# INTERNATIONAL ATHEROSCLEROSIS SOCIETY
# HARMONIZED GUIDELINES ON
# PREVENTION OF ATHEROSCLEROTIC
# CARDIOVASCULAR DISEASE

## Full Report

Atherosclerotic cardiovascular disease (CVD) is the foremost killer in developed countries and is assuming increasing importance in developing countries. The World Health Organization projects that CVD will become the primary cause of death worldwide by the year 2020 (1,2). This prediction depends in part on anticipated progress in reducing deaths from infectious diseases throughout the world.

The causes of atherosclerotic CVD are multiple. Many of the contributing factors relate closely to lifestyle (3). These include cigarette smoking, atherogenic diets, overweight/obesity, and sedentary life habits (physical inactivity). To effectively forestall the predicted pandemic of atherosclerotic CVD, massive national efforts must be made to modify lifestyle trends. All of the risk factors deserve attention in public policies, particularly agricultural and tobacco policies, in education of the public, and in creation of opportunities for healthful physical activity. The International Atherosclerosis Society (IAS) is committed to supporting national and regional public health efforts to reduce the burden of atherosclerotic CVD worldwide.

Parallel with the rising prevalence of atherosclerotic diseases has been an advance in preventing the clinical sequelae of these diseases--major coronary events and strokes. Our ability to reduce the latter results in no small part from a better understanding of the underlying causes of CVD, which are called *risk factors* (4). Two approaches to risk factor modification are recognized, namely, public health strategies and clinical approaches. The former focuses on population life habits, whereas the latter makes use of both therapeutic lifestyle changes and medications. The development of drugs to reduce risk factors promises to produce remarkable reductions in the incidence of CVD in high-risk persons. The clinical approach nonetheless extends beyond high-risk patients; the medical profession has a responsibility to identify persons who are at risk for CVD in the long term and to employ appropriate clinical strategies to augment the public health approach in these persons. For example, some individuals at moderate risk may require drug therapies to control individual risk factors so as to prevent CVD in the long run.

This document is directed primarily to health professionals, with the purpose of providing guidelines on clinical management of risk factors to reduce risk for CVD. In the past decade, a large number of guidelines for CVD prevention have been developed by professional organizations and national societies. These guidelines increasingly offer "evidence-based" recommendations and have gone beyond earlier "consensus" recommendations. The evidence mounted in guidelines has been enriched by many powerful randomized controlled trials. Even so, other lines of evidence—epidemiological studies, clinical experimentation, and expert judgment—contribute when clinical trials fail to answer pressing clinical questions.

This document was prepared by the Executive Committee of the IAS and ratified by the IAS Executive Board and a majority of the IAS Member Society presidents. Its purpose is to harmonize and integrate existing guidelines for the clinical management of risk factors for atherosclerotic CVD. The existing guidelines provide an extensive review of the scientific evidence underlying their recommendations. The current document does not attempt to re-examine all of the available evidence.

Instead it abstracts the evidence reviewed by several expert panels. Besides acknowledging the sources that contributed to the IAS harmonized guidelines, key references are inserted into the text for background information. They should not be taken as the sole basis for the recommendations. The reader is referred to the original reports of expert panels for documentation of the scientific basis for particular recommendations. It must be noted nonetheless that in the effort to harmonize existing guidelines, an element of judgment was required by the IAS Executive Committee to link the different guidelines into a coherent whole.

In this harmonization process, useful formation has been obtained from guidelines that focus on particular CVD risk factors, e.g., major risk factors, such as cigarette smoking (5-8) hypertension (9-12) high blood cholesterol (13,14) and diabetes (15-19), or underlying risk factors, such as overweight/obesity (20-22) physical inactivity (23-25), and atherogenic diets (3,26,27). In addition, guidelines were also surveyed that offer recommendations on global risk factor management in higher risk patients or for primary prevention (28-33). Some of these guidelines are available on-line, whereas others can be obtained only in print. For a review of the current status of CVD risk factors, the United States National Cholesterol Education Program (NCEP) Adult Treatment Panel III (14) was consulted carefully. ATP III further provided up-to-date guidance on management of high blood cholesterol in adults. Although discrepancies on recommendations can be found among existing guidelines, the results of many clinical trials during the past decade make possible congruence in most recommendations. In most part differences in guidelines fall under specialized areas and do not alter the general principles of clinical CVD prevention. This effort at harmonization will emphasize areas of agreement on major issues, and 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.

