Chapter **45**

The Growing Burden of Risk from High Blood Pressure, Cholesterol, and Bodyweight

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High blood pressure, cholesterol, and bodyweight are responsible for a large and increasing proportion of the global burden of disease. Although historically these risks have been regarded as "Western," their impact is now recognized as global: they are already leading causes of disease in middle-income countries and of emerging importance in low-income countries (Ezzati and others 2004; WHO 2002). This chapter presents an evidenced-based review of the impact of high blood pressure, cholesterol, and bodyweight; the cost-effectiveness of relevant interventions; and the economic benefits of interventions. The chapter focuses on personal interventions—that is, those that are mediated largely by interpersonal actions and take place at the individual level. As such, the chapter should be considered as complementary to chapter 44 on lifestyles, which addresses populationwide interventions.

Prevention strategies have been broadly classified as individual based (also known as high risk) or population based (Rose 1985). The former typically involve screening to detect individuals above a certain threshold level of an individual risk factor—for example, people with hypertension—followed by personal interventions for those individuals. In contrast, the population-based approach aims at lowering mean risk-factor levels and shifting the population distribution of exposure in a favorable direction (Rose 1985). One example would be by reducing salt content in manufactured foods, thereby lowering blood pressure levels on a populationwide basis. Such an approach has the potential to produce large and lasting changes in disease incidence but requires substantial sociopolitical investments. Another approach is an evolution of the individual-based strategy in which treatments are targeted to those at high absolute risk of cardiovascular disease (CVD) rather than those with single risk-factor levels above traditional thresholds, such as hypertension or obesity (Jackson and others 1993). Such an approach appears to be highly cost-effective, with the potential to substantially reduce CVD rates when combined with populationwide interventions (Murray and others 2003).

EPIDEMIOLOGY

Elevated blood pressure, cholesterol, and bodyweight are all established risk factors for CVD and, in the case of bodyweight, for other diseases, such as diabetes, certain cancers, and osteoarthritis. The associations between blood pressure (Asia Pacific Cohort Studies Collaboration 1999, 2003a; Prospective Studies Collaboration 2002); cholesterol (Asia Pacific Cohort Studies Collaboration 2003b; Law, Wald, and Thompson 1994; Prospective Studies Collaboration 1995); and body mass index (BMI) (Asia Pacific Cohort Studies Collaboration 2004; Willett and others 1995) and CVD are direct and continuous from relatively low levels, indicating that optimal levels are about 115/75 millimeters of mercury (mmHg), 3.8 millimoles per liter (mmol/l), and 21 kilograms per square meter (kg/m^2), respectively (figure 45.1).

Although some studies suggest *J*- or *U*-shaped associations (Calle and others 1999; Cruickshank 1994; D'Agostino and

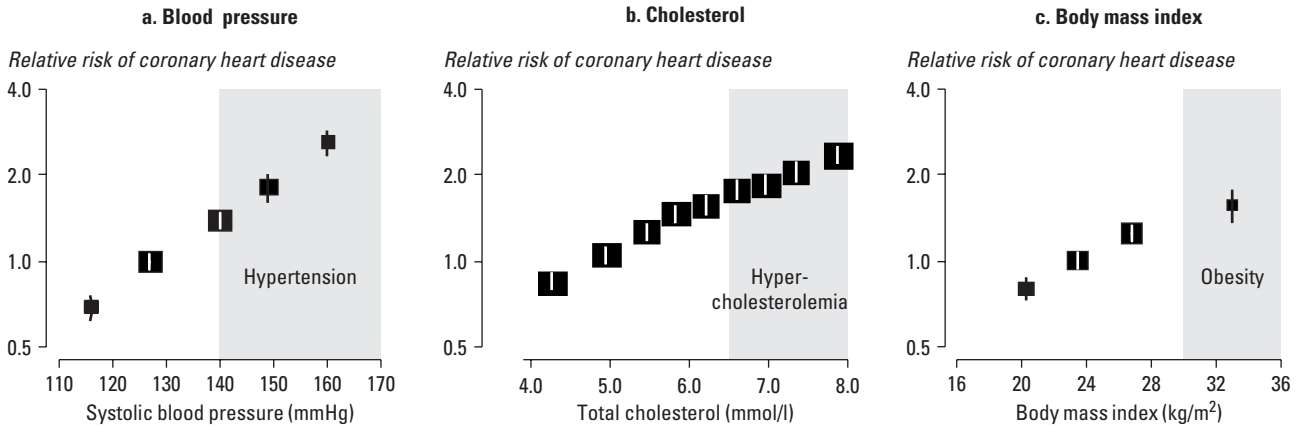


Figure 45.1 Continuous Risks of Blood Pressure, Cholesterol, and Body Mass and Coronary Heart Disease Risk

others 1991; Farnett and others 1991; Field and others 2001; Iso and others 1989; Kannel, D'Agostino, and Silbershatz 1997; Stewart 1979; Troiano and others 1996), low levels of these risk factors are unlikely to cause CVD. Rather, such associations more likely reflect incipient disease, which itself produces both a fall in risk-factor levels and an increase in CVD risk (Alderman 1996; Flack and others 1995; MacMahon and others 1997; Manson, Willett, and Stampfer 1995; Neaton and Wentworth 1992; Sleight 1997a, 1997b; Stevens and others 1998). No trial evidence points to a *J*-curve association for blood pressure, despite including patients with below average blood pressure (Hansson and others 1999; McMurray and McInnes 1992; Pfeffer 1993; Staessen and others 1997).

The continuous associations between blood pressure, cholesterol, and bodyweight and CVD demonstrate the lack of a biological justification for current threshold levels, such as those that define hypertension. Indeed, most of the disease burden resulting from these three risk factors occurs in the large majority of the population with nonoptimal levels but without hypertension, hypercholesterolemia, or obesity. Hence, this chapter avoids those terms and instead uses high blood pressure, high cholesterol, and high bodyweight, defined as nonoptimal levels of these risk factors (that is, over 115/75 mmHg, 3.8 mmol/l, or 21 kg/m^2, respectively).

The strength of the proportional associations of these risk factors with CVD is similar for most population subgroups. Although they attenuate with age, they remain strong and positive in the oldest age groups. Overall, in middle-aged populations, a 10 mmHg lower systolic blood pressure (SBP) is associated with a roughly 30 to 40 percent lower stroke risk and 20 to 25 percent lower ischemic heart disease (IHD) risk, a 1 mmol/l lower cholesterol level is associated with about a 15 to 20 percent lower stroke risk and 20 to 25 percent lower IHD risk, and a 2 kg/m^2 lower BMI is associated with an 8 to 12 percent lower stroke and IHD risk and an approximately 20 to 30 percent lower diabetes risk.

BURDEN OF THE DISEASE, CONDITION, OR RISK FACTOR

Epidemiological data on blood pressure, cholesterol, and bodyweight levels are predominantly available from developed countries; however, evidence indicates that these risk factors are important and increasing in many other countries. Surveys in developing countries suggest increases in these risks occur early in the path to industrialization (Bobak and others 1997; Evans and others 2001; Suh 2001; Wu and others 1996). Good evidence also documents risk-factor levels rising after people migrate to more urbanized settings (Poulter and Sever 1994) in Africa (Poulter 1999; Poulter, Khaw, and Sever 1988), China (He, Klag, and others 1991; He, Tell, and others 1991), and the Pacific islands (Joseph and others 1983; Salmond and others 1985; Salmond, Prior, and Wessen 1989). The World Health Organization's *Global Burden of Disease* study demonstrated that CVD was a leading cause of death in many regions and that most adults in developed and developing countries have nonoptimal blood pressure, cholesterol, and bodyweight levels (Ezzati and others 2004; WHO 2002). Indeed, even using traditional cutoff points, these risk factors are prevalent: of 140 subgroups defined by age, sex, and region, 45 percent had a mean SBP equal to or greater than 140 mmHg, 25 percent had mean cholesterol levels over 5.5mmol/l, and 45 percent had mean BMI levels of at least 25 kg/m^2.

