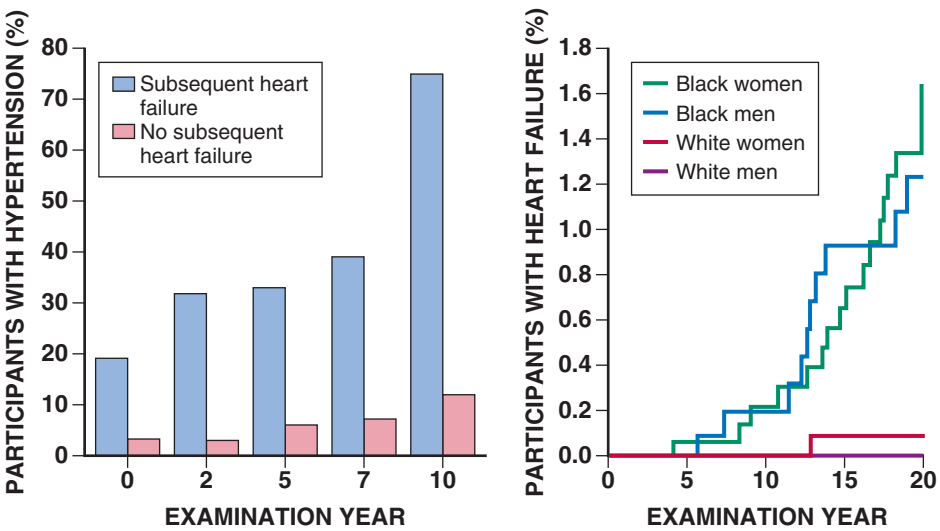

FIGURE 2-3 Role of hypertension in the development of HF in black Americans. In the CARDIA study, note the striking association of hypertension identified as a young adult with the subsequent development of HF and the significant variance in risk for the eventual development of HF in blacks versus whites. *(From Bibbins-Domingo K, Pletcher MJ, Lin F, et al: Racial differences in incident heart failure among young adults. N Engl J Med 360:1179, 2009.)*

Response to Therapy

Black Americans, as well as Hispanics, have been underrepresented in clinical trials of HF, particularly early ACE inhibitors studies. With small numbers of black Americans in the U.S. studies and none in European studies, only post hoc analyses can be done to extrapolate the results to sparse racial/ethnic groups. Black American representation in U.S.-based trials has been higher than that in multinational trials, but except for the Vasodilator Heart Failure Trials, which were performed in all-male Veterans Administration medical centers, black American representation in clinical trials is still lower than their estimated 25% to 30% representation of all HF patients in the United States. In the V-HeFT II trial, which compared enalapril with the vasodilator combination of hydralazine and isosorbide dinitrate, although the overall results of the trial favored

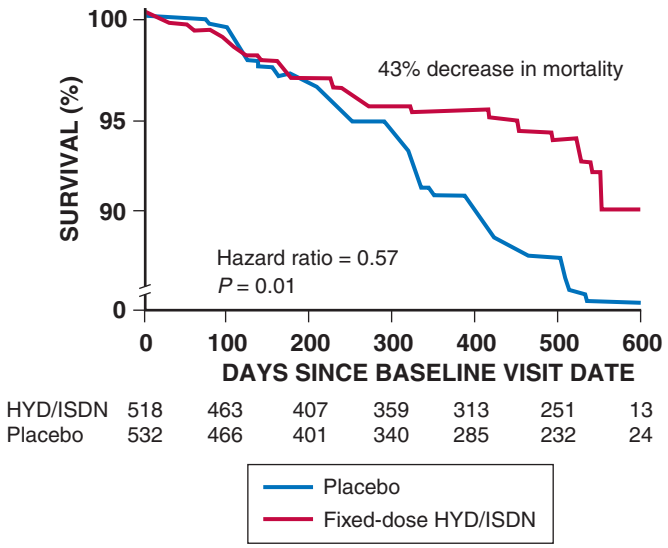

FIGURE 2-4 Primary results from the African American Heart Failure Trial demonstrating a 40% survival advantage for blacks receiving isosorbide dinitrate (ISDN)-hydralazine (HYD) plus standard medical therapy versus placebo plus standard medical therapy. *(From Taylor AL, Zeische S, Yancy CW, et al: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 351:2049, 2004.)*

enalapril, in post hoc analysis by racial groups there was a differential effect of the ACE inhibitor—it had greater benefit in white patients, whereas vasodilators had greater benefit in black patients.[75,76] The contemporary A-HeFT trial confirmed the significant mortality advantage of combined isosorbide dinitrate and hydralazine added to neurohormonal antagonism in blacks (**Fig. 2-4**; **see Chapter 25**).[77] The black American response to beta blockers for HF has been somewhat contradictory: a post hoc analysis of the U.S. carvedilol studies suggested a similar benefit in reducing hospitalization rates across all races; however, numbers of black Americans were very small. In contrast, a real-world population in a large health care system showed a 40% to 50% lesser benefit in the black American patients with HF who were taking beta blockers. This difference remained in effect even when adjusting for the use of evidenced-based beta blockers.[78]

Current HF guidelines have generalized recommendations to include all population subgroups while recognizing the limitations of this approach. In contrast to the greater uncertainty in the treatment effect of ACE inhibitors and beta blockers in black Americans, significant effects of the combination of isosorbide dinitrate and hydralazine on mortality and hospitalization were demonstrated in the A-HeFT trial.[77] Current guidelines give high priority to the use of this combination in addition to ACE inhibitors and beta blockers in black American patients with persistent symptoms of HF. However, in programs in which there have been consistent efforts to improve care, black Americans enjoy the same benefits from evidenced-based care as other races do.[79]

Heart Failure in Hispanics

Epidemiology, Etiology, and Clinical Features

Data on the incidence of HF in Hispanics have not been abundant, which may be multifactorial, including poor data capture under ethnicity classification and poor enrollment of Hispanics in registries. In the MESA cohort of 6814 individuals (21.9% Hispanics) with a mean age of 61.3 years, the incidence of HF in Hispanics was 3.5 per 1000 person-years as compared with 2.4 per 1000 person-years in non-Hispanic whites and 4.6 per 1000 person-years in non-Hispanic blacks.[80] Once controlled for hypertension and diabetes, there was no difference among the ethnic groups. Much of the data on the prevalence of HF in Hispanics comes from review of hospitalization rates in various communities. The American Heart Association's Get with the Guidelines database provides an opportunity to examine large groups of patients in more than 250 hospitals across the country. From January 2005 through December 2008, Hispanics accounted for 6.0% of hospitalizations for HF.[81] Hispanic patients were significantly younger than whites (63 versus 78 years) and had lower ejection fractions with more diabetes and hypertension. Notwithstanding these differences, Hispanic patients had lower in-hospital mortality than whites did. Care was equitable across all racial and ethnic groups. Quality care, however, may not be available to all Hispanic groups. Elderly Hispanic patients may have a higher rate of readmissions if admitted to Hispanic-serving hospitals versus hospitals that do not specifically serve Hispanics. This difference may be due to language preferences among older Hispanics, in whom English fluency may not be common.[82,83] Hispanic patients admitted for acute decompensated HF also tend to be younger than white patients and have more renal insufficiency.[83] In a review of Medicare beneficiaries from 1990 to 2000, the prevalence of hospitalization for HF increased in all racial and ethnic groups and rose with increasing age. When compared with non-Hispanic whites, the likelihood of hospitalization for HF was 1.2 times higher in Hispanic beneficiaries. However, rates of in-hospital mortality were lower in both blacks and Hispanics than in whites. Hispanics were also more likely than whites to be discharged home.[84] With the growing number of older Hispanics, the prevalence of HF with preserved ejection fraction (HFpEF) should be considered. From Get with the Guidelines from 2005 to 2010, 46% of the Hispanics had a diagnosis of HFpEF and 54% had HF with a reduced ejection fraction (HFrEF) as compared with 55% and 45% of non-Hispanic whites, respectively. Multivariate analysis showed a significantly higher risk for mortality in Hispanics with HFpEF than in non-Hispanic whites, but not in those with HFrEF. Quality of care and performance measures did not vary by ethnicity, once again providing evidence of lack of disparity in care in centers in which quality outcome programs exist.

Response to Therapy

Little is known about the differential effects of medications on Hispanics given the small numbers of patients enrolled in the randomized clinical trials. Disparities in device therapy have been noted, and fewer cardioverter-defibrillators are implanted in Hispanics, blacks, and women who would otherwise be eligible patients. There is, however, no reason to withhold evidence-based medical therapy and device therapy.

SUMMARY

The risk for heart disease and stroke affects all ethnic and racial populations in the United States. However, there are important differences regarding risk for CVD and outcomes in different populations in the United States. Although a complete explanation for these differential outcomes is not apparent at this time, it probably reflects a complex interplay of cultural, political, physiologic, and genetic variances among the different populations. Because of the untoward consequences of heart disease, it is imperative that the practice of cardiovascular medicine address the nuanced risk profiles and different manifestations of disease within varied populations.

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3 Ethics in Cardiovascular Medicine

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Ethical issues are inherent in medicine, and cardiology is no exception. The breadth of cardiovascular disease means that almost every ethical challenge in medicine arises. These disorders affect all age groups, range from highly acute to chronic, entail variable prognoses, and have a wide range of impact on patients' lives. Moreover, cardiac disease accounts for significant health care cost and public health burden. Although many ethical issues that cardiologists face are not unique to cardiology, certain issues have particular salience, and special considerations are raised by cardiac disease and its treatment.

This chapter considers five broad categories of ethical issues: (1) informed consent and shared decision making; (2) end-of-life care; (3) ethics of clinical research; (4) resource allocation; and (5) conflict of interest (COI). Within each category, issues of particular or unique relevance in cardiology are highlighted.

INFORMED CONSENT AND SHARED DECISION MAKING

Working with patients to make decisions that reflect their values and goals is essential to the physician-patient relationship. This commitment has firm ethical underpinnings in the principles of respect for autonomy and beneficence. In contrast with paternalistic conceptions that might have prevailed in the past, it is now accepted that patients should be free from unwanted treatment and able to choose treatments that match their values and interests. Of importance, the courts have also recognized patients' rights to make medical decisions, and recent policy and research efforts have elevated patient-centeredness and shared decision making as national priorities.

A legal and ethical standard for most procedures and many interventions, informed consent is designed to ensure that patients understand a proposed treatment, appreciate the risks, benefits, and alternatives, and voluntarily agree to the treatment. The four key elements of informed consent are (1) assessment of the patient's decision-making capacity, (2) disclosure of relevant information, (3) assessment of the patient's understanding of the information, and (4) ensuring that the patient's decision is voluntary and made free from coercion or undue influence.[1,2] Although signed informed consent forms attesting that these steps have occurred are the norm in the United States, such forms are primarily a token of the process that facilitates documentation. It is ultimately the disclosure, understanding, and consent that are the key ethical values to be realized.

Signed informed consent typically is sought for discrete decisions about procedures or diagnostic tests involving appreciable risk. As a rule, formal consent is not obtained for medical therapy, even for medicines and interventions such as warfarin or antiarrhythmic therapy that carry important risks. This difference is driven more by convention and practicality than by real ethical distinctions. Developing and implementing processes that inform and involve patients in these decisions and result in treatments that match their goals are clear ethical responsibilities.

A growing appreciation has emerged for the importance of shared decision making in clinical medicine and of active research aimed at identifying deficiencies and improving practices of shared decision making.[3] Innovative strategies have included decision aids that range from interactive modules to simple and individualized forms.[4] Numerous practical barriers to effective shared decision making are recognized. A generic barrier is the difficulty of communicating and having patients understand risk, benefit, and uncertainty. Probabilistic reasoning is challenging to communicate, and estimates of individual risk and benefit are often unavailable or unknown. Efforts to improve risk communication using pictograms depicting absolute risk and individualizing risk estimates offer promise.[5,6] Decision aids incorporating these tools have increased patient knowledge of relevant procedural risks and benefits and represent progress toward evidence-based approaches for fulfilling these ethical commitments.[4]

Shared decision making also requires successfully eliciting patients' values and priorities. This can be challenging in the absence of long-term relationships and in the context of logistical and financial pressures that promote "efficiency." Additionally, because patients may not understand exactly what is at stake in many situations, helping patients to articulate their goals of care is essential. Many decision aids explicitly incorporate values clarification elements that help to address this barrier.

Two common decisions in cardiology pose special and illustrative challenges regarding shared decision making. The first involves treatment for chronic stable angina. Therapies vary significantly, ranging from coronary artery bypass grafting (CABG) to percutaneous coronary interventions (PCIs) to medical treatment—yet the principal goal often is symptom control and not prolongation of survival. These decisions should be guided by patients' goals, but available data suggest that patient involvement is often minimal.[7] One reason for this lack of involvement is the "stuttering" or staggered decision-making process that characterizes these situations. In the process of evaluating and treating angina, there are numerous treatment and diagnostic options and multiple points at which the patient may be involved, from decisions regarding an initial stress test to those about catheterization and intervention. The ultimate decision about intervention, however, often is made while the patient is sedated and at times by interventionalists with incomplete knowledge of the patient's priorities or overall clinical picture. Properly carving out time for discussion, figuring out ways to communicate risk and downstream decisions early in the process, and adequately incorporating patients' goals into these decisions are challenging but important tasks. Developing and using standardized decision aids for such common interventions could be helpful.

A different challenge surrounds use of implantable cardioverter-defibrillators (ICDs) for primary prophylaxis. Communicating the preventive nature of the therapy, the absence of symptomatic benefit, and the long- and short-term risks can be difficult. Proper discussion about ICD implantation also should be intertwined with discussions regarding quality of life and goals of care and should address options for deactivation. Recent studies have found significant variability in these discussions. Cardiologists often stress benefits and guideline-based indications for therapy. Patients often overestimate benefits and are uncertain about risks and quality-of-life implications of ICD therapy.[8,9] Of interest, only 37% of physician respondents in one survey thought that patient preferences mattered "a great deal," and

12% thought they mattered "very little" or "not at all" in this context.[10] If physicians do not think patients' preferences matter, it is no surprise that efforts to engage patients in decision making are not more common. ICD decisions, however, are preference-sensitive. Despite a clear mortality benefit in properly selected patients, these decisions involve trade-offs between living with heart failure and risk of sudden death, some risk of complications, and a need for regular monitoring.[11]

Coronary artery disease (CAD) treatment and ICD decisions illustrate the importance and difficulty of shared decision making. In the CAD case, patients' values and involvement are important because of the lack of mortality difference or obvious superiority of different treatment approaches and real qualitative differences including risks. Practical barriers to implementing shared decision making, as noted, complicate involvement. In the ICD case, medical benefits and risks are clear. However, they can be difficult to communicate, "lived" risks and benefits can only be ascertained through individual patients' values and goals, and many physicians appear reluctant to engage patients in these decisions.

END-OF-LIFE CARE

All medical fields face ethical challenges regarding care at the end of life. These challenges go back to Hippocrates and the dawn of medicine. Cardiovascular disease remains the leading cause of death in the United States, accounting for an estimated 811,940 deaths—almost a third of all deaths—in 2008.[12] Some cases are acute, but most involve a chronic phase that permits end-of-life discussions. Cardiologists must be prepared to face a wide variety of end-of-life challenges. They must regularly work with patients and families to make decisions about when to pursue aggressive treatment in the face of high-mortality conditions, when to withdraw support, and when to initiate do not resuscitate (DNR) orders.

These challenges are ubiquitous and their ethical and legal underpinnings generally well established. However, cardiologists face a special set of challenges in caring for patients with advanced heart failure and those who rely on medical devices. These challenges are growing with increasing prevalence of heart failure and rapid expansion and improvement in mechanical circulatory support.[13]

Addressing the needs of today's advanced heart failure patient is increasingly complex, as medical and device therapies improve while mortality and morbidity remain high. As illness progresses, patients and physicians both have to prepare for the worst while hoping for the best, particularly when patients are candidates for advanced therapy with transplantation or placement of a ventricular assist device (VAD). American College of Cardiology/American Heart Association (ACC/AHA) guidelines specifically recognize the need for advance care planning and palliative care involvement in advanced heart failure, and there has been support for early involvement and integration of palliative care specialists into VAD/transplant evaluations.[14] This development is due to increasing recognition that palliative care specialists offer more than hospice care and that a model of "preparedness planning" incorporating advance care discussions and goals clarification can facilitate care that coheres with patients' values. This model can be particularly helpful when sudden events or changes in clinical status arise and is entirely consistent with aggressive treatment plans.[15] Further research will help to optimize timing of discussions, clarify roles of palliative care specialists and cardiologists, and improve communication.

Deactivation of implantable devices is an important component of end-of-life care. Guidelines from the Heart Rhythm Society and European Heart Rhythm Association explicitly state that implantable defibrillators and pacemakers in particular can, and should, be deactivated when patients so choose.[16,17] These positions follow long-established ethical and legal analysis. Respecting patients' autonomy entails allowing them to be free from unwanted medical interventions, even life-prolonging interventions. Again, well-established ethical and legal reasoning demonstrate that withdrawing device support or treatment that is no longer desired by the patient, but may prolong life, is not ethically different from not implanting the device in the first place. The lethal process is the underlying disease state and not the physician's action. This is the basis on which these activities are both ethically and legally distinguished from physician-assisted suicide (PAS) or active euthanasia. It is widely accepted as justifying the withdrawal of such therapies as mechanical ventilation, artificial nutrition and hydration, and dialysis. Despite relative consensus in the scholarly literature, the process of deactivation still raises concerns on the part of many practitioners.[18]

The greatest controversy has focused not on ICDs but rather on pacemakers (in pacemaker-dependent patients) and VADs for three principal reasons. First, deactivation of continuously "active" devices typically results in death in the very short term. Second, these devices, once implanted, replace a normal function of the heart and do not themselves generally cause discomfort or harm. Third, dependency on pacemakers in particular is sometimes intentionally induced in attempts to control tachyarrhythmia.[19,20] Consequently, some have argued that deactivating these devices, particularly if a patient is otherwise not acutely ill, represents a form of PAS or active euthanasia. Indeed, some European countries do not officially allow pacemaker deactivation in pacemaker-dependent patients.[17]

The emotional difficulties related to these decisions are obvious. However, no ethically or legally defensible basis exists for refusing to acknowledge a patient's informed, authentic request to deactivate any cardiac device, regardless of the immediacy of death as a consequence. A long legal history favors honoring such requests, and physicians routinely withdraw other forms of treatment, including dialysis and mechanical ventilation, with similar features. The right to be free from unwanted intervention is clearly conceptually distinct from PAS and euthanasia. As recognized in available guidance documents, providers uncomfortable with a deactivation procedure may refuse to perform it but should refer the patient to a willing provider if that is indeed the patient's wish.

Important practical challenges remain. All published data suggest that the option of ICD deactivation in particular is inadequately communicated to patients both at the time of implantation and subsequently.[18] This shortcoming probably reflects discomfort with deactivation and absence of training regarding these discussions. Patients should be made aware of deactivation options, particularly in the face of advancing illness or receipt of shocks, whether appropriate or inappropriate.