In spite of general agreement on the science of recommendations, national and regional guidelines are affected differently by considerations of costs and priorities in health care. In some countries, such as the United States, single payer systems do not exists; consequently, availability and costs of medical care vary widely for different subpopulations. United States treatment guidelines therefore are largely "science based," and cost considerations are given less attention. It is expected that various payment organizations will adjust guidelines according to payment priorities. In other countries that have a single-payer system, guidelines typically are fashioned at the outset to accord with national resources and priorities. And in still other countries, particularly in developing nations, resources for clinical prevention are severely limited. In these countries, CVD prevention, of necessity, must give way to other priorities, i.e., basic nutrition and infectious diseases. Nonetheless, the prevalence of CVD in many developing countries is on the rise, and increased attention must be given to both public health and clinical prevention. It is the intention of this document to provide an infrastructure for CVD prevention guidelines in all countries.

The guidelines outlined in this report are divided into four major sections. First, the risk factors for atherosclerotic CVD will be classified and reviewed. Second, methods of risk stratification, i.e., global risk prediction, will be assessed. Third, strategies for clinical intervention to reduce risk for major CVD events will be outlined and proposed. And fourth, special considerations on management of CV risk factors will also be discussed.

## Risk Factors for Atherosclerotic CVD

The risk factors for atherosclerotic CVD are divided into three major categories: underlying risk factors; major, independent risk factors; and emerging risk factors. This classification was recently proposed by NCEP ATP III (14). Although agreement on the placement of risk factors in the different categories is not universal, this three-part division provides one rational classification that accords in general with most others. The risk factors of each category will be described, and a summary of efficacy of interventions to modify the risk factors will be provided.

When reviewing the influence of different factors on CVD risk, it is important to keep in mind the current paradigm for development and progression of atherosclerotic disease. Currently two major phases of atherogenesis are recognized. First, *stable atherosclerotic plaques* gradually develop over a period of many years (34). When these plaques become advanced enough, they can produce chronic ischemic syndromes such as classical angina pectoris. Second, when atherosclerosis becomes advanced, some plaques can degenerate into *unstable atherosclerotic lesions*. These lesions are prone to plaque rupture; and rupture initiates coronary thrombosis, which is responsible for acute coronary syndromes (unstable angina and myocardial infarction) (35-37). Prevention strategies aim to delay the development of both types of lesions: first, delaying the formation of stable plaques, and second favoring the prevention of unstable plaques and their rupture. Persons with advanced atherosclerosis generally carry a high risk for acute coronary syndromes; hence they deserve highest priority in clinical prevention. Nonetheless, an important goal for both public health and clinical approaches is primary prevention of atherosclerosis itself. Although public health approaches are the best way to reduce the burden of atherosclerotic disease in populations, clinical primary prevention of atherosclerosis through the control of risk factors is warranted for many persons (28-33).

### Underlying Risk Factors

*Atherogenic diet*. The nutrient composition of the diet contributes to the development of atherosclerotic disease in several ways. Among these, high intakes of saturated fatty acids and cholesterol promote atherogenesis by raising the serum cholesterol level (27). Epidemiological studies demonstrate that populations that consume large quantities of saturated fatty acids and cholesterol have higher serum cholesterol levels and higher rates of CHD than do populations with lower intakes of these nutrients (38,39). Although no large, diet-heart clinical trials have been conducted to test whether reducing intakes of saturated fats and cholesterol in the diet will reduce risk for CHD, meta-analyses of several smaller clinical trials strongly suggest that substituting unsaturated fatty acids for saturated fatty acids in the diet will lower serum cholesterol levels and reduce incidence of CHD (14,27).

Other dietary factors also associate with CHD risk, either in a positive or negative way (14,27). Factors that seemingly increase risk for CHD are *trans* fatty acids, whereas putative protective factors include unsaturated fatty acids (N-9, N-6, and N-3), folic acid, fruits and vegetables, anti-oxidant vitamins, alcohol, and higher intakes of plant sterols and viscous fiber (14). In addition, CVD risk may be increased by high intakes of sodium and low intakes of potassium, magnesium, and calcium, all of which may raise the blood pressure (9). Support for the beneficial effects of N-9 fatty acids comes from the Seven Country Study in which high-intakes of N-9 fatty acids were associated with lower rates of CHD (38). Higher intakes of N-9 and low consumption of saturated fatty acids are characteristic of the "Mediterranean diet." A large body of epidemiological data supports a CHD-reducing action of moderate alcohol consumption (40-42). Limited clinical trial data support benefit from higher intakes of N-3 fatty acids (43-45). In spite of several lines of evidence that oxidative stress

contributes to CHD risk, clinical trials of anti-oxidant vitamins have failed to confirm a protective action (46,47). It should be noted however that these studies were limited to high-risk patients and vitamins were given as a supplement. Several epidemiological studies suggest that population diets rich in anti-oxidants are accompanied by reduced risk for CHD. Finally, numerous recent studies document that high intakes of plant stanol/sterols or viscous fiber lower serum cholesterol levels beyond what can be achieved by reducing intakes of saturated fatty acids and cholesterol (48-50).

