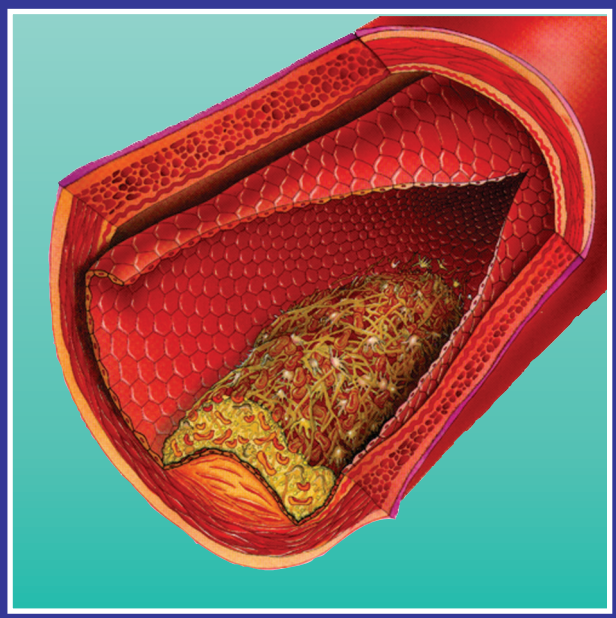
International Atherosclerosis Society

Harmonized Clinical Guidelines on Prevention of Atherosclerotic Vascular Disease



EXECUTIVE SUMMARY

International Atherosclerosis Society (IAS) Harmonized Clinical Guidelines on Prevention of Atherosclerotic Vascular Disease were prepared by the IAS Executive Board.
The guidelines were ratified by a majority of member societies of the IAS.

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Harmonized Clinical Guidelines on Prevention of Atherosclerotic Vascular Disease

EXECUTIVE SUMMARY

International Atherosclerosis Society

The International Atherosclerosis Society (IAS), incorporated in 1979, promotes, at an international level, the advancement of science, research, and teaching in the field of atherosclerosis and related disease. The IAS endeavors to achieve these objectives by promoting the exchange of existing knowledge; encouraging new research ventures and interdisciplinary approaches; establishing visiting fellowships for young investigators; fostering the dissemination of knowledge by organising international symposia, workshops, courses, and meetings; and through the association with a scientific journal.

Membership is open to active researchers who join one of the 50 IAS national or regional constituent societies or who join as individual members from countries without a national affiliated society. There are 10,265 individual members of the IAS. These members are represented in the IAS by the Executive Board. This board is elected by representatives of the 50 constituent societies. It consists of 10 members including the officers of the IAS, members at large, the president of the upcoming International Symposium on Atherosclerosis, and the senior adviser.

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Executive Summary

Introduction

Atherosclerotic cardiovascular disease (CVD) is the foremost killer in developed countries and is becoming increasingly common in developing countries. The major atherosclerotic diseases include coronary heart disease (CHD), stroke, and peripheral arterial disease. The causes of atherosclerotic CVD are multifactorial. Many of the contributing factors are related closely to lifestyle. These include cigarette smoking, atherogenic diets, overweight/obesity, and sedentary life habits (physical inactivity). The International Atherosclerosis Society (IAS) is committed to supporting national public health efforts to decreasing atherosclerotic CVD worldwide by reducing the population burden of these lifestyle factors. In addition the IAS recognizes that some persons in the general population are at higher risk for CVD and require clinical intervention to reduce both CVD morbidity and mortality. Advances in clinical management of such persons make it possible to appreciably reduce their risk. Such advances involve a combination of therapeutic lifestyle changes and drug therapies. The clinical strategy for CVD risk reduction represents an important and necessary extension of the public health approach.

This document summarizes the IAS harmonized guidelines for the clinical reduction of atherosclerotic CVD risk. The rationale for these recommendations and appropriate references are provided in the full report of these guidelines. This executive summary is not referenced. The IAS recommendations are directed primarily to the medical profession. In the past decade, guidelines for CVD prevention have been developed by several professional organizations and national societies. The IAS has attempted to harmonize and integrate these other guidelines to provide a rational multifactorial strategy that can be adapted for use worldwide. Particular attention was given to guidelines produced by expert bodies representing both national and international cardiovascular organizations. Especially noteworthy are the educational programs sponsored by United States National Heart Lung and Blood Institute (NHLBI) for cholesterol, blood pressure, and obesity, the International Task Force for Prevention of Coronary Heart Disease, the World Health Organization, the joint European Cardiovascular Societies, the American Heart Association (AHA), the American College of Cardiology, and various national and international societies for hypertension and diabetes. The recent Third Report of the Adult Treatment Panel (ATP III) of the NHLBI-sponsored National Cholesterol Education Program (NCEP) provides a particularly detailed review of the evidence for clinical intervention to reduce risk for CVD. The IAS has paid special attention to the ATP III report, its extensive review of the literature, and its evidence statements in the development of its recommendations. Although recommendations from these various bodies are not completely congruent, the results of many clinical trials during the past decade require a similarity of treatment guidelines. Where discrepancies exist, they generally are in special areas and do not alter the general principles of clinical CVD prevention. This effort at harmonization will emphasize areas of agreement on major issues; it also will consider reasons for discrepancies on guidelines for special issues. In these latter areas, considerable room exists for clinical judgment in implementation of preventive strategies.

The IAS recognizes that cardiovascular guidelines must be adapted by national or regional societies to accord with national health policy and available resources. Physicians to individual patients must further adapt them according to patient needs. The IAS recommendations thus represent a set of principles that require modification where appropriate to nations or individuals. An excellent example of adaptation of IAS guidelines is provided by Pocket Guide to Prevention of Coronary Heart Disease prepared by the International Task Force for Prevention of Coronary Heart

Disease. This Pocket Guide to Prevention of Coronary Heart Disease was prepared in cooperation with the IAS under the terms of the affiliation agreement between these organizations.

This summary of IAS guidelines will be divided into three major sections: (a) risk assessment for selection of patients for clinical intervention, (b) clinical management of CVD risk factors, and (c) special issues in CVD prevention.

RISK ASSESSMENT FOR SELECTION OF PATIENTS FOR CLINICAL INTERVENTION

The selection of patients for clinical intervention for prevention of CVD is done through identification of high-risk conditions and risk factors for CVD. These contributors to CVD risk are summarized in Table 1. High-risk conditions are listed in Table 1A. Three categories of risk factors that contribute to CVD risk include underlying risk factors, major risk factors, and emerging risk factors (Table 1B).

Prevention in High-Risk Patients

Persons who have high-risk conditions deserve immediate and intensive clinical intervention to reduce risk for major CVD events. These conditions include established CHD, clinical forms of non-coronary atherosclerotic disease, diabetes occurring in high-risk populations, and the presence of multiple risk factors leading to a high risk for future CVD events (e.g. 10-year risk for CHD > 20%). Many controlled clinical trials document the efficacy of high-risk prevention. The essential approach to prevention of future CVD events in high-risk patients is through reduction of those risk factors for CVD listed in the Table 1B.

Primary Prevention

When persons carry major risk factors but *do not* manifest one of the high-risk conditions, clinical intervention may still be required to reduce either short-term risk or long-term risk. Selection of patients for clinical intervention for primary prevention depends on estimates of absolute CVD risk and/or on severity of individual risk factors. Assessment of absolute risk gives priority to the major risk factors. The usual method for estimating absolute risk is to determine 10-year risk for *hard* CHD events (myocardial infarction + coronary death). Absolute risk for total CVD events (acute coronary syndromes, coronary death, coronary artery procedures, and stroke) typically is about twice that estimated for hard CHD events.

Risk categories. Categories of 10-year risk warranting clinical intervention vary according to national health policy from one country to another. A 10-year risk for CHD of > 20% is commonly classified as a *high-risk status.* ATP III guidelines further identify a 10-year risk of 10-20% as *moderately high risk.* A 10-year risk of < 10% can be called *low-to-moderate risk* depending on the number of risk factors present. ATP III moreover recognizes a category of *high lifetime risk* for individuals whose 10-year risk is < 10% but who have two or more major risk factors or a severe single risk factor, e.g. heavy cigarette smoking, persistent hypertension, hypercholesterolemia, and type I diabetes. Several risk-assessment algorithms have been developed for estimating 10-year risk for CHD events. Two of these—Framingham and PROCAM— are most commonly employed.

Framingham risk scoring. In the United States, the most widely used algorithm is that developed by the Framingham Heart Study (see Table 2 for men and Table 3 for women). The risk factors included in the Framingham calculation of 10-year risk recommended by ATP III are *age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking.* Diabetes is not listed in this calculation because ATP III guidelines designated diabetes in the United States as a *CHD risk equivalent* and recommended that it be treated

separately as a high-risk condition. In other Framingham algorithms, diabetes is counted as a risk factor and is included in 10-year risk assessment. For risk estimation, the first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and HDL cholesterol are required. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Total cholesterol and HDL cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis. The blood pressure value used is that obtained at the time of assessment, regardless of whether the person is on anti-hypertensive therapy. However, if the person is on anti-hypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk (see Tables 2 and 3). The average of several blood pressure measurements is needed for an accurate measure of baseline blood pressure. The designation "smoker" means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death (hard CHD) is estimated from total points and the person is categorized according to absolute 10-year risk as indicated above (see Table 1). Computer-based risk estimates based on Framingham risk equations can be obtained through the Internet at the website of the National Heart, Lung, and Blood Institute (www.nhlbi.nih.gov). Estimates of risk by computer are more accurate because they employ risk factors as continuous variables rather than dichotomous variables as used with paper score sheets (Tables 2 and 3).

PROCAM risk scoring. Another recognized risk assessment tool was developed for men from the PROCAM study based on residents of Munster, Germany (see Table 4). Risk factors included in the PROCAM algorithm are *cigarette smoking, blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, family history of myocardial infarction, diabetes,* and *age*. As with the Framingham Point Score, the number of points for each risk factor is calculated; the 10-year risk for fatal or non-fatal myocardial infarction or sudden coronary death is based on total points score. Computer-based risk estimates based on PROCAM risk equations can be obtained through the Internet at the website of the International Task Force for Prevention of Coronary Heart Disease (www.CHD-taskforce.com). Recently the International Task Force has added a new calculator to estimate risk of myocardial infarction by *Neural Network Analysis* (based upon data from the PROCAM study in men aged 40 to 65 years). Finally, *Pocket Guide to Prevention of Coronary Heart Disease* prepared by the International Task Force provides details of risk assessment along with regional adjustment factors for risk scoring with the PROCAM algorithm.

Comparison of Framingham and PROCAM algorithms. The IAS website (www.athero.org) contains links to the websites for Framingham and PROCAM risk-assessment tools.The IAS recognizes both algorithms as valid tools for risk assessment. The two algorithms provide similar, although not identical, estimates of 10-year risk. Several differences can be noted, particularly for men. The Framingham algorithm reduces points for total cholesterol and smoking with advancing age, which PROCAM does not. Therefore, for smokers or hypercholesterolemic men < 50 years, Framingham risk estimates are higher than PROCAM; consequently hypercholesterolemic and/or smoking men in this age range often are classified as having 10-20% risk by Framingham, whereas their estimated 10-year risk is < 10% by PROCAM. These higher estimates in Framingham produced by hypercholesterolemia and smoking track with a high lifetime risk. Differences between the two algorithms decline after age 50, and in older patients who are smokers or hypercholesterolemic, PROCAM estimates often are somewhat higher. With these exceptions, in most other patients the two algorithms will give the same categories of 10-year risk, i.e., > 20%, 10-20%, and < 10%. Finally, with the PROCAM *Neural Network Analysis* the interaction between age and other risk factors should lead to a scoring adjustment.

It should be noted that Framingham, but not PROCAM, provides a 10-year risk assessment for men > 65 years. Framingham but not PROCAM also has a risk algorithm for women. In the future, PROCAM should complete a risk-assessment tool for women. Preliminary indications are that PROCAM estimates for women will be lower than with Framingham, but it must be noted that Framingham estimates for women already are much lower than for men with the same risk factor profile. Therefore, any differences in estimates between PROCAM and

Framingham for women will be of little therapeutic significance.