ETHICS OF CLINICAL RESEARCH

Cardiology has been revolutionized by clinical research, and evidence-based therapy undergirds much of current care. Nevertheless, outcomes are still unacceptable for many conditions, and effective therapies have not been identified for many major causes of morbidity and death. Therapies with novel mechanisms and targets continue to emerge, and further study of existing therapies lacking an adequate evidence base is needed. Clinical research is as important as ever; addressing its ethical challenges also is critical.

The overarching goal of research ethics and human subjects protections is to minimize exploitation.[21] In clinical medicine, a primary focus is on promoting the individual patient's best interests; in research, the primary focus is on developing scientific knowledge. This shift creates an opportunity for exploitation of research subjects; they are used to advance knowledge that will benefit others in society.

Research that successfully avoids exploitation is guided by eight ethical principles: (1) collaborative partnership with relevant community stakeholders; (2) social value; (3) scientific validity; (4) fair participant selection; (5) favorable risk-benefit ratio accounting for risks and benefits to both subjects and society; (6) independent review; (7) informed consent when possible; and (8) respect for participants (**Table 3-1**).[22]

Two critical components of this framework are that informed consent alone is never sufficient to make a study ethical and that basic elements of study design have fundamental ethical implications.

TABLE 3-1 Eight Principles of Ethical Clinical Research*

ETHICAL PRINCIPLE	DEFINITION/BENCHMARK
Collaborative partnership	Investigators identify and involve relevant stakeholders in planning and conduct of research.
Social value	Research addresses a clinical need and may lead to meaningful improvements in practice.
Scientific validity	Study design and endpoints are chosen in order to ensure that the clinical question is answered.
Fair participant selection	Participants are selected on the basis of scientific considerations and in order to maximize benefit and minimize risks.
Favorable risk-benefit ratio	Potential physical, psychological, social, and economic risks to participants are minimized and justified by potential for benefit to participants and society.
Independent review	Research is reviewed by an independent body with appropriate human subjects protections knowledge, scientific expertise, and knowledge of participants.
Informed consent	Recruitment materials and strategies are appropriately designed to optimize potential participant's understanding of important study details and ensure the absence of undue influence or coercion.
Respect for participants	Procedures are in place to recognize participants' contribution by ensuring dissemination of results, monitoring the well-being of participants, and protecting their confidentiality.

**Modified from Emanuel EJ, Wendler D, Grady C, et al. An ethical framework for biomedical research. In Emanuel EJ, Grady C, Crouch RA, et al (eds): The Oxford Textbook of Clinical Research Ethics. New York, Oxford University Press, 2008, pp 123-135.*

Studies that are inadequately powered to detect key endpoints do not have adequately defined inclusion or exclusion criteria, or do not reflect the population in which a therapy would be delivered are unethical. They lack social value, fail to respect participants' contributions, and squander scarce research resources.[23]

Perhaps the most widely known principle of ethical study design in the context of randomized trials is the concept of *clinical equipoise*. Investigators and individual clinicians are rarely completely ambivalent about the benefits of different "arms" in a study. Clinical equipoise requires legitimate uncertainty within the field of experts regarding which of two or more comparison groups in a trial is superior.[24] Although the specific concept of equipoise as a standard has been criticized, legitimate uncertainty by the group of experts about treatment superiority is essential for a trial to be ethical in most circumstances.[25,26] Determining adequate uncertainty, however, can be challenging. Varying levels are inevitable, and no standards exist for assessing whether the body of experts is in "enough doubt" to allow randomization. In some trials, for example, trials comparing PCI or CABG and medical therapy for CAD, qualitative differences between treatments can complicate these comparisons.

Just as it can be difficult to determine whether legitimate uncertainty is present at a study's outset, the job of data and safety monitoring boards (DSMBs) to determine whether equipoise has been sufficiently disturbed during the course of a trial to warrant stoppage due to futility, benefit, or harm can be difficult. Early stoppage is often controversial, in part because it tends to result in overestimated benefit, may compromise collection of clinically important secondary endpoints, and can leave substantial clinical uncertainty about long-term risks and benefits.[27,28] Continued randomization in the presence of inadequate uncertainty is, however, unethical. Controversies in cardiology regarding early stoppage of trials of perioperative beta blockade, fractional flow reserve (FFR)-guided revascularization, and lipid-lowering therapy have all illustrated the difficulties and impact of these decisions.[27,29,30]

The ethical requirement for informed consent also can pose significant challenges in cardiac research, particularly in acute illness. Clinical treatment of conditions such as acute myocardial infarction (AMI), cardiac arrest, or acute decompensated heart failure often takes place under circumstances in which consent is either impossible or highly problematic. Even when patients are asked for consent, their true understanding and level of engagement are frequently minimal because of their illness.

Federal regulations allow an exception from informed consent (EFIC) for research in emergency settings where consent is not possible within an appropriate timeframe. Although still controversial to some extent, it is generally recognized that EFIC research in emergency settings can be ethical.[31] The EFIC regulations have appropriately stringent requirements, including that: (1) informed consent must not be feasible in the timeframe within which enrollment must occur; (2) the condition under study must be life-threatening; (3) current treatment must be unsatisfactory or unproved; (4) the study must offer some prospect of direct benefit; (5) risks and benefits must be reasonable in light of the condition; (6) the trial could not be carried out in a population that can provide consent; and (7) investigators must conduct community consultation and public disclosure.[32] These regulations are designed to maximize the extent to which research participation coheres with critically ill patients' overriding interest in survival with maximal cognitive functioning.

The community consultation requirement has been particularly controversial, in part because it is not required for other types of research and in part because its primary purposes remain somewhat ambiguous. Moreover, federal guidance only specifies very broad metrics by which community consultation can be assessed, established criteria for interpreting community feedback are lacking, and consultation efforts may take many different forms and involve considerable expense.[33,34]

EFIC studies represent a small proportion of cardiology trials, principally those dealing with cardiac arrest and cardiogenic shock. However, many acute cardiac trials involve significant barriers to consent. It is well documented, for example, that consent is suboptimal in STEMI trials.[35] This is not surprising in view of the urgency of this clinical situation, the time frame within which treatment must be given, and the presence of significant symptoms in affected patients. Moreover, patients' surrogates are often under the same time pressures and in significant distress. Clear regulatory provisions to allow adaptations to the consent process in these circumstances are lacking, as is evidence on how best to involve patients in decisions. Of interest, the GISSI and ISIS trials of thrombolytic therapy in the 1980s explicitly did not ask patients or surrogates for consent on the basis that consent was thought to be an unjustifiable and unproductive burden in the context of AMI.[36] Although this approach probably would not be accepted today, ascertaining how to involve patients meaningfully while recognizing unavoidable barriers to consent that are intrinsic to these clinical circumstances is an important priority.[35]

A final research ethics issue that will grow in an era of health system reform is the integration of research into clinical practice.[37] With continued migration to electronic record systems and increasing emphasis on comparative effectiveness and "real world" research, the traditional separation between research and clinical medicine may dissolve. This development has important advantages, particularly in addressing declining and sluggish research enrollment, but it poses challenges. Comparative effectiveness studies, for example, that examine commonly used treatments may ideally be performed on a large scale within health systems. The ethical standards for institutional review board (IRB) review and informed consent for these trials may plausibly differ from trials involving new agents.[38] Similarly, the paradigm of partnerships between payers such as the Centers for Medicare & Medicaid Services (CMS) or other large insurers with the National Institutes of Health (NIH) and other research

funders may create circumstances where coverage of innovative treatment is contingent upon trial participation.[39,40] These programs, as well as U.S. Food and Drug Administration (FDA) programs to facilitate accelerated review and approval in the context of treatment for serious or life-threatening conditions, attempt to balance patients' need for access to innovative therapy with the need for rigorous evaluation before these therapies are distributed for clinical use.[41] These potentially productive paths for improving health care blur distinctions between research and clinical care, involve clinicians in research activities in new ways, and require further work to define adequate protections.

RESOURCE ALLOCATION

Some of the most prevalent and troublesome challenges in cardiology relate to resource allocation. Cardiology care is expensive, numerous high-technology, high-cost interventions are available and effective, and patient demand and expectations (whether informed or not) are high. At the same time, the need for judicious use of resources is increasingly recognized in an era of rising costs and health care system change. What is often underrecognized is the underlying ethical nature of these decisions. Data regarding relative costs and benefits of particular treatments inform decisions, but decisions ultimately rely on ethical frameworks for valuing specific outcomes and costs.

Significant variability has been demonstrated in the use of many cardiac procedures. Although some variability is appropriate and reflects acceptable differences in clinical judgment, excessive geographic variability and use in cases that do not comply with guidelines, as has been demonstrated in use of PCI for stable coronary disease, for example, raises concerns.[42] The principal mechanism by which cardiology has tackled challenges of resource allocation and over-use has been through development of *appropriate use criteria* (AUC). AUCs represent an important step forward in the attempt to ensure that care is being provided in a way that is evidence-based and appropriate. AUCs have been used to examine practice patterns and to facilitate estimates of the magnitude of inappropriate use, for example, of PCI and implantable devices.[43] Although these estimates have been controversial and are, of course, inexact to some degree, AUCs have facilitated an important shift toward standardization and reduction of inappropriate care.

AUCs generally are directed at identifying use of treatment or diagnostic modalities for which there are data to support clinical benefit. Many difficult decisions, however, require fundamentally ethical judgments about what constitutes value. One obvious example is selection of patients for transcatheter aortic valve replacement (TAVR). TAVR has revolutionized treatment of severe aortic stenosis in patients who are not good surgical candidates, most of whom are of advanced age and often have limited life expectancy and multiple comorbid conditions. Particularly because these procedures are paid for predominantly by Medicare, use of TAVR has significant implications for U.S. health care costs at a time of increasing awareness of the need to constrain costs. Significant attention has thus been focused on evaluating cost-effectiveness of this therapy. Published analyses have produced variable results, and estimates will surely change as experience with this therapy evolves and in the context of different patient populations.[44,45] What cannot be ignored, however, is that decisions regarding use must balance patients' comorbidities, likelihood of benefit, and life expectancy. The relevance of age is more controversial. Striking these balances will be inevitably difficult but is an essential ethical task.

Overt resource allocation decisions are part of everyday practice in advanced heart failure management. Because of the fixed supply of transplantable organs, the interests of the population of potentially eligible and eligible transplant candidates must be balanced. Rationing is unavoidable when giving an organ to one patient means that another may die. These decisions have become more commonplace as heart failure prevalence rises and the supply of transplantable organs remains fixed. Screening processes designed to identify those likely to have the best outcomes are critical, although challenges remain regarding how to assess and weigh various factors. In particular, assessing the relevance of variations in social and economic support, age, and comorbidity often complicates transplant eligibility decisions, and there is a need for continued discussion along with additional data on how best to weigh and evaluate these factors in a way that ensures justice but appropriately favors good outcomes among recipients of a truly scarce resource.

The option of left ventricular assist device (LVAD) implantation for destination therapy or as a bridge to transplantation or transplant candidacy raises somewhat different resource allocation challenges. Although the supply of transplantable organs is absolutely fixed and the need for explicit rationing of organs overt, this is not the case with mechanical devices. There is no shortage of VADs; placing a VAD in one patient does not entail denying this therapy to another. Associated costs, however, are significant, and outcomes with VADs are highly variable because of requirements for complex aftercare and the potential for numerous devastating complications. Predictors of good outcomes are thus critical to consider, both for patients' interests and for wise use of resources. However, the "moral weight" of various risk factors in this context is less clear than in transplantation.[46] Particularly when VAD candidates have relative contraindications (be they social or medical) but will clearly die without mechanical support, it becomes essential to consider whether giving those patients a chance is "worth" the investment. Striking this balance requires continued research into predictors of outcomes, but as in the TAVR case, it also requires clinicians to confront, as practitioners in the field and as members of society, long-avoided questions regarding rationing and value in health care.

CONFLICT OF INTEREST

Addressing COI has been a priority in cardiology and across all of medicine.[47] As defined by the Institute of Medicine, COIs are "circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest."[48] The primary interest of cardiologists is to promote the well-being of their patients and, if they are engaged in research, to produce reliable and valid generalizable knowledge. Secondary interests may be securing grants, obtaining promotion, participating in departmental governance or professional societies, and securing income. Of importance, these secondary interests are not unethical. Indeed, many are laudatory. COIs arise because these secondary interests may compromise a professional's primary interest and judgment.

Of note, situations that create the *appearance* of conflict are not essentially different, at a practice or policy level, from situations in which true compromise of judgment actually occurs.[49] The central consideration in addressing and managing COI is to create contexts in which inappropriate influences are minimized and in which observers can feel confident that they know and can reliably trust professional judgments. The structure of different types of conflicts may vary, but the cornerstones of most attempts at addressing COI are three: (1) disclosure, (2) management and oversight, and (3) prohibition or conflict avoidance.

Powerful influences can affect at least five stages of clinical research (**Table 3-2**).[50] Interestingly, data suggest that industry sponsored research is highly methodologically rigorous, particularly at the design and patient enrollment stages.[51,52] Where industry sponsorship has created the most significant COI problems is around dissemination of results. Here, studies have demonstrated marked tendencies toward publishing positive results, selective publication of studies, including infrequent publication of negative studies or the multiple publications of positive results, potential bias in interpretation of results, alteration of endpoints between design and publication, and failure to report results completely.[51-54] For example, major controversies surrounding the trials of COX-2 inhibitors rofecoxib and celecoxib involved selective reporting of data critical to assess these drugs' risks and benefits.[55-57]

TABLE 3-2 Stages of Clinical Research and Potential Conflict of Interest

STAGE OF RESEARCH	POTENTIAL AREAS OF CONFLICT
Study conception	Choice of primary study question may be driven by multiple potential interests.
Research design	Fundamental design elements (e.g., sample size, randomization scheme, choice of endpoints) differently advance competing interests (securing marketing indication versus clinical usefulness).
Subject recruitment	Biased selection or follow-up may compromise data integrity.
Data analysis	Choice of analytic methods or exploration (or absence of exploration) of alternative explanations can have heavy impact on findings.
Dissemination	Negative findings may not be submitted for publication or may be downplayed in reports. Positive results may be published multiple times.

In assessing and addressing COIs, an important point is that they are not all the same. Thus, it is essential to determine (1) the likelihood that a secondary interest might distort professional judgment and (2) the seriousness of harm that might result from a conflict.[58] Even if a conflict is likely to arise, fewer safeguards may be necessary if the seriousness of resulting harms is minimal. Conversely, serious harms, such as potential for disability or death—even if the likelihood of conflict is low—may necessitate more stringent safeguards.

The main safeguards to minimize the impact of conflicts of interest are three: (1) disclosure, (2) management, and (3) prohibition. Although disclosure may be necessary, it may not be sufficient in many cases. Disclosure often places responsibility for resolving the conflict on the least powerful member of a health team: the patient.[59] Although disclosure is a meaningful component of addressing COI in research, efforts to promote dissemination of patient-level data, for example, have the potential to mitigate conflicts in far more meaningful ways.[60]

Within clinical practice, COI also is an inherent and pervasive concern. From interactions with drug representatives to basic reimbursement strategies, multiple interests are at stake in clinical medicine that compete with the primary goal of advancing patient care. Fee-for-service medicine, for example, explicitly incentivizes overtreatment. Capitated payment, on the other hand, incentivizes undertreatment. These tensions are unavoidable and must be balanced, are not mitigated by mere disclosure, and require solid data to facilitate evidence-based and rational approaches.

CONCLUSIONS

There is no shortage of ethical challenges in cardiology today, and many do not have easy answers. However, we can continue to make progress in addressing them. Deep conceptual questions may persist, but rigorous research can result in evidence-based approaches to ethical challenges in the same way that it can inform clinical decisions. Implementation and evaluation of decision aids to improve shared decision making and strategies to address COI, for example, can maximize desirable outcomes. Further research into communication regarding device implantation and into the costs and benefits of innovative therapies can better inform patients' and physicians' decisions. These challenges cannot be eliminated, but they can be addressed and our approaches improved.

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4 Clinical Decision Making in Cardiology

Harlan M. Krumholz

Clinical decision making is central to all patient care activities. It involves making a diagnosis and selecting actions from among alternatives. Clinicians are continually faced with decisions, some that are made deliberately and others urgently. In most cases, these decisions must be made under conditions of uncertainty. Some decisions can be made in full partnership with patients; others must be made on behalf of patients. With today's growing array of diagnostic and therapeutic options and escalating health care costs, there is an emerging focus on decision making.

This chapter highlights key issues in clinical decision making in cardiology. The true breadth of the science of clinical decision making is enormous, spanning disciplines that include statistics, sociology, psychology, economics, and political science. The many issues that require consideration include hypothesis generation and refinement, use and interpretation of diagnostic tests, causal reasoning, diagnostic verification, therapeutic decision making, and cognitive tools and pitfalls.[1] This last category comprises heuristics, clinical prediction rules, and other tools. Despite the broad scope of this topic, clinicians should be familiar with a key set of concepts that can enhance their decision-making skills and promote the best interests of each patient.

DIAGNOSTIC DECISION MAKING: GENERAL CONSIDERATIONS

Making the correct diagnosis by using the least harmful and least costly approach is critical to the proper care of patients. Diagnoses can classify patients by their underlying pathophysiology, prognosis, and response to therapy. Delays in diagnosis, or an incorrect diagnosis, can have marked adverse consequences.

Many conceptual models underlie the way in which clinicians approach diagnosis. *Deductive inference* starts with a hypothesis that can be tested. Observations and test results can be assessed for their consistency with the hypothesis. *Inductive inference* starts with empiric observations and then develops an applicable hypothesis. Medical diagnosis is often based on inductive inference, asking the question "Given the patient's condition, what is the likelihood of different diseases?"

DIAGNOSTIC TESTING

Good decision making requires a thorough understanding of the strengths and limitations of each diagnostic test. Test characteristics convey information about the performance of a test and can be expressed in terms of sensitivity, specificity, likelihood ratio, and positive and negative predictive values. For clinicians to be able to incorporate diagnostic test results into clinical decision making, they should be familiar with the following definitions.

Sensitivity and Specificity

Sensitivity: among people who have the disease, the proportion with a positive test result (true positive)

Specificity: among people without the disease, the proportion with a negative test result (true negative)

Knowledge of these test characteristics can assist in the interpretation of results and their implications for the patient. High-sensitivity tests have low false-negative rates. A test with a high sensitivity will give a positive result in almost all persons with the condition being tested. Thus a negative result on a test with high sensitivity makes the diagnosis highly unlikely, essentially ruling out the condition. Conversely, a test with high specificity will have a low false-positive rate. A test with a high specificity will give a negative result in virtually all persons without the condition being tested.

Studies that define the sensitivity and specificity of a certain test may also be flawed, and clinicians should be alert to problems with these estimates. In high-quality studies, the diagnostic test should be compared with a gold standard that is measured independently. Stable estimates of test characteristics require large study populations. Nevertheless, issues of generalizability arise, because published test characteristics tend to reflect the performance of the test in excellent centers, with experienced clinicians using the most advanced technology.