*Overweight/obesity*. Increased body mass index (BMI: $kg/m^2$) conveys greater risks for CVD. Classifications of body weight based on BMI generally accepted in the United States and Europe (20,21,51) and a modification for the population in the Asian-Pacific region (52,53) are shown in the following table:

| 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<br>Class I obesity<br>Class II obesity<br>Class III obesity | ≥ 30<br>30-34.9<br>35.0-39.9<br>≥ 40 | ≥ 25<br>25-29.9<br>≥ 30 |

Overweight and obesity are accompanied by increased risk for CHD (54). The strength of this association is greatest in young adults and middle age, but apparently declines with age. It must be kept in mind nonetheless that the increased risk for CHD in overweight/obese patients is duein large part to accompanying major and emerging risk factors.

Abdominal obesity predicts CVD risk factors out of proportion to total body fat (55-58). Waist circumference is positively correlated with abdominal fat content and provides acceptable clinical measure of a patient's abdominal fat content. The following sex-specific cutpoints have been recommended to identify ***abdominal obesity*** in most United States and European populations (20,21,51). The identified cutpoints for defining abdominal obesity probably are not appropriate for all populations (59). Different sets of waist circumference have been identified for Asians in the Western Pacific Region (52) and for the Japanese population (53). The cutpoints for the identification of abdominal obesity thus probably should be population-specific and may even be different for different nations within a geographical region. The following cutpoints for abdominal obesity has been proposed for different populations:

| | Europe and United States | Asian Pacific Region | Japan |
|---|---|---|---|
| Men | ≥ 102 cm (≥ 40 in) | ≥ 90 cm | ≥ 85 cm |
| Women | ≥ 88 cm (≥35 in) | ≥ 80 cm | ≥ 90 cm |

*Physical inactivity*. Several lines of evidence demonstrate that regular exercise exerts a protective effect against CVD. By implication, physical inactivity is a risk factor for CVD. The American Heart Association has made this formal designation (23,24), and evidence-based reports are in accord (25). Controlled clinical trials have not been carried out to directly test the protective effect of regular exercise on CVD risk; nonetheless, many smaller trials have demonstrated a favorable effect of exercise on other known CVD risk factors (20,21,25).

*Genetic influences*. There is no doubt that genetic factors influence CVD risk. The contribution of genetic abnormalities is observed most strongly in monogenic disorders resulting in development of major risk factors in severe form. Several of the risk factors also have been shown to be under polygenic influence. The common occurrence of particular risk factors or constellations of risk factors in different races further supports the importance of genetic factors in the causation of atherosclerotic CVD.

Major, Independent Risk Factors

*Cigarette smoking*. In many societies, cigarette smoking is the foremost preventable cause of death (5-8). In spite of a reduction in smoking in some countries, cigarette smoking worldwide continues to rise. It is a powerful contributor to risk for CHD and other forms of CVD. Smoking raises risk for CVD in a dose-dependent manner in both men and women. The mechanisms for increased risk are not fully understood but seemingly are multifactorial. Moreover, smoking cessation reduces risk for CVD events; the decline in risk begins within a few months of quitting smoking. Randomized, primary-prevention clinical trials of smoking cessation have revealed substantial reduction in subsequent cardiovascular events in quitters.

*High blood pressure.* Elevations in blood pressure are positively associated with CHD, stroke, heart failure, renal failure, and recurrent CVD (9-12). High blood pressure promotes the development of coronary atherosclerosis, and blood pressure levels are positively and continuously related to the risks of major CHD events (myocardial infarction and coronary death). The relationship occurs across a broad range of blood pressure levels, and patients with even high-normal levels of blood pressure carry an increased risk for CHD. High blood pressure likewise enhances carotid atherosclerosis and produces "small vessel" disease in the brain, both of which are common causes of stroke. Both systolic and diastolic blood pressures are positively and continuously related to stroke risk in all populations. The slope for stroke risk associated with blood pressure is about one-third higher than for CHD. The incidence of stroke increases strongly with age, and the majority of cases of blood pressure-associated cerebrovascular disease occurs in the older population. Elevated blood pressure produces both thrombotic (ischemic) stroke and hemorrhagic stroke. In persons who have suffered a major vascular event, there is a continuous and positive association between blood pressure levels and recurrence of stroke and CHD.

Other important consequences of hypertension are heart failure and renal disease. Patients with a history of hypertension have at least six times greater risk of
heart failure than do normotensive persons. Moreover, hypertension pairs with diabetes as the two most common causes of chronic renal failure.