The issue of diabetes. The position of diabetes in risk-assessment algorithms is a topic of on-going consideration. In higher risk populations, patients with diabetes carry a high risk for CVD. However, the absolute risk for CVD in patients with diabetes varies depending on type of diabetes, age, and population baseline risk. ATP III designated diabetes as a high-risk condition because of the high average risk in patients with diabetes in the United States; ATP III thus recommended intensive risk-factor management, similar to that given to patients with established CHD. This has the advantage of simplifying guidelines, and it recognizes diabetes as a multifactorial risk condition. Nonetheless, clinical judgment is required for selection of types and intensity of risk-factor management in patients with diabetes, depending on modifying factors. For these reasons, diabetes is not included in the ATP III's recommended Framingham risk scoring (Tables 2 and 3). An alternate approach advocated by some investigators is to count diabetes as a risk factor and to incorporate it into absolute risk assessment algorithms along with other major risk factors. This approach is taken by PROCAM (Table 4) and is appropriate when a large fraction of patients with diabetes do not have a high 10-year risk.

Risk assessment beyond Framingham and PROCAM. Absolute risk in individuals is determined in large part by the major risk factors, but risk can be modified by other influences including the underlying risk factors and the emerging risk factors (Table 1B). Other "risk factors" yet to be discovered undoubtedly contribute to risk as well. Studies are underway to incorporate factors other than major risk factors into risk assessment tools. For example, PROCAM has gone beyond Framingham by identifying triglycerides and family history of myocardial infarction as *independent risk factors.* There is a growing body of evidence that the underlying and emerging risk factors carry some independent prediction of risk. To date however their relation to CVD has not been quantified adequately to incorporate them into absolute risk estimates. Nonetheless, the likelihood that other factors are at play is suggested by differences in CVD rates in different populations. Although population differences in CVD must be explained in part by variations in established risk factors, regional differences almost certainly influence the severity of other factors as well. It has been proposed that these regional differences can be used as a basis to modify the risk estimates obtained with available risk algorithms. This approach however will be problematic unless the burden of established risk factors for each population has been well defined. To date such information for most regions is not available. Unfortunately, long-term prospective studies, such as those from Framingham and PROCAM, have not been carried out for most regions of the world.

Clinicians in practice have two rational options for estimating absolute risk algorithms as a guide to primary prevention. The first is to base clinical decisions exclusively on one of the absolute risk algorithms (e.g. Framingham or PROCAM), which places a patient into a particular risk category, e.g. 10-year risk of < 10%, 10-20%, or > 20%. The other is to employ one of these two algorithms to obtain an initial categorization of risk and then to raise or lower the risk assignment by *one category* after evaluating all of the available underlying and emerging risk factors, i.e., whether they are present or absent. Underlying risk factors to be evaluated include an *atherogenic diet, overweight/obesity,* and *physical inactivity,* and in the case of Framingham, *family history of CHD.* In addition, average rates of CVD of the population in which the patient resides can also count as an underlying risk factor. Emerging risk factors consist of serum elevations of *apolipoprotein B, small LDL particles, lipoprotein (a), C-reactive protein, fibrinogen,* and *homocysteine. Impaired fasting glucose* or *impaired glucose tolerance* further can count as emerging risk factors. The detection of *advanced subclinical atherosclerosis* through imaging modalities also apparently imparts increased risk for CVD beyond the established risk factors. If changing the risk category based on underlying and emerging risk factors is undertaken, as many of these other risk factors as available should be taken into account; excessive emphasis on a single emerging risk factor is to be discouraged. Changing a risk category must be based on clinical judgment because no quantitative methods are available for this purpose.

Metabolic syndrome as a risk indicator. With the worldwide increase in overweight/obesity

and sedentary life habits, an alternate pattern of risk factors is emerging. This pattern consists of several metabolic risk factors occurring in individuals and is designated as the *metabolic syndrome.* The risk factors that compose the metabolic syndrome and ATP III criteria for the clinical diagnosis of the metabolic syndrome are presented in Table 5. The IAS adopts these diagnostic criteria for routine clinical management; however, it recognizes that attempts are being made to refine and extend clinical assessment of the metabolic syndrome. The absolute risk for CVD conveyed by the metabolic syndrome in different populations has not been determined with certainty. *The IAS does not identify the metabolic syndrome per se as a high-risk condition.* Risk assessment in persons with the metabolic syndrome should first be based on the major risk factors. Nonetheless, there is growing evidence that the metabolic syndrome represents a common major multiplex risk factor in many populations and deserves increased attention in the clinical setting. Patients with the metabolic syndrome deserve intensive therapeutic lifestyle changes to reduce the severity of the syndrome. If adjustment of risk categorization is made through the use of underlying and emerging risk factors, the risk factors of the metabolic syndrome may be taken into consideration in this adjustment.

CLINICAL MANAGEMENT OF CVD RISK FACTORS

Underlying Risk Factors

Much of the increase in CVD worldwide can be attributed to a growing prevalence of the underlying risk factors. Besides cigarette smoking, the modifiable risk factors in this category are an atherogenic diet, overweight/obesity, and physical inactivity. Although these risk factors are primarily targets for public health strategies, the health care profession can support these strategies by intervention on these risk factors in individuals with increased CVD risk.

Atherogenic diet. The globalization of the food market has introduced atherogenic foods to all nations. Traditional eating habits in many nations that once protected against CVD are disappearing. Physicians should counter this trend by instructing their patients at risk for CVD to modify their diets according to the principles outlined in Table 6.

Overweight and obesity. Changing lifestyles and especially urbanization have produced a worldwide epidemic of overweight and obesity. This epidemic is most manifest in the United States, but the prevalence of obesity is increasing at an alarming rate in many parts of the world, especially in Asia. A greater prevalence of obesity will be largely responsible for the increase in CVD and diabetes throughout the world. The following shows classifications of body weight and body mass indexes (BMIs) that are generally accepted in the United States, Europe, and the Asian Pacific region.

Body Weight Category	Europe and United States	Asian-Pacific Region
	Body Mass Index (kg/m^2)	Body Mass Index (kg/m^2)
Underweight	<18.5	<18.5
Normal	18.5-24.9	18.5-22.9
Overweight (moderate risk)	25-29.9	23-24.9
Obesity	≥30	≥25
Class I obesity	30-34.9	25-29.9
Class II obesity	35-39.9	≥30
Class III obesity	≥40	

When physicians encounter persons who are overweight or obese, they should introduce the principles of management outlined in Table 7.

Physical inactivity. Over 60% of the world's population is sedentary and is not physically active enough to gain the health benefits of exercise. Physical inactivity further contributes to overweight/obesity. Clinicians should encourage their sedentary patients to adopt the principles of physical activity outlined in Table 8.

Major Risk Factors

Cigarette smoking. The World Health Organization estimates that 4 million people die each year from cigarette smoking. At current rates of smoking worldwide, this number will increase to 10 million over the next decade. Smoking in the developing world is especially alarming. In China alone, 2,000 people die each day from smoking-induced diseases. At least one-third of all CVD is the result of cigarette smoking. Physicians should make every effort to discourage smoking and to assist in smoking cessation among their patients. Principles of clinical intervention on cigarette smoking are outlined in Table 9.

Hypertension. Approximately 690 million people worldwide have hypertension. At least 3 million die directly from hypertension annually, and the condition contributes to many other deaths. The prevalence of hypertension increases with age; in fact, in some populations up to half of the population over age 60 has elevated blood pressure. Hypertension is a major risk factor for stroke, CHD, heart failure, and kidney failure. About 30 million people worldwide have had a hypertension-related stroke; among these, 5 million die each year. Thanks to improved detection and treatment of hypertension, hypertension has been better controlled and stroke incidence has declined in some countries. Even so, seven out of every 10 people with hypertension are not being treated adequately. Physicians are urged to pay close attention to current recommendations for treatment of hypertension (Table 10). These recommendations generally harmonize the recommendations of the World Health Organization-International Society of Hypertension and the United States Joint National Committee on Hypertension VI (JNC VI). Application of these recommendations to persons with hypertension would greatly reduce hypertension-induced co-morbidities.

Elevated LDL cholesterol. An elevation of serum LDL cholesterol is a primary risk factor for CHD; some elevation of serum LDL is required to initiate and maintain atherogenesis. Populations that have very low levels of LDL cholesterol generally have low rates of CHD even when other CVD risk factors are present. Recent clinical trials have shown the benefit of LDL-lowering drugs (statins) in high-risk patients. Other LDL-lowering drugs (bile acid sequestrants, nicotinic acid, and ezetimibe) reduce LDL levels about half as much as statins. These other drugs can be combined with statins to enhance LDL reduction. Although LDL-lowering drugs will reduce risk, they must be used judiciously in primary prevention because of their high cost. ATP III indicates that LDL-lowering drugs are "cost effective" in patients at moderately high risk by current standards in some countries; however, in other countries they are considered to be too expensive in this category of risk. Because of the relatively high cost of LDL-lowering drugs, cutpoints for their initiation in persons whose 10-year risk is < 20% is restricted in many countries. As cost of drugs declines, these drugs will be used more widely. Table 11 presents a general approach for management of elevated LDL cholesterol in different risk categories.

Low HDL cholesterol. In higher risk populations, a low serum HDL-cholesterol level is consistently associated with increased risk for CHD. At least three mechanisms have been postulated for this association. First, a low HDL commonly reflects the presence of atherogenic remnant lipoproteins; second, a low HDL typically occurs in the presence of non-lipid risk factors of the metabolic syndrome; and third, HDL may directly protect against atherosclerosis and a low level may allow for accelerated atherogenesis. There is only limited clinical trial evidence that HDL-raising therapies will protect against CHD. However, a low HDL level deserves clinical attention as outlined in Table 12.

Diabetes mellitus. Over 90% of all cases of hyperglycemia (plasma glucose ≥ 126 mg/dL; ≥ 7.0 mmol/L) are present in a condition called type 2 diabetes. Less common is type 1 diabetes. According to current estimates, over 120 million people worldwide have type 2 diabetes Because of the global epidemic of obesity, this number is expected to rise to over 230 million by 2010 and to over 300 million by 2025. The medical complications of diabetes are manifold: CHD, stroke, peripheral arterial disease, blindness, renal failure, and amputations. All patients with diabetes deserve appropriate clinical management, as recommended by both diabetes and cardiovascular societies. Table 13 summarizes these key recommendations. Since type 2 diabetes is characterized by a constellation of risk factors (the metabolic syndrome), therapy of type 2 diabetes requires attention to all risk factors. Clinical trials document benefit of treating multiple risk factors in patients with type 2 diabetes. Likewise, risk factor management is needed in patients with type 1 diabetes.

Family history of premature CVD. Persons with a strong family history of premature CVD are at increased risk for major CVD events. A positive family history can be defined as the presence of CVD in a male first-degree relative before age 60 or female first-degree relative before age 65. At least two factors contribute to risk in a person who has a positive family history. First, the family may be genetically predisposed to early onset CVD; and second, CVD often occurs in families because of a shared atherogenic environment, i.e., family habits of cigarette smoking, obesity, physical inactivity, and consumption of an atherogenic diet. For these reasons, special attention must be given to individuals who have a family history of premature CVD. They should be carefully tested for the presence of genetic risk factors, e.g. familial hypercholesterolemia and other dyslipidemias, hypertension, insulin resistance and impaired fasting glucose, and thrombotic disorders. In addition, these persons should be carefully questioned about lifestyle that could predispose to CVD. Finally, in view of higher risk accompanying a positive family history, an intensive search for all CVD risk factors - major, underlying, and emerging risk factors - can be justified. Moreover, when risk factors are identified, their appropriate management is indicated.

Aging as a risk factor. Advancing age is a risk factor for CVD. This is due in large part to the cumulative damage of other risk factors on the arterial tree. The most explicit example is the progressive accumulation of atherosclerotic plaque burden with age. Plaque burden predisposes to major vascular events. Nevertheless a growing body of evidence indicates that major vascular events can be reduced by risk factor management in older subjects even when atherosclerosis is advanced. Clinical trials of both blood pressure control and LDL-lowering therapy have demonstrated a reduction in vascular events in older persons. For many years there was skepticism as to whether control of risk factors would reduce major vascular events in older persons. Any remaining doubt has been dispelled through recent clinical trials. Because of the aging of the world's population, physicians are increasingly called upon to make decisions about use of risk reducing therapies in older persons. Certainly first priority for therapy goes to persons who fall into the high-risk categories; these include persons with established CHD, other forms of clinical atherosclerotic disease, diabetes, and multiple risk factors. Clinical judgment is required as to when to introduce medical therapies for primary prevention in older persons. Measurements of subclinical atherosclerosis may assist for deciding when to use cholesterol-lowering drugs. In persons not deemed to be at high risk, a reasonable approach may be to intervene on established risk factors - smoking, hypertension, hypercholesterolemia, and diabetes. In all cases clinical judgment is required when intervening on risk factors in older persons who have co-morbidities that affect quality of life and that may reduce life expectancy.

Emerging Risk Factors and the Metabolic Syndrome

Persons who have emerging risk factors may be at increased risk for CVD (Table 1). When they occur in the presence of the metabolic syndrome, risk may be compounded. Although the emerging risk factors are associated with increased risk for CVD, there are important

unresolved issues about their relationship to CVD. In general the pathophysiological mechanisms responsible for their relationship are not known. Further the strengths of their relationship to CVD are not as well established as for the major risk factors. For these reasons, measurement of emerging risk factors is optional, and if measurements are obtained, clinical judgment is required for their use in risk assessment. General principles for approaching the emerging risk factors are outlined in Table 14.

A prothrombotic state can be assumed to be present in patients with the metabolic syndrome. Among the risk factors of the metabolic syndrome, a prothrombotic state is highlighted because of evidence that anti-platelet therapy will reduce risk for major atherosclerotic events. Moreover, even when the metabolic syndrome is not present, anti-platelet therapy will reduce risk for major thrombotic events, i.e., acute coronary syndromes and stroke. Consequently, aspirin therapy is indicated for most high-risk patients (Table 1). Some authorities further recommend use of low-dose aspirin in individuals at moderately high risk, i.e., 10-year risk for CHD, 10 to 20%. It has been estimated that appropriate use of low-dose aspirin therapy could save 40,000 lives per year by reducing major vascular events in high-risk patients. General principles of anti-platelet therapy are summarized in Table 15.

The metabolic syndrome represents a combination of underlying, major, and emerging risk factors (Table 5). The prevalence of the metabolic syndrome is on a steep rise worldwide because of the increasing obesity and sedentary lifestyles. The prevalence of the metabolic syndrome probably exceeds that of type 2 diabetes by a factor of three-to-four. Persons with the metabolic syndrome should be identified in clinical practice. The current clinical approach to the syndrome is to focus on appropriate management of accompanying risk factors. Priority is given to management of underlying risk factors with therapeutic lifestyle changes (Tables 6, 7, and 8). Associated major risk factors should be treated according to the principles outlined in this document, and appropriate clinical attention should be given to the presence of emerging risk factors (Table 14).

SPECIAL ISSUES IN CVD PREVENTION

Special Considerations on Management of Cardiovascular Risk Factors

Major CVD risk factors (e.g., cigarette smoking, hypertension, serum lipid disorders, and diabetes) are common in many populations. IAS guidelines generally describe clinical approaches to control of mild-to-moderate risk factors occurring in the general population. If these approaches were to be followed thoroughly, the burden of cardiovascular disease in societies would be greatly reduced. However, in some individuals, risk factors occur in severe or unusual forms. It is beyond the scope of this document to address the management of these particular forms. Standard reference sources should be sought. However, in this section, three issues will be addressed briefly: (a) special disorders of lipid and lipoprotein metabolism and (b) special issues that arise in different gender and age groups as well as in racial and ethnic differences in susceptibility to cardiovascular disease, and (c) considerations for differences in national and regional venues.

Management of Specific Dyslipidemias

Very high LDL cholesterol (≥ 190 mg/dL; ≥ 4.9 mmol/L) often is of genetic origin. Early detection and early intervention with cholesterol-lowering drugs can prevent premature CVD and prolong life. *Very high triglycerides* (≥ 500 mg/dL; ≥ 5.7 mmol/L) carry increased risk for acute pancreatitis and usually require triglyceride-lowering drugs combined with very low fat diets. Lesser increases in triglycerides (150-499 mg/dL; 1.7-5.7 mmol/L) often signify the presence of the metabolic syndrome but may indicate genetic hyperlipidemias (familial hyperlipidemia or familial combined hyperlipidemia). In these conditions, priority goes to attaining LDL cholesterol and non-HDL cholesterol targets and introducing therapeutic lifestyle changes (Tables 6-8); use of

triglyceride-lowering drugs depends on clinical judgment. *Diabetic dyslipidemia* represents atherogenic dyslipidemia occurring in patients with type 2 diabetes; again, LDL cholesterol is the primary target of therapy, and non-HDL cholesterol, the secondary target.

Special Considerations According to Age, Gender, and Racial and Ethnic Groups

Premature CVD occurs commonly in middle-aged men (35-65 years) in high-risk populations. To prevent premature death in middle-aged men special attention should be given to detection and management of CVD risk factors. Although women 45-75 years typically have a lower incidence of CVD than men of the same age, women at higher risk should be identified; such include women who are smokers or who have the metabolic syndrome, type 2 diabetes, hypertension, or hypercholesterolemia. It should be noted that women have similar propensities to stroke and diabetes as men, and particular attention should be given to blood pressure control and diabetes prevention. Recent clinical trials do not support the concept that post-menopausal estrogen replacement therapy will reduce the risk for CVD. The risk issues of older persons were discussed under age as a major risk factor. Young adults should be examined for one or more of the major risk factors: smoking, hypertension, hypercholesterolemia, and type 1 diabetes. In young adults, all categorical major risk factors deserve clinical intervention.

Some populations are particularly susceptible to particular risk factors and exhibit different patterns of CVD. For example, black populations of African origin are prone to hypertension. Caucasians often manifest cholesterol disorders and other dyslipidemias. Several populations in the Middle East have been reported to have relatively low levels of HDL cholesterol. Native Americans are susceptible to insulin resistance and diabetes. South Asians and South East Asians also have a high prevalence of insulin resistance and commonly develop the metabolic syndrome, diabetes, and coronary heart disease. The Japanese appear to have a low baseline risk for CHD, but have a relatively high prevalence of hypertension and stroke. This variability in disease prevalence must be taken into account when adapting the IAS guidelines for different racial and ethnic groups.

Special Considerations for Differences in National and Regional Venues

In different countries and regions of the world atherosclerotic CVD varies in its incidence, prevalence, and manifestations. Differences depend on both racial susceptibility and national lifestyle. For this reason, clinical guidelines for prevention of CVD must be adapted and modified according to national and regional requirements. Moreover, in many populations, medical resources are limited and clinical management of risk factors must be restricted to those at highest risk. One approach that has been taken by many countries is to identify high-risk patients and to make pharmaceutical therapies available for them. For the remainder of the population, risk factor control in primary prevention is relegated to the public health approach. If this approach is necessary, more attention should be given to prevention and/or reduction of risk factors in the general population, i.e., prevention and cessation of smoking, encouragement of regular physical activity, introduction of means to reduce the prevalence of obesity, and modification of an atherogenic diet in the population. Dietary modification will require cooperation from government on health policy and from the food industry. The prevalence of hypertension is relatively high in most countries of the world; but even in the wealthier countries, control of hypertension in the general population is relatively poor. Inexpensive medications for treatment of hypertension are widely available, and increasingly, their use must be considered an element of the public health approach. It is also expected that the costs of cholesterol-lowering drugs will decline rapidly over the next decade so that they will become more widely available for treatment of lipid disorders, even for primary prevention. Thus, the current guidelines should be viewed as a strategy for CVD prevention as much as for use in the treatment of individual patients. It is expected that providing a state-of-the-art blueprint for clinical CVD prevention will serve as a resource for development of national and regional strategies at all levels for preventing CVD worldwide.