The test characteristics, moreover, are not always an intrinsic feature of the test. Practitioner skill and patient factors may affect the performance of some tests. For example, it is difficult to assign a sensitivity and specificity to transthoracic echocardiography for the detection of a vegetation, because the performance of the test may vary with the skill of the technician, the quality of the equipment, and the acoustic windows and cooperation of the patient.[2] By contrast, computed tomography (CT) images tend not to vary by patient and therefore have a more consistent sensitivity and specificity. In considering the characteristics of a test that varies by patient, it is important to take into account circumstances of each clinical situation. The variation in interpretations, even with the same studies, also is often not appreciated. Repeated studies of angiography have demonstrated that clinical interpretations often do not agree with panel assessments or autopsy reports or simulated lesions.[3]

Predictive Values

Positive predictive value: among those with a positive test result, the proportion of people who have the disease

$$PPV = sens \times prev/[sens \times prev + (1 - spec) \times (1 - prev)]$$

Negative predictive value: among those with a negative test result, the proportion of people who do not have the disease

$$NPV = spec \times (1 - prev)/[(1 - spec) \times prev + spec \times (1 - prev)]$$

These values convey information about how the test result translates into the likelihood that a particular patient has the disease. The key insight about predictive values is that unlike sensitivity and

specificity, they are highly dependent on disease prevalence. If the prevalence is low, a positive highly specific test will still not yield a high likelihood of disease (i.e., the test has a low positive predictive value despite the exemplary test characteristic). The implication is that even with a test with high specificity, the screening of a low-risk population will still yield many false positives.

Example: A young woman comes to your office with a result of a positive exercise stress test as indicated by electrocardiographic changes but with good exercise tolerance. The test was ordered for atypical chest pain. She has no traditional risk factors for coronary artery disease, including family history, and wonders whether this test is likely to be an indication that she has heart disease. To make a point, pretend that her risk of disease is 1 in 1 million and that the stress test has a sensitivity and specificity of 75%; then for every 4 million women in her risk group, 4 have disease and 3 have a positive test result. Of the almost 4 million without disease, 1 million have a positive test result. Therefore, for every 1 million positive test results, only about 3 would represent a true positive. Even if the screening test had a sensitivity of 100% and specificity of 99%, then for every 10 million women screened, 10 have disease and 10 have a positive test result. Of the approximately 10 million without disease, 100,000 have a positive test result. Thus for every approximate 100,000 positive test results, only 9 would represent a true positive.

Bayes Theorem. The Bayes theorem expresses how the probability of disease should change with new information. The posterior, or post-test, probability is a function of the prior, or pre-test, probability (or disease prevalence) and the likelihood ratio. This theorem provides a way to revise estimates based on new information. In essence, it relates a conditional probability: the probability of A given B. Conceptually, it formalizes the incorporation of previously obtained information into the interpretation of new information. A test that does not change a prior belief may be unnecessary.

Likelihood Ratio

Likelihood ratio (LR): the ratio of the probability of a certain test result in people who have the disease to the probability in people who do not have the disease

$$LR+ = sens/(1 - spec)$$

$$LR- = (1 - sens)/spec$$

The post-test odds that a patient has the disease can be calculated with the LR: pre-test odds × LR. An LR value of 1.0 does not modify the post-test probability, thus indicating a test that provides no useful information.

Defining Abnormal

Another important issue in the use of diagnostic tests is the definition of *normal*. By convention, test results are often characterized in a binary fashion (normal/abnormal), which is a translation from a continuous result. Ideally, test results are translated into quantitative post-test estimates. For example, noting that an exercise stress test result is abnormal is much less informative than providing an estimate that a patient has ischemic heart disease based on a result that takes into account the exercise time, the symptoms, the blood pressure response, and the type of electrocardiographic changes. Not all "positive" tests have the same meaning for a patient.

Considerations in Test Ordering

Decisions about test ordering are often difficult, because too few studies have compared alternative testing strategies for patients with a given set of signs and symptoms. A test can reduce uncertainty about a diagnosis and estimates of risk, but the key issue is whether patients undergoing the test have better outcomes than those who are not tested. In current practice, there is substantial variation in testing patterns that seem independent of the patient's characteristics.[4]

The construct of *number needed to treat* (NNT) also can apply to screening tests.[5] The number needed to screen, which is defined as the number of people who need to be screened over a defined period to prevent an adverse event, takes into account the number of people tested to identify those with a specific condition that may be amenable to a specific treatment strategy. The metric can convey how many must be tested for one individual to experience a benefit.

Example: A middle-aged man with hyperlipidemia is about to be started on statin therapy. You remember a recent article that identified a single-nucleotide polymorphism that predicts the risk of myopathy and can identify individuals with a risk of almost 20%. Then you realize that in the published study, of more than 8000 patients taking a statin only about 10 cases of myopathy, which were reversible, were attributable to this single-nucleotide polymorphism. The potential benefit is very modest (it could avoid a reversible adverse event) and the number screened is high, raising questions about the usefulness of this test in practice.[6]

When making decisions about whether to recommend diagnostic tests, clinicians should envision the actions that would occur based on the results. If findings would not change clinical strategies in ways that are likely to improve outcomes or reduce future testing, then the test probably should not be ordered. Platelet reactivity testing may currently fit into this category because the benefit is unclear.[7] Ultimately, more evidence that addresses how particular testing strategies relate to patient outcomes is needed.

Decisions about testing need to consider the risks of the test itself as well as the downstream risks and benefits of the procedures and tests that may occur as a result of a positive test. For example, radiation exposure as a result of testing can be quite substantial.[8] Moreover, even if a test does not have intrinsic risk, it may lead to more interventions, eventually resulting in net harm and wasteful use of scarce resources—a phenomenon designated the "cascade effect" by Mold and Stein.[9] At every step of deciding about diagnostic testing, the clinician should be sure how a test result will be used and how it will promote the best interests of the patient.

Professional societies are now identifying tests that are not useful so as to reduce overuse of tests and procedures.[10] The American College of Cardiology is producing *appropriate use criteria*, for guidance regarding the strength of evidence for tests and procedures in cardiovascular medicine.[11] The criteria state, "An appropriate diagnostic or therapeutic procedure is one in which the expected clinical benefit exceeds the risks of the procedure by a sufficiently wide margin such that the procedure is generally considered acceptable or reasonable care." The methodology, shown in **Figure 4-1**, is based largely on expert opinion and the medical literature. It rates the tests and procedures into three categories: "appropriate," "may be appropriate," and "rarely appropriate." The American College of Cardiology introduced these documents in 2005 with a focus on radionuclide imaging but has since expanded them substantially.

THERAPEUTIC DECISION MAKING

Decisions about therapy involve weighing risks and benefits to determine the best course of action, and understanding the goals of the patient. The key questions for clinical decision makers are whether an intervention can improve the quantity and/or quality of the patient's life, and how the risks, benefits, and requirements align with the patient's preferences. Moreover, the benefit is often best understood in a probabilistic framework, because most interventions do not provide a guaranteed benefit for each person who is treated.

Clinicians should be aware of the strength of the evidence in support of therapeutic decisions. The strongest evidence derives from well-conducted randomized trials. Observational studies and case series can provide useful information but usually are less definitive. Extrapolation from knowledge of pathophysiology provides the weakest evidence, because what seems reasonable does not always produce the expected outcomes when subjected to rigorous evaluation by trials. Regardless of design, clinicians should not assume that all published studies, including randomized trials, are high-quality and should not rely solely on summaries of studies. An understanding of the evidence requires the expert clinician to engage directly with the literature.

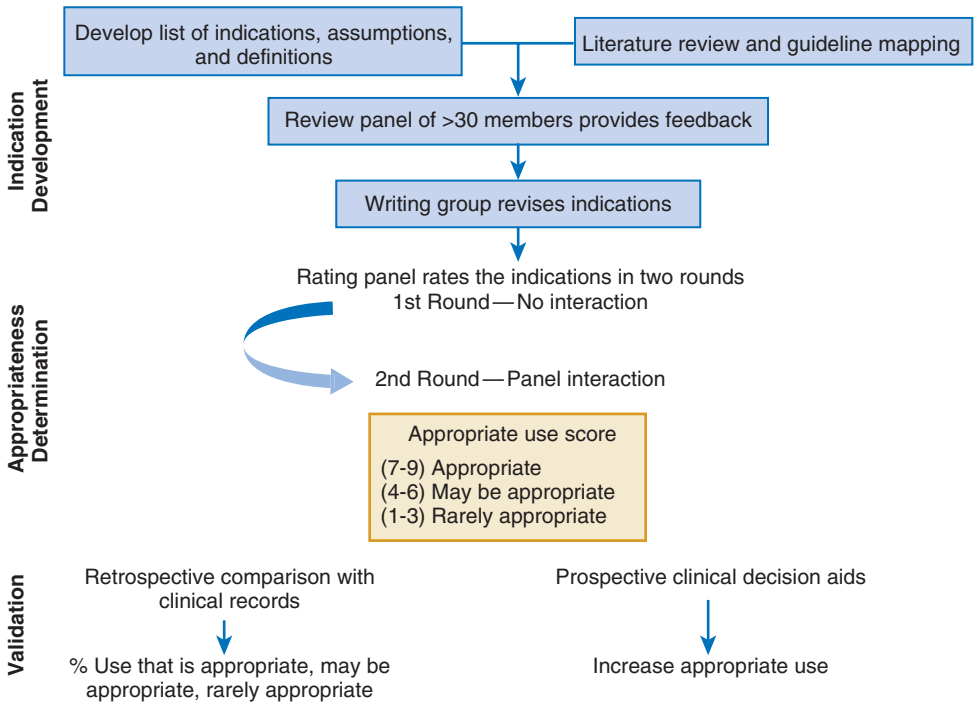

FIGURE 4-1 Appropriate use methodology.

Clinical practice guidelines from the American College of Cardiology and the American Heart Association synthesize the literature and provide recommendations with information about the strength and type of evidence.[12] Level of evidence A is associated with evidence derived from multiple randomized trials or meta-analyses. Level of evidence B is based on a single trial or nonrandomized trials or nonrandomized studies. Level of evidence C is based solely on the consensus opinion of experts, case studies or standard-of-care, which may be derived primarily from causal reasoning. The recommendations are also organized into class I (should be performed or administered), II (some uncertainty, with IIa favoring treatment more strongly than IIb), and III (not recommended). Similar approaches, such as that of the European Society of Cardiology, are used internationally.

Unfortunately, even if high-quality studies are available, precise estimates of risks and benefits are not often available for individual patients. Although the internal validity of a study may be strong, the external validity, or generalizability, may be less clear, because patients in routine practice often do not resemble those enrolled in trials.[13] Extrapolation of the trial results may be difficult. Moreover, the average effect may not be relevant for each patient.[14]

Decision Analysis

Decision analysis in medicine was developed to make explicit the assumptions that are relevant to a choice and reveal the expected outcomes, with the associated probabilities. The method takes into account the probabilities of different outcomes and the value (or utility) of various outcomes from the patient's perspective. By repeating the analysis with varying assumptions about probabilities and utilities, this approach can reveal the sensitivity of a decision to particular factors, and under what conditions a specific strategy is favored. A decision analysis cannot mandate a choice. It is a tool to assist in illuminating the trade-offs inherent in a decision that occurs under conditions of uncertainty.

Example: The decision about whether to administer fibrinolytic therapy to patients who are 80 years and older was controversial when the therapy was first introduced. Some clinicians had concerns that the bleeding risk might offset the benefit of restoring blood flow in the coronary artery. A decision analysis modeled the decision, incorporating estimates of the risks and benefits of therapy.[15] In addition, the analysis evaluated the decision across a range of estimates for risk and benefit. The study demonstrated that across a broad range of estimates of risk and benefit, the decision to treat was, on average, favored. The analysis provided the insight that even a small relative reduction in risk produced a substantial absolute reduction in the number of deaths that overshadowed the risk of bleeding. Using the best estimates for benefit, the decision favored treatment until the risk of hemorrhagic stroke rose to above 4%.

Evaluating the Evidence

The interpretation of evidence has many subtleties. Several topics bear particular emphasis, because they are commonly the source of misunderstanding, potentially leading to compromise in the quality of decisions.

P Values. Statistical issues play a key role in therapeutic decision making. The *P* value, in particular, has taken on great weight in clinical studies. This value represents the probability that the result observed, or a more extreme one, could have occurred under the null hypothesis. The *P* value does not convey the probability of the alternative hypothesis. In fact, under the right conditions, the probability that the null hypothesis is false may be low even with a *P* value less than 0.05.[16] There are other views about how to approach statistical inference. Bayesian statisticians reject *P* values in favor of the approach of using data to update their estimates of a certain parameter. Support for the bayesian approach is growing, but hypothesis testing continues to dominate.[17]

Because the *P* value is so commonly used in clinical research, clinicians need to be aware of several key issues. First, the threshold of 0.05 for statistical significance is arbitrary. A *P* value of 0.04 implies that the data could occur 4% of the time if the null hypothesis is true, and a *P* value of 0.06 would suggest the data would occur 6% of the time. Is the difference between 6% and 4% enough to reject the null hypothesis in one case and accept it in another? Second, *P* values do not inform clinical importance. A large study sample can produce a small *P* value despite a clinically inconsequential difference between groups. Clinicians need to examine the size of the effects in addition to the statistical tests of whether the results could have occurred by chance.

Expressions of Benefit and Risk. Clinical decisions involve the balancing of benefit and risk. The expression of benefit and risk can influence decisions. Clinicians need to understand these expressions, which form the foundation for making decisions from clinical evidence.

The relative benefit (or risk) of an intervention is often expressed as a relative risk or odds ratio. *Risk* is the probability of an event, and *odds* is the probability an event will occur against the probability that it will not occur. A probability of 25% (1 in 4) represents odds of 1 : 3 or 1/3. The *relative risk ratio* of an event conveys the relative probability that an event will occur when two groups are compared. The *odds ratio* expresses the odds of the event in one group compared with another.

Despite its widespread use, the odds ratio is less helpful than relative risk in clinical decision making. The expressions are similar when baseline event rates are low (<5%) but deviate with higher risk and larger treatment effects.[18] The odds ratio can express associations, but unlike the risk ratio, it cannot express the relative size of the treatment effect; if clinicians assume it to be equivalent to risk, it may lead to overestimates of the treatment effect when the outcome is common.

The relative benefit of any intervention may vary depending on patient characteristics, which are often explored in subgroup analyses. For example, fibrinolytic therapy was effective in the treatment of suspected acute myocardial infarction (AMI), and subgroup analyses revealed the benefit to be substantial in patients with ST elevation but not in those without it.[19] The challenge is that subgroup analyses introduce the possibility that associations have occurred only by chance. In the Second International Study of Infarct Survival (ISIS-2), the investigators provided perspective on subgroup analyses by demonstrating that patients born under the astrologic sign of Gemini or Libra were significantly less likely to benefit from fibrinolytic therapy. Thus subgroup analysis is capable of producing important insights, but findings must be interpreted with caution.

A weakness of relative benefit estimates is that they do not convey information about what is achieved for patients at varying levels of risk. A small relative reduction in risk may be meaningful for a high-risk patient, whereas a large relative reduction may be inconsequential for a very low-risk patient. Absolute risk reduction, the difference between two rates, varies with the risk of an individual patient. For example, a risk ratio of 2.67 does not distinguish between baseline risks of 80% and 30% and between 0.08% and 0.03%. In one case, the absolute difference is 50% (5000/10,000) and in the other, it is 0.05% (5/10,000). In one case, 1 person of 2 is benefited and in the other, 1 of 2000 is benefited. Unfortunately, absolute benefit is not emphasized adequately in many articles.[20]

NNT, which can be calculated as the inverse of the absolute risk reduction, represents the number of people who need to be treated to prevent an adverse event. NNTs constitute a useful approach to express risk and benefit that incorporates the patient's baseline risk and are a convenient way to express a trial result. For decision making with an individual patient, the baseline risk, which cannot be assumed to be the same as that of people in a trial, will strongly influence the estimate. Therefore, the NNT from a trial may need to be modified for an individual patient.

Example: Physicians and their patients are often in a position to decide about whether aspirin should be used for primary prevention of cardiovascular disease. To make the example easier, let us assume that the patient is male and a physician, the group for which the most data are available. Some of the best information about this topic is from the Physicians' Health Study (PHS) Research Group, which enrolled 22,071 doctors in a randomized, double-blind, placebo-controlled trial of the effect of 325 mg of aspirin every other day (versus placebo) on cardiovascular risk.[21] The study was terminated early because the findings strongly favored aspirin. The investigators reported a 44% reduction in the risk of an AMI. The relative reduction sounds impressive, but the absolute reduction in risk is less compelling. The overall risk of an AMI in this population was low, 440 per 100,000 per year in the placebo group. Thus, a 44% reduction in a low-risk population averted only approximately 186 events per 100,000 treated (in the trial, 100 AMIs [93% nonfatal] were averted, with 54,560 per year of treatment). In other words, approximately 540 physicians needed to take aspirin every other day for a year for 1 person to avoid an AMI. The other 539 did not experience a benefit. On the other hand, there was a strong trend toward a doubling of the admittedly small risk of incurring a hemorrhagic stroke (relative risk, 2.14; 95% confidence interval, 0.96 to 4.77; $P = 0.06$). Overall, there were 11 extra hemorrhagic strokes. For every 9 AMIs that were avoided, there was 1 additional hemorrhagic stroke. The overall risk of stroke was slightly but nonsignificantly elevated in the aspirin group (relative risk, 1.22; 95% confidence interval, 0.93 to 1.60; $P = 0.15$), which also represented 11 extra strokes. The risk of death was not significantly different in the two groups (relative risk, 0.96; 95% confidence interval, 0.80 to 1.14; $P = 0.64$). The expression of the result as an absolute risk reduction provides a perspective for the individual patient that is easier to understand than the relative reduction in risk. The main point is that the reporting of a large relative reduction in risk provides only part of the relevant information to make this decision, and that presentation can affect the decision.

Personalized Care

Patient characteristics should influence decisions. First and foremost, as noted in the section on shared decision making, the decision must be aligned with the patient's preferences, values, and goals. In addition, risk stratification should be used to estimate patient risk and to provide a perspective on the absolute risks and benefits. This approach generally uses the results of statistical models that have identified prognostic factors and incorporated them into a tool that may assist clinicians. For example, statin therapy may produce a substantial relative risk reduction but will have only a small benefit for those with the lowest risk.[22,23] In another example, investigators found that only patients with a 10-year risk of cardiac events greater than 6% had a net benefit from aspirin therapy to prevent cardiovascular disease.[24] The presence of comorbid illnesses and competing risks also is important, because adding years of life is different from substituting causes of death. Socioeconomic status also may influence decisions. In countries in which patients bear the costs of health care, patients may need to make decisions based on affordability, and clinicians cannot be indifferent to these practical issues. Some studies also show that the comparative effectiveness of strategies may vary based on a patient's socioeconomic status.