The utility of blood pressure-lowering emerges from a large number of clinical trials with anti-hypertensive drugs (60-67). The benefit of therapy has been shown in patients in various countries, and efficacy of therapy extends to both sexes, middle-aged and elderly patients, various races and ethnic groups, and differing socioeconomic status. Reducing blood pressure with pharmacological therapy decreases cardiovascular mortality, and protects against stroke, major coronary events, heart failure, progression to renal disease, progression to more severe hypertension, and all-cause mortality (9-12).

*High LDL cholesterol*. Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that increased levels of LDL cholesterol are a major and independent risk factor for CHD (13,14). Early clinical trials with both dietary therapy and drug therapy provided evidence that LDL-lowering will reduce risk for CHD (68). The benefit of LDL-lowering therapy is strongly confirmed by recent clinical trials with HMG CoA reductase inhibitors (statins) (47,69-73). To date there have been four major clinical trials in high-risk patients, i.e., in patients with established CHD and other high-risk states. These trials revealed that statin therapy substantially reduces risk for acute coronary syndromes (myocardial infarction and unstable angina), coronary procedures, and stroke. Risk reduction occurred in all subgroups studied, i.e., smokers and non-smokers, hypertensive and non-hypertensive patients, patients with and without low HDL, patients with and without diabetes, men and women, and middle-aged and older patients. In addition, two other large statin trials of primary prevention demonstrated a marked reduction in relative risk for new onset CHD. All subgroups examined likewise benefited. Taken together, these trials document that for every one percent lowering of LDL-cholesterol concentrations the risk for CHD declines by approximately one percent. Reductions of LDL cholesterol and CHD risk best fit a log-linear relationship, as has been observed in many epidemiological studies. A recent clinical trial showed that high-risk patients demonstrated CVD risk reduction regardless of baseline LDL levels, even with very low LDL-cholesterol concentrations.

*Low HDL cholesterol*. In prospective epidemiological studies, low levels of serum HDL cholesterol associate with increased CHD morbidity and mortality (4,14,30,74). Data from epidemiological studies reveal that a low HDL cholesterol is an *independent risk factor* for CHD. In fact, among the lipid risk factors, low HDL levels usually correlate most highly with CHD risk.

The mechanistic relationship between low HDL-cholesterol levels and development of CHD remains to be fully determined (14). Several lines of evidence suggest that HDL directly participates in atherogenesis. For example, some genetic forms of HDL deficiency in humans display increased risk for CHD. In genetically modified animals, high levels of HDL protect against development of atherosclerosis (75-77). *In vitro* studies further suggest a protective effect of high HDL; for example, HDL promotes efflux of cholesterol from foam cells, the type of cell occurring in atherosclerotic lesions (78). HDL moreover has antioxidant and anti-inflammatory properties that could inhibit atherogenesis (79-81).

These interactions of HDL with the arterial wall, however, cannot fully account for the epidemiological relationship between low HDL levels and CHD rates. Certainly a low HDL concentration correlates with other atherogenic factors, e.g., elevations in triglycerides and remnant lipoproteins (82,83), small LDL particles (84-87), insulin resistance (88), proinflammatory and prothrombotic states, and hypertension (89-91). Consequently low HDL cholesterol is not as strongly *independent* in its prediction of CHD as suggested by usual multivariate analysis, i.e., its independence is partially confounded by some risk factors that are not routinely measured, e.g., *emerging risk factors.*

There are no drugs, available for clinical practice, that specifically raise serum HDL cholesterol. However, fibrates and nicotinic acid cause substantial increases in HDL cholesterol. Several primary and secondary prevention trials provide relatively strong evidence that these agents will reduce risk for major coronary events (92-100).

*Diabetes*. Diabetes is defined as a confirmed elevation of fasting blood glucose [≥ 126 mg/dL (≥ 7.0 mmol/L)]. Clinical diabetes is a major risk factor for CVD (15-19), and it contributes importantly to CVD and its complications (101-107). Two well-recognized forms of diabetes are Types 1 and 2. Type 1 diabetes, commonly called juvenile diabetes, is secondary to autoimmune destruction of pancreatic beta cells. Type 2 diabetes usually has onset in adulthood and is characterized by variable combinations of insulin resistance and reduced insulin secretion. Both types of diabetes raise the risk for all forms of atherosclerotic disease. Hyperglycemia per se probably promotes the development of atherosclerosis; however, many patients with diabetes have concomitant cardiovascular risk factors that accelerate atherogenesis. A growing body of literature point out that many people with diabetes from higher risk populations carry an absolute risk for major coronary events similar to that of non-diabetic people with established CHD (46,108,109). This finding led the ATP III to designate diabetes in the United States as a *CHD risk equivalent* (14); as such, all CVD risk factors in patients with diabetes should be treated as intensely as in patients with established CHD. It was recognized that some patients with diabetes (e.g., young adults with type 1 diabetes and older persons with mild hyperglycemia) may not have a CHD risk equivalent and therefore may require less intensive therapy of risk factors. For such patients, physicians can use clinical judgment when adjusting management of risk factors.

An additional factor must be taken into account when considering the risk for CVD associated with diabetes. Risk for new-onset CVD and risk after onset for CVD must be distinguished. Abundant evidence indicates that patients with diabetes carry a worse prognosis for CVD mortality after onset of CVD than do persons without diabetes. In fact, mortality at time of myocardial infarction is twice as high in those with diabetes as in those without (110-112). Further, long-term mortality after myocardial infarction is twice as high in survivors of acute events in the presence of diabetes compared to the non-diabetic state (108,113-118). This worsening of prognosis following onset of CVD in patients with diabetes must be taken into consideration when decisions are made about intensity of risk factor management in primary prevention. It was one factor that led ATP III to designate diabetes as a high-risk condition in the United States even in those patients whose absolute risk for first CVD event is below that of patients with established CVD.

It should be noted that in persons with diabetes from lower risk populations, the absolute risk for future CVD events can be below that of patients with established CHD. There are several categories of lower risk populations (38,119-122). First, in some racial and ethnic groups, baseline risk for CVD is relatively low, and the addition of diabetes as a risk factor does not raise absolute risk to the level found in other populations. In particular, in lower risk populations that practice healthy life habits, CVD can be relatively low even when hyperglycemia is present. And second, younger persons with either type 1 or type 2 diabetes may be at relatively low risk in the short term even though they live in "high-risk" societies. It must be noted however that as these individuals age and as duration of diabetes increases, their risk for CVD rises progressively. At some point most of these individuals become "high-risk" patients. The latter is particularly so when they acquire additional risk factors. Finally, mild hyperglycemia is common in older persons; and if these individuals do not have other risk factors, their risk does not qualify them as CHD risk equivalents.

Clinical trials involving patients with diabetes confirm that effective treatment of hyperglycemia reduces risk for microvascular disease (123,124). Moreover, the available results are consistent with a reduction of macrovascular disease, although a fully convincing proof is lacking (123,124). On the other hand, clinical trials document that major cardiovascular events can be reduced by treatment of both hypertension (124,125) and elevated levels of serum lipids, especially LDL cholesterol (47,71,73,126-128) in patients with diabetes.

*Family history of premature atherosclerotic disease*. Most of the research on family history as a risk factor comes from studies that specify CHD as the endpoint. Prospective studies denote that a family history of premature CHD is an *independent* risk factor even when other risk factors are taken into account (129-141). When a first-degree relative has premature CHD, relative risk for CHD is 2-12-fold higher than that of the general population (142-144). Risk rises in proportion to the number of first-degree relatives affected. Familial clustering CHD risk appears polygenic in origin, and not Mendelian recessive or dominant inheritance (145). Siblings of CHD-affected, first-degree relatives have the highest relative risk, presumably due to shared sociocultural environment, exposures, and genetics. Although several risk factors, e.g., blood pressure, lipids and lipoproteins, Lp(a), and obesity have an inherited component, they do not fully account for familial aggregation of CHD in several studies (146,147). In the Framingham Heart Study, analysis of family history of CHD did not demonstrate sufficient incremental risk for family history to be included in risk assessment equations. Nonetheless, other studies provide strong evidence that a family history of premature CHD is an *independent* risk factor (129-141). For example, in the PROCAM study (74) family history proved to be a major, independent risk factor. For this reason, it was included in the absolute risk assessment algorithm.

*Age*. Risk for CVD rises progressively with advancing age in both men and women (4). This increase in risk appears to be due to two factors. First, the prevalence of risk factors—hypertension, lipid disorders, and diabetes—rises with aging. But in addition, atherosclerosis is a cumulative process. The progressive accumulation of increasing amounts of atherosclerosis raises the risk for vascular disease independent of risk factors. In persons with advanced atherosclerosis, the likelihood of major cardiovascular events is much higher than in those with little or no atherosclerosis, even at the same level of risk factors.

At any given age in adulthood, men are at higher risk than are women. Thus, male sex is a risk factor relative to female sex. In many populations, absolute risk for CHD in women lags behind that of men by 10 to 15 years. After the menopause, particularly after surgical menopause, this lag time appears to be diminished; nonetheless some lag persists even into old age.

## Emerging Risk Factors

*Emerging lipid risk factors*. These risk factors include elevations in triglycerides, small lipoprotein particles (small LDL and small HDL), lipoprotein (a) [Lp(a)], and apolipoproteins B and CIII. Low levels of apolipoprotein AI also are an indication of increased CHD risk.

Meta-analyses of epidemiological studies confirm that elevated serum triglyceride levels are an *independent* risk factor for CHD (148,149). Nonetheless, whether triglycerides per se are the true

atherogenic agents or whether elevated triglyceride are a marker for increases in triglyceride-rich remnant lipoproteins is uncertain; most investigations however point to elevated remnants as the culprit in the triglyceride-CHD relationship (150-152). But beyond remnant lipoproteins, high triglycerides often engender small lipoprotein particles (small LDL and small HDL); these latter also have been implicated in atherogenesis. No clinical trials designed to study effects of triglyceride lowering in hypertriglyceridemic patients have been designed or completed. On the other hand, clinical trials in which triglyceride-lowering drugs were employed as the primary therapy have frequently showed a reduction in major coronary events (92-99).

In several studies (153-157), but not all (158,159), elevations in *lipoprotein (a)* [Lp(a)] have been associated with increased risk for CHD. Lp(a) is a modified form of LDL that may have enhanced atherogenicity. The cholesterol of Lp(a) is included in the measurement of LDL cholesterol, but this inclusion may underestimate the atherogenic potential of the Lp(a) component of LDL. *Apolipoprotein B* (apo B) is a marker for all atherogenic lipoproteins in both LDL and triglyceride-rich lipoproteins (TGRLP). Several studies have shown that serum total apo B is a strong predictor for CHD, even stronger than LDL cholesterol in some reports (160-171). Highly correlated with total apo B is non-HDL cholesterol (total cholesterol – HDL cholesterol) (172,173); a few reports suggest that non-HDL is a better predictor of CHD than is LDL (174-177). ATP III identified non-HDL cholesterol as a secondary target of lipid-lowering therapy in patients with hypertriglyceridemia; in such patients, LDL cholesterol remained the primary target. High levels of apolipoprotein CIII (apo CIII) are an indicator of increased remnant lipoproteins and have been correlated with increased risk for CHD (178-182). Conversely, low apolipoprotein AI (apo AI), which is correlated with HDL cholesterol, is positively associated with CHD risk.

*Prothrombotic state*. Most acute coronary syndromes are the product of thrombosis secondary to disruption of the endothelium covering coronary plaques (36). Both platelets (183-185) and coagulation factors contribute to coronary thrombosis. A concept has emerged that patients having a *prothrombotic state* are prone to more severe coronary syndromes in the presence of coronary plaque disruption. Presumably a shifted balance of thrombotic over fibrinolytic factors favors formation of larger thrombi. For example, factors that may favor larger thrombi are platelet hyperaggregability, and high plasma levels of fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and D-dimers. Epidemiological studies indicate that high levels of fibrinogen (186-189), PAI-1 (190-192) and D-dimers (193) are associated with increased risk for CHD. Other hemostatic factors reported to be associated with increased coronary risk include activated factor VII, tissue plasminogen activator (tPA), von Willebrand factor, factor V Leiden, protein C, and antithrombin III. The precise mechanisms whereby hemostatic or prothrombotic states predispose to major cardiovascular events remain to be determined; nonetheless, the fact that aspirin, other antiplatelet therapies, and anticoagulants can reduce risk for CVD indicates that modification of the coagulation system can reduce risk. Unfortunately, no simple laboratory tests are available to detect a prothrombotic state. Even so, evidence is strong that some patients are at increased risk for thrombotic events. For example, one component of the metabolic syndrome has been reported to be a prothrombotic state, especially because of high levels of PAI-1 (195-197).

Both primary and secondary prevention trials have been carried out with antiplatelet drugs, and they generally show that these drugs will reduce risk for major cardiovascular events. For example, the Antithrombotic Trialists' Collaboration reviewed 287 studies involving 135,000 patients who received antiplatelet therapy versus control and 77,000 patients who received different antiplatelet regimens. Meta-analysis revealed that antiplatelet therapy reduced the combined outcome of any serious vascular

event by about one quarter; non-fatal myocardial infarction by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth (with no apparent adverse effect on other deaths) (198).

*Proinflammatory state*. At a pathological level atherosclerosis is a chronic inflammatory condition. In addition, the presence of a proinflammatory (high-cytokine) state appears to be a risk factor for acute coronary syndromes. Recent reports specify high levels of serum inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), as predictors of major coronary events (199-204). Elevations of other specific cytokines or related factors (interleukin-6, soluble intercellular adhesion molecule type 1 (sICAM-1), VCAM, E-selectin, and P-selectin have been found to be predictive of primary and secondary coronary events (205). Several mechanisms have been implicated to explain this association. For example, certain infections, e.g., *Chlamydia pneumoniae* and cytomegalovirus within the atherosclerotic lesions, have been postulated to increase arterial wall inflammation. In addition, the major risk factors (i.e., cigarette smoking, hypercholesterolemia, and diabetes) may induce arterial inflammation and thereby predispose to plaque rupture. Finally, hs-CRP levels are elevated in persons who are overweight/obese, particularly those with abdominal obesity; adipose tissue per se have been shown to produce cytokines that elicit increased production of hs-CRP by the liver. Presumably, a high-cytokine state could activate macrophages within the arterial wall and predispose to plaque rupture. Some investigators speculate that the action of smoking cessation and cholesterol-lowering therapy to reduce risk for CHD is related to reduction of their proinflammatory effects (206,207). In fact, several therapies have been reported to reduce hs-CRP levels and through anti-inflammatory actions potentially lower risk for CHD; among these are weight loss, aspirin, clopidogrel, statins, ACE inhibitors, PPARα agonists such as fibrates, PPARγ agonists such as thiazolidinediones, and nicotinic acid (208).

*Insulin resistance/glucose intolerance*. Insulin resistance denotes an impairment in the cellular actions of insulin. It leads to hyperinsulinemia, and in some persons, to glucose intolerance. Insulin resistance is typically the result of overweight/obesity, physical inactivity, and genetic susceptibility. It is commonly associated with several metabolic risk factors. As a portion of persons with insulin resistance age, they experience a decline in secretion of insulin by pancreatic beta-cells. In such patients, glucose levels rise. First they develop impaired glucose tolerance, then impaired fasting glucose [glucose 110-125 mg/dL (6.0-7.0 mmol/L)], and finally, type 2 diabetes.

The relation of insulin resistance to CVD risk is not well understood. Some studies report that hyperinsulinemia and/or insulin resistance is a *risk factor* for CVD (209-211). Other investigations indicate that impaired glucose tolerance, another indicator of insulin resistance, is associated with increased risk for CVD (212-214). However, because of the association of insulin resistance with other metabolic risk factors, it has been proposed that insulin resistance is primarily a "marker" for CVD risk, but not a causative risk factor (58,215-218). Even so, several investigators suggest mechanisms whereby insulin resistance per se could accelerate the development of CVD (219,220).

In the UK Prospective Diabetes Study, treatment of patients with the insulin-sensitizing drug, metformin, appeared to reduce cardiovascular deaths (119) but to date no clinical trials have tested whether drugs that specifically reduce insulin resistance also lower risk for CVD in subjects without diabetes However, it has been shown that both therapeutic lifestyle changes and insulin sensitizing drugs (metformin) will delay the onset of type 2 diabetes in patients with impaired fasting glucose (221).

Aggregation of Risk Factors

*Multiple major risk factors*. A common pattern of risk factors in higher risk populations is the aggregation of multiple major risk factors. Multiple major risk factors are especially common in middle-aged and older persons in whom age counts as a risk factor. The risk for CHD/CVD has been evaluated in large prospective studies such as the Framingham Heart Study (4), the PROCAM Study (74), the MONICA study (222-224), the ARIC study (225-227), the Cardiovascular Health Study (228-230), and many others (231,232). Estimations of risk accompanying multiple major risk factors have been the basis of "global risk assessment" used in many cardiovascular prevention guidelines.

Two lipid risk factors that often are paired are total cholesterol and HDL cholesterol. This has led to wide use of the total cholesterol to HDL cholesterol ratio (TC/HDL) (233-235). In prospective studies the risk of CHD increases in a log-linear fashion with increasing TC/HDL-C ratio; risk has been noted to rise more sharply at TC/HDL-C ratios >5.0. One reason that the TC/HDL-C is a powerful predictor is because elevated TC concentrations are an indicator of elevated atherogenic lipoproteins whereas a low HDL-C is a marker for the metabolic syndrome (see below).

*Metabolic syndrome: multiple metabolic risk factors*. 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; this aggregation of risk factors goes by several names: metabolic syndrome (236), insulin resistance syndrome (237,238)**,** the deadly quartet (239), and the metabolic syndrome (240,241). According to ATP III, the risk factors that make up the metabolic syndrome are the following:

- Atherogenic dyslipidemia
  - Elevated triglycerides
  - Elevated small, dense lipoprotein
  - Low HDL cholesterol
- Elevated blood pressure
- Insulin resistance $\pm$ glucose intolerance
- Prothrombotic state
- Proinflammatory state

ATP III cholesterol guidelines (14) proposed a clinical diagnosis for the metabolic syndrome. This syndrome is based on risk factors that can be readily identified in clinical practice. According to ATP III, the diagnosis of the metabolic syndrome can be made on the basis of three of five of the following risk factors:

- Increased waist circumference*
- Elevated triglyceride $\geq$ 150 mg/dL ($\geq$ 1.69 mmol/L)
- Reduced HDL cholesterol
  - Men < 40 mg/dL (< 1.0 mmol/L)
  - Women < 50 mg/dL (< 1.3 mmol/L)
- Elevated blood pressure
  - Systolic blood pressure $\geq$ 130 mmHg
    or diastolic blood pressure $\geq$ 85 mmHg
- Elevated fasting glucose $\geq$ 110 mg/dL ($\geq$ 6.0 mol/L)

* The definition of increased waist circumference appears to be population specific (20,21,51,53), as indicated by recommended cutpoints:

| | Europe and United States | Asian Pacific Region | Japan |
|---|---|---|---|
| Men | ≥ 102 cm (≥40 in) | ≥ 90 cm | ≥ 85 cm |
| Women | ≥ 88 cm (≥ 35 in) | ≥ 80 cm | ≥ 90 cm |

An alternate approach to the diagnosis of the metabolic syndrome has been proposed by the World Health Organization (242). This approach begins with the assumption that insulin resistance is the underlying component of the metabolic syndrome and it requires evidence of insulin resistance for diagnosis, i.e., impaired fasting glucose, impaired glucose tolerance, categorical hyperglycemia, or hyperinsulinemia. Other components that confirm the diagnosis are those listed by ATP III. In contrast, the ATP III diagnosis places more emphasis on obesity being the primary underlying cause of the metabolic syndrome as it views insulin resistance as one of several CVD risk factors.

**Risk Stratification**

Great advances have been made in the medical prevention of major cardiovascular events. These advances have led to the emergence of the high-risk strategy for prevention of CVD. This strategy requires that first priority be given to identification of individuals who have high-risk conditions that warrant intensive medical intervention. At the same time, persons who have underlying and major risk factors but have not yet acquired a high-risk status deserve varying degrees of medical attention. Thus, the first step of clinical prevention is stratification according to absolute risk for future CVD. In this section, the categories of risk will be reviewed.

<u>High-Risk Conditions</u>

A high-risk condition is that which carries an unusually high risk for future clinical events resulting from atherosclerosis. The majority of atherosclerotic events occur in the coronary arteries. Hence one approach to defining a high-risk state is to relate it to the absolute risk for developing CHD. The use of CHD as an endpoint has the advantage of being an endpoint in several large epidemiological studies, which allows for projections of absolute risk based on major risk factors. A general consensus has emerged that high-risk conditions are those that impart a risk for major coronary events (myocardial infarction + coronary death) of 2% per year (or > 20% per 10 years). This is the level of risk that has been reported for European patients with stable angina pectoris (243,244) and for patients in the placebo groups of large clinical trials of cholesterol-lowering therapy (70,71). At this level of risk for major coronary events, the risk for major cardiovascular events (acute coronary syndromes, stroke, and coronary artery procedures) is about twice as high, i.e., about 40% per 10 years. The list of high-risk conditions can be described briefly. They are divided by ATP III guidelines into established CHD and *CHD risk equivalents*. The latter are characterized by a high risk for future CHD events (i.e., > 20% per 10 years) in the absence of manifest CHD (14).

*Established CHD*. Patients who have already manifested clinical coronary disease are at high risk for future cardiovascular events. This high risk can be attributed to several factors, i.e., advanced atherosclerotic disease, known risk factors, and likely, genetic susceptibility for major vascular events. Disorders that constitute established CHD include a history of the following:

- Acute coronary syndromes (unstable angina and myocardial infarction)

- Stable angina pectoris

- Coronary artery procedures (angioplasty or bypass surgery)

*Non-coronary forms of clinical atherosclerotic disease*. The presence of clinical atherosclerotic disease in non-coronary arteries also conveys a high risk for future cardiovascular events, particularly acute coronary syndromes. Included among these disorders is a history of the following:

- Peripheral arterial disease [classical symptoms or ankle/brachial blood pressure index (ABI) < 0.9] (245-250)

- Abdominal aortic aneurysm (251)

- Carotid artery disease [carotid transient ischemic attacks (TIAs), carotid strokes, or > 50% obstruction of a carotid artery] (252-258)

*Multiple major risk factors and 10-year risk > 20%*. The presence of multiple major risk factors can confer a high-risk status, i.e., 10-year risk for *hard* CHD > 20%. To detect this level of risk in individuals, absolute risk assessment must be carried out according to established algorithms. Absolute risk status is determined by two components: (a) the number and intensity of major risk factors and (b) baseline risk. The major risk factors are discussed in the preceding section. Baseline risk depends on a composite of several factors other than the major risk factors. They include sex, demographic characteristics, and seemingly, underlying and emerging risk factors. Several algorithms have been developed for absolute risk assessment. They depend largely on the major risk factors and have been largely population-specific. These algorithms typically separate men and women because of differences in baseline risk between the two sexes. The two most widely used risk-assessment tools are the Framingham algorithm developed from the residents of Framingham, Massachusetts and the PROCAM algorithm based on residents of Munster, Germany. Each of these risk assessment algorithms can be discussed briefