Principles for National and Regional Guidelines on Cardiovascular Disease Prevention

A Scientific Statement From the World Heart and Stroke Forum*

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In the global effort to reduce suffering and death from CVD, the World Heart and Stroke Forum (WHSF) Guidelines Task Force of the World Heart Federation (WHF) recommends that every country develop a policy on CVD prevention. National policy should grow out of systematic and ongoing dialogue among governmental, public health, and professional clinical groups. National policy should set priorities for public health and clinical interventions appropriate to the country. It should also be the foundation for the development of national guidelines on CVD prevention, which are the focus of the present document.

Cardiovascular disease (CVD) is a leading cause of global mortality, accounting for almost 17 million deaths annually. Nearly 80% of this global mortality and disease burden occurs in developing countries. In 2001, CVD was the leading cause of mortality in 5 of the 6 World Health Organization (WHO) worldwide regions. Of concern in developing countries is the projected increase in both proportional and absolute CVD mortality. This can be related to an increase in life expectancy due to public health advances, which reduce perinatal infections and nutritional deficiencies in infancy, childhood, and adolescence, and in some countries to improved economic conditions. This increasing longevity provides longer periods of exposure to CVD risk factors and thus a greater probability of clinically manifest CVD. The concomitant decline of infections and nutritional disorders (competing causes of death) also increases the proportional burden due to CVD. Adverse lifestyle changes accompanying industrialization, urbanization, and increased discretionary income increase the degree of exposure to CVD risk factors. Altered diet with increased fat and total caloric consumption and increased tobacco use are prevalent lifestyle trends. Demographic changes coupled with adverse lifestyle changes will accelerate the number of deaths due to CVD worldwide, many of which will be premature in the developing countries. Although continuation of this adverse trend is not inevitable, the CVD disease patterns now present in the economically developed countries are, in fact, becoming established in developing countries, as noted in the World Health Report 2002[1] (Data Supplement Figure I).

Whereas the causes of CVD are common to all parts of the world, the approaches to its prevention at a societal or individual level will differ between countries for cultural, social, medical, and economic reasons. Although national guidelines will embrace the principles of CVD prevention recommended in this report, they may differ in terms of the organization of preventive cardiology, risk factor treatment thresholds and goals, and the use of medical therapies. The recommendations in this report focus on clinical management of patients with established CVD and those at high risk; however, it is essential that each country include a societal approach to CVD prevention. As stated in the WHO publication *Integrated Management of Cardiovascular Risk*,[2] "Epidemiological theory indicates that, compared with intensive individual treatment of high-risk patients, small improvements in the overall distribution of risk in a population will yield larger gains in disease reduction, when the underlying conditions that confer risk are widespread in the population." Each country should seek to implement national clinical guidelines directed toward high-risk individuals and give equal importance to developing low-risk population strategies.

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The Data Supplement, which contains Figures I through VI, is available with the online version of this article at http://www.circulationaha.org.

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Nomenclature and Profile of the Various Cardiovascular Risk Factors

A great advance in the prevention of CVD has resulted from the identification of measurable factors that predict the development of CVD. These factors are termed *risk factors*. Several risk factors are direct causes of CVD; these are termed *major risk factors* and include tobacco smoking, high blood pressure, high serum LDL cholesterol, and elevated glucose. A low level of HDL cholesterol is also considered a major risk factor because it independently predicts the incidence of CVD. A final major risk factor is advancing age; chronological age is considered a risk factor because it also independently predicts CVD. Age per se does not cause CVD but may reflect the accumulation of atherosclerosis, the severity of which predicts the likelihood of suffering a major CVD event. Persons who have multiple major risk factors generally are more likely to experience a CVD event than those with a single risk factor. Many prospective epidemiological studies provide estimates of the relative contributions of each major risk factor to CVD risk. Prediction equations have been developed from these estimates and can be used to estimate risk for individuals. Risk estimate based on risk equations is termed *total CVD risk*.

In clinical practice, it is convenient to categorize total risk estimates into high, intermediate, and lower risk. Patients with established CVD are said to be at high risk because they are highly likely to experience new CVD events in the next 10 years. However, some asymptomatic patients with multiple risk factors, particularly those with type 2 diabetes, may carry as high a risk for future CVD events as patients with established CVD. These persons with multiple risk factors likewise are said to be at high risk. Multiple risk factors also typically are required to elevate persons to the intermediate-risk category, whereas most persons with only a single risk factor are at lower short-term risk. Nonetheless, even single risk factors, if severe and sustained, can lead to premature CVD and should not be ignored in clinical practice.

Other risk factors, in addition to the aforementioned major risk factors, may further contribute to total risk. They are underlying risk factors and emerging risk factors. The underlying risk factors are overweight/obesity, physical inactivity, atherogenic diet, socioeconomic and psychosocial stress, family history of premature CVD, and various genetic and racial factors. To some extent, the underlying risk factors affect risk by acting through the major risk factors, and they also appear to influence risk in ways unrelated to the major risk factors. Although these underlying risk factors likely add an independent component to total risk, their contribution has been difficult to distinguish in prospective studies from their effects on major risk factors; for this reason, they generally are not included in clinical predictive equations. Nonetheless, the underlying risk factors apparently affect population baseline risk. Thus, the available predictive equations may not be applicable equally to all populations. The major risk factors are similar in relative predictive power in different populations, but absolute estimates of risk are variable. Differences in the underlying risk factors probably account for much of this variability in absolute risk.