Risk-Treatment Paradox

Several studies have shown a risk-treatment paradox in which the higher-risk patients are least likely to receive interventions that are expected to provide a benefit.[25,26] This pattern is paradoxical in that the high-risk patients would be expected to have the most to gain from an intervention that reduces risk, assuming that the relative reduction in risk is constant across groups defined by their baseline risk. The source of the paradox is not known, although some investigators have suggested that it is related to an aversion to the treatment of patients with limited functional status.[27] This treatment pattern concentrates the intervention among the patients with the least absolute benefit. Clinicians may want to guard against this tendency.

Outcomes and Timing

Additional considerations in assessing the potential effect of interventions include the outcome that is evaluated and the time period assessed. Although articles about patients with cardiovascular disease often focus on cardiovascular events, including cardiovascular death, patients would be expected to have more interest in all-cause mortality. If averting cardiovascular death merely leads to death from other causes, then this focus is of little value for the patient. The issue is particularly important in older patients who have other conditions, often called competing risks.[28] Quality of life and health status are commonly neglected in clinical studies but are very important to patients. Patients may not value short-term mortality benefits if other conditions and complications diminish their quality of life during the time that is gained. Thus, narrowly focusing on specific outcomes may obscure important insights about an intervention. The challenge is that evaluating many outcomes in a trial can increase the likelihood of false-positive findings.

Surrogate Outcomes

In evaluating evidence, clinicians should be particularly attuned to the outcomes that are assessed. Ideally, interventions are assessed for their effect on a patient's quality or quantity of life. Many studies use surrogate outcomes, measures that are more distally related to the patient's experience but are expected to be related to a patient's quality or quantity of life. These surrogate outcomes often reflect information about a patient's biology and have prognostic value in epidemiologic studies. It is not possible, however, to know that an intervention that modifies a surrogate outcome has the expected

effect on patients. There are many examples in medicine of changes in surrogate measures that did not translate into benefits for patients (see Chapter 6).[29,30] Clinicians evaluating the medical literature should know whether the outcome reflects the patient's experience. Prominent examples in which surrogates were not proxies for outcomes are studies of torceptrapib,[31] dalceptrapib,[32] niacin,[33] fenofibrate,[34] blood pressure,[35] and hemoglobin A_{1c} levels.[36] In the case of lipids, guidelines that focus on targets were based on extrapolations from clinical trials and accepted that low-density lipoprotein (LDL) levels were perfect surrogates for clinical outcomes, even as the literature increasingly failed to support that view.

Efficacy/Effectiveness

Efficacy is what is achieved by interventions under ideal circumstances, such as in the setting of a clinical trial. In contrast, effectiveness describes the effect in actual practice. There are many reasons why actual practice is different from the trial environment. Patients may differ in their biologic response or their adherence to intervention protocols and may be treated by less skilled physicians who have less infrastructure support. Therapeutic decisions are often based on the assumption that the efficacy and the effectiveness of interventions are identical, which is not always the case.

Completeness of Evidence

In evaluating the evidence, an additional consideration for clinicians is completeness of that evidence. The medical literature is skewed by publication bias. Such selective publication can distort the available evidence, compromise systematic reviews and meta-analyses, impair evidence-based clinical practice, and undermine guideline recommendations. Studies suggest that less than half of the trials registered in ClinicalTrials.gov, the Internet-based registry managed by the U.S. National Library of Medicine, were published.[37] Even trials funded by the National Institutes of Health are frequently not published.[38] Many trials that are published lack complete safety data.[39] Data that are not published can have important public health implications as was demonstrated in the case of Vioxx.[40] Clinicians are handicapped by not knowing what is absent from the literature and should at least be aware that information about the safety and effectiveness profile of interventions may not be complete. This unfortunate fact heightens the uncertainty surrounding treatment decisions.

External Factors

Clinicians frequently are faced with external influences that may affect their clinical decision making to the detriment of the best interests of patients. Defensive medicine, practiced to protect against future litigation, can expose patients to unneeded tests and procedures. Financial incentives, whether overt or hidden, should be excluded from the decision-making process. Any incentives that exist, even in the form of regular payment, should be transparent. Relationships with industry or others that could be perceived as compromising objectivity should be made clear to patients.

ACCURACY OF STUDY RESULTS

An important aspect of clinical decision making is the validity of the primary information on which the decisions are based. Clinicians need to ensure that the evidence is coherent and consistent. Errors can occur in analysis, interpretation, or reporting of results, and disagreement among experts is common. Excellent clinicians recognize the possibility that the information they have been provided is not correct, and they must be prepared to review primary data as necessary.

COGNITIVE ERRORS

Even with good information, cognitive errors can undermine clinical decisions.[41] Some examples of these errors are described next.

Heuristics or Rules of Thumb

Clinicians tend to rely on heuristics, or rules of thumb, to assess probabilities and support complex cognitive tasks required for decision making. These heuristics can be useful because they allow shortcuts in reasoning, but they also are vulnerable to important errors and can undermine decisions.

Many medical heuristics are familiar. Occam's razor suggests that a clinician should choose the simplest explanation for a set of observations. Sutton's law, named for the bank robber who explained that he robbed banks "because that's where the money is," encourages clinicians to focus their attention where they will get the most yield.

A representative heuristic leads clinicians to estimate probability by how readily they can remember examples. Clinicians may estimate the probability of a disease because of its ease of recall. Thus, a more recent experience with a certain illness may make someone believe it is more common than it is. A clinical encounter in which the patient suffered a rare adverse event from a medication could lead a clinician to avoid that treatment. The anchoring heuristic leads people to stay with their initial impressions. This heuristic can mislead if clinicians do not refine initial impressions. A form of this heuristic, called premature closure, can lead clinicians to inappropriately stop pursuing alternative explanations.

Framing Effects

Like their patients, clinicians are sensitive to the framing of information. That is, the same truth is acted on differently, depending on the way the information is presented. Clinicians (and patients) need to recognize their sensitivity to the framing of the data. Clinicians are more likely to use a new therapy when presented with the relative reduction in risk, rather than the absolute reduction.[42,43] Physicians can address this error by reframing decisions and being aware of the effect of the presentation of the data on perceptions of benefit.

Blind Obedience

The unwavering acceptance of the diagnosis of an authority (test or person) can lead to ignoring discordant information. Wise clinicians have the courage to question authority when the information does not provide a clear answer. The persistence of good decision makers and their refusal to blindly follow the crowd often lead to important insights. The best interests of the patient should guide clinicians and give them the strength to respectfully question authority, when appropriate.

SHARED DECISION MAKING

Clinical decisions are not the sole domain of physicians. Professional societies are moving to endorse the importance of shared decision making.[44,45] The principle of autonomy mandates that patients retain control over their bodies and, except in rare circumstances, must consent to undergo interventions. Informed consent is the cornerstone of this concept, but other approaches that promote information sharing are also needed.[46,47] Patients report that they want to be involved in decision making. One study of patients who had experienced an AMI found that two thirds preferred active engagement in decisions.[48]

Shared decision making can be understood as having five phases: assess, advise, agree, assist, and arrange. The clinician must first assess the patient. Then the clinician should advise the patient of the options, including benefits and risks. Next, the clinician and the patient should agree on a plan that is aligned with the patient's preferences and values. The clinician should then assist the patient in implementing the plan. Finally, the patient and the clinician should arrange for follow-up evaluation.

Unfortunately, patients do not always have a good understanding of benefit and risk. For example, in a study of patients who had

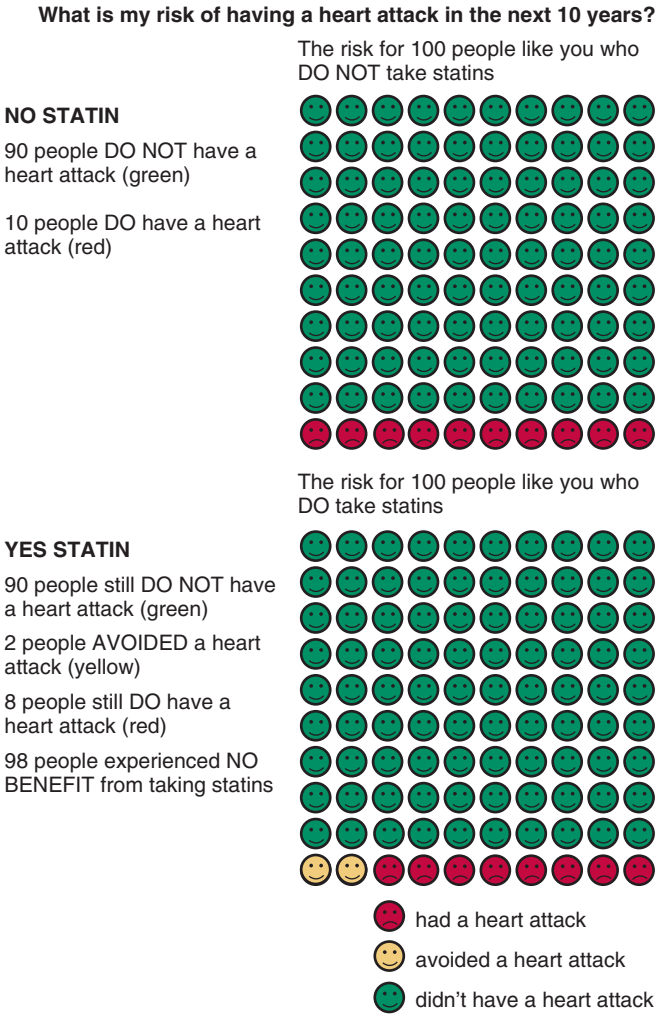

FIGURE 4-2 Decision support tool for acute myocardial infarction with and without use of statins. *(Courtesy Dr. Victor Montori, Mayo Clinic, Rochester, Minn.)*

consented to elective percutaneous coronary intervention (PCI), which does not improve survival or prevent AMI in this context, 75% thought it would prevent an AMI and 71% felt it would improve survival.[49] Moreover, only 46% could identify at least one possible complication. Among this group, 67% stated that for making decisions, they should be involved at least equally with the physician. Other studies also have found that patients often have unrealistic expectations of benefit.[50,51]

Like physicians, patients are susceptible to framing effects.[52] The manner in which information is presented, including the order in which it is provided, may be influential. Patients tend to view more favorably and be more likely to choose a therapy that is presented in relative rather than absolute terms, because the relative effect is almost always much greater than the absolute change.

Some techniques have been proposed to help clinicians convey risk and promote shared decisions.[53] First, clinicians should avoid descriptive terms such as "low-risk," which may not have a consistent meaning among patients and may be difficult for them to interpret. In expressing risk as ratios, a consistent denominator should be used (e.g., 40 of 1000 and 5 of 1000 instead of 1 in 25 and 1 in 200). Clinicians should offer various perspectives to encourage multiple ways of considering risk and should use absolute numbers rather than relative risks. Visual aids also are useful to overcome barriers to understanding for patients with poor numeracy or literacy skills. Innovative approaches are emerging, including tools designed by experts for use by clinicians and patients at the point of care[54,55] (**Figs. 4-2** and **4-3**).

SYSTEMS OF CARE

It is important to view good clinical decision making as a team effort, rather than an individual skill. It is thus an effort that can occur only in the context of good systems. System errors, including problems with policies and procedures, and inefficient processes and communication obstacles, commonly contribute to incorrect information that fosters mistakes in decision making.[56] Lack of decision support can lead to overlooking sources of error. Lack of systems to diagnose and learn from decision-making errors will increase the likelihood that such errors will occur again.

CONCLUSIONS

Clinical decision making is the cornerstone of good clinical care. Physicians must not only have knowledge of the field but be prepared to use it in ways that optimize the care and outcomes of patients. Good judgment requires an ability to interpret evidence, weigh risks and benefits, and understand and promote the preferences and values of patients.

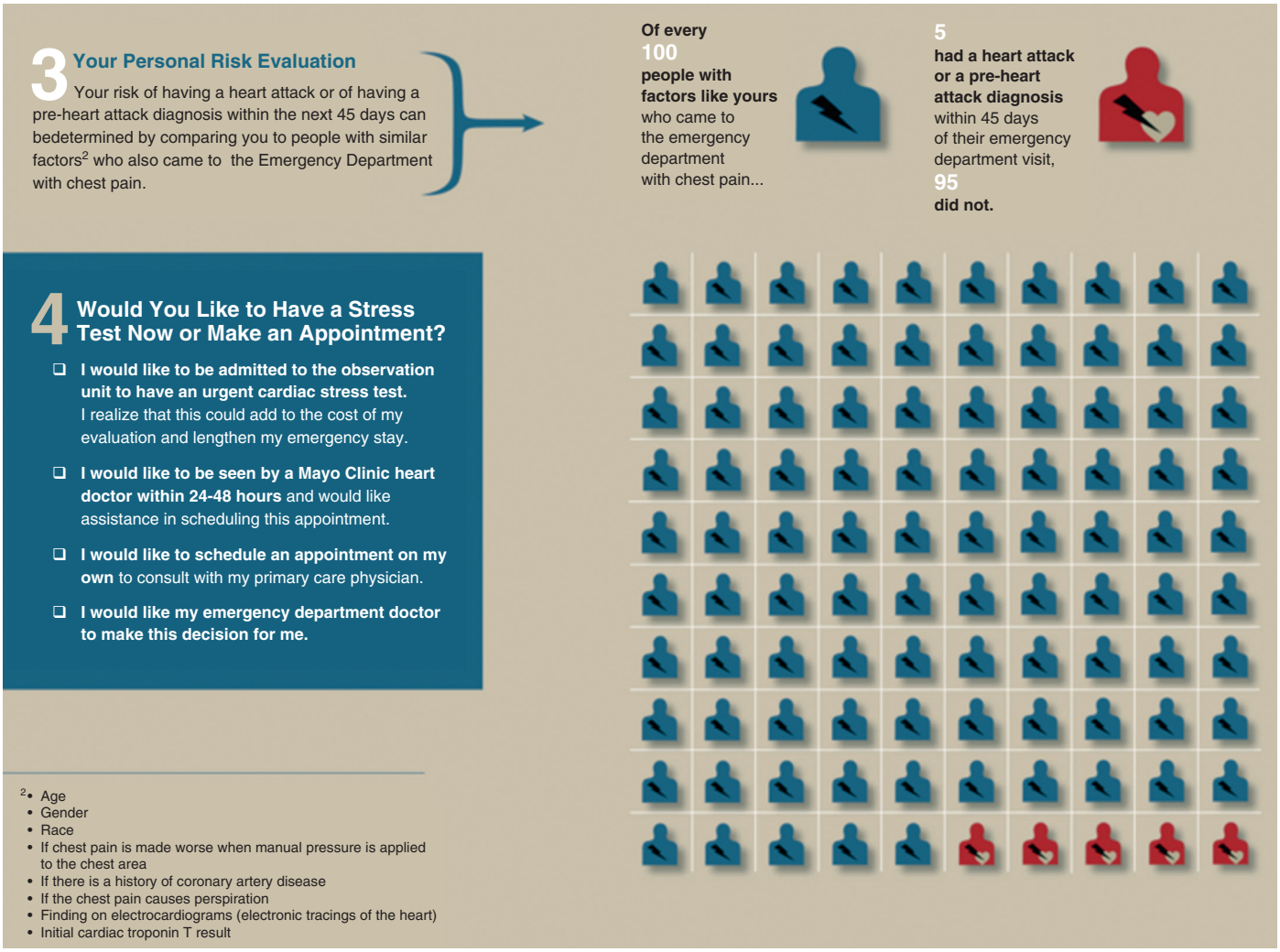

FIGURE 4-3 Risk assessment tool for diagnosis of acute myocardial infarction/pre–acute myocardial infarction within 45 days of presentation to the emergency department. *(Courtesy Dr. Victor Montori, Mayo Clinic, Rochester, Minn.)*

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5 Measurement and Improvement of Quality of Care: Relevance to Cardiovascular Clinical Practice

Frederick A. Masoudi and John S. Rumsfeld

Although the quality of health care is important for all stakeholders, the primary perspective of this chapter is that of cardiovascular clinicians. Our goals are to help cardiovascular clinicians understand the definition and importance of quality of care, and the relevance of quality of care measurement and improvement in current cardiovascular practice. We focus on measuring health care quality and uses of quality measurements, as well as improving quality of care, with examples of *quality improvement* (QI) approaches.

DEFINING QUALITY OF CARE

Quality of care generally is defined as the extent to which health care delivery optimizes the outcomes, or the "end results," of care. In the United States, the Institute of Medicine (IOM) has more specifically defined quality of care as "the degree to which health care systems, services, and supplies for individuals and populations increase the likelihood for desired health outcomes in a manner consistent with current professional knowledge."[1] Key outcomes of care include survival, patient health status (i.e., symptom burden, functional status, and health-related quality of life), morbidity (e.g., acute myocardial infarction [MI] or heart failure hospitalization), patient experience (e.g., satisfaction), and cost-effectiveness.

The IOM has further proposed six domains of quality (**Table 5-1**), specifying that high-quality health care is effective, safe, equitable, timely, efficient, and patient-centered. Quality of care can thus be conceptualized as the extent to which these domains are optimized to improve outcomes of care. Accordingly, quality measures either should focus on at least one of these six domains of quality or should directly measure outcomes of care. QI is the action undertaken to improve one or more of these six domains in order to improve health outcomes.

Unfortunately, despite tremendous therapeutic advances in the past 50 years, well-recognized deficiencies in health care delivery are manifest, as suboptimal quality and outcomes of care persist. Health care spending in the United States exceeds that of any other country, but American health care does not achieve commensurately high scores on most metrics of quality of care or health outcomes.[2] Marked geographic variation in per capita health care utilization and spending are well recognized, yet consistent correlation between spending and health outcomes is lacking. For example, significant variation in the use of cardiovascular testing and procedures that is not explained by case-mix does not clearly translate into better patient outcomes.[3]

Numerous studies have documented *underuse* of guidelines-indicated care, unexplained variation in care delivery, and outcomes that may reflect *overuse* or inconsistent quality of care delivery, and *misuse*, including avoidable complications and medical errors, all of which contribute to suboptimal outcomes. Gaps in quality can result from deficiencies in any of the IOM quality domains (see Table 5-1). For example, effective therapies may not be provided to eligible patients (e.g., statin therapy in a patient with a recent MI). Providers and health care systems may fail to minimize exposure of patients to unnecessary risk (e.g., prescribing drugs that carry a high risk of adverse drug-drug interaction). Clinicians may prescribe suboptimal or ineffective therapies (e.g., routine primary-prevention implantable cardioverter-defibrillator placement in a patient with mild left ventricular systolic dysfunction) or may recommend use of resource-intensive care for marginal benefit (e.g., routine intra-aortic balloon pump use for high-risk percutaneous coronary intervention). Care delivery may be excessively delayed or may be delivered differentially based on patient age, sex, race/ethnicity, or insurance status. Patients may not be engaged in their care to focus principally on the health outcomes of highest import (e.g., quality of life in addition to quantity of life). Deficiencies in any of these areas contribute to observed variations in quality of care and patient outcomes. These deficiencies, coupled with rising health care costs, have raised interest in health care reform, in which measurement and reporting of quality of care are central to clinical practice.