Health Burden

The *Global Burden of Disease* study assessed the burden attributable to nonoptimal levels of these risks (table 45.1) (Ezzati

Table 45.1 Global Burden of Disease Attributable to Nonoptimal Blood Pressure, Cholesterol, and BMI by Region, 2000

Condition	High-mortality developing countries[a]	Low-mortality developing countries[b]	Developed countries[c]	World total
Attributable deaths (thousands)				
Blood pressure	1,969	2,205	2,966	7,140 (12.8%)
Cholesterol	1,405	849	2,161	4,415 (7.9%)
BMI	399	775	1,417	2,591 (4.6%)
Attributable DALYs (thousands)				
Blood pressure	20,630	20,277	23,363	64,270 (4.4%)
Cholesterol	15,602	8,609	16,227	40,438 (2.8%)
BMI	6,408	11,115	15,892	33,415 (2.3%)

Sources: Ezzati and others 2004; WHO 2002b.

Note: The burden of disease estimated to be attributable to nonoptimal blood pressure (mean SBP > 115 mmHg), cholesterol (mean > 3.8 mmol/l), and body mass index (mean > 21 kg/m^2) in 2000. A, B, C and D designations in specific notes below are as follows: A = very low child mortality and very low adult mortality; B = low child mortality and low adult mortality; C = low child mortality and high adult mortality; D = high child mortality and high adult mortality; E = high child mortality and very high adult mortality.

a. The high-mortality developing countries include those in Africa, America D, the Eastern Mediterranean D, and Southeast Asia D.

b. The low-mortality developing countries include those in America B, Eastern Mediterranean B, Southeast Asia B, and the Western Pacific B.

c. The developed countries include those in America A, Europe, and the Western Pacific A.

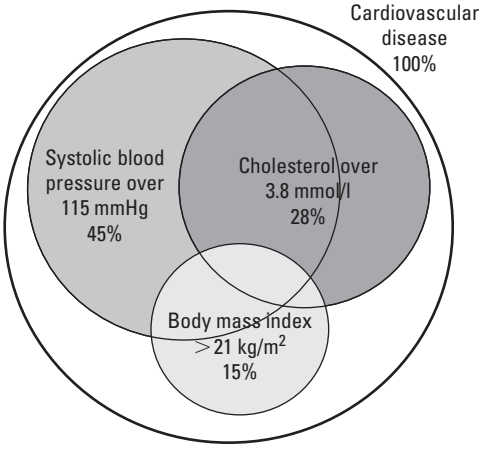
and others 2004; WHO 2002). The burden for blood pressure was related to deaths and disability-adjusted life years (DALYs) from IHD, stroke, hypertensive disease, and other CVD; endpoints for cholesterol included IHD and stroke; and endpoints for BMI were IHD, stroke, hypertensive disease, diabetes, certain cancers, and osteoarthritis. Globally, 7.1 million deaths were attributed to high blood pressure in 2000, 4.4 million to high cholesterol, and 2.6 million to high BMI. This burden was shared approximately equally among the sexes. A large fraction occurred in middle age, especially in developing countries, and this factor, together with the frequently debilitating nature of nonfatal CVD, accounted for a large number of DALYs.

More of the DALY burden was experienced in developing countries than in developed countries, reflecting the large populations in developing countries and their already high risk-factor levels. In all regions, most CVD is attributable to the combined effects of high blood pressure, cholesterol, and bodyweight levels (figure 45.2).

Table 45.2 shows the burden resulting from the overlapping or multicausal etiology of diseases. Analyses of the combined impact of these and other major cardiovascular risks indicate that the joint contribution of established risks is responsible for 83 to 89 percent of the IHD burden and 70 to 76 percent of the stroke burden worldwide (Ezzati and others 2003; Ezzati and others 2004).

Financial Burden

The economic impact of high blood pressure, cholesterol, and bodyweight levels can be estimated indirectly using the foregoing data—namely, that more than two-thirds of the CVD burden can be attributed to those risks. In addition, more than three-quarters of type 2 diabetes is caused by high bodyweight (Ezzati and others 2004; WHO 2002). Hence the economic impact of nonoptimal levels of those risks will be at least two-thirds that due to CVD and diabetes. A recent report highlighted the economic impact of CVD in developing economies, noting that a high proportion of the CVD burden occurs among adults of working age (Leeder and others 2004). In Brazil, China, India, Mexico, and South Africa, conservative



Source: Ezzati and others 2004; WHO 2002.

Note: Individual and joint contributions of high blood pressure, cholesterol, and body weight to global cardiovascular burden are shown, with the size of each circle proportional to the size of burden (as measured in DALYs) (WHO 2002). The percentages indicate the attributable burden for each risk factor, and the overlap shows disease caused by joint or mediated effects.

Figure 45.2 Global CVD Burden Caused by High Blood Pressure, Cholesterol, and Bodyweight

Table 45.2 Individual and Joint Contributions of Seven Selected Risk Factors to the Burden of CVD by Region

Disease	Percentage of the regional disease burden	Population attributable fractions for individual risk factors (percentages)	Overall population attributable fraction (percent)
High-mortality developing countries			
Stroke	1.6	High blood pressure (56), high cholesterol (18), high BMI (7), low fruit and vegetable intake (12), physical inactivity (6), tobacco (7), alcohol (2)	65–71
IHD	3.0	High blood pressure (44), high cholesterol (54), high BMI (11), low fruit and vegetable intake (33), physical inactivity (21), tobacco (8), alcohol (4)	80–87
Low-mortality developing countries			
Stroke	4.7	High blood pressure (58), high cholesterol (13), high BMI (11), low fruit and vegetable intake (10), physical inactivity (5), tobacco (8), alcohol (7)	67–74
IHD	3.2	High blood pressure (45), high cholesterol (48), high BMI (22), low fruit and vegetable intake (31), physical inactivity (22), tobacco (8), alcohol (3)	79–87
Developed countries			
Stroke	6.0	High blood pressure (72), high cholesterol (27), high BMI (23), low fruit and vegetable intake (12), physical inactivity (9), tobacco (22), alcohol (0)	81–86
IHD	9.4	High blood pressure (58), high cholesterol (63), high BMI (33), low fruit and vegetable intake (28), physical inactivity (22), tobacco (22), alcohol (−0.2)	89–93
World			
Stroke	3.1	High blood pressure (62), high cholesterol (18), high BMI (13), low fruit and vegetable intake (11), physical inactivity (7), tobacco (12), alcohol (4)	70–76
IHD	4.0	High blood pressure (49), high cholesterol (56), high BMI (21), low fruit and vegetable intake (31), physical inactivity (22), tobacco (12), alcohol (2)	83–89

Source: Ezzati and others 2003.
Note: See notes to table 45.1 for a breakdown of the regional groupings.

estimates indicated that at least 21 million years of future productive life are lost because of CVD each year. Although no detailed data exist on the direct economic burden of the individual risk factors, the costs of CVD treatment in developing countries are significant. In South Africa, for example, 2 to 3 percent of gross domestic product was devoted to the direct treatment of CVD, or roughly 25 percent of all health care expenditures (Pestana and others 1996). For many middle-income countries, high body mass is already an important cause of health inequities (Monteiro and others 2004).

Current expenditure in developed countries provides an indication of possible future expenditure in developing countries. For example, estimated direct and indirect costs of CVD in the United States were US$350 billion in 2003. In 1998, US$109 billion was spent on hypertension, or about 13 percent of the health care budget (Hodgson and Cai 2001). Studies are limited but suggest that obesity-related diseases are responsible for 2 to 8 percent of all health care expenditures in developed countries. For example, in 1991, 2.5 percent of health care costs in New Zealand were attributable to obesity (Swinburn and others 1997), and in 1996, US$22 billion was attributed to obesity-related CVD in the United States, equivalent to 17 percent of CVD-related health expenditures (G. Wang and others 2002).

INTERVENTIONS

Data on the choice of interventions for blood pressure, cholesterol, and bodyweight and their effectiveness are now presented.

Choice and Classification of Interventions

A variety of population-based and personal interventions could potentially be used to address the risks associated with

high blood pressure, cholesterol, and bodyweight. Of the personal interventions discussed in this section—lifestyle and dietary, pharmacological, and surgical interventions—two main strategies exist for choosing whom to treat: those above certain threshold values of *single* risk-factor levels and those above certain values of absolute cardiovascular (or global) risk, which is determined by the levels of *multiple* factors.

Targeting treatments by levels of a single risk factor (such as hypertension) does not effectively focus on overall risk of developing CVD, which is mainly determined by the net effects of other risk factors. For example, the predicted 10-year CVD risk for someone with an SBP of 140/90 mmHg can vary from 5 to 50 percent depending on the number of concomitant risk factors. The number of people who would need to be treated to prevent an event can therefore vary by an order of magnitude, even if they have the same blood pressure levels. Thus, a treatment strategy based only on individual risk-factor levels is likely to result in high-risk patients being undertreated and many patients at relatively low risk being treated with little absolute benefit, which is unlikely to be the best allocation of scarce health care resources.

The absolute-risk strategy was developed in New Zealand (Jackson and others 1993) and has been adopted extensively elsewhere, for example, by the British Hypertension Society (Ramsay and others 1999) and the Joint Task Force of European and other Societies on Coronary Prevention (Wood and others 1998). The absolute CVD risk is estimated using risk assessments such as the Framingham risk function (Anderson and others 1991) or the Prospective Cardiovascular Munster Study score (Assmann, Cullen, and Schulte 2002) on the basis of the number and severity of CVD risk factors. Targeting treatments at those at high absolute risk rather than those above arbitrary thresholds ensures a favorable ratio of benefits to risks. It can be expected to reduce events in the large proportion of people who are, for example, nonhypertensive but who still have nonoptimal blood pressure (Rose 1981). Combinations of personal interventions targeted at those at high absolute risk also have the potential of being highly cost-effective.

The simplest indicator of high absolute risk is established CVD, principally myocardial infarction, angina, stroke, or transient ischemic attack. For example, without preventive treatment, people who have had a myocardial infarction face an annual risk of death from coronary heart disease of about 5 percent (Law, Watt, and Wald 2002). That risk persists indefinitely—probably for the rest of a person's life—and varies little with age or sex.

However, many individuals with no history of CVD are at similar elevated risk for future CVD as a result of constellations of elevated risks. Thus, the distinction between primary and secondary prevention is somewhat artificial and could lead to undertreatment of many high-risk individuals. While recognizing that the distinction is somewhat arbitrary, this chapter discusses the cost-effectiveness of efforts to manage those without previous CVD, and chapter 33 reviews the management of those with known vascular disease. A unifying system targeting treatments at those at highest risk, either with CVD or multiple risk factors, is likely to be highly cost-effective because more than 75 percent of events occur in the 5 to 10 percent of people with CVD or specific clusters of risk factors (Haq and others 1999; Tosteson and others 1997).

The limitations of the individual-risk-factor approach, together with increasing evidence that the thresholds do not have any biological justification, have motivated the adoption of strategies that take other risk factors into account. Although the most complete way of doing so is using the absolute-risk strategy outlined earlier, one intermediate strategy involves lowering the thresholds of blood pressure or lipid levels at which treatment is initiated if one or more additional CVD risk factors, such as diabetes, are present (Chobanian and others 2003).

Intervention Effectiveness

This section summarizes data on the effectiveness of population-based interventions and personal interventions (lifestyle and dietary interventions and pharmacological and surgical interventions). The studies concerned have mainly been conducted in developed countries.

Population-Based Interventions. Investigators have undertaken a variety of population-based community intervention studies, mostly in developed countries in the 1970s and 1980s (for further details see chapter 44). These studies have tended to be multifactorial projects testing whether comprehensive community programs could produce favorable changes in such risk factors as bodyweight, cholesterol, and blood pressure and in CVD morbidity and mortality (Schooler and others 1997). In general, they included a combination of populationwide and individual interventions, including messages disseminated through local associations, sports clubs, the media, and food associations; healthy food options at restaurants and worksite cafeterias; food labeling at supermarkets; face-to-face communication at meetings and distribution of educational materials; smoking restrictions; and competitions to develop healthy food. Except in Finland, the projects had mixed results, although many demonstrated significant effects with respect to individual components of the interventions. The limitations of many of the projects include inability to detect small but potentially important changes in risk factors, short duration of intervention and follow-up, and issues with outcome measures. Some have also suggested that those trials with less favorable results may have lacked adequate community support and public policy initiatives (Feinleib 1996; Mittelmark and others 1993; Schooler and others 1997; Susser 1995).

A number of population-based interventions have also taken place in developing countries, including the following:

- In China, the Tianjin Project showed a significant reduction in sodium intake in men after three years of intervention, and after five years, the prevalence rates of both hypertension and obesity decreased among 45- to 65-year-olds (Schooler and others 1997).
- In Chile, the Mirame Project was a three-year intervention program designed to provide and evaluate strategies to promote healthy lifestyles among schoolchildren and their families. Nissinen, Berrios, and Puska (2001) report a significant positive effect on some risk factors for the intervention schools.
- In Mauritius, government-led initiatives resulted in a change in the composition of cooking oil from mostly palm oil, which is high in saturated fatty acids, to wholly soybean oil, which is high in unsaturated fatty acids. From 1987 to 1992, total cholesterol concentrations fell significantly, and the estimated intake of saturated fatty acids decreased, with much of this finding reportedly resulting from the change in cooking oil (Uusitalo and others 1996).

An effective populationwide intervention draws together different kinds of feasible activities that combined produce a synergistic effect (Nissinen, Berrios, and Puska 2001; Puska 1999). Even though the projects and trials were undertaken in a range of different communities and used a variety of methods and interventions, several common themes emerge. Some of the important elements of a successful program that enables individuals to adopt healthier lifestyles include the following:

- clear responsibility for coordinating prevention efforts, with credible agencies with good communication methods carrying out long-term education programs
- intersectoral collaboration, with multiple messages sourced from different organizations, including health sector entities, nonhealth government agencies, schools, workplaces, religious organizations, and voluntary agencies
- collaboration with the food industry to ensure the availability of reasonably priced healthier food options, with food labeling that presents relevant information in a clear, reliable, and standardized format
- realistic multiyear time frames.

Lifestyle and Dietary Personal Interventions. Many guidelines have concluded that lifestyle modifications, such as weight loss, healthy diet (such as one rich in potassium and low in sodium), physical activity, and moderate alcohol consumption are effective in reducing blood pressure (see, for example, Chobanian and others 2003). Trials indicate that a reduction of salt intake lowers blood pressure, with larger blood pressure reductions in the elderly and in those with higher initial blood pressure levels (Law, Frost, and Wald 1991; Whelton and others 1998). An increase in daily fruit and vegetable intake may also lower blood pressure, and when combined with an increase in low-fat dairy products and a reduction in saturated and total fat, may lower blood pressure even more (Appel and others 1997). Weight reduction lowers blood pressure in proportion to the amount of weight lost (Whelton and others 1998), and physical activity appears to lower blood pressure in a way that may be independent of weight loss. High levels of alcohol intake are associated with blood pressure elevation, which is reversible by reducing intake (Kaplan 1995).

Dietary approaches to lowering total cholesterol and low-density lipoprotein (LDL) cholesterol typically involve reduced intake of dietary fats, particularly saturated fats. Evidence suggests a dose-response relationship between saturated fatty acid intake and LDL cholesterol levels (NCEP Expert Panel 2002). Plant sterols and stanols have recently been incorporated into foods such as margarine and can reduce LDL cholesterol by about 10 percent; however, this approach is currently relatively expensive (Law 2000). Dietary advice may also suggest increasing the intake of viscous fiber—for instance, in the form of cereal grains, fruits, and vegetables—because these dietary sources may enhance the lowering of LDL cholesterol. Maintaining bodyweight in the desirable range and engaging in moderate physical activity complement these dietary strategies (NCEP Expert Panel 2002).

Increases in obesity have been related to declines in energy expenditure (for example, reductions in physical activity and adoption of a more sedentary lifestyle) and a higher intake of energy-dense but micronutrient-poor foods, such as most processed foods (WHO 2003b). A variety of trials have recorded beneficial health effects, with weight reduction achieved by a combination of interventions (NHLBI Obesity Education Initiative Expert Panel 1998). These interventions include dietary counseling and therapy that involves a decrease in daily caloric intake and a reduction in saturated fats and total fats. An increase in physical activity is an important component of weight-loss therapy. Behavioral strategies revolving around self-monitoring of eating habits, stress management, problem solving, and social support may also complement these approaches. Overall, however, the effects of lifestyle modifications to reduce weight and maintain the weight loss are relatively poor, with many reports finding that weight returns to baseline levels after several years.

Pharmacological and Surgical Personal Interventions. Randomized trials have shown that medications to lower blood pressure effectively reduce the risk of stroke, IHD, and heart failure. Results from meta-analyses of more than 40 different trials

published in 2003 included about 210,000 participants and more than 8,000 stroke and 11,000 IHD events (Blood Pressure Lowering Treatment Trialists' Collaboration 2003; Fox and EUROPA Investigators 2003; Law, Wald, and Rudnicka 2003; Lawes and others 2004; Pepine and others 2003). The trials may be broadly classified into three groups: (a) drug versus placebo trials, (b) more intensive regimens to lower blood pressure versus less intensive regimens, and (c) drug versus drug trials.

The drug versus placebo trials achieved the greatest reductions in blood pressure, and a dose-response relationship was apparent between blood pressure reduction and reduced risk of stroke. Overall, the trials indicated that a 10 mmHg reduction in SBP would result in a 32 percent reduction in stroke risk and a 14 percent relative reduction in IHD risk. This finding is consistent with the size of associations observed in cohort studies.

Clear evidence indicates that all the major drug classes have similar effects on the risk of stroke and coronary heart disease per mmHg reduction in blood pressure (Blood Pressure Lowering Treatment Trialists' Collaboration 2003; Lawes and others 2004). The only clear evidence of clinically important, class-specific effects are with agents that block the renin-angiotensin system, which reduce diabetes incidence by about one-quarter, and with calcium channel blockers, which reduce heart failure less than other agents (although this result may be partly caused by misclassification, because a known side effect of calcium channel blockers is ankle edema, which is a diagnostic component of heart failure). Because all agents lower blood pressure by about the same modest amount and because their effects on blood pressure are additive (Law and others 2003), the key issue seems to be which combinations of two or more drugs should be provided and how long-term adherence can be maximized.

Over the past three decades, numerous trials have assessed the effect of different cholesterol-lowering interventions (Law, Wald, and Rudnicka 2003; Law, Wald, and Thompson 1994). The placebo-controlled trials can be broadly classified into those testing fibrates, statins, and other interventions (mostly dietary interventions, but also some other interventions such as resins and niacin). The statins are the most effective in lowering total and LDL cholesterol, with reductions of more than 1 mmol/l in most trials. A good correlation has been found between reduction in total cholesterol and relative risk reduction. This finding suggests, as for trials investigating blood pressure lowering, that even though some drugs are more effective in achieving greater reductions in risk factors, their effect on disease outcomes is similar per unit reduction of cholesterol. Overall, a 1 mmol/l reduction in total cholesterol is associated with a 21 percent relative risk reduction in IHD and a 17 percent reduction in risk of stroke. Again, this finding is consistent with the epidemiology, with the proviso that the vast majority of strokes in clinical trials were ischemic.

In clinical trials of statins, the relative risk reduction in cardiovascular events is similar at all levels of baseline cholesterol, extending to levels below 5 mmol/l total cholesterol, and is also consistent among patients who are and are not taking concurrent blood pressure lowering and other medications (Heart Protection Study Collaborative Group 2002). Similar findings are observed with treatments to lower blood pressure (Progress Collaborative Group 2001), indicating that these treatment effects are independent. This finding is plausible, because they act through different mechanisms and because observational studies do not suggest a large interaction (Neaton and Wentworth 1992).

The benefits of lowering blood pressure and cholesterol are achieved surprisingly rapidly: for most outcomes, risk appears to be fully reversed within 6 to 18 months of beginning treatment. For example, individuals with cholesterol lowered in the past two or more years are at approximately the same coronary heart disease risk as otherwise identical individuals whose cholesterol has been at that level for decades (Law, Wald, and Thompson 1994).

Pharmacological agents for weight loss that have been subject to randomized controlled trials include dexfenfluramine, sibutramine, orlistat, and phentermine/fenfluramine (although the last has been withdrawn because of a reported association between the drugs and valvular heart disease). Overall, trials suggest only modest weight-loss effects, with an average net weight loss of 1.5 kg after eight weeks and 2 to 3 kg after one year (NHLBI Obesity Education Initiative Expert Panel 1998). A systematic review of orlistat trials indicated a pooled net weight loss of 1.2 kg at 12 weeks, 2.9 to 3.4 kg at one year, and 2.5 to 2.4 kg at two years (O'Meara and others 2001). Results of a systematic review of trials assessing sibutramine were similar (O'Meara and others 2002), with fewer data available on long-term sustained weight loss.

Investigators have also undertaken several randomized controlled trials to assess the effects of different surgical interventions, generally in individuals with a BMI equal to or greater than 35 or 40 kg/m^2. Weight loss resulting from gastric bypass varied from 50 to 100 kg six months to a year following surgery (NHLBI Obesity Education Initiative Expert Panel 1998). Overall, several trials suggest that surgery resulted in about 23 to 37 kg more weight loss than conventional treatment and that this loss was maintained for eight years (Clegg and others 2002). Furthermore, gastric bypass surgery appears to be more beneficial than gastroplasty or jejunoileal bypass.

In relation to compliance and adherence with pharmacological therapy, population surveys have demonstrated that, even in industrial countries, high blood pressure is either untreated or inadequately controlled in about 70 to 75 percent of patients and that adherence to medications among patients suffering from chronic disease is only about 50 percent (WHO 2003a). The extent of poor adherence is likely to be even greater in

developing countries given the relative lack of health services and inequities in access. Pharmacotherapy faces a variety of potential barriers, including the symptomless nature of the conditions, a lack of knowledge or denial of risk, the complicated nature of drug regimens, the risk of side effects (real and perceived), and the costs of treatment.

Health providers may use multiple strategies to increase compliance and adherence. Patient-centered interventions include involving individuals in the decision-making process; providing individualized patient education and disease counseling and adapting treatment to patients' lifestyles; simplifying dosing schedules; providing drug information leaflets, medication charts, and special reminder packaging for medications; holding group sessions for education and family-oriented disease management therapies; and implementing automated telephone assessment and self-care education calls with nurse follow-up (Haynes and others 2003).

Strategies may also aim to increase physician adherence, and interventions may include the use of guidelines, peer review and audit, and prompts to remind physicians to review risks and medications (Ebrahim 1998; NCEP Expert Panel 2002). These strategies obviously do not address issues pertaining to resources and access in poor countries.

Several trials and overviews have attempted to assess the value of different interventions to improve compliance and adherence; however, issues have arisen in connection with the generalizability of the interventions, the low statistical power in many trials, the lack of description of all parts of interventions, and the assessment of complex interventions without assessment of the separate effects of the intervention components. Haynes and others' (2003) systematic review concludes that, overall, no single approach to improving adherence can be recommended. Simpler treatment regimens can sometimes improve adherence and treatment outcomes for both short- and long-term treatments. Several complex strategies, including combinations of more thorough patient instructions and counseling, easier access to care, reminders, close follow-up, supervised self-monitoring, family therapy, and rewards for success can improve adherence and treatment outcomes in some patients. However, even the most effective interventions did not lead to large improvements in adherence or treatment outcomes and were relatively resource intensive. By contrast, Connor, Rafter, and Rodgers's (2004) systematic review indicates improved adherence and clinical outcomes with fixed-dose combination treatment or unit-of-use packaging.

Few good, evidence-based strategies to improve obesity management are currently available, although reminder systems, brief training interventions, shared care, inpatient care, and dietitian-led treatments may all be worth further investigation (Harvey and others 2003). Thus, a clear need for innovations still exists to help people follow medication prescriptions as well as dietary and lifestyle advice.

COST-EFFECTIVENESS OF INTERVENTIONS

Costs include expenditures required to identify and treat risk factors as well as expenditures for treating CVD when it is not prevented. Where possible, this chapter deals with the separate sources of costs for several reasons. First, the costs for identifying those requiring treatment vary significantly by level of economic development and by urban versus rural location. In many situations in developing countries, such costs will make most or all forms of screening beyond a determination of CVD history unaffordable. Second, in some countries, such as India, that are large producers of generic drugs, prices are reported to be lower than in most other drug-producing or -importing countries. Third, this approach allows researchers and policy makers to understand the constituent costs so that they can examine where cost reductions may be most beneficial. Fourth, it clarifies what expenditures may be required as a result of changes in decisions about the treatment of risk factors. Finally, many people in developing countries do not have access to hospitals for acute management of CVD events. Nonetheless, increased expenditure on treating risk factors may lead to significant reductions in the costs of treating subsequent CVD events for many countries. Ultimately, the net effect is reflected in cost-effectiveness analyses. Unless otherwise stated, costs are in 2001 U.S. dollars.

The costs of personal interventions include the costs of patient screening (identifying high-risk patients), drugs and their acquisition, clinic visits, health care workers' time, laboratory tests, and travel. Annual drug costs for medications to lower blood pressure and cholesterol vary widely by country and depend on whether generics are available and used. For example, according to the *International Drug Price Indicator Guide* (Management Sciences for Health 2004), annual costs in 2002 of generic 40 mg lovastatin ranged from US$14 in Barbados to US$217 in Costa Rica, and on-patent statins can cost almost a US$1,000 a year in the United States. Because drug costs vary by up to two orders of magnitude across countries, results of cost-effectiveness analyses are particularly sensitive to their input prices. Table 45.3 presents some sample prices. The costs of these medications have dropped considerably in recent years, and now the annual costs for hydrochlorothiazide (25 mg), atenolol (50 mg), and captopril (50 mg), are US$2, US$4, and US$9, respectively (Management Sciences for Health 2004). Statins will become increasingly affordable as simvastatin joins lovastatin in coming off patent (2006 in the United States and already off patent in Germany and the United Kingdom).

The estimated number of visits to manage high blood pressure and cholesterol, under traditional paradigms, ranges from two to six per year at costs ranging from US$3 to US$20 per visit across the six regions assessed, but note that generally many fewer tests and less follow-up is required with a strategy

Table 45.3 Annual Costs of Selected Cardiovascular Medications

Medication	United States (2002 US$)[a]	Average international price (2002 US$)	Projected polypill[b]
Beta-blocker	32–365	3–15	n.a.
Diuretic	6–37	1–3	n.a.
Statin	180–864	11–147	n.a.
Aspirin	2	1–6	n.a.
Angiotensin-converting enzyme inhibitor	65–365	1–19	n.a.
Total	285–1,633	17–190	20–40

Sources: U.S. prices: Murray 2004; international prices: Management Sciences for Health 2004.
n.a. = not applicable.
a. Based on average wholesale prices.
b. Based on a moderate increase from the sum of the lowest-cost generic components.

based on absolute risk. Diagnostic testing for cholesterol in the United States using a general laboratory is reimbursed at US$6 for total cholesterol, US$16 for a complete lipoprotein cholesterol fractionation analysis, and US$6 for triglycerides (Xact Medicare Services 2003). Point-of-care one-step enzymatic strips that require only a few drops of blood from a finger stick and that can process total cholesterol in minutes cost less than US$3 per test (Greenland and others 1987). A basic metabolic panel for those on diuretics or for measuring renal function is US$12. The costs attributed to patient time and travel for visits have not been estimated for many countries, but they were recently estimated at US$12 to US$26 per visit in the United States, depending on age and sex (Prosser and others 2000).

A review of studies to date highlights several issues regarding cost-effectiveness analyses, including the significant variations in terms of calculations of cost per life year saved. The two most important aspects of the cost-effectiveness of any primary intervention are the future risk for CVD of the population treated and the costs of the medications.

Population-Based Interventions

Given the strong association between CVD and high blood pressure, cholesterol, and body mass, most guidelines for those risk factors begin by recommending lifestyle modifications. Although these benefits can lead to changes in risk factors, their effect on CVD events is not well documented. However, on the basis of assumptions about cholesterol and blood pressure reduction from population-based lifestyle education programs and given the relatively low cost of the interventions—US$5 to US$17 per person per year (Tosteson and others 1997)—the cost-effectiveness of such programs may be reasonable. However, the cost-effectiveness ratios of these interventions were sensitive to the cost of the intervention as well as to the expected reduction in the risk factor. For example, a community intervention that expects a 4 percent reduction in total serum cholesterol and costs US$5 per person annually targeted would save more than US$2 billion over 25 years of the program. When the North Karelia (Puska 1999) estimates were used in a cost-effectiveness analysis in the United States (Tosteson and others 1997), the cost-effectiveness ratios ranged from being cost saving to US$88,000 (in 1985 U.S. dollars) per life year saved, depending on the percentage reduction in cholesterol (1 to 4 percent).

Personal Interventions to Lower Blood Pressure or Cholesterol in Developed Countries

A common finding of cost-effectiveness analyses of primary prevention of CVD by means of lowering blood pressure and cholesterol is the wide variability in cost-effectiveness ratios, depending on underlying risk, age, and costs of medications. For personal interventions using drug treatment for lowering blood pressure and cholesterol levels, no single cost-effectiveness analysis adequately summarizes experience in the developed countries. Collectively, the studies evaluating hypertension treatment in Australia, New Zealand, the United States, and the Scandinavian countries suggest a range of cost-effectiveness ratios from US$4,600 to more than US$100,000 per life year gained when applied to the entire adult population without further risk stratification (Kupersmith and others 1995). Compared with the entire population, for those at high risk with diastolic blood pressures over 105 mmHg and older than 45, hypertension treatment can cost as little as a few hundred dollars per life year gained or can even be cost saving (Johannesson and others 1991).

Investigators have reported that primary prevention with cholesterol-reducing medications is less attractive overall than other interventions, such as hypertension treatment, from a cost-effectiveness perspective, although once again this finding is likely to differ considerably now that statins are off patent.

Reported cost-effectiveness ratios have ranged from US$10,000 to US$2 million per life year gained (Hay, Yu, and Ashraf 1999), whereas dietary interventions for cholesterol reduction are more favorable, with ratios of around US$2, 000 per quality-adjusted life year (QALY) (Prosser and others 2000). For cholesterol treatment, Prosser and others (2000) find cost-effectiveness ratios of US$50,000 per QALY for on-patent statins among those at highest risk (high cholesterol levels and multiple risk factors) and up to US$1.4 million per QALY among low-risk females when compared with dietary strategy alone. The cost per life year gained in the primary prevention trial of the West of Scotland Coronary Prevention Study among high-risk individuals treated with pravastatin was about US$30,000 (Caro and others 1997). Using the same criteria, Downs and others (1998) find that the cost per life year saved in the Air Force/Texas Coronary Atherosclerosis Prevention Study cohort with average cholesterol levels was more than US$100,000. In general, younger and older age groups tend to have the least favorable cost-effectiveness ratios. For younger groups, this finding probably reflects their overall lower risk and the many years of treatment required before realizing a benefit. For the elderly, high cost-effectiveness ratios may reflect other competing causes of death and the delay of up two years between treatment and benefit seen in most primary prevention trials.

Personal Interventions to Lower Blood Pressure or Cholesterol in Developing Countries

No trials of blood pressure, cholesterol, or body mass lowering have been conducted solely in developing countries. As a result, we have derived assessments of cost-effectiveness by extrapolating from results in developed countries presented earlier. Goldman and others (1991) report that a decline in the cost of lovastatin by 40 percent, once generic, would result in a roughly 30 percent reduction in the cost-effectiveness ratio. However, this finding does not take into account that both the underlying epidemiology and the costs can be quite different across and within countries and regions.

Murray and others (2003) compare 17 nonpersonal and personal health service interventions or combinations of interventions in the 14 epidemiological subregions defined by the World Health Organization (WHO) as part of its Choosing Interventions That Are Cost-Effective (WHO-CHOICE) initiative. The nonpersonal interventions included health education through the mass media and legislative efforts to reduce salt intake, improve blood pressure generally, and reduce cholesterol and obesity levels. The personal interventions included treatment with statins of those above two different cholesterol-level thresholds (greater than 6.2 mmol/l or greater than 5.7 mmol/l), treatment with beta-blockers and diuretics of those above two different hypertension thresholds (greater than 160 mmHg or greater than 140 mmHg), and treatment of individuals with both hypertension and increased cholesterol with all three medications. Finally, the effects of combination treatment with a beta-blocker, diuretic, statin, and aspirin were modeled for four groups defined on the basis of absolute risk (10-year probability of a cardiovascular event of 5, 15, 25, or 35 percent).

Intervention effects were based on systematic reviews of randomized trials or meta-analyses. Population health effects caused by the interventions were based on stochastically simulating populations on the basis of age, sex, and risk factor distribution of smoking, hypertension, cholesterol, BMI, and smoking in the 14 subregions, both with and without the various treatments to determine the effect. The effects of the intervention were then translated into DALYs using a standard multistate modeling tool. Costs include both program-level costs (media, training, and administration) and patient-level costs (medicines, health care visits, diagnostic tests). All costs were based on a standard ingredients approach and on regional estimations. The costs of CVD events were not included.

The results are summarized in table 45.4. The incremental cost-effectiveness ratios for the strategy assessing absolute risk and using the triple combination of beta-blocker, statin, and aspirin with or without the addition of health education and salt legislation ranged from US$138 per DALY saved (absolute risk greater than 35 percent) in the Africa E region to US$4,319 per DALY saved (absolute risk greater than 5 percent) in the Latin America and the Caribbean B region. These estimates are in international or purchasing-power parity dollars (see chapter 15 for an explanation). Table 45.4 also shows the approximate equivalent costs in U.S. dollars and explains the conversion from the WHO-CHOICE estimates. The nonpersonal interventions, including efforts to reduce salt intake in processed foods, were less costly than the personal interventions. Personal interventions based on treatment guidelines were cost-effective; however, when the strategies for treating high cholesterol or hypertension were compared with the absolute-risk approach, they were not favorable and were dominated by the latter, meaning that the absolute-risk approach of treating those with a greater than 35 percent risk averted more DALYs and cost less than either the blood pressure or cholesterol strategies. For an example of a country-specific analysis, see box 45.1.

Several recent publications have suggested that combination treatments of medications to lower blood pressure, statin, aspirin, and perhaps other agents such as folate could more than halve cardiovascular risk (Wald and Law 2003; WHO 2002; Yusuf 2002). This suggestion is especially relevant for developing countries, given that suitable components are all now off patent. Good evidence indicates that single-pill combinations increase adherence to drug regimens (Connor, Rafter, and Rodgers 2004) and reduce supply and transport costs. We used a Markov model to evaluate the cost-effectiveness of such a hypothetical pill or combination packaging of the individual medications. We modeled the effect of a pill that included half

Table 45.4 Comparison of the Cost-Effectiveness of Absolute Risk with Treatment According to Either Blood Pressure or Lipid Targets Alone in Addition to Population-Based Strategies, Selected WHO Regions

Region	Strategy	Risk (percent)	Incremental cost-effectiveness ratio (cost/DALY saved)[a]	
			International $	US$
Africa E	Prevention (SL and/or HE)		Dominated[b]	
	Targeted risk factors[c]		Dominated[b]	
	Absolute risk[c] (TRI)	35	138	42
		25	778	295
		15	1,445	639
Latin America and the Caribbean B	Prevention (SL)		127	65
	Prevention (SL + HE)		145	74
	Targeted risk factors[c]		Dominated[b]	
	Absolute risk[d] (TRI + SL + HE)	35	286	178
		25	1,598	1,058
		15	2,391	1,664
		5	4,319	3,075
Southeast Asia B	Prevention (SL)		70	18
	Prevention (SL + HE)		127	32
	Targeted risk factors[c]		Dominated[b]	
	Absolute risk[d] (TRI + SL + HE)	35	301	133
		25	1,197	578
		15	2,094	1,120
		5	3,952	2,233
Western Pacific B	Prevention (SL)		97	18
	Targeted risk factors[c]		Dominated[b]	
	Absolute risk[d] (TRI + SL + HE)	35	1,124	423
		25	1,278	564
		15	2,092	1,042
		5	4,028	2,135

Source: Murray and others 2003.

B = low child mortality and low adult mortality; E = high child mortality and very high adult mortality; HE = health education through the mass media to reduce cholesterol; SL = legislation to decrease the salt content of processed foods, including appropriate labeling and enforcement; TRI = treatment with aspirin, beta-blockers, and a statin.

a. Costs of prevention and nondrug costs for treatment according to absolute risk are converted at an estimated regional average ratio of exchange rate to purchasing-power parity rate; drug costs are not converted, assuming drugs to be imported at world prices. The share of drug costs in total treatment cost, as a function of risk, is taken from the estimates for India in table 45.6 and assumed to be the same for all regions.

b. Dominated strategies were both less effective and more costly than comparator strategies.

c. Treating SBP greater than 140 mmHg or 160 mmHg or total cholesterol greater than 5.7 mmol/l or 6.2 mmol/l (220 or 240 mg/dlL).

d. Risk refers to 10-year risk of CVD greater than or equal to the number listed.

of the standard doses of hydrochlorothiazide, atenolol, lisinopril, lovastatin, and aspirin on overall morbidity and mortality in treating those without prior CVD. We did not include folate because no randomized trials had shown that it reduced CVD events at the time of the analysis. The assumptions of the relative risk reductions were based on those of Wald and Law (2003). The strategies compared were for treating various high-risk populations (absolute risk for CVD greater than 15, 25, and 35 percent over 10 years. We applied the model to a population of 1 million adults over the age of 35, with the costs and benefits seen from a societal perspective and with the intervention run for 10 years. We calculated estimates for one representative country from each region where demographic and risk factor data existed. Unlike the WHO-CHOICE analysis, this analysis separated use of the intervention according to those with and without established CVD. Table 45.5 presents the results.

Table 45.6 shows the breakdown of events averted and costs for India. Even though the absolute numbers differ for other countries, the relative differences between the different groups receiving the "polypill" compared with the groups not receiving

Box 45.1

Example of Country-Specific Analysis: South Africa

In another analysis, researchers (Gaziano 2001) compared the approach based on absolute risk with blood pressure guidelines in South Africa. The analysis used country-specific epidemiology and, where available, applied local cost data. The study compared six strategies for initiating drug treatment—two different blood pressure levels (160/95 mmHg and 140/90 mmHg) and four different levels of absolute CVD risk over 10 years (40, 30, 20, and 15 percent)—to a strategy of no treatment. The methodology differed from the WHO-CHOICE study because of the availability of local data. Data on diabetes prevalence were included to further refine risk estimates. Also the actual mix of medications was used to assess costs with actual current drug-use patterns, which included the use of some nongeneric medications.

The table displays the results. The four absolute-risk strategies had the four lowest incremental cost-effectiveness ratios. The strategy of initiating antihypertensive therapy for those individuals with a predicted 10-year CVD risk greater than 40 percent had an incremental cost-effectiveness ratio of US$700 per QALY gained compared with no treatment. The absolute risk of CVD greater than 30, 20, and 15 percent had larger and increasing cost-effectiveness ratios. Treatments based on the 1995 South African guidelines and the Joint National Commission VI guidelines were both more costly and resulted in fewer QALY gains than the 15 percent absolute-risk strategy and were therefore dominated by the less costly absolute-risk treatment strategies.

Furthermore, the results showed that the cost-effectiveness ratios were quite sensitive to the costs of treatment for hypertension, especially medication costs. Further analysis revealed a threshold point for an annual treatment cost of US$53. Below this threshold, the 40 percent absolute-risk strategy cost less and increased the number of life years gained compared with the no primary prevention strategy and is therefore cost saving. In South Africa, annual treatment with diuretics and beta-blockers could be provided for less than US$40.

Incremental Cost-Effectiveness Ratios for Selected Hypertension Management Strategies over 10 Years, South Africa

	Incremental cost-effectiveness ratio[a]	
Treatment	**US$/QALY**	**US$/life year saved[b]**
No treatment	n.a.	n.a.
Absolute risk of CVD > 40 percent	700	900
Absolute risk of CVD > 30 percent	1,600	2,100
Absolute risk of CVD > 20 percent	4,900	6,700
Absolute risk of CVD > 15 percent	11,000	18,000
Target level 160/95 mmHg (1995 South African guidelines)[c]	Dominated[d]	Dominated[d]
Target level 140/90 mmHg (Joint National Commission VI guidelines)	Dominated[d]	Dominated[d]

Source: Gaziano and others 2005.
n.a. = not applicable.
a. Each strategy's costs and effects are compared with those of the preceding less costly strategy.
b. Total and incremental life years not shown.
c. Compared with an absolute risk of CVD greater than 15 percent because the 1995 South African guidelines are dominated by the former.
d. A dominated strategy is one that is both more expensive and less effective than the preceding strategy to which it is compared.

Table 45.5 Incremental Cost-Effectiveness Ratios of a Multidrug Regimen by World Bank Region Compared with a Baseline of No Drug Treatment *(2001 US$/DALY)*

Region	35 percent risk	25 percent risk	15 percent risk	5 percent risk
East Asia and the Pacific	830	1,440	2,320	3,820
Europe and Central Asia	940	1,450	1,960	3,620
Latin America and the Caribbean	920	1,470	2,420	3,740
Middle East and North Africa	720	1,290	2,190	4,030
South Asia	670	1,250	1,932	3,020
Sub-Saharan Africa	610	1,170	1,920	2,960

Source: Authors' calculations.
Note: The regimen includes aspirin, a beta-blocker, a thiazide diuretic, an angiotensin-converting enzyme inhibitor, and a statin. The risk refers to a 10-year risk of CVD.

Table 45.6 Polypill Cost-Effectiveness Estimates for a Population of 1 Million Adults at Varying Levels of Risk for CVD Treated for 10 Years in India

Costs and effects	Comparison with no polypill	Absolute risk of a CVD event over 10 years			
		> 35 percent	> 25 percent	> 15 percent	> 5 percent
Total cost (2001 US$ millions)	23.5	34.5	51.4	92.2	205.2
Profile of total costs					
Percentage attributable to inpatient stay	12.0	6.0	3.0	1.0	0.3
Percentage attributable to ambulatory care	0	29.0	40.0	49.0	54.0
Percentage attributable to labor	75.0	36.0	21.0	9.0	2.0
Percentage attributable to pharmaceuticals	0	23.0	31.0	38.0	42.0
Percentage attributable to laboratory expenses	12.0	6.0	3.0	1.0	0.0
Effects[a]					
Number of myocardial infarction cases averted	n.a.	10,200	14,400	21,300	31,800
Number of stroke cases averted	n.a.	5,200	7,000	12,400	19,600
Number of coronary heart disease deaths averted	n.a.	10,500	13,500	19,600	25,900
Number of stroke deaths averted	n.a.	5,900	7,500	10,500	14,200
Number of life years saved	n.a.	39,000	51,000	67,000	98,000
Number of DALYs gained	n.a.	41,000	57,000	86,000	134,000
Incremental cost-effectiveness (US$/DALY)	n.a.	300	990	1,500	2,430

Source: Authors' calculations.
n.a. = not applicable.
a. Each strategy compared with no polypill.

it are similar for all countries. Although the total costs for treating lower-risk patients increase, so do the benefits, and the overall incremental cost-effectiveness ratio remains relatively favorable. The proportion of costs shifts away from those attributable to hospital care when no primary prevention is initiated to costs attributable to ambulatory care and pharmaceuticals when more lower-risk patients are treated.

Interventions to Reduce Bodyweight

No large-scale randomized trials of weight reduction as an isolated intervention are available on which to base estimates of the benefits of weight loss in lowering the risk of coronary heart disease. Thus, costs per life year saved would have to be modeled to project benefits. In one such analysis, a school-based educational program to reduce obesity among middle school students reported a cost of US$4,300 per QALY (L. Wang and others 2003). However, this analysis assumed that the weight loss would be maintained throughout adulthood, but the high relapse rates found in weight reduction studies do not bear out this assumption (Serdula and others 1999). Further research is needed to evaluate the benefits of weight reduction in relation to reducing CVD events and the long-term sustainability of weight loss before reliable cost-effectiveness estimates can be made.

Distributional and Equity Consequences

Failing to translate available evidence from industrial countries about CVD prevention strategies into practicable solutions for developing countries would have clear equity implications, especially when CVD is a large and growing problem in developing countries and when safe and effective interventions that were once extremely expensive are now available for a few cents a day. Because access to cardiovascular health care in developing countries often depends on patients' ability to pay, the poor would stand to benefit the most from a low-cost intervention such as a polypill.

Some see CVD as exclusively a disease of the affluent in developing countries; however, in many developing countries, the transition of CVD to becoming a disease of the poor has already begun—a transition already seen in developed countries around the world. A recent analysis of the distribution of major cardiovascular risks by poverty levels has shown that many cardiovascular risks already affect the poor in the world's poorest countries (Ezzati and others 2004; WHO 2002). Combating the trend requires highly effective, low-cost solutions relevant for most or all of those at risk in developing countries, in contrast to the investments in high-tech treatment interventions that have commonly occurred to date.

ECONOMIC BENEFITS OF INTERVENTION

In the cost-effectiveness analyses, most of the gains are reported in cost savings either from particular interventions, such as decreased hospitalizations resulting from the improved combination therapy of the polypill, or from a more efficient means of screening those at highest risk through an absolute-risk approach. Those who do not die from the sequelae of poorly controlled risk factors for CVD suffer from serious chronic illness, such as stroke and congestive heart failure. Those chronic diseases can result in significant impairments, thereby preventing those affected from continuing to work and sometimes also requiring the services of other family members, who themselves end up having to leave the workforce. Further losses resulting from disability include the loss of wages for major wage earners and their families and the state's losses in terms of disability compensation. Leeder and others (2004) estimate that in 2000 the cost of CVD disability payments in South Africa equaled US$70 million.

However, many other indirect economic gains or losses are not included in the economic analysis, such as gains or losses in productivity. Leeder and others (2004) report that, at current CVD mortality rates, the potential productive years of life lost (defined as those years between the ages of 35 and 64) will nearly double by 2030. Those later adult working years are particularly important, given the many years of investment in skills through formal education and experience that would be lost. Preventing CVD would therefore improve the size and skills of the workforce and would therefore aid economic development. For those reasons, the Commission for Macroeconomics and Health has recommended that any intervention that costs less than triple a country's per capita gross domestic product be regarded as cost-effective (WHO 2001). Many of the combination cardiovascular preventive approaches outlined in this chapter comfortably satisfy that criterion.

RESEARCH AND DEVELOPMENT AGENDA

The cost-effectiveness data reviewed in this chapter indicate that the best use of resources for personal-level interventions for preventing CVD mediated by high blood pressure, cholesterol, and bodyweight would be combination medications targeted to those at high absolute risk. This strategy represents a considerable departure from existing paradigms, such as hypertension treatment. Research and development is therefore required in several areas to develop, implement, and evaluate this strategy. This research could include several themes as follows:

- Refine absolute risk-based treatment in developing country settings:
  - Evaluate optimal communications to the public and to health professionals that explain the rationale for this new paradigm and its advantages over traditional paradigms, such as hypertension treatment. One barrier to adopting preventive therapy based on absolute risk has been its relative complexity compared with dichotomous diagnosis-based strategies, such as hypertension–no hypertension.
  - Develop simple methods for predicting absolute risk using straightforward, inexpensive, direct measures, such as physical examination, clinical history, and on-site tests. These methods would likely involve low-cost algorithms completed by a multipurpose health care worker involving, for example, the collection of data on age, sex, tobacco use, blood pressure, waist circumference, and urine dipstick results. The development of different levels of screening protocol may also be needed in certain settings.
  - Calibrate existing algorithms for different disease rates and cardiovascular profiles in developing countries.
  - Develop treatment algorithms that can easily be adopted in resource-poor settings by, for example, multipurpose health care workers.
  - Develop methods for predicting absolute risk on the basis of the probability of lost healthy life years as well as the probability of a clinical event. This strategy could mean developing an index of healthy life years at risk from a cardiovascular event in the next five years, which would require taking case fatalities into consideration and discounting. A major barrier to adopting a strategy based on absolute risk has been the absence of a time-based measure and, hence, the equal value placed on preventing an event at a young and at an old age.
- Develop and evaluate combination treatments:
  - Carry out new research on the ideal combinations for different patient groups and populations at different stages of the health transition. Local initiatives would be needed to determine the ideal combination of medications based principally on cost, tolerability, and ability to lower risk-factor levels. One default set of interventions could be an angiotensin-converting enzyme inhibitor (for example, enalapril or lisinopril); a diuretic (such as hydrochlorothiazide or chlothalidone); a statin (for instance, simvastatin or lovastatin); and low-dose aspirin.
  - Measure the potential costs and benefits of adding other active agents, such as vitamins or diabetic medications.
  - Quantify the extent of improved access, acceptability, and tolerability for people with symptomatic vascular disease who have established indications for those medications.
  - Evaluate the benefits and costs in developing countries with large-scale clinical trials and demonstration projects, both among patients who have established indications (compared with usual care) and among those

who do not have clear indications but are still at high risk (compared with a placebo).
    - Evaluate the advantages and disadvantages of a polypill versus unit-of-use packs and other novel delivery strategies.
- Investigate weight-loss initiatives:
    - Develop strategies to improve the effectiveness of personal interventions to reduce bodyweight in developing countries.
    - Evaluate the use of gastric surgery for weight loss in the extremely obese in selected settings.
- Assess technology:
    - Screen which technologies should be transferred to developing countries on the basis of cost-effectiveness criteria.
    - Design new technologies specifically for use by community health workers (for example, point-of-care devices).
- Review public and personal health services:
    - Carry out a critical evaluation of community health workers versus trained health professionals in delivering simplified screening and treatment regimens.
    - Provide guideline assistance for CVD prevention and management to regional and country-specific ministers of health and policy makers.
    - Support demonstration projects to determine the limitations for managing chronic conditions in resource-poor settings.

CONCLUSIONS

The analyses presented in this chapter indicate that providing off-patent blood pressure and cholesterol-lowering medications targeted at those at high absolute risk seems to be a cost-effective strategy. Currently available personal interventions to prevent or reduce high BMI are likely to be much less cost-effective.

An approach based on absolute risk will still involve choosing some level below which people are not recommended for personal treatments, which will leave some people at risk of progression of vascular disease. This issue exists with current paradigms and underscores the need for parallel improvements in population-based prevention. The strategy based on absolute risk must be regarded as complementary to populationwide initiatives that address the root causes of CVD—in particular, the societal determinants that lead to high salt and saturated fat in the diet in relation to high blood pressure and cholesterol and high-energy diets coupled with decreasing physical activity in relation to high bodyweight. Preventing and reducing those risks in developing countries will reduce the need for medication-based prevention strategies in the coming decades.

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