Emerging risk factors are factors that are correlated with CVD risk in prospective or case-control studies, but the strength of their correlation and/or their prevalence in the population is less than that for the major risk factors. For this reason, the emerging risk factors generally are not included in risk-prediction equations. Among the emerging risk factors are various lipid factors [triglycerides, apolipoproteins, lipoprotein(a), and lipoprotein subfractions] and nonlipid factors (insulin resistance, prothrombotic markers, and proinflammatory markers). Similarly, subclinical atherosclerosis may also be useful in predicting the risk of CVD events. Because the emerging risk factors are not incorporated into risk predictions, their use in clinical practice must be individualized and based on clinical judgment. Most importantly, they should not be given more priority in risk assessment than that given to the major risk factors.

Concept of Total CVD Risk

In general, the benefits of interventions on particular risk factors are related more to the magnitude of the preintervention total CVD risk than to relative risk associated with a single, specific risk factor. Therefore, determination of total CVD risk is critical to recommendations on the effective and efficient management and control of CVD risk at both population and individual levels. Total CVD risk is a measure of the number of events in a defined population per unit of time (eg, CVD events per 1000 in 55- to 64-year-old men per year). In effect, a total risk compares a person's or population's risk with a zero risk. The combined effects of all risk factors determine total CVD risk, and often, modest increases in multiple risk factors have a greater impact on CVD risk than a significant increase in 1 risk factor.

For example, a 46-year-old woman with high blood pressure (170/100 mm Hg), but who is a nonsmoker, is nondiabetic, and has a total cholesterol level of 5.5 mmol/L and HDL cholesterol level of 1.5 mmol/L, has an absolute CVD risk of $<$4/100 in 5 years. In contrast, a 62-year-old smoking man without diabetes and with a lower blood pressure (150/90 mm Hg) but with a slightly higher total cholesterol level (6.0 mmol/L) and a slightly lower HDL level (1.2 mmol/L) has an absolute CVD risk of $>$20/100 in the next 5 years. Moreover, although blood pressure–lowering drugs would reduce the relative CVD risk by at least one quarter in both patients, the woman's risk would fall from 4% to 3% (ie, a 1% absolute risk reduction in the next 5 years), whereas the man's risk would fall from 20% to 15% (ie, a 5% absolute risk reduction in the next 5 years). Appropriately, most practitioners would treat the first patient in concordance with national guidelines; unfortunately, many clinicians might not start a blood pressure–lowering drug in the second patient.

Total CVD Risk and Policy Development: Efficacy and Cost Issues

Several risk factors that are only moderate often incur a greater total risk in the short term than does a single, severe risk factor. Risk assessment in both individuals and populations must take this fact into account. The greatest efficacy of treatment occurs in patients who are at highest risk. Thus,

persons who are at higher total risk will attain greater reductions in absolute risk with any given lowering of risk factors. Giving priority in risk-reduction therapies to patients at higher total risk will produce a substantial reduction in total CVD events. Furthermore, more high-risk individuals will benefit; in other words, the number needed to treat over a given period of time to achieve prevention of 1 CVD event will be fewer in higher-risk persons than in lower-risk persons.

One important issue to consider in CVD prevention is cost of medical management. In traditional medical practice, priority in spending has gone to treatment of persons who already manifest disease. However, there is increasingly a demand on the part of society to prevent the chronic diseases that rob individuals of health in their later years. Among the latter, heart disease, stroke, and chronic renal failure are high on the list. Moreover, advances in medical practice now make it possible to prevent or to delay the onset of these diseases. Consequently, prevention is assuming increasing importance. On the other hand, adding prevention to conventional medical practice increases the cost and cuts into the overall healthcare budget of individuals and nations. Consequently, the health policy of each nation must determine what portion of the total healthcare budget can go into prevention and what portion must go into treatment of existing disease. Medical economists have attempted to compare benefits of prevention and treatment through estimations of "cost-effectiveness." Estimates of benefits have been made for both and have been expressed in terms of quality life extension. These estimates suggest that the greatest cost-effectiveness for prevention occurs for individuals at high short-term risk, whether they have established CVD or not. Most of the more economically privileged nations can readily afford to institute preventive measures in high-risk individuals. However, considerable controversy exists about where to draw the line for primary prevention in lower-risk persons with the use of public funds. In societies with higher socioeconomic levels, primary prevention in the clinical setting can be employed in intermediate-risk persons. In less economically privileged societies, even high-risk prevention may strain available resources. Regardless of healthcare policy for clinical intervention, in all societies, public health measures can be instituted for primary prevention, and these are highly cost-effective. These include programs to discourage cigarette smoking, to promote appropriate nutrition, and to encourage physical activity. The cardiology and medical communities can play a major role in public health efforts for primary prevention of CVD.

Total CVD Risk for Specific Individuals

The principle of assessing the total or global risk associated with multiple risk factors was first introduced in New Zealand in 1993, in relation to the management of blood pressure.[3] The following year, the European Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension proposed total multifactorial risk as the primary determinant of drug treatment for both blood pressure and blood lipids in preventing the development of coronary heart disease (CHD).[4] The US National Cholesterol Education Program (Adult Treatment Panel II),[5] published in the same year, also recommended, for the first time, assessing and managing lipids in the context of other cardiovascular risk factors. The principle of global risk was also supported by conclusions of the 27th Bethesda Conference[6] (Matching the Intensity of Risk Factor Management with the Hazard of Coronary Disease Events), followed by the Sixth report of the Joint National Committee on High Blood Pressure,[7] the AHA Prevention V Conference,[8] the International Task Force on Coronary Heart Disease,[9] the WHO/International Society of Hypertension Guidelines for Management of Hypertension,[10] the National Cholesterol Education Program (Adult Treatment Panel III),[11] and, most recently, the Third Joint European Societies' Task Force on CVD Prevention in Clinical Practice[12] and the Seventh report of the Joint National Committee on High Blood Pressure.[13] All of these guidelines since 1993 have embraced, to different extents, the principle of multifactorial or global risk assessment as a basis for deciding whom to treat with drugs, although patients with hypertension and end-organ damage such as renal failure or younger patients with hypertension and dyslipidemias whose short-term risk may be low also can benefit from medical therapy directed toward a single risk factor. Because physicians deal with the whole patient and therefore every aspect of their risk of CVD, the principle of total risk assessment and management is consonant with the practice of medicine.

A number of tools for estimating risk of CHD or other atherosclerotic diseases have been developed over the past 10 years, including risk score charts, risk assessment algorithms, and computer software programs. They are all based on the same principle, and many have used Framingham data.[14] Ideally, coronary or CVD risk prediction should be based on a prospective population cohort study undertaken in the population to which the risk score is to be applied. This is because total risk of CVD may differ from one country to another, and the contribution of individual risk factors may also differ to some extent from one part of the world to the other. The published examples of coronary or CVD predictions include the Systematic Coronary Risk Evaluation (SCORE)[15] Project in liaison with the Third Joint European Societies' risk charts (Data Supplement Figures II and III); the New Zealand cardiovascular risk assessment and management chart (Data Supplement Figure IV), which provides estimates of both CVD risk and the likely benefit of therapy to lower blood pressure or lipids; the Sheffield Tables[16]; the Joint British Societies' coronary risk prediction chart and associated software program[17]; and the ATP III 10-year Risk Estimates for men and women[11] using Framingham Point Scores[14] (Data Supplement Figures V and VI), which are also available as a computer program. Most of these risk tools are based on the Framingham function. In addition, computer software programs are available based on the PROCAM study of men in Germany,[18] PRECARD from a prospective cohort study of Danish men and women,[19] and the European Society's HeartScore.

First, when we use the European Society of Cardiology's SCORE charts (Data Supplement Figure II or III) as an example, an individual's short-term risk of developing a CVD event (myocardial infarction or stroke) over the next 10 years

is found by locating the appropriate box in the chart based on the knowledge of age, gender, smoking status, systolic blood pressure, and total cholesterol level. The New Zealand chart (Data Supplement Figure IV) estimates CVD rather than CHD, but the risk is over a shorter period, 5 years rather than 10. Systolic and diastolic pressure are both used, as well as the ratio of total to HDL cholesterol. The total cholesterol/HDL cholesterol ratio improves coronary risk prediction, particularly for women and for those in the middle range of cholesterol. The Framingham tables (Data Supplement Figures V and VI) produce a numerical score that also corresponds to a short-term 10-year CHD risk (myocardial infarction and CHD death). Although all of these charts, tables, and computer programs estimate CHD or CVD risk for an individual, it must to be emphasized that some individuals will be at higher risk than is evident from these calculations. Patients with clinically established CHD, other atherosclerotic disease, and diabetes; patients with hypertension associated with end-organ damage or familial dyslipidemias; patients with a family history of premature CVD; and those with low HDL cholesterol or raised triglyceride levels also may be at higher risk than indicated by the charts. Use of the Framingham risk function has certain limitations. Although it depends on the population, it or any other algorithm that is derived from a different region may not accurately predict total risk in another population. Nevertheless, coronary risk charts or computer programs can have several useful functions: An individual's total risk of developing a CHD or CVD event over a defined time period can be read from a chart without any calculations.

Second, relative risk can readily be estimated by comparing the risk in one cell with any other in the same age group or with a table of average or low risk.

Finally, the chart can be used to illustrate the effect of changing from one risk category to another.

Although young people are generally at lower risk, this will rise steadily as age increases. In the European recommendations, short-term risk estimates for clinical decisions in young adults and subjects in early middle age are made to project risk to age 60 years. For example, if the projected risk to age 60 years places a person in the high-risk category, this person can be treated accordingly with more intensive monitoring and earlier intervention. In this way, individuals with low CVD risk today, but who will become high risk in the long term unless there is lifestyle and, where appropriate, therapeutic intervention, can also be identified and treated earlier.

Concept of a Continuum From Low- to High-Risk CVD Prevention

The concept of total CVD risk also challenges the traditional classification of prevention into tertiary, secondary, and primary. Most patients with established CVD have developed symptomatic disease because they are at high risk, and the management of these multiple risk factors will over the longer term determine their risk of recurrent disease. Healthy individuals at high risk are usually no different (and many will already have asymptomatic atherosclerosis) from those who have declared their disease; all are at high risk of developing and dying from a CVD event. Thus, prevention of CVD at a population and individual level should be considered as a continuum from low to high risk: those at highest risk are patients with clinically manifest CVD, followed by individuals without known CVD at different levels of risk from high to low. The risk for an individual within a population is not just a function of their absolute ranking in relation to others but on the overall risk of the population in which they live. A "low-risk" individual in a high-risk population may actually be at higher total CVD risk than a "high-risk" individual in a low-risk population. The risk of an individual should always be judged in the context of the CVD risk of the population as a whole.

An assessment of the determinants of total CVD risk should be a major determinant of priority setting for CVD prevention and management policy at both the clinical and population level, and guideline recommendations should emphasize interventions on all CVD risk factors rather than on single risk factors.

Established Atherosclerotic Vascular Disease

People who present with symptoms or history of atherosclerotic vascular disease (AVD), ie, CHD, stroke, or peripheral arterial disease, are at high risk of recurrent nonfatal and fatal cardiovascular events. Although the initial prognosis of these patients is determined by the extent of tissue damage to heart or brain, the longer-term prospects are strongly influenced by the extent of their atherosclerotic process, lifestyle, and other risk factors responsible for expression of atherosclerotic disease. CHD dominates the clinical presentation of atherosclerosis and accounts for a large majority of CVD patients. Of those with other manifestations of atherosclerosis in the form of stroke or peripheral arterial disease, many will also have CHD, which is a frequent cause of death. Population-based autopsy studies have shown a strong correlation between the severity of atherosclerosis in one arterial territory and involvement of other arterial beds. Therefore, the prevention of atherosclerosis and its complications is the same regardless of which arterial territory becomes symptomatic. For practical purposes, no distinction needs to be made between those presenting with CHD and other forms of atherosclerosis in terms of lifestyle intervention and risk factor management for blood pressure, lipids, and hyperglycemia. However, specific drug therapies may differ according to the clinical expression of atherosclerotic disease and its complications (eg, preference for β-blockers or angiotensin-converting enzyme [ACE] inhibitors for blood pressure control in CHD patients).

CHD is the most common clinical manifestation of atherosclerosis. Sudden cardiac death in the community is often the first manifestation of CHD and is the terminal event in more than half of CHD patients.[20] Acute myocardial infarction and unstable angina account for approximately one third of all cases, whereas exertional angina is the most common clinical manifestation of this disease, accounting for more than one half of all cases presenting in the community. Because the majority of individuals with CHD survive their first symptomatic presentation, the potential to reduce the risk of recurrent events and death is considerable. Surveys of contemporary clinical practice around the world, however, show

that lifestyle and risk factor management, including the use of prophylactic medical therapies, falls far short of evidence-based national guidelines on CVD prevention. To further reduce the risk of recurrent CHD events and death, the standards of preventive care must be raised.

Patients with atherosclerosis of the carotid, vertebral, and cerebral arterial circulations can present with transient episodes of cerebral ischemia (transient ischemic attack) or a full stroke (either thrombotic or embolic), which can leave them temporarily or permanently disabled. Prevention of hemorrhagic stroke is not included here because the pathology is not usually atherosclerosis; however, because of its association with hypertension as a modifiable risk factor, it must be considered to benefit from medical treatment. The risk of recurrent cerebrovascular disease is determined by multiple risk factors, particularly hypertension. In addition, patients with cerebrovascular disease due to thrombosis usually have CHD as well. Therefore, their risk factors should be managed on the assumption that they have CHD in order to broadly reduce their risk of CVD events. Although it is beyond the scope of this discussion, embolic stroke associated with atrial fibrillation deserves attention as a major preventable entity.

Atherosclerosis of the peripheral arteries usually presents clinically with aneurysmal dilatation of the aorta, aortic dissection, and, most commonly, progressive ischemia ("intermittent claudication") of the lower limbs. Although an aortic aneurysm or dissection can be life threatening, atherosclerosis of the lower limb arteries is usually not, although patients can develop critical ischemia of the foot requiring amputation. However, almost all patients with atherosclerosis of the peripheral arteries also have CHD and therefore are at increased risk of a nonfatal coronary event or coronary death. The risk factors for atherosclerosis of the peripheral arteries are the same as those for the coronary circulation, although smoking is a particularly powerful risk factor for atherosclerosis of the aorta and lower limbs. Therefore, patients with peripheral atherosclerotic disease should also have their risk factors managed in the same way as those with CHD to reduce their risk of CVD complications. In addition, peripheral arterial disease is a powerful predictor of major coronary events. Therefore, the presence of peripheral atherosclerotic disease places a person in a high-risk category.

Patients with CHD or other atherosclerotic disease are considered to be at high risk. There is no practical utility in further quantifying their total risk of a future CVD event because risk stratification will not alter recommendations for target goals of risk factor therapy.

Asymptomatic Atherosclerotic Vascular Disease

The medical technology to detect asymptomatic atherosclerotic disease is already available for coronary atherosclerosis, carotid/vertebral atherosclerosis, and peripheral arterial disease. This technology has revealed the ubiquity of AVD, as understood by pathologists many years ago. Emerging methodologies can aid in the detection of AVD before clinical symptoms. The cost of this technology emphasizes the benefits and importance of primordial preventive strategies, as discussed elsewhere in this article. The objective of detecting asymptomatic AVD in apparently healthy individuals is to intervene in order to slow disease progression, if possible to induce regression, and to reduce the risk of thrombotic complications, thereby reducing the risk of a first nonfatal or fatal coronary or other atherosclerotic disease event.

Before screening technology is used in routine clinical practice, the following screening criteria should be met: (1) The noninvasive technique for detecting CHD or other atherosclerotic disease is valid, precise, easy, and acceptable. (2) The risk of symptomatic disease, eg, angina, CHD death, or stroke, has been quantified. (3) The screening strategy, intervention, and follow-up policy are defined. (4) Trained staff and facilities for screening and intervention are available. (5) Screening and intervention results in a reduction in clinical events: CHD and other atherosclerotic morbidity and mortality. (6) Screening has no adverse effects. (7) Cost of screening and intervention is affordable, appropriate for the healthcare system, and justified by the outcome.

For CHD, CT can identify coronary calcification as a surrogate for coronary atheroma. In addition, CT and MRI are evolving technologies for the detection of epicardial disease. The impact of coronary atheroma on perfusion of the myocardium can also be objectively assessed noninvasively with a variety of techniques including radionuclide scintigraphy, stress echocardiography, and exercise ECG testing. However, most of these techniques detect obstructive coronary atheroma, and each has limitations as a sensitive and specific test for the diagnosis of CHD in an asymptomatic individual. Asymptomatic atherosclerotic disease of the aorta, carotid, brachial, and lower limb arteries can also be detected by noninvasive techniques, including MRI, carotid ultrasound, brachial reactivity, ankle-brachial pressure index, and tibial artery blood flow velocity by Doppler ultrasound.

More research is needed to evaluate the incremental value and cost-effectiveness of these techniques compared with conventional risk factors in assessing the absolute risk of developing symptomatic disease. Randomized controlled trials are also required to evaluate the impact of noninvasive screening and intervention programs for CHD or other atherosclerotic disease on subsequent CVD morbidity and mortality. Until such evidence is available, screening for asymptomatic disease with advanced technologies should be considered investigational, with the exception of ankle-brachial pressure index, and studies should be performed to confirm their cost-effectiveness before adoption for use in a given region.

High-Risk Populations

The rising prevalence of CVD worldwide is in part a reflection of a rising prevalence of CVD risk factors in many nations. Among these are increasing prevalence rates of cigarette smoking, hypertension, lipid disorders, diabetes, and older people. Changing life habits across broad populations is responsible for the emergence of most of these risk factors. Cultural changes are such that multiple risk factors in individuals are common. To stem the rising tide of CVD worldwide, it will be necessary to attack the causes of CVD risk factors. These underlying causes include increasing obesity, decreasing physical activity, and changes in the

composition of the diet. To modify these underlying risk factors, CVD specialists must team with primary healthcare providers, epidemiologists, and public health officials to modify behavioral characteristics of individuals. CVD specialists can assist in the identification of problem areas and serve as a catalyst for change. It is logical that preventive efforts in whole populations should be broad based and directed toward reducing all the risk factors simultaneously.

At the same time, even within a single nation there can be subpopulations that are at higher risk than others because of either genetic or racial factors or unique exposures to environmental factors. Indeed, many epidemiological studies reveal that socioeconomic status can be an independent predictor of risk. Some of the excess risk dependent on advantaged socioeconomic status can be explained by the major, independent risk factors and their root causes. However, other factors such as psychosocial stress, behavioral factors, and access to the medical care system may raise the risk in persons who are economically disadvantaged.

Physicians should play an increasing role in public health medicine. Not only can their national health societies take an active part in public health issues, but they have an opportunity to convey the public health (preventive) messages in their daily interactions with patients. When patients are being treated for various medical complaints, the physician should not overlook the chance to deliver a broader message. In fact, societal changes that lead to an increased prevalence of cardiovascular risk factors also provide greater access to personalized healthcare. The prevention message should be built into routine patient care.

The public health approach to prevention of CVD has several components, including government policy, educational efforts, industrial policy, and testing for risk factors. Physicians are appropriately involved at every level. Particularly important are screening programs for risk factors. Screening is best done in the medical setting where appropriate follow-up and advice are available. However, when prevalence of certain risk factors is identified in subpopulations, mass screenings may be more efficient and cost-effective.

Management of Specific and Total Risk Factors in Patients and Populations

The overall objective of CVD prevention in patients with clinically established AVD or asymptomatic individuals at high risk is the same: to reduce the risk of subsequent major CHD or other AVD events. Secondary prevention for patients with established AVD has traditionally been distinguished from primary prevention for asymptomatic high-risk individuals, but this distinction is artificial because the majority of individuals at high risk are also likely to have advanced subclinical atherosclerosis. Thus, prevention of CVD at a population and individual level should be considered a continuum. Those at highest risk are patients with clinically manifest CVD, followed by asymptomatic CVD individuals and by individuals with a high risk factor profile. Because the biology of AVD and the distribution of risk overlap in these 3 groups, a high intensity of lifestyle intervention and risk factor management can be justified.

Lifestyle

Intervention in relation to tobacco cessation, healthy food choices, weight control, and physical activity is the foundation of preventive cardiology. Diets associated with a low CVD risk will differ in terms of food composition around the world. Although pharmacological, interventional, and device-oriented interventions may depend on national economic factors, lifestyle interventions can be implemented worldwide.

Physicians and other health professionals should set an example for patients with AVD, high-risk individuals, and the general population by not smoking themselves. A physician's firm advice that a patient should stop smoking is the most important first step. The goal is complete cessation and avoidance of passive smoking. The only important difference between current recommendations is in the use of nicotine replacement therapy, especially for patients with AVD. Nicotine chewing gum and transdermal nicotine patches can double the cessation rates compared with a placebo. The use of nicotine patches has been tested successfully in patients who have coronary disease without any adverse effects, but caution in the use of nicotine replacement therapies is still required. Patients should not smoke while they are using these nicotine delivery preparations because doing so may exacerbate symptoms. The antidepressive drug bupropion is an additional treatment to help individuals quit.

An atherogenic diet contributes to CVD in many populations. A healthy diet is low in saturated and trans-fatty acids and low in dietary cholesterol. The amount of saturated and trans-fatty acids in the diet should be $<$10% of total calories, and the dietary cholesterol intake should be $<$300 mg/d. A useful recommendation for individuals at high risk is to reduce the quantity of food they consume by 20% to 25%, reduce animal fats, and decrease the amount of salt added to foods in cooking and at the table. A good example of a diet low in saturated fat and cholesterol is the traditional Mediterranean diet; in this diet, unsaturated fats replace most of the saturated fat. The traditional Japanese diet is also low in saturated fat but high in complex carbohydrates. Both of these diets are associated with the best life expectancy in the world. For prevention of CHD and other AVD, the best advice is to use a diet low in saturated fatty acids by replacing them in part with monounsaturated and polyunsaturated fatty acids as well as with complex carbohydrates. These principles are reflected in all the recommendations. Physicians should emphasize the importance of diet in relation to reducing weight, lowering blood pressure and blood cholesterol, controlling blood glucose in diabetic patients, and reducing the propensity to thrombosis. Alcohol should be considered in the context of dietary advice. Although moderation in the use of alcohol should always be advised, further restriction may be necessary in those who are overweight (to reduce calories), particularly in patients with elevated blood pressure and elevated serum triglycerides. The intake of salt (sodium chloride) should also be reduced to $<$5 g/d in patients with high blood pressure. The goals of dietary counseling have to be defined on a national basis, together with the practical recommendations for translating such goals into the selection, preparation, and consumption of foods.

The goals and recommendations for weight management vary on the basis of geographic region. In Western Europe and the United States, body mass index <25 but >20 kg/m^2 is associated with the lowest risk of CVD and CHD. As people become overweight (BMI >25 and <30 kg/m^2), CVD risk increases, and with obesity (BMI >30 kg/m^2) all-cause mortality increases, largely because of an increase in CVD mortality. Overweight is also associated with an increased risk of stroke. Central adiposity, defined as an increased intra-abdominal fat mass, is associated with an adverse risk factor profile, including insulin resistance, and, as assessed by waist-to-hip circumference ratio, is more strongly associated with risk of CHD and other CVD than general adiposity assessed by body mass index. Reducing weight will reduce blood pressure and plasma LDL cholesterol, raise HDL cholesterol, and lower triglycerides and will decrease glucose intolerance. It should be emphasized that the aforementioned numbers for BMI have been determined for Western Europe and the United States and may be lower for other regions and countries.

The relevance of physical activity in helping weight control and favorably modifying other risk factors should be explained. A balance in caloric intake and energy expenditure is fundamental to any program that seeks to alter and maintain ideal body weight. Regular physical activity is associated with a lower risk of death from CVD and CHD. Physical activity helps to prevent obesity, is associated with lower levels of plasma LDL cholesterol and triglycerides and higher levels of plasma HDL cholesterol, and lowers blood pressure. Exercise-based cardiac rehabilitation in patients with established coronary disease has been shown to reduce total cardiovascular and coronary mortality.

Blood Pressure

Hypertension is a major cause of stroke and contributes to an increased risk of recurrent myocardial infarction in patients with CHD. Treatment of hypertension is therefore important as a primary and secondary prevention strategy. Several trials in coronary patients with blood pressure–lowering drugs, β-blockers and ACE inhibitors, particularly after myocardial infarction, have demonstrated a reduction in both recurrent myocardial infarction and all-cause mortality.[13] Similarly, treatment of high blood pressure has been shown to lower the occurrence of fatal and nonfatal stroke. International, continental, and national recommendations advise treating hypertension in patients with established atherosclerotic disease, and a blood pressure target of <140/90 mm Hg is common to all. In healthy individuals there is agreement across all recommendations that the decision to start treatment depends both on the blood pressure level and the overall CHD or CVD risk as well as the presence of subclinical CVD or end-organ damage. Markers such as left ventricular hypertrophy, a marked reduction in glomerular filtration rate, proteinuria, and retinal hemorrhages and/or exudates with or without papilledema are all associated with an increased risk at any given blood pressure level. Echocardiography is a more sensitive marker of left ventricular hypertrophy than electrocardiography, and echocardiographic left ventricular hypertrophy is associated with an increased risk of CVD morbidity and mortality. Microalbuminuria in diabetic and in nondiabetic patients is also associated with increased risk. Systolic blood pressure is as strongly, or even more strongly, associated with CVD risk as diastolic blood pressure. In some clinical trials of hypertension, cardiovascular events correlate more closely with achieved systolic pressure than diastolic pressure. Recent trials on isolated systolic hypertension have added to evidence regarding the importance of systolic blood pressure in risk assessment and management.

International, continental, and national guidelines now recommend that treatment of hypertension in healthy individuals be based on both the systolic and diastolic values and the coexistence of other atherosclerotic disease risk factors and aforementioned comorbidities. For some individuals the level of blood pressure is deemed sufficiently high to merit antihypertensive treatment in its own right, regardless of its clinical context. For others a decision to treat is taken in the context of absolute CHD or CVD risk. The definition of high risk differs between guidelines in terms of both the levels of systolic and diastolic blood pressure and the levels of absolute CHD or CVD risk. The optimal blood pressure to be achieved by treatment has not been established in randomized controlled trials, but the blood pressure goal is the same for international, continental, and some national guidelines, and the risk of events has been shown to increase continuously with increasing blood pressures.

In clinical practice, it is important to set a blood pressure target for an individual and to try to achieve it with a minimum of side effects. Several classes of drugs have been shown in randomized controlled trials to reduce the risk of CHD and CVD: diuretics, β-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers. Local costs and patient characteristics should be taken into account in the selection of antihypertensive drugs. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT)[21] results indicate improved or comparable cardiovascular outcomes among patients given thiazide diuretics for treatment of hypertension and lend support to the potential for lower-cost strategies.

Blood Lipids and Lipoproteins

A strong, independent relationship exists between serum LDL cholesterol levels and risk for CHD and to a lesser extent for other CVD end points. The relationship between other serum lipids (HDL cholesterol and triglycerides) and the risk of atherosclerotic disease is more complex. Like blood pressure, the relationship between serum LDL cholesterol and risk of CVD (principally CHD) increases continuously as LDL cholesterol levels rises, starting from levels that are considered to be within the so-called normal range. Therefore, like blood pressure, the dividing line between individuals requiring clinical intervention is determined operationally by epidemiological data, randomized controlled trials, and economic considerations. Standard risk equations have a diminished reliability in familial dyslipidemias, particularly familial hypercholesterolemia. Affected patients are at very high risk of aggressive premature atherosclerosis and suffer early coronary morbidity and mortality. For these patients, lipid-lowering therapies and other forms of treatment are

essential regardless of the presence of other cardiovascular risk factors. Although these other risk factors also need to be effectively addressed in patients with these familial dyslipidemias, lowering LDL cholesterol should be the primary objective.

For patients with established CHD or other atherosclerotic disease and even for those with diabetes or hypertension, there is randomized controlled trial evidence that modifying lipids, principally reducing LDL cholesterol, irrespective of the initial values, reduces the risk of recurrent coronary disease, stroke, and all-cause mortality. Thus, for asymptomatic individuals, international, continental, and national guidelines now recommend that treatment of blood lipids, in the absence of familial dyslipidemia, should be based on absolute risk.

Hyperlipidemias secondary to other diseases are common, including abuse of alcohol, hypothyroidism, diseases of the kidney and liver, and diabetes, particularly in the presence of a nephropathy. Therefore, it is always important to exclude these diseases with an appropriate clinical assessment and tests before introducing drug therapy.

Although goals for total cholesterol and LDL cholesterol have been set, there is insufficient evidence to justify goals for triglycerides and HDL cholesterol. Instead, these measurements should be used to identify individuals at high multifactorial risk of CHD or other atherosclerotic disease and possibly used as secondary considerations in the selection of lifestyle and drug interventions.

Several classes of lipid-lowering drugs have been shown in randomized controlled trials to reduce clinical events: 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins), fibrates, bile acid sequestrants (resins), and nicotinic acid derivatives. All 4 classes of drugs, but not all drugs within each class, have been shown in clinical trials to reduce myocardial infarction and sudden death.[11] A new class, cholesterol absorption blockers, reduces LDL cholesterol but has not yet been tested in clinical trials to determine the effect on cardiovascular morbidity and mortality. The statin drugs are the most widely used of the lipid-lowering drugs because they are highly effective in lowering LDL levels and because they are well tolerated. Increasingly, other lipid-lowering drugs are used in combination with statins in patients with severe hyperlipidemias or complex dyslipidemias.

Blood Glucose

Mounting evidence suggests that aggressive blood glucose lowering with insulin in patients with myocardial infarction, both during the hospital admission and 1 year after it, reduces mortality. Although there is no specific randomized controlled trial evidence for blood pressure lowering in patients with atherosclerotic disease and diabetes, the subgroup analyses of patients with diabetes and myocardial infarction in trials of β-blockers and ACE inhibitors have shown a similar treatment benefit for patients with and without diabetes. Similarly, there is no direct trial evidence of cholesterol lowering in patients with diabetes, but subgroup analyses in large statin trials showed reductions in CHD events at least as large in patients with diabetes as in nondiabetic patients.[11] In individuals with diabetes but no symptomatic AVD, glucose control has been shown in randomized controlled trials to reduce the risk of microvascular complications in both type 1 and type 2 diabetes. In addition, in the UK Prospective Diabetes Study of type 2 diabetes, there was a favorable trend for glycemic control reducing the risk of myocardial infarction.[22] Blood pressure reduction in the same trial significantly reduced the risk of myocardial infarction, and this result is consistent with the subgroup analyses of patients with diabetes in other primary prevention trials of hypertension that showed a reduction in cardiovascular morbidity and mortality at least as good as that seen in nondiabetic individuals.

Other Risk Factors

Although risk assessment is principally focused on aspects of lifestyle, blood pressure, lipids, and diabetes, there are other risk factors for CHD and other AVD. These include psychosocial factors, markers of inflammation, thrombogenic factors, insulin resistance, and genetics. However, the benefit of clinical interventions directed to each of these factor profiles remains to be determined through controlled clinical trials.

Prophylactic Medical Therapies

In individuals at high multifactorial risk of developing CHD or other AVD, there is evidence from randomized controlled trials that prophylactic aspirin reduces risk.[23] There is growing agreement across international, continental, and national guidelines that persons at intermediate or high risk ($>$10% per 10 years) for hard CHD events (myocardial infarction or CHD death) may benefit from 75 to 160 mg/d of aspirin. For patients with established CHD or other atherosclerotic disease, aspirin ($\geq$75 mg) or other platelet-modifying drug is universally recommended. The meta-analysis of antiplatelet trials after myocardial infarction demonstrates a significant reduction in all-cause mortality, vascular mortality, nonfatal reinfarction of the myocardium, and nonfatal stroke for those receiving antiplatelet therapy. In several studies of anticoagulation after myocardial infarction, systemic anticoagulants reduced the risk of all-cause mortality and coronary death.[23] This drug class is used selectively in patients at high risk of systemic embolization or in patients unable to take aspirin.

In a meta-analysis of β-blockers after myocardial infarction, there was also evidence of a significant reduction by therapy in all-cause mortality and in particular sudden cardiac death, as well as nonfatal reinfarction.[24] The benefit was greatest in those with left ventricular dysfunction or supraventricular or ventricular tachyarrhythmias. Therefore, a β-blocker is recommended in patients with no contraindications after myocardial infarction.

A meta-analysis of ACE inhibitors has confirmed a similar benefit in regard to all-cause mortality for this drug class in patients with myocardial infarction with symptoms or signs of heart failure at the time of acute myocardial infarction, in those with impaired systolic ventricular function (ejection fraction $<$40%), and in patients at high risk with preserved systolic function.[25] Because most trials of β-blockers and ACE inhibitors were single-drug trials, the use of both drugs versus one or the other has not been studied. Patients with clinical CHF after myocardial infarction have also been

shown to have a benefit from angiotensin receptor blocker therapy comparable to that from ACE inhibitors.

As mentioned, for asymptomatic individuals, international, continental, and national guidance now recommends that irrespective of the initial LDL cholesterol values, treatment with LDL-lowering drugs, in the absence of familial dyslipidemia, should be based on absolute risk.

Screening Relatives

A detailed family history of CHD or other atherosclerotic disease should be part of the assessment of all patients. The risk of CHD increases when a first-degree family relative has a history of premature CHD. Risk factor screening should be considered in first-degree relatives of any patient developing CHD at an early age: before 55 years in men and before 65 years in women. In this context, the multifactorial risk will be higher than that estimated from the coronary risk chart. When familial dyslipidemia is suspected, particularly familial hypercholesterolemia (family history of premature CHD, blood cholesterol >8.0 mmol/L, with or without stigmata or hyperlipidemia), screening all first-degree relatives with a full lipoprotein profile is essential.

National and International Guidelines on CVD Prevention

Similarities and Differences

An international consensus has emerged among guidelines regarding priorities for CVD prevention, risk factor assessment, and management, including the use of drug therapies. However, this consensus mainly comes from guidelines developed in the United States, Europe, Australia, and New Zealand. For much of the world, especially the developing countries in the Asia-Pacific region, Africa, and South America, there are few data on risk factors and CVD and few published guidelines. The strongest agreement across international, continental, and national guidelines is for patients with established CHD or other AVD. These patients are recognized by cardiologists and other physicians as the top priority for prevention, and there is general agreement on the need for lifestyle intervention, blood pressure reduction, cholesterol reduction, and the use of prophylactic drug therapies: aspirin, β-blockers, ACE inhibitors, and LDL-lowering drugs. Although the same or similar blood pressure goal has been specified in all guidelines, this is not so for cholesterol. There are some differences between guidelines on cholesterol goals for patients with CHD and CVD, but this is of practical importance only to a small minority of patients; most have cholesterol levels that are untreated and remain above the standards of the most conservative of cholesterol targets. Otherwise, it is important to set a treatment target for LDL cholesterol in patients with AVD at a national level. The same principle applies to patients with diabetes mellitus.

For healthy individuals, there is also agreement across international, continental, and national guidelines on the principle of basing the decision to treat blood pressure or lipids on absolute multifactorial risk of CVD. However, the practical application of this principle differs between guidelines in terms of the method of risk calculation, the absolute level of risk at which to intervene, and the risk factor thresholds themselves. All of these differences should be resolved at a national level by taking account of the scientific evidence and the resources available to deliver effective multifactorial intervention.

International Call to Action to Address the Challenge

Because CVD is a global problem, societies of cardiology can and will benefit through international professional collaboration. The International Heart Health Conferences issued declarations on prevention of CVD in 1992 (Victoria Declaration),[26] in 1996 (Catalonia Declaration),[27] in 1998 (Singapore Declaration),[28] and most recently in 2001 (Osaka Declaration).[29] The Singapore Declaration particularly is a valuable description of the intellectual and organizational principles that should underlie programs to prevent CVD. The principles are broadly divided into those pertaining to the structure of preventive programs and those pertaining to the political will to proceed to action. Preventive efforts have been mounted by international organizations with more specific agendas for longer periods of time, and thus the present document is a logical extension of international collaborative efforts that have been in place since 1992.

The idea of political will, consistent with an activist agenda, is that prevention will get nowhere if clinicians, researchers, and others who want to advance the cause of CVD prevention do not accept personal responsibility to assume a leadership role. In the section on physical and organizational infrastructure of prevention, the Singapore Declaration specifies the importance of nongovernmental organizations and professional health organizations such as the WHF. The WHSF quite specifically requests in this document that continental and national societies of cardiology and related professional organizations assume leadership of continental and national programs to prevent further increases in the occurrence of CVD. Societies of cardiology have the professional authority to not only ask government to allocate resources for care of patients with CVD but also to ask government, be it continental, national, or local, to incorporate prevention of CVD into legislation whenever relevant.

Strategic Principles for the Development of National Clinical Guidelines

On the basis of and following the sequential approach of this document, the WHSF of the WHF recommends 10 strategic principles to serve as a template for the development of national clinical guidelines:

1. Governments, national societies, and foundations should collaborate to develop clinical and public health guidelines for CVD prevention that target risk factors.
2. Evidence-based guidelines should incorporate professional judgment on the translation of such evidence into effective and efficient care addressing all areas of CVD risk.
3. The assessment of total CVD risk should be based on epidemiological risk factor data appropriate to the population to which it is applied.

4. Policy recommendations and guidelines should emphasize a total risk approach for CVD prevention.
5. The intensity of interventions should be a function of the total risk of CVD, with lower treatment thresholds for higher-risk patients.
6. National cardiovascular societies/foundations should promote routine prospective collection of validated national vital statistics on the causes and outcomes of CVD for use in the development of national policies.
7. National professional societies should inform policymakers of risk factor targets and drug therapies for prevention of CVD that are culturally and financially appropriate to their nation and ask the government to incorporate prevention of CVD into legislation whenever relevant.
8. National professional societies/foundations should facilitate CVD prevention through education and training programs for health professionals.
9. National professional societies should assess the achievement of lifestyle, risk factor, and therapeutic targets defined in the national guidelines.
10. Health professionals should include prevention of CVD as an integral part of their daily clinical practice.

Although the focus of these recommendations is clinical, it is recognized that a population approach to CVD prevention is the foundation of all clinical strategies in preventive cardiology. The WHSF strongly endorses the World Health Report 2002 recommendations that urge countries to adopt policies and programs to promote population-wide interventions such as reducing use of tobacco, reducing saturated fat in the national diet and salt in processed foods, encouraging higher consumption of fruits and vegetables, and encouraging weight reduction and exercise.

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