RELEVANCE OF QUALITY OF CARE IN CARDIOVASCULAR PRACTICE

Too often, cardiovascular clinicians perceive quality of care primarily as indicating more careful documentation in the medical record or satisfying quality metrics to meet payer or other requirements. This narrow view is reinforced in the current health care environment, in which quality measurement and reporting are often placed in a "regulatory" context and often are executed separately from clinician-patient interactions and clinical decision making. In reality, the interaction of patients and clinicians is central to high quality of care, in keeping with the impact of clinical decisions (e.g., therapeutics prescribed or procedures done) on patient outcomes. Hence, cardiovascular clinicians should play a central role in how quality is measured and how health systems are modified to optimize quality and patient outcomes.

Indeed, there are multiple reasons why cardiovascular providers should engage in quality of care measurement and improvement. First, quality of care reflects the degree to which clinicians practice evidence-based medicine. Inherent in evidence-based medicine is consideration of both the best available scientific evidence and individual patient factors and preferences. In an optimal scenario, informed patients, who understand the state of their health and the potential risks and benefits of health interventions ranging from prevention to acute and chronic disease management, interact with clinicians who observe the tenets of evidence-based medicine.

TABLE 5-1 Institute of Medicine Domains of Highest-Quality Health Care

QUALITY DOMAIN	BRIEF DEFINITION
Effective	Providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and overuse, respectively)
Safe	Avoiding harm to patients from the care that is intended to help them
Equitable	Providing care that does not vary because of personal characteristics such as sex, ethnicity, geographic location, and socioeconomic status
Timely	Reducing waits and sometimes harmful delays for both those who receive care and those who give care
Efficient	Avoiding waste, including the waste of resources and patient time, as well as waste of equipment, supplies, ideas, and energy
Patient-centered	Providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions; this type of care attends to patients' physical and emotional needs, maintaining or improving their quality of life, and gives them the opportunity to be the locus of control in decision making.

From Institute of Medicine, Committee on Quality Health Care in America: Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC, National Academies Press, 2001.

Second, quality of care is increasingly tied to maintenance of certification and licensure, particularly with regard to involvement in practice improvement. Medical education is evolving to a model of life-long learning, in which the principles of quality of care are integrated with clinical knowledge and decision making. Intrinsic to this new framework, cardiovascular clinicians will need to have the skills of quality of care measurement and improvement in addition to medical knowledge.

Third, quality of care lies at the center of health care system improvement. The outcomes of health decisions of patients and cardiovascular clinicians depend on the environment (including community and health care system attributes) in which these decisions are made. From the perspective of the cardiovascular clinician, quality of care includes not only their actions but also patient access, engagement, and behavior; the context and methods of health care delivery; and multiple aspects of the health care system, ranging from information technology support to ancillary personnel support to health system policy and incentives. Ultimately, although clinical knowledge and skill are essential for high-quality care, they are not sufficient; a primary driver of high-quality health care and QI is the health care delivery system.

Finally, quality of care provides a means for professional accountability. In today's health care environment, performance-based reimbursement and public reporting of quality of care measures are increasingly prevalent. Evolving models of health care delivery and reimbursement that are being pursued in the United States, such as accountable care organizations and integrated delivery systems, invariably emphasize performance on quality measures that reflect one or more of the IOM quality domains (see Table 5-1) and the direct measurement of patient outcomes. Measures of health care value (outcomes as a function of costs of care) are increasingly used to characterize cardiovascular practice, including linkage to incentives or disincentives, or both.

Cardiovascular clinicians should therefore have a strong interest in participating in robust and clinically relevant quality of care measurement and improvement efforts, health care delivery design and payment programs. Moreover, the concept of professionalism includes not only clinical knowledge but also excellence in the delivery of health care and accountability for that care. Quality of care—through measurement and improvement of the IOM domains of quality and patient outcomes—directly speaks to health care delivery and accountability. Accordingly, quality of care is central to professionalism in cardiovascular medicine.

TABLE 5-2 Current American College of Cardiology/American Heart Association (ACC/AHA) Performance Measure Sets

TOPIC AREA	PUBLICATION YEAR (WITH UPDATE)	PARTNER ORGANIZATIONS
Heart failure	2005 (2011)	ACC/AHA (inpatient) ACC/AHA/AMA-PCPI (outpatient)
Chronic stable coronary artery disease	2005 (2011)	ACC/AHA/AMA-PCPI
Hypertension	2005 (2011)	ACC/AHA/AMA-PCPI
ST-elevation and non-ST-elevation myocardial infarction	2006 (2008)	ACC/AHA
Cardiac rehabilitation	2007 (2010)	AACVPR/ACC/AHA
Atrial fibrillation	2008	ACC/AHA/AMA-PCPI
Primary CVD prevention	2009	AHA/ACCF
Peripheral artery disease	2010	ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS
Percutaneous coronary intervention	2013	ACCF/AHA/SCAI/AMA-PCPI/NCQA
Cardiac imaging	2014 (est.)	ACCF/AHA/ACR/AMA-PCPI/NCQA

AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation; ACCF = American College of Cardiology Foundation; ACR = American College of Radiology; AMA-PCPI = American Medical Association–Physician Consortium for Performance Improvement; CVD = cardiovascular disease; NCQA = National Committee for Quality Assurance; SCAI = Society of Cardiovascular Angiography and Interventions; SIR = Society of Interventional Radiology; SVM = Society of Vascular Medicine; SVN = Society of Vascular Nursing; SVS = Society of Vascular Surgeons.

MEASURING HEALTH CARE QUALITY AND USES OF QUALITY MEASUREMENTS

This section discusses types of quality measures, the uses of measures, commonly used data sources for quality measurement, and possible limitations of quality measures, including the potential for unintended consequences.

Types of Quality Measures

Donabedian's seminal treatise, published more than 50 years ago, delineated a conceptual framework for measuring health care quality that endures to the present: characterizing quality according to structure, process, and outcome.[4] Although measurement has extended beyond these three domains, these constructs remain central to understanding the quality of health care. The American College of Cardiology/American Heart Association (ACC/AHA) have described in detail the methodologic principles of developing various types of measures.[5-8]

Structural measures are specific attributes of the health care delivery system that are used as surrogates for the care delivered. Examples are procedural volume and accreditation status. In general, such measures are only weak surrogates and frequently are considered inadequate if more robust metrics of quality are available.[9,10]

Process measures reflect the actions of providers, such as the prescription of a medication, and are among the most commonly used metrics of quality. For example, the Centers for Medicare & Medicaid Services (CMS) has used processes of care for acute MI and heart failure as part of its Hospital Compare quality reporting system since 1995[11]; the ACC/AHA have developed several sets of process measures for specific cardiovascular procedures and conditions (**Table 5-2**). Operationally, process measures are generally selected from among the care processes with strong support in practice guidelines (e.g., class I recommendations in the ACC/AHA

TABLE 5-3 Attributes of Measures of Process, Outcome, and Value in Health Care

MEASURE TYPE	MEASURE ATTRIBUTES
Process[5]	Evidence-based Interpretable Actionable Explicit numerator and denominator Valid Reliable Feasible
Outcomes[6]	Clear explicit definition of appropriate patient sample Clinically coherent variables for risk adjustment Sufficiently high-quality and timely data Designated time of covariate and outcome ascertainment Standardized period of outcome assessment Analysis accounting for multilevel organization of data Disclosure of methods used
Value/efficiency[7]	Integration of both quality and cost Valid cost measurement and analysis No or minimal incentive to provide poor-quality care Proper attribution of the measure

guideline recommendation taxonomy). Not all strong guideline recommendations are appropriate for adoption as quality measures, however; such measures should possess additional attributes that support their use for quality measurement (**Table 5-3**).

Process measures have substantial face validity because they focus on therapies and approaches that have been established in clinical studies and are readily interpretable. However, they generally require clinical data, thus requiring resources for data abstraction. The exclusion of individual patients from a process measure denominator because of contraindications to treatment is viewed favorably by clinicians but is controversial. Such exclusions increase the burden of data collection but enhance the clinical validity of these measures. Moreover, there is not always a demonstrated association between higher performance on process measures and better patient outcomes.[12] Finally, process measures may "top out," in that performance is consistently high and the measures lose the capacity to discriminate meaningfully among institutions, as has been the case with many of the process measures for acute MI and heart failure that are reported to the public.[13]

In view of the limitations of structural and process measures, a greater emphasis has been placed on outcomes measures. Suitable outcomes measures have several attributes (see Table 5-3), perhaps the most important of which is risk adjustment.[6] Risk, or "case mix," adjustment can address concerns that differences in outcomes reflect differences in patient populations being cared for. Robust risk adjustment requires advanced statistical methods, and is generally limited by the extent of availability of accurate data variables (e.g., patient characteristics) to include in risk models. Outcome measures are appealing because they are patient-centered, can be applied to all patients (as opposed to process measures, which apply only to a discrete "denominator" of patients), and reflect the actions of the health care system.[14] Risk adjustment methods must be valid, however, and some outcomes of great importance to patients such as health status are not currently measured systematically in large populations. Furthermore, unlike process measures, outcomes measures do not explicitly inform the targets for QI.

Measures of value—broadly defined as quality delivered as a function of cost—have emerged as part of the quality measurement portfolio.[15] Of importance, cost alone is not synonymous with value; the easiest way to minimize cost is to withhold care, whereas value explicitly incorporates quality. Attributes of measurements of value have been enumerated (see Table 5-3)[7]; developing robust measures of value involves the challenges attendant to measuring quality as well as those associated with measuring costs.

In response to escalating costs and concerns that variation in care delivery may in part reflect overuse, the ACC, in conjunction with partner societies, have developed *appropriate use criteria* (AUC). These criteria provide ratings of the appropriateness of care for several cardiovascular diagnostic and therapeutic modalities for a range of commonly encountered clinical scenarios.[16] Because the AUC are based on clinical scenarios that may not exactly reflect individual patient situations, and because the criteria are derived from expert consensus, their role in quality measurement and reporting is evolving.

Composite measures, which formally aggregate multiple aspects of quality, are appealing because of the various structures, processes, and outcomes that can be measured for a particular condition or procedure.[17] Developing composite measures is complex, and should be guided by an explicit methodology.[18] These measures have the advantage of combining various domains of quality but can obscure the impact of component measures and can decrease the understanding of where action for improvement is needed.

Data Sources

In general, quality measures are most useful when compared against an external standard (e.g., a "benchmark" of similar practice or national performance). Although single-center data can on occasion provide useful insights for local quality assessment and improvement, data used to characterize quality are most useful when compared across patients, providers, and settings. Sources meeting these criteria are often categorized as "claims" (also known as "administrative") data or clinical data, each of which has distinct strengths and limitations. Ultimately, any measurement of quality will be no more robust than the quality of the data upon which it is based.

Insurance payers maintain data bases of claims for services as a means of identifying and paying for health services delivered to their members. Claims data have several strengths. First, they tend to include large numbers of patients, although this depends on the payer involved. Second, because these data are already collected for other purposes, there is lower incremental expense to use claims data for this purpose. Finally, claims data use a consistent standard (e.g., International Classification of Diseases [ICD]-9 codes) for each claim.

However, several factors significantly limit the value of claims data. Because their primary purpose is to facilitate billing, claims data are constrained in their capacity to inform clinical inferences. For example, claims data are limited with regard to measuring severity of disease, indications and results of procedures, and differentiating comorbid conditions from complications. Moreover, diagnostic codes may be discordant with clinical diagnoses established by clinicians.[19] Claims data also are specific to the population receiving insurance from the entity that creates the data base. Finally, claims data require substantial time to elapse before they are adequately complete for use. Thus measurements with these data will lag with respect to current practice. The usefulness of claims data as a component of quality measurement is largely dependent on the specific use. In some cases, claims and clinical data perform similarly for case mix adjustment at the institutional or hospital level for cardiovascular conditions.[20] However, when used for risk adjustment of outcomes at the patient level, clinical data generally provide better calibration and discrimination than claims data alone.[21]

Clinical data are appealing as the foundation of quality measurements for several reasons. The primary advantage of clinical data is their specificity with regard to clinical details, such as severity of disease, coexisting conditions, and indications for and results of procedures. For example, identifying contraindications to the use of a particular medication in a quality measure is likely to be incomplete using claims data, whereas clinical data are more likely to include the relevant information. Limitations to clinical data also are recognized. Clinical data generally are more expensive and difficult to obtain in large populations compared with claims data. Aside from national clinical registry programs (discussed further on), there are few sources of clinical data using consistent data standards and adequate in reach and scope to characterize quality on a large scale. Data in medical records, including electronic health records (EHRs), typically do not use standardized definitions and may not include the specific elements necessary to compose a quality measure.

National clinical registry programs are currently the most widely used clinical data to measure quality. In the United States, the National Cardiovascular Data Registry program of the ACC and partner organizations (www.ncdr.com), the AHA Get With the Guidelines program (www.heart.org), and the Society of Thoracic Surgeons (STS) National Database (www.sts.org) are the most widely implemented cardiovascular registry programs. These programs provide quality measurements with national benchmarks using detailed standardized clinical data and can support QI initiatives.[22]

In some cases, clinical and claims data are used together for quality measurement purposes. This approach is often used to take advantage of the detailed clinical data from a registry program for a specific episode of care (e.g., a percutaneous coronary intervention or a hospitalization for heart failure) and the assessment of events after that episode from claims data (e.g., death or rehospitalization). These hybrid data sources, though sharing the advantages and disadvantages of their component sources, can permit assessments of longitudinal outcomes with a robust clinical foundation.

The increasing deployment of EHRs in the United States creates opportunities and challenges for quality measurement. EHRs have potential as sources of large amounts of clinical data but do not constitute a panacea for how to measure quality. EHRs are not superior to paper records with respect to data structure and definitions, or in ensuring that particular data are collected, unless they are specifically modified to do so. Moreover, EHR systems are not necessarily interoperable among institutions, limiting the extent to which they can be used for multi-institutional quality assessment without further efforts. Experience suggests that EHRs must evolve considerably to achieve their full potential as a source of robust, reliable data for quality measurement.[23]

Uses of Quality Measures

Quality measurements serve a range of purposes, but in broad terms they can be considered as supporting QI (see later section, Improving Quality of Care) or accountability for care (e.g., public reporting).[24] The distinction between these two uses is important: Although a broad range of measures may be suitable for the purposes of self-evaluation, benchmarking, and informing QI, measures that will be used for accountability must withstand the scrutiny of those who are measured and the intended consumers of those measures.[25] The use of measures for accountability requires greater validity, reliability, and reproducibility of the measures, including the quality of the data that underlie the measures, as well as attribution of the measures.[26] The ACC/AHA and other measure developers apply specific standards and nomenclature to identify those measures that are appropriate for accountability purposes (e.g., those designated as "performance measures") or those that are intended for QI purposes (designated as "quality metrics" or "test metrics").[25] In the United States, most measures intended for the purposes of accountability are reviewed and endorsed by the National Quality Forum (www.nqf.org).

The past two decades have witnessed the evolution of programs that use quality measures for the purposes of accountability. These include public reporting of quality measures (e.g., CMS Hospital Compare); "pay for reporting," whereby participation in reporting efforts (but not the specific results) results in financial incentives; and "pay for performance," whereby reimbursement is tied to the specific results of outcomes (e.g., the CMS Value-Based Purchasing program). Professional organizations also are taking leadership roles in public reporting efforts based on clinical registry data, such as the STS voluntary public reporting program for cardiovascular surgery.[27]

Ostensibly, accountability programs are intended to improve quality by introducing meaningful incentives for better performance. Systematic reviews of the existing literature suggest that although public reporting stimulates efforts to improve quality,[28] there is not consistent evidence that it results in better quality or influences decisions by the consumers of health care services.[29,30] The heterogeneous results of accountability programs likely reflect the variability in these programs in terms of what is measured, the contexts of implementation, and the incentive structures.

Concerns About Quality Measures: Unintended Consequences

Efforts to measure and improve quality can potentially result in unintended consequences. For example, focusing on one process of care could detract from attention to others; incentives to increase rates of treatment could result in overtreatment in some cases; or threats of penalties for providers for adverse procedural outcomes or inadequate risk adjustment methods could result in biases against performing that procedure in high-risk patients.[31,32] These concerns support the importance of monitoring for potential unintended consequences as part of performance improvement efforts and programs. To date, however, QI and accountability efforts generally have not been evaluated with the rigor and to the extent of other medical interventions.[33] Accountability also may incentivize "gaming" the measurement system, which undermines its credibility with regard to meaningful QI and increases the importance of rigorous data quality/audit programs.

Improving Quality of Care

The principal reason to measure quality of care should be to inform meaningful improvement in health care delivery. As noted, QI, often also referred to as performance improvement, is the set of actions undertaken to improve one or more of the six IOM domains of quality (see Table 5-1) in order to improve health outcomes. Various studies have helped delineate key components of successful QI efforts, yet a number of activities familiar to cardiovascular clinicians have been found to be largely ineffective.

Imploring clinicians to "do more" or "do better" in terms of following guidelines or documenting care is generally ineffective. Perhaps surprisingly, traditional continuing medical education and didactic lectures, utilization management, and the availability of clinical practice guidelines also are ineffective in achieving QI.[34] On the other hand, the availability of quality measures with benchmarking (also called "audit and feedback") can be successful, particularly when tied to health care delivery system improvement.

Successful QI involves identifying suboptimal performance in one or more aspects of quality of care, and then matching QI activities to effectively improve performance. Data with benchmarking is central to choosing meaningful targets for improvement (see **Fig. 5-1**). Once QI targets are chosen, a primary emphasis for QI activities should be system changes to support higher quality care delivery. Examples are use of the EHR for computerized order entry to avoid prescription errors and to provide automated drug-drug interaction alerts, development of and adherence to standardized order sets and care pathways (e.g., for acute MI patients), implementation of a multidisciplinary care team approach, efforts to promote care coordination, and effective engagement of patients in decision making.

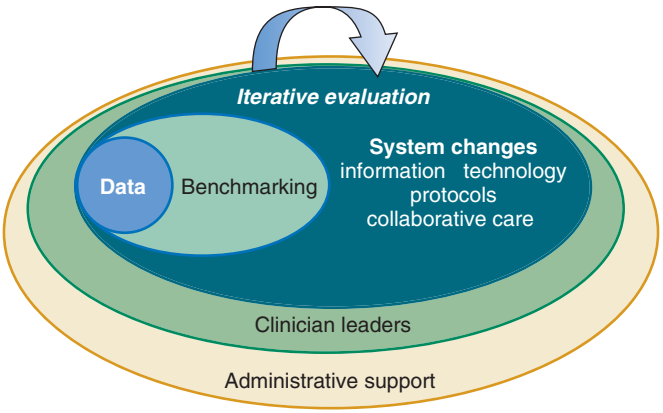

FIGURE 5-1 Key components of quality improvement. *(From Rumsfeld JS, Dehmer GJ, Brindis RG: The National Cardiovascular Data Registry: Its role in benchmarking and improving quality. US Cardiol 6:11, 2009.)*

QI is most successful as a "team sport"; it should be focused not on an individual clinician but on a multidisciplinary team. Moreover, QI should be responsive to specific gaps in performance over time, striving to continuously improve the delivery system. QI efforts should be evaluated in an iterative fashion, to assess progress in performance improvement and to monitor for unintended consequences. The measurement of the impact of QI, which can be considered part of "health care delivery research," should be increasingly important in the future.[35]

Clinical leaders—those who are engaged in and committed to quality measurement and improvement—are critical to successful QI efforts. Increasingly, training in quality measurement and QI is available to cardiovascular clinicians. Many hospitals and health systems are training clinical staff in quality. Organizations such as the ACC are embedding quality measurement and performance improvement into educational programs; these programs will increasingly support the performance improvement requirements of maintenance of certification and licensure.

Administrative support also is crucial for successful QI. This includes not only financial support of quality measurement and improvement efforts, but also clear institutional leadership goals and commitment with regard to achieving the highest quality of care. Indeed, among the most consistent and powerful drivers of QI is the culture of a practice or institution. For example, in an evaluation of hospital characteristics associated with 30-day mortality rates after acute MI, those hospitals that fostered "an organizational environment in which clinicians are encouraged to solve problems creatively" had, in addition to having both physician and nurse quality champions, significantly lower mortality rates.[36]

QI may be carried out at local levels (i.e., community/practice/hospital) or at regional, health system, national, or international levels. In other words, QI goals and strategies for performance improvement can be defined as part of local or broader-reaching quality initiatives; however, the principles of QI are the same for each of these, and the QI activities ultimately must be executed at the local level following the key factors noted in Figure 5-1. Several well-known approaches to QI are briefly described in the remainder of this section, including Plan-Do-Study-Act (PDSA), Lean, and Six Sigma.

Some Approaches to Quality Improvement

Fruitful QI requires the integration of the components described previously (see Fig. 5-1) into a specific framework for action. Perhaps the most widely used framework for QI in health care is PDSA. This model—developed by Associates in Quality Improvement (www.apiweb.org)—has been embraced by the Institute for Healthcare Improvement as the approach to plan health QI (www.ihi.org). PDSA is composed of two interdependent steps: first, formulating a plan by setting goals, establishing metrics of success, and identifying changes to implement; and second, testing these changes in an iterative PDSA cycle (**Fig. 5-2**). The goals should be measurable, time-delimited, and realistic. The measures should address at least one of the IOM domains of quality (see Table 5-1) but should also include ways to characterize possible adverse consequences of the improvement effort. Then, in evaluating changes, each step of the PDSA cycle contributes to the understanding of the impact of the change, both positive and negative, thus informing future cycles of improvement.

The Lean approach builds on PDSA by specifically targeting wasteful health care processes. Lean was originally developed at Toyota to improve the efficiency of production of automobiles. Not surprisingly, with the rapid growth of medical expenditures and the understanding that more spending does not necessarily translate to better quality, the use of Lean in health care settings has expanded rapidly. In essence, the Lean QI approach includes a focus on patient needs, an explicit evaluation of complex processes of care delivery in a given setting, and the identification and improvement of those components of the process that do not promote one or more of the IOM domains of quality (see Table 5-1) for improvement. The process of care mapping (e.g., the specific steps of how care is delivered in the emergency room, on a ward, or in the office), empowering all members of the health care team to help identify targets, and improving delivery in an iterative fashion are hallmarks of Lean.[37] Studies of the Lean approach suggest that it is an effective means of improving efficiency, by both reducing cost and improving quality.

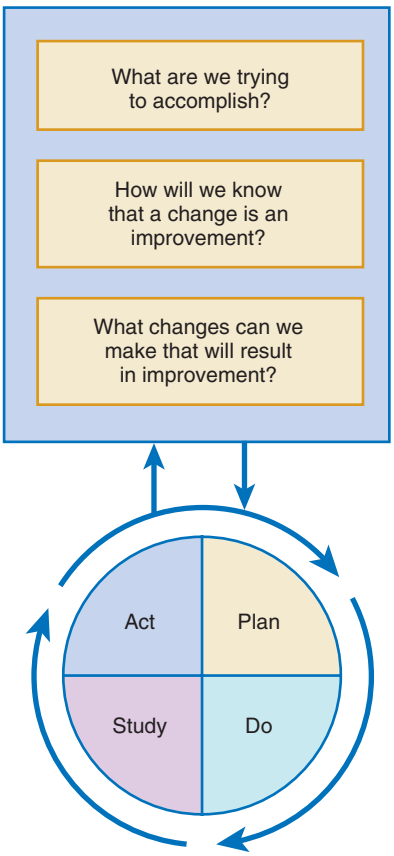

FIGURE 5-2 The PDSA (Plan-Do-Study-Act) cycle of quality improvement. *(From the Institute of Healthcare Improvement [www.ihi.org], attributed to Langley GL, Nolan KM, Nolan TW, et al: The Improvement Guide: A Practical Approach to Enhancing Organizational Performance. 2nd ed. San Francisco, Jossey-Bass Publishers, 2009.)*

Another well-known QI approach that builds on PDSA is Six Sigma, which focuses on reducing unnecessary variation in care delivery. The term *Six Sigma* stems from statistical process control, which aims to execute care processes with error rates that are six standard deviations below average. Unfortunately, medical errors generally occur at much higher rates.[38] Hence, Six Sigma emphasizes reducing errors in processes of care such as medication prescriptions or medical procedures (i.e., minimizing unnecessary procedural complications) through five steps, which constitute a modification of PDSA—namely, Define, Measure, Analyze, Improve, and Control.[39] The last step emphasizes ongoing monitoring of care processes once error rates/variation has been reduced, such that additional QI can be applied if variation/error rates increase. Lean and Six Sigma may be combined (Lean Six Sigma) for QI that leverages a PDSA approach to target reductions in wasteful processes of care and minimizing variation/error rates in care delivery.

CONCLUSIONS

Quality of care—the extent to which health care delivery optimizes patient outcomes—is becoming a core competency for cardiovascular clinicians. It is the practice of evidence-based medicine as well as accountability of care, both of which help define professionalism. Quality, or performance, improvement is increasingly central to clinical training and life-long medical education for cardiovascular clinicians, including maintaining certification and licensure.

Quality measurement and improvement are now an essential part of cardiovascular practice, as well as for the broader health care system. Quality measures—be they structural, process, outcome, value, or composite—depend on the extent of underlying scientific evidence, the validity of data sources, and clear specification. They can be used for QI as well as in accountability programs such as public reporting and "pay for performance." Meaningful QI stems

from using data with benchmarking to identify targets for improvement, making system changes to support high-quality care delivery, and having adequate clinical leadership as well as administrative support. Robust, iterative evaluation of QI efforts is of critical importance, both to assess the impact of these efforts on intended quality measures and to monitor for unintended consequences.

Ultimately, cardiovascular clinicians should be fully engaged in quality of care, to help ensure that quality measurement, QI, and accountability programs are clinically meaningful, not just a regulatory burden. Only in this way will quality of care efforts truly promote health care that is more effective, safe, equitable, timely, efficient, and patient-centered and that translates into improved patient outcomes.

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Improving Quality of Care

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6 Critical Evaluation of Clinical Trials

Elliott M. Antman

Despite many decades of advances in diagnosis and management, cardiovascular disease (CVD) remains the leading cause of death in the United States and other high-income countries, as well as many developing countries.[1] Managing the burden of CVD consumes 16% of overall national health care expenditures in the United States; interventions to treat CVD are therefore a major focus of contemporary clinical research. Therapeutic recommendations are no longer based on nonquantitative pathophysiologic reasoning but instead are evidence-based. Rigorously performed trials are required before regulatory approval and clinical acceptance of new treatments (drugs, devices, and biologics) and biomarkers.[2] Thus the design, conduct, analysis, interpretation, and presentation of clinical trials constitute a central feature of the professional life of the contemporary cardiovascular specialist.[3,4] Case-control studies and analyses from registries are integral to epidemiologic and outcomes research but are not strictly clinical trials and are not discussed in this chapter.[5,6]

CONSTRUCTING THE RESEARCH QUESTION

Before embarking on a clinical trial, investigators should review the FINER criteria for a good research question (**Table 6-1**) and the phases of evaluation of new therapies (**Table 6-2**) and should familiarize themselves with the processes of designing and implementing a research project, good clinical practice, and drawing conclusions from the findings (**Fig. e6-1**).[3,4,6-10] A clinical trial may be designed to test for superiority of the investigational treatment over the control therapy but also may be designed to show therapeutic similarity between the investigational and the control treatments (noninferiority design) (**Fig. 6-1**; **Table 6-3**).

In a noninferiority trial, investigators specify a noninferiority criterion (M) and consider the investigational treatment to be therapeutically similar to control (standard) therapy if, with a high degree of confidence, the true difference in treatment effects is less than M (see Fig. 6-1).[11,12] Specification of the noninferiority margin M involves considerable discussion between the investigators (advocating for clinical perception of minimally important difference) and regulatory authorities (advocating for assurance that the investigational treatment maintains a reasonable fraction of the efficacy of the standard treatment based on previous trials).[11,12] The investigational therapy may satisfy the definition of noninferiority but may or may not also show superiority over the control therapy.[13] Thus superiority can be considered a special case of noninferiority, in which the entire confidence interval for the difference in treatments falls in favor of the investigational treatment (see Fig. 6-1). Investigators can stipulate that a trial is being designed to test both noninferiority and superiority (see Table 6-3). For a trial that is configured as a noninferiority trial, it is acceptable to test for superiority conditional on having demonstrated noninferiority.[14] Because of the subjective nature of the choice of M, the reverse is not true—trials configured for superiority cannot later test for noninferiority unless the margin M was prespecified.

Regardless of the design of the trial, it is essential that investigators provide a statement of the hypothesis being examined, using a format that permits biostatistical assessment of the results (see Fig. e6-1). Typically, a null hypothesis (H_0) is specified (e.g., no difference exists between the treatments being studied) and the trial is designed to provide evidence leading to rejection of H_0 in favor of an alternative hypothesis (H_A) (a difference exists between treatments). To determine whether H_0 may be rejected, investigators specify type I (α) and type II (β) errors, referred to as the false-positive and false-negative rates, respectively. By convention, α is set at 5%, indicating a willingness to accept a 5% probability that a significant difference will occur by chance when there is no true difference in efficacy. Regulatory authorities may on occasion demand a more stringent level of α—for example, when a single large trial is being proposed rather than two smaller trials—to gain approval of a new treatment. The value of β represents the probability that a specific difference in treatment efficacy might be missed, so that the investigators incorrectly fail to reject H_0 when there is a true difference in efficacy. The power of the trial is given by the quantity $(1 - \beta)$ and is selected by the investigators—typically, between 80% and 90%.[7] Using the quantities α, β, and the estimated event rates in the control group, the sample size of the trial can be calculated with formulas for comparison of dichotomous outcomes or for a comparison of the rate of development of events over a follow-up period (time to failure). Table 6-3 summarizes the major features and concepts for superiority and noninferiority trials designed to change the standard of care for patients with a cardiovascular condition.

CLINICAL TRIAL DESIGN

Controlled Trials

The *randomized controlled trial* (RCT) is considered the gold standard for the evaluation of new treatments (**Fig. 6-2**). The allocation of subjects to control and test treatments is not determined but is based on an impartial scheme (usually a computer algorithm). Randomization reduces the likelihood of patient selection bias in allocation of treatment, enhances the likelihood that any baseline differences between groups are random so that comparable groups of subjects can be compared, and validates the use of common statistical tests. Randomization may be fixed over the course of the trial or may be adaptive, based on the distribution of treatment assignments in the trial to a given point, baseline characteristics, or observed outcomes (see Fig. 6-2A).[15] *Fixed* randomization schemes are more common and are specified further according to the allocation ratio (equal or unequal assignment to study groups), stratification levels, and block size (i.e., constraining the randomization of patients to ensure a balanced number of assignments to the study groups, especially if stratification [e.g., based on enrollment characteristics] is used in the trial). During the course of a trial, investigators may find it necessary to modify one or more treatments in response to evolving data (internal or external to the trial) or a recommendation from the trial's data safety monitoring board (DSMB)—that is, to implement an *adaptive* design (see Fig. 6-2B).[15] Adaptive designs are most readily implemented during phase II of therapeutic

COMPARING SUPERIORITY AND NONINFERIORITY DESIGNS

	Null hypothesis	Alternative hypothesis
Superiority	$H_0 : P_{Test} = P_{Control}$	$H_A : P_{Test} < P_{Control}$
Noninferiority	$H_0 : P_{Test} \geq P_{Std} + M$	$H_A : P_{Test} < P_{Std} + M$

FIGURE e6-1 Statistical design of superiority and noninferiority trials. In both superiority and noninferiority trials, the investigators propose a null hypothesis (H_0) with the goal of the trial being to reject H_0 in favor of the alternative hypothesis (H_A). To determine whether the null hypothesis may be rejected, before initiation of the trial, the type I (α) and type II (β) errors are specified (*not shown*). In superiority trials, α is usually two-sided, whereas it is one-sided in noninferiority trials. The quantity ($1 - \beta$) is referred to as the power of the trial. M = margin for noninferiority. P_{Std} = proportion of subjects experiencing the event of interest in the standard treatment group.

development. Regulatory authorities are concerned about protection of the trial integrity and the studywise alpha level when adaptive designs are used in registration pathway trials.[15] The most desirable situation is for the control group to be studied concurrently and to comprise subjects distinct from those of the treatment group. Other trial formats that have been used in cardiovascular investigations include nonrandomized concurrent and historical controls (**Fig. 6-3A, B**), crossover designs (see Fig. 6-3C), withdrawal trials (see Fig. 6-3D), and group or cluster allocations (groups of subjects or investigative sites are assigned as a block to test or control). Depending on the clinical circumstances, the control agent may be a placebo or a drug or other intervention used in active treatment (standard of care).

TABLE 6-1 FINER Criteria for a Good Research Question

F	Feasible
I	Interesting
N	Novel
E	Ethical
R	Relevant

From Hulley SB, Cummings SF, Browner WS, et al: Designing Clinical Research. 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2007.

TABLE 6-2 Phases of Evaluations of New Therapies

PHASE	FEATURES	PURPOSE
I	First administration of new treatment	Safety—is further investigation warranted?
II	Early trial in patients	Efficacy—dose ranging, adverse events, pathophysiologic insights
III	Large scale comparison versus standard treatment	Registration pathway—definitive evaluation
IV	Monitoring in clinical practice	Postmarketing surveillance

Modified from Meinert C: Clinical trials. Design, conduct, and analysis. New York, Oxford University Press, 1986; and Stanley K: Design of randomized controlled trials. Circulation 115:1164, 2007.

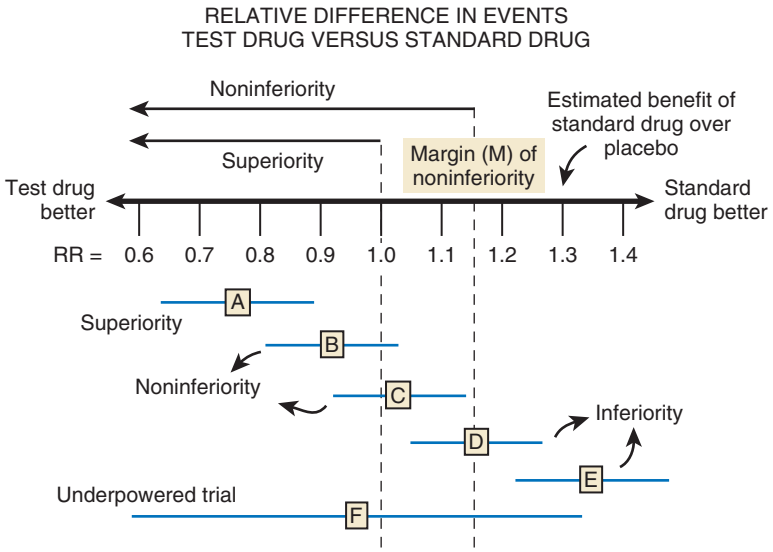

FIGURE 6-1 Example of design and interpretation of noninferiority trials. The margin (M) for noninferiority is prespecified based on previous trials comparing the standard drug with placebo. Examples of hypothetical trials A to F are shown, of which some (trials B and C) satisfy the definition of noninferiority. Trial A not only satisfies the criteria for noninferiority but, because the confidence interval is entirely to the left of a relative risk of 1.0, also shows superiority of the test drug over the standard drug.

Other Forms of Controlled Studies

Trials in which the investigator selects the subjects to be allocated to the control and treatment groups are *nonrandomized, concurrent control studies* (see Fig. 6-3A). In this type of trial design, clinicians do not leave the allocation of treatment in each patient to chance, and patients are not required to accept the concept of randomization. It is, however, difficult for investigators to match subjects in the test and control groups for all relevant baseline characteristics, introducing the possibility of selection bias, which could influence the conclusions of the trial. Clinical trials that use *historical controls* compare a test intervention with data obtained earlier in a nonconcurrent, nonrandomized control group (see Fig. 6-3B). Potential sources for historical controls include previously published trials in cardiovascular medicine and electronic data bases of clinic populations or registries. The use of historical controls allows investigators to offer the treatment(s) being investigated to all subjects enrolled in the trial. The major drawbacks are the potential for bias in the selection of the control population and failure of the historical controls to reflect accurately the contemporary picture of the disease under study.

The *crossover* design is a special case of the RCT in that each subject serves as his or her own control (see Fig. 6-3C). The appeal of this design is that the same subject is used for both test and control groups, thereby diminishing the influence of interindividual variability and allowing a smaller sample size. However, important limitations to a crossover design are the assumptions that the effects of the treatment assigned during the first period have no residual effect on the treatment assigned during the second period, and that the patient's condition does not change during the periods being compared.

In a *fixed sample size* design, the trialists specify the necessary sample size before patient recruitment, whereas in an *open or closed sequential* design, subjects are enrolled only if the evolving test-control difference from previous subjects remains within prespecified boundaries.[15,16] Trials with a fixed design can be configured to continue until the requisite number of endpoints is reached (event driven), thus ensuring that enough endpoints will occur to provide intended power to evaluate the null and alternative hypotheses. When both the patient and the investigator are aware of the treatment assignment, the trial is said to be *unblinded*. *Single-blind* trials mask the treatment from the patient but permit it to be known by the investigator, *double-blind* trials mask the treatment assignment from both the patient and the investigator, and *triple-blind* trials also mask the actual treatment assignment from the DSMB and provide data only in the form of group A and group B categories.

Withdrawal Studies

A *withdrawal* study evaluates the patient's response to discontinuation of treatment or reduction in the intensity of treatment for a cardiovascular condition (see Fig. 6-3D). Because patients previously experiencing incapacitating side effects would have been taken off the test intervention, they are not available for withdrawal. This bias toward selection of patients who tolerate a test intervention can overestimate benefit and underestimate toxicity associated with the treatment. In addition, changes in the natural history of the disease in a given patient may influence the response to withdrawal of therapy.

Factorial Design

In a *factorial* design, multiple treatments can be compared with control within a single trial through independent randomizations (**Fig. 6-4**). Because patients with CVD typically receive multiple therapies, the factorial design is more reflective of actual clinical practice than trials in which only a single intervention is randomized. Multiple comparisons can be efficiently performed in a single large factorial design trial that is smaller than the sum of two independent clinical trials. Each intervention should be evaluated individually against control and the possibility of interaction between the factors should be evaluated, because the validity of comparisons within each factor depends on the absence of interaction. Factorial designs may not be appropriate if there is an a priori reason to anticipate interactions (e.g., resulting from related mechanisms of action) (see Fig. 6-4).

TABLE 6-3 Trial Designs to Replace Standard of Care

PARAMETER	SUPERIORITY	NONINFERIORITY	
		Objective 1	Objective 2
Goal	Test beats control	Test beats placebo	Test as good as standard
H_O H_A	$P_{test} = P_{control}$ $P_{test} < P_{control}$	Assessment of test made against putative placebo	$P_{test} \geq P_{standard} + M$ $P_{test} < P_{standard} + M$
Source of data	Trial	Historical data	Trial
Type I error	Set by regulatory authorities, typically 0.05	Set by regulatory authorities, typically 0.05	Set by regulatory authorities, typically 0.05
Type II error (power)	Set by investigator	N/A	Set by investigator
Major threats to validity	Assay sensitivity; bias	Assay constancy	Assay sensitivity; bias
Inferential reasoning from trial	Results in study cohort yield estimate of $P_{test} - P_{control}$ in population of patients with same clinical characteristics and disease state	Combining results from the trial ($P_{test} - P_{standard}$) and historical data ($P_{standard} - P_{placebo}$) yields estimate of ($P_{test} - P_{placebo}$) in population of patients with same clinical characteristics and disease state	Results in study cohort yield estimate of $P_{test} - P_{standard}$ in population of patients with same clinical characteristics and disease state
Generalizability to universe of *all* patients with the disease state	Related to enrollment criteria; the more restrictive they are, the less generalizable are the results to the entire universe of patients with the disease state	Enrollment criteria of prior trials and medical practice concurrent with those trials determines generalizability of estimate of $P_{standard} - P_{placebo}$ to contemporary practice	Related to enrollment criteria; the more restrictive they are, the less generalizable are the results to the entire universe of patients with the disease state

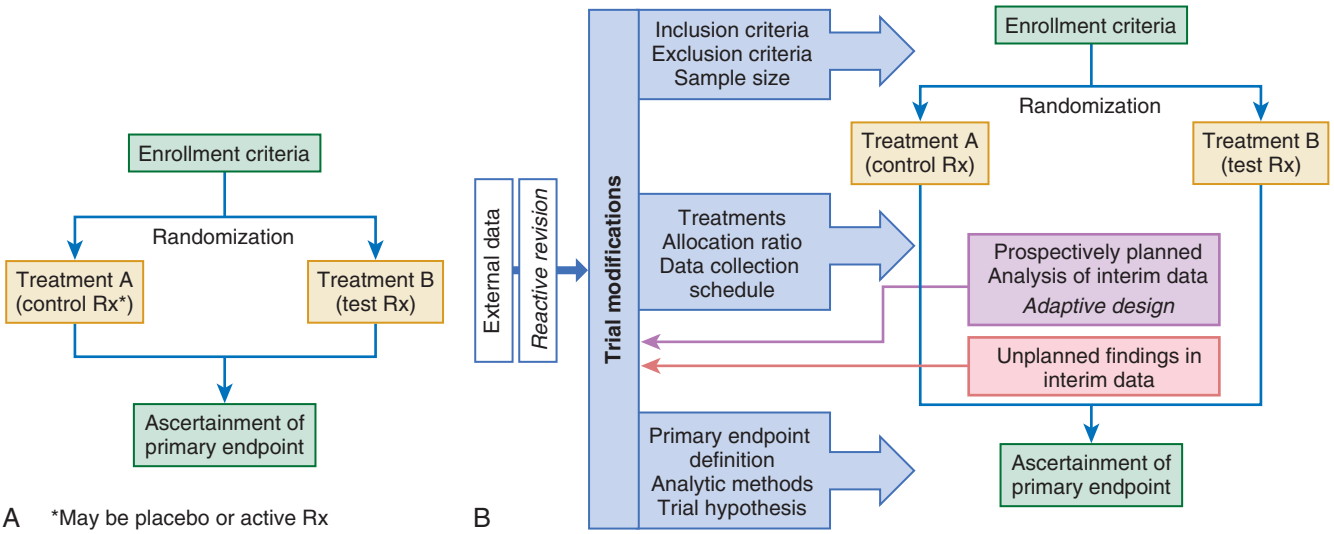

FIGURE 6-2 A, Basic structure of a randomized control trial (RCT). The investigators specify the enrollment criteria for the study population. Allocation to the treatment groups occurs through a randomization scheme, subjects are followed, and the primary endpoint is ascertained. **B,** The design of the RCT may be modified at the major levels shown. When the modification is in response to data external to the trial, it is referred to as a reactive revision (*left side*). When the investigators prospectively plan an analysis of interim data for the purposes of modifying the trial, it is referred to as an adaptive design. Unplanned findings in interim data (e.g., data safety monitoring board recommendation) also may provoke a modification of the trial design. *(Modified from Antman E, Weiss S, Loscalzo J: Systems pharmacology, pharmacogenetics, and clinical trial design in network medicine. Wiley Interdiscip Rev Syst Biol Med 4:367, 2012.)*

Selection of Endpoint of Clinical Trial

Evaluation of new treatments in the face of rising costs and reduced mortality rates for cardiovascular illnesses has resulted in two major approaches to the selection of endpoints. The first is to use a composite endpoint with a perceived logical grouping of events, whereby each of the elements of the endpoints is believed to be affected by the treatments being studied. During the course of a trial but before unblinding, investigators may assess the aggregate (all treatment groups combined) event rate for the primary endpoint to ascertain whether the initial estimates of the event rate in the control arm and the anticipated treatment effect of the intervention were reasonable.[16] A low aggregate event rate may reflect inaccuracies in the control rate or treatment effect; investigators may respond by modifying the sample size or expanding the definition of the primary endpoint (see Fig. 6-2B).

Some investigators use a term such as MACE (*m*ajor *a*dverse *c*ardiac *e*vents) to refer to the composite endpoint that they selected, but readers need to evaluate the methods sections in clinical trial reports rigorously, because such phrases may be used differently across trial groups. This situation may improve in the future, as a result of a movement toward standardization of the definitions of endpoints in RCTs.[17] Interpretation of composite endpoints is challenging when the various component elements show different quantitative or qualitative responses to a new treatment. For example, the new treatment may reduce a nonfatal element such as hospitalization for heart failure but may increase total mortality. Efforts to address the complexities of composite endpoints include evaluating the total number of endpoints (first element as well as recurrent nonfatal components) as well as novel weighting schemes using matched pairs of patients in the treatment and control groups to calculate a "win ratio."[18,19]

The balance of benefit and risk associated with a new treatment may be described using terms such as *net clinical benefit*, *net clinical outcome*, or *NACE* (*n*et *a*dverse *c*ardiac *e*vents). Such terms typically

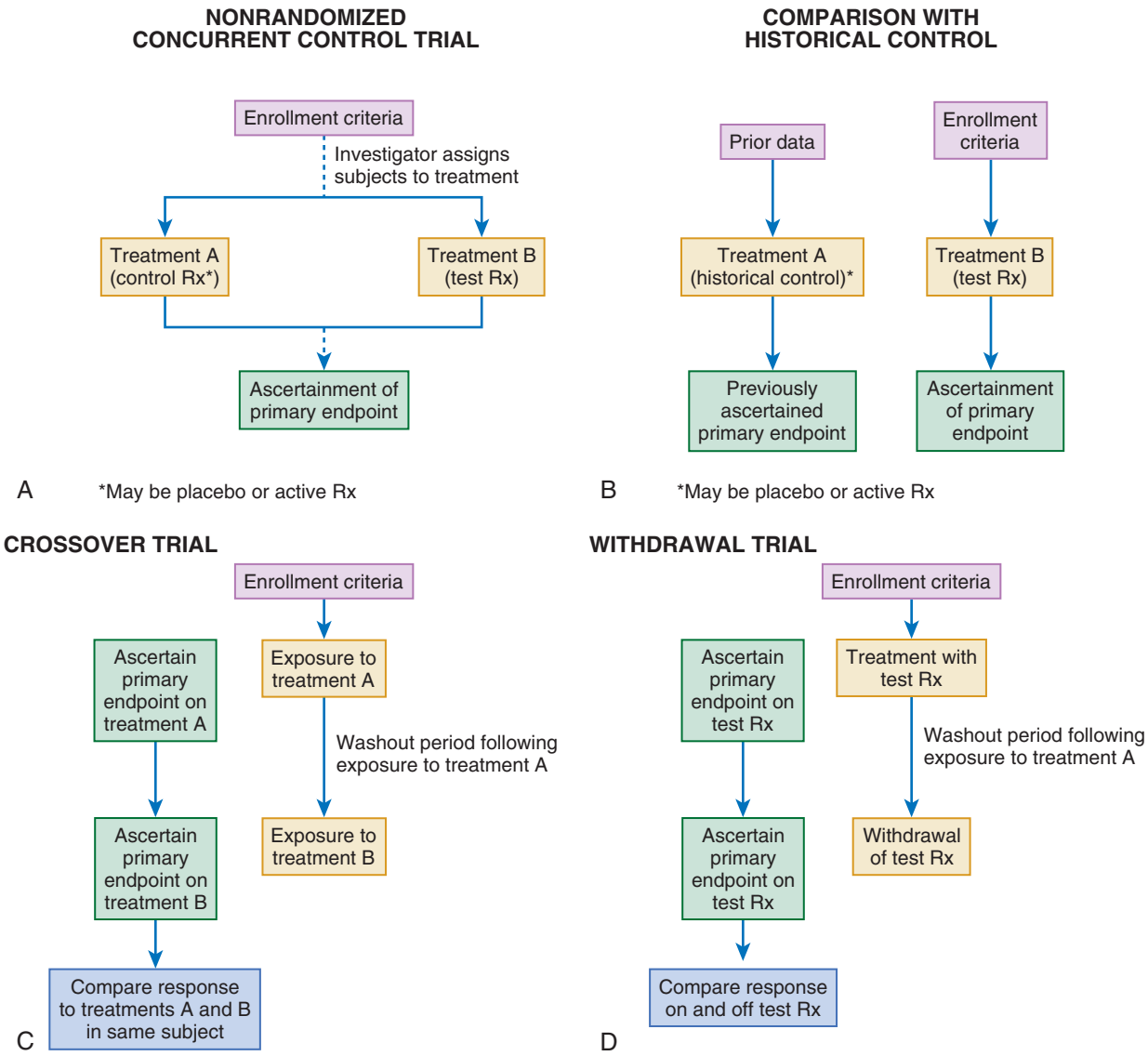

FIGURE 6-3 Other forms of controlled studies. **A,** Features of nonrandomized concurrent control trial. **B,** Design features of a trial using an historical control group. **C,** Design features of a crossover trial. (For an example of this type of trial to evaluate an intervention for angina pectoris, refer to Cole PL, Beamer AD, McGowan N, et al: Efficacy and safety of perhexiline maleate in refractory angina. A double-blind placebo-controlled clinical trial of a novel antianginal agent. Circulation 81:1260, 1990.) **D,** Design features of a withdrawal trial. (For an example of the use of this type of trial to evaluate the use of digoxin in patients with chronic heart failure, refer to Packer M, Gheorghiade M, Young JB, et al: Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 329:1, 1993.)

combine elements of efficacy and safety (e.g., cardiovascular death, nonfatal myocardial infarction [MI], nonfatal stroke, nonfatal major bleed) and provide clinicians with a summary statement about what to expect from a new treatment. Although this is appealing, controversy remains because of a lack of agreement on weighting schemes to interpret composite endpoints, especially when nonfatal safety elements (e.g., bleeding) are combined with efficacy elements (e.g., prevention of MI).

Another approach is to use a surrogate endpoint as a substitute for measuring more traditional clinical outcomes.[20] Surrogate endpoints are attractive to investigators because they often are measured on an interval (continuous) scale and can lead to trials with a smaller sample size. However, the field of cardiology is replete with examples of trials configured around surrogate endpoints that not only failed to demonstrate benefit but actually uncovered harm (e.g., increased mortality) associated with a new treatment. Surrogate endpoints are useful if they lie in the causal pathway of a disease and if interventions that affect them are reliably associated with changes in clinical outcomes. **Figure e6-2** illustrates a range of settings in which surrogate endpoints failed to serve as useful substitutes for measuring "hard" clinical events in cardiovascular trials.

KEY ISSUES

During the Course of the Trial

Contemporary trials require surveillance of multiple issues on a regular basis (**Fig. e6-3**). The determination as to whether an event (efficacy, safety) has occurred is the responsibility of a clinical events committee (CEC). Members of a CEC typically are experts in the field, remain blinded to the treatment assignment, and adjudicate events according to a charter established before initiation of enrollment.[17] Because it would not be possible for investigators to maintain equipoise as the events in a trial begin to accumulate, the DSMB assesses the data at prespecified intervals to ascertain whether the accumulating evidence strongly suggests an advantage of one treatment (**Fig. e6-4**).[21]

A critical aspect of a trial that impacts the analysis and interpretation of the findings is missing data. Subjects who initially agree to participation in an RCT may decline to continue to take a blinded study drug at some point during the course of the trial. Rather than ceasing follow-up in such subjects (i.e., censoring the data), trialists should strive to obtain follow-up data by asking subjects who stop taking a study drug to allow the investigators to obtain follow-up on

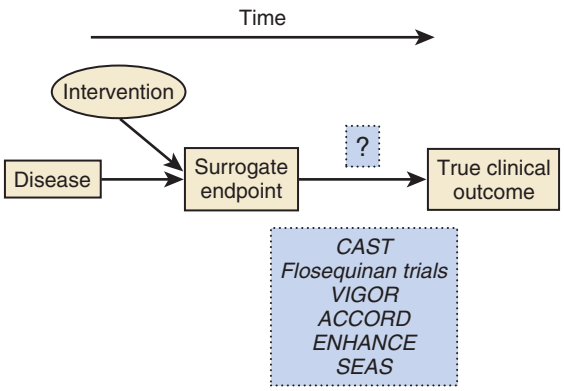

FIGURE e6-2 Surrogate endpoints. Selection of a surrogate endpoint in a clinical trial provides reliable information for clinicians if the surrogate endpoint is in the causal pathway of the disease with respect to clinical outcomes and the intervention acts on the surrogate endpoint so as to truly affect clinical outcome. Some examples of trials in cardiovascular medicine for which this paradigm failed are CAST (Cardiac Arrhythmia Suppressor Trial); studies of flosequinan; VIGOR (Vioxx GI Outcomes Research); ACCORD (Action to Control Cardiovascular Risk in Diabetes); ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression); and SEAS (Simvastatin and Ezetimibe in Aortic Stenosis). *(Modified from Fleming TR, DeMets DL: Surrogate end points in clinical trials: Are we being misled? Ann Intern Med 125:605, 1996.)*

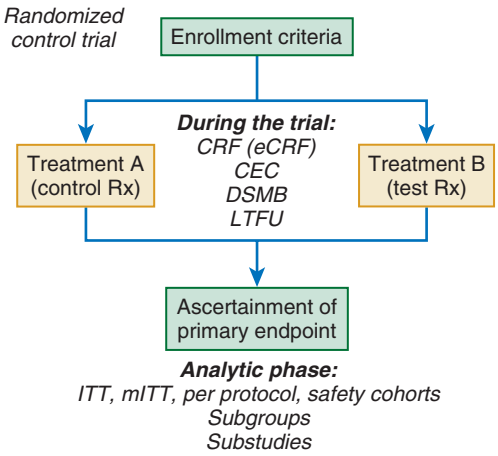

FIGURE e6-3 Conduct during recruitment and follow-up of subjects in the trial and during the analytic phase. The case report form (CRF) is an important barometer of the quality of the data being collected at investigative sites. Surveillance procedures need to be in place for central review of the data being submitted to trap for key items such as any violations of the enrollment criteria, range check errors (e.g., number of digits or units for age, weight, biomarkers, etc.), adequacy of the information being submitted for suspected endpoint events, and timely submission of adverse events (a regulatory reporting responsibility). Many of these tasks are facilitated by the use of an electronic CRF (eCRF) that can be completed using an Internet-based interface. The complexity of monitoring the tasks may be handled by a contract research organization (CRO) that has a large staff capable of visiting the enrolling sites. Additional quality checks that typically are conducted by a CRO include source document verification (inspection of primary medical record) for suspected endpoint events and random sampling of subjects who did not experience any events. Retention of subjects in the trial and minimizing loss to follow-up (LTFU) also are key quality measures. CEC = clinical events committee; DSMB = data safety monitoring board; ITT = intention to treat; mITT = modified intention to treat.

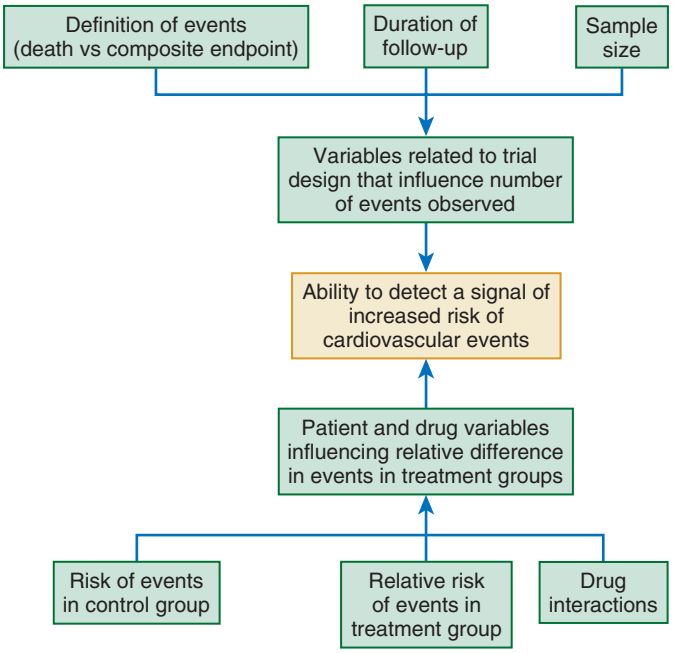

FIGURE e6-4 Detection of treatment effects in clinical trials. Factors related to trial design (*top*) and to the patient and drug being investigated (*bottom*) are shown. The interplay of these factors influences the ability to detect a treatment effect in a clinical trial. *(Reproduced with permission from Antman EM, DeMets D, Loscalzo J: Cyclooxygenase inhibition and cardiovascular risk. Circulation 112:759, 2005.)*

them either through office visits, telephone contact, or review of their medical records.[22,23] Every effort also should be made to track patients who move during the course of the trial to avoid "loss to follow-up."[23]

Stopping boundaries to guide the DSMB are usually agreed on before the initiation of enrollment. Such stopping boundaries need to take into account the uncertainty of the evidence at iterative interim looks at the data and the play of chance, which may produce a situation in which one treatment appears to be favorable. During these interim looks at the data, members of the DSMB inspect the differences between treatment groups expressed as a standardized normal statistic (Z_i). Usually, Z_i plots depict evidence of superiority of the test treatment in the upward (positive) direction and inferiority of the test treatment in the downward direction.[21]

Stopping boundaries may be symmetric (**Fig. 6-5**) or asymmetric. Investigators and DSMB members may agree to use an asymmetric stopping boundary scheme that requires less compelling evidence to cross a lower bound for inferiority of a new treatment when an acceptable standard treatment is clinically available and the new treatment is associated with safety concerns (e.g., intracranial hemorrhage during the evaluation of a new fibrinolytic). The DSMB may also be called on to determine whether a particular dose group should be discontinued (adaptive design) (see Fig. 6-2B) and whether the trial is futile (e.g., that conditional on the data accumulated at the -*i*th look, there is only a 10% chance that H_0 would be rejected at the end of the trial).

	Active A 5000	*Placebo A 5000*
Active B 5000	Active A Active B 2500	Placebo A Active B 2500
Placebo B 5000	Active A Placebo B 2500	Placebo A Placebo B 2500

Total enrollment = 10,000 patients

Evaluation of drug A alone and in combination with drug B:

Active A/Placebo B vs Placebo A/Placebo B = Difference$_1$ = D_1

Active A/Active B vs Placebo A/Active B = Difference$_2$ = D_2

Treatment effect of drug A in the absence of drug B = D_1

Treatment effect of drug A in the presence of drug B = D_2

Grand summary of treatment effect of drug A = $D_1 + D_2$

Effect of drug B on treatment effect of drug A = $D_2 - D_1$

FIGURE 6-4 Factorial design of clinical trial. In this example, 10,000 patients are randomized to receive or not receive two interventions (drug A and drug B). Each patient will fall into one of the following four categories: Active A/Active B, Placebo A/Active B, Active A/Placebo B, Placebo A/Placebo B. *Definitions/equations at bottom:* Differences in event rates for the comparisons permit an assessment of the treatment effect of drug A in the presence and absence of drug B. See text for further discussion. *(From Antman E: Medical therapy for acute coronary syndromes: an overview. In Califf R, Braunwald E [eds]: Acute Myocardial Infarction and Other Acute Ischemic Syndromes. Philadelphia, Current Medicine, 1996, pp 10.1-10.25.)*

During the Analytic Phase of the Trial

Before unblinding the results of the trial (i.e., revealing patient outcomes by treatment group to the investigators), investigators should have finalized a statistical analysis plan (SAP). Key features of the SAP include a definition of the cohorts of trial subjects to be analyzed (**Table 6-4**), the statistical test(s) to be used to analyze the primary endpoint (e.g., for comparison of proportions or time to event), conventions for handling missing data,[22,24] time windows for analyzing data (e.g., randomization through common study end date), and

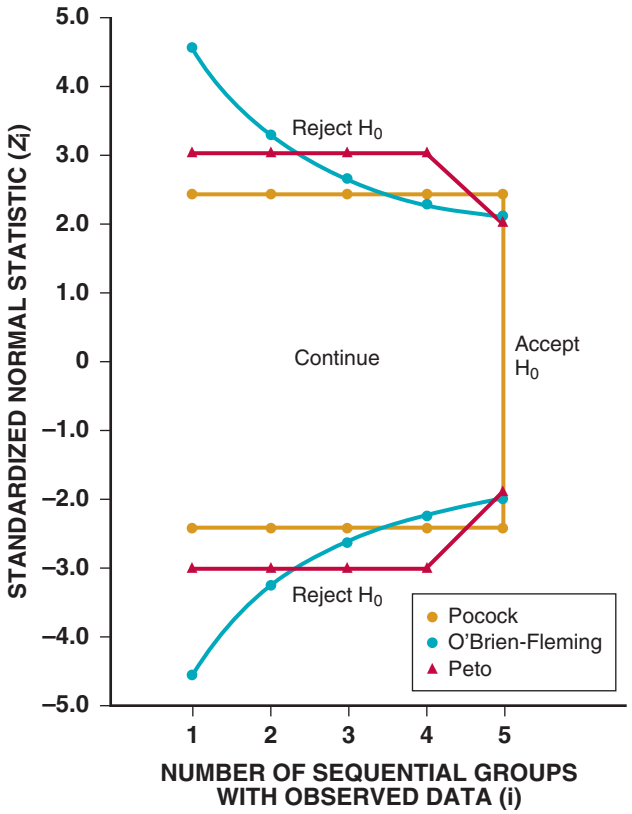

FIGURE 6-5 Sequential stopping boundaries used in monitoring a clinical trial. Shown are three sequential stopping boundaries for the standardized normal statistic (Z_i) for up to five sequential groups (of patients enrolled in the trial by the -*i*th analysis), with a final two-sided significance level of 0.05. *(From Friedman LM, Furberg CD, DeMets DL: Fundamentals of Clinical Trials. 4th ed. New York, Springer Verlag, 1998.)*

TABLE 6-4 Examples of Definitions of Analytic Cohorts in a Clinical Trial

ANALYTIC COHORT	REFERENCE DATE	EXCLUDE IF PROTOCOL VIOLATIONS DISCOVERED	REQUIRE THAT SUBJECT RECEIVED AT LEAST ONE DOSE OF STUDY DRUG	TREATMENT ASSIGNMENT FOR ANALYTIC PURPOSES
Intention to treat	Randomization	No	No	As per randomization
Modified intention to treat	May start at initial dose of study drug	No (may vary)	May introduce this requirement	As per randomization
Per protocol	Initial dose of study drug	Yes	Yes	Usually as per randomization, but sensitivity analyses that account for actual treatment received may be performed
Safety	Usually at time of initial dose of study drug	No	Yes	Usually as per actual treatment received, but sensitivity analyses that use treatment assigned at randomization may be performed

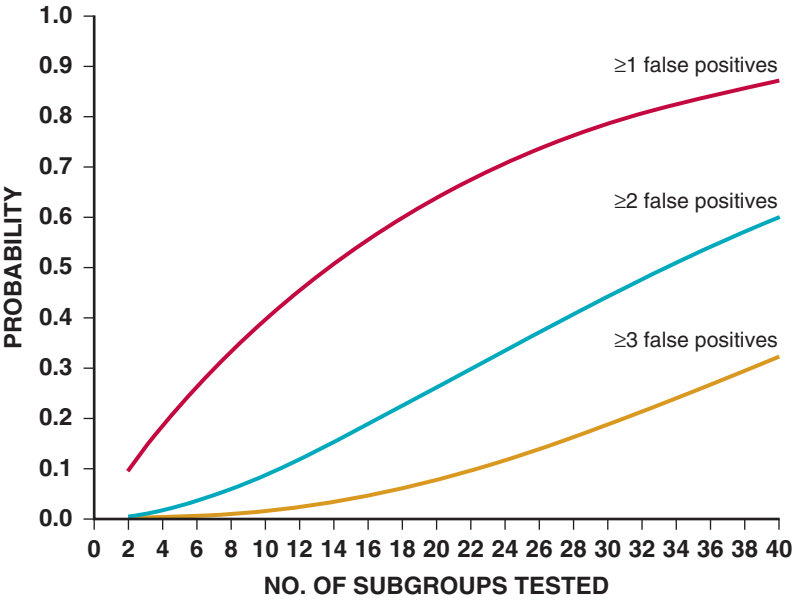

FIGURE 6-6 Probability that multiple subgroup analyses will yield at least one (*red line*), two (*blue line*), or three (*yellow line*) false-positive results. *(From Lagakos SW: The challenge of subgroup analyses—reporting without distorting. N Engl J Med 354:1667, 2006.)*

subgroups of interest (see Fig. e6-3). Depending on the exact definitions used for the analytic cohorts (see Table 6-4), the denominators may vary; this may lead to slight variations in the estimates of event rates and treatment effects. Ideally, the main results of the trial will be similar in the intention to treatment and per protocol cohorts. If they are not, an explanation should be sought from additional analyses of the data.

Missing data present a serious challenge to analysis of trial results. Depending on the mechanism leading to the missing data, the information is considered in one of three categories: (1) missing completely at random, where "missingness" is unrelated to the study (e.g., flood destroys case report forms); (2) missing at random, where the characteristics of the subject can account for differences in the distribution of missing data (e.g., elderly subjects have more missing visits than younger subjects); and (3) missing not at random, where "missingness" depends on the value of the missing observation. The last category is especially problematic because it is likely to be informative and nonignorable—for example, subjects assigned to the test intervention are more likely to have side effects and drop out of the study.[22] Biostatisticians advise against using simple adjustment methods for dealing with missing data (e.g., analyzing only subjects who complete the trial, or a single imputation such as carrying the last observation forward). They recommend, instead, using statistical models based on the data and performing sensitivity analyses to examine the robustness of the trial findings.[22]

Not all patients will respond to a given treatment in a clinical trial to the same extent. The role of pharmacogenomics in determining the response to therapeutic agents is discussed in **Chapter 9**. Because not all patients will respond to a given treatment, it is of clinical interest to inspect the data stratified by subgroups of interest.[25] Although such an approach initially may seem appealing, a number of considerations limit the investigator's ability to draw conclusions from subgroup analyses. Typically, subgroups involve univariate analyses of the data (e.g., men versus women) but the clinical picture is more complex, such that an individual patient will belong to multiple subgroups. Responses in subgroups should be evaluated by an interaction test, which determines whether the relative efficacy of treatments differs among the subgroups being examined. A *quantitative* interaction is said to be present when the treatment effect varies in magnitude but not in direction across subgroups.[25] A *qualitative* interaction is said to be present when the direction of the treatment effect varies among the subgroups.[25] Note that a qualitative interaction also must be a quantitative interaction. Of importance, the multiplicity of subgroup analyses inflates the false-positive rate (**Fig. 6-6**). Rather than relying on a *P* value for a subgroup response, investigators and readers should focus on a graphic display of subgroup data depicting the point estimates and confidence intervals for the treatment effect. Such an approach provides a summary of the range of plausible treatment effects observed in a trial.

MEASURES AND DETECTION OF TREATMENT EFFECT

Events in a clinical trial may be measured on a nominal (dichotomous), categorical, or interval (continuous) scale.[26] Clinical trials reports should use descriptive statistics, graphic displays, and estimates of the precision of the observations appropriate for the scale of measurement being used in the trial.[26] A common assessment in a cardiovascular trial is comparison of the proportions of patients experiencing a dichotomous event (e.g., dead versus alive) during the follow-up period of the trial. When the outcome is an undesirable cardiovascular response and the data are arranged as investigational group compared with control group, a *relative risk* (RR) or *odds ratio* (OR) of less than 1 indicates benefit of the investigational treatment (see Fig. 6-1).

Interpretation of the treatment effect should take into account the absolute risk of the outcomes. The *absolute risk difference* (ARD) is the difference in events in the treatment group and the control group and is particularly useful when expressed as the number of patients that must be treated ($N = 1/\text{ARD}$), or *number needed to treat* (NNT), to observe the beneficial effect in one patient. Similarly, the absolute risk increase (ARI) in adverse events with the investigational treatment can be converted into the *number needed to harm* (NNH). By comparing the NNT and NNH for a given treatment, clinicians can assess the risk-benefit balance and also benchmark the treatment effects of the new therapy against other treatments used in contemporary cardiovascular practice. Another useful metric is to express the outcome for every 1000 patients treated.

The NNT (or NNH) should be interpreted in the context of the time frame of the trial. For example, in patients with an acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), use of prasugrel instead of clopidogrel over 14.5 months is associated with an NNT of 46 (to prevent one event of CV death, MI, or stroke) and NNH of 167 (to cause one excess major bleed) (**see Chapter 55**).[27] Use of rosuvastatin (versus placebo) in apparently healthy persons with a low-density lipoprotein cholesterol less than 130 mg/dL but elevated C-reactive protein level is associated with a 5-year NNT value of 20 (to prevent one event of MI, stroke, revascularization, or death) (**see Chapter 42**).[28] In some therapies, the balance of NNT and NNH is even more complex, because a treatment may have an early hazard (e.g., cardiac surgery versus PCI) but be more effective over time[29]; the balance of NNT and NNH also may vary according to the baseline risk at the time of randomization.[30]

The interplay of variables set by investigators during the design of a clinical trial, the characteristics of the patients studied, and the features of the treatment being investigated influence the relative difference in events in the treatment groups (see Fig. e6-4). The interface of the patient and the treatment may change over the course of exposure to the treatment (e.g., lower risk of events over time as the patient moves from the acute to chronic phases of a disease), and background therapy also may change during the course of the trial (e.g., with treatments added or removed or doses modified). Although these considerations can influence the likelihood of a "positive" trial, they also have an impact on the ability to detect a signal of harm (**Fig. e6-5**).

FUTURE PERSPECTIVES

Trialists, peer reviewers, and journal editors now have checklists and templates that codify the reporting of clinical trials (**Table e6-1**).

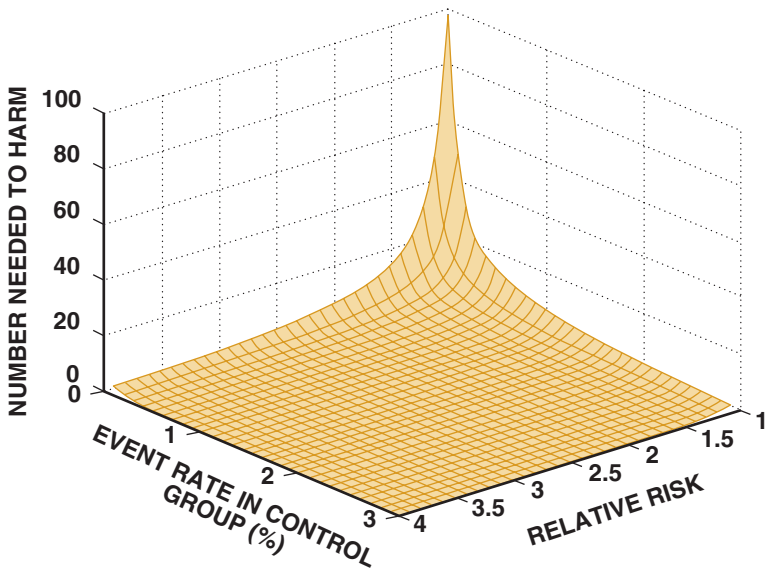

FIGURE e6-5 Number needed to harm. The relationship of the event rate in the control group and the relative risk of cardiovascular events with the treatment being investigated determines the number of patients who need to be treated with the drug to observe one cardiovascular event (number needed to harm). The surface generated can be used to understand the relative ease or difficulty of detecting a signal of harm with a particular treatment (e.g., cyclooxygenase inhibition). *(Reproduced with permission from Antman EM, DeMets D, Loscalzo J: Cyclooxygenase inhibition and cardiovascular risk. Circulation 112:759, 2005.)*

TABLE e6-1 Checklist of Information for Inclusion in Reports of Clinical Trials

Introduction
Clear statement of a priori hypothesis and specific research objective(s)
Methods
Study as designed; include: 1. Planned study population, including controls 2. Inclusion and exclusion criteria 3. Planned subgroup analyses 4. Prognostic factors that may affect study results 5. Outcome measures and minimum difference(s) to be considered clinically important 6. Planned treatment interventions 7. Method of assignment of subjects to treatments (for example, randomization method, stratification blinding or masking procedure, matching criteria) 8. Planned sample size, power calculations 9. Use of data safety and monitoring board and rules for stopping the study 10. Methods of statistical analysis in sufficient detail to permit replication
Results
Study as conducted; include: 1. Inclusive dates of accrual of study population 2. Sample size achieved 3. Report of extent of follow-up 4. How many subjects were excluded or withdrew and the reasons 5. Demographics and clinical characteristics of the study population, including controls 6. How the study as conducted deviated from the study as planned and the reasons (for example, compliance) Study findings; include: 1. Cohorts analyzed (e.g., intention to treat) 2. Estimates of treatment effects, stated as comparisons among treatment groups (for example, differences in risks, rates, or means of outcome measures, as well as exact *P* values, not just $P < 0.05$) 3. Measures of precision for outcome measures and for estimates of treatment effects (e.g., confidence intervals) 4. Summary data and appropriate descriptive statistics 5. Complications of treatment 6. Repository where original data can be obtained
Discussion
Interpretation of study finding Results considered in the context of results in other trials reported in the literature

Modified from Working Group on Recommendations for Reporting of Clinical Trials in Biomedical Literature: Call for comments on a proposal to improve reporting of clinical trials in the biomedical literature. Ann Int Med 121:894, 1994; Stanley K: Evaluation of randomized controlled trials. Circulation 115:1819, 2007.

TABLE 6-5 Questions to Ask When Reading and Interpreting the Results of a Clinical Trial

Are the Results of the Study Valid?
Primary Guides
1. Was the assignment of patients to treatment randomized? 2. Were all patients who entered the trial properly accounted for and attributed at its conclusion? a. Was follow-up complete? b. Were patients analyzed in the groups to which they were randomized?
Secondary Guides
1. Were patients, their clinicians, and study personnel "blind" to treatment? a. Were the groups similar at the start of the trial? b. Aside from the experimental intervention, were the groups treated equally?
What Were the Results?
1. How large was the treatment effect? 2. How precise was the treatment effect?
Will the Results Help Me in Caring for My Patients?
1. Does my patient fulfill the enrollment criteria for the trial? If not, how close is my patient to the enrollment criteria? 2. Does my patient fit the features of a subgroup in the trial report? If so, are the results of the subgroup analysis in the trial valid? 3. Were all the clinically important outcomes considered? 4. Were important concomitant treatments described? 5. Are the likely treatment benefits worth the potential harm and costs?

Modified from material in Guyatt GH, Sackett DL, Cook DJ: The medical literature: Users' guides to the medical literature: II. How to use an article about therapy or prevention: A. Are the results of the study valid? JAMA 270:2598, 1993; Guyatt GH, Sackett DL, Cook DJ: The medical literature: Users' guides to the medical literature: II. How to use an article about therapy or prevention: B. What were the results and will they help me in caring for my patients? JAMA 271:59, 1994; and Stanley K: Evaluation of randomized controlled trials. Circulation 115:1819, 2007.

Clinicians can refer to guides for reading and interpreting clinical trials (**Table 6-5**).[31] These advances, however, deal only with clinical trials that reach the point at which they are reported in a publicly available format. Considerable concern has been expressed in the past that some clinical trials, especially those with negative results, were never reported. The introduction of a requirement to register clinical trials in an online repository (e.g., www.clinicaltrials.gov) was an important step forward, but specific details typically are limited on such postings. Current requirements that clinical trials post a final study report within a reasonable period after study completion (1 year) will assist those investigators planning future trials, clinicians seeking the latest information about treatments, and writing committees charged with creating guidelines documents who need up-to-date and complete data to formulate recommendations. The full impact of this requirement has not yet been realized, however.[32]

Additional directions for RCTs in the future include (1) involving patients in structuring research questions assessing the value of health care options,[33] (2) engaging community representatives in the planning of trials (community-based participatory research),[34] and (3) using a patient's electronic medical record to embed randomization between treatment options.[3,4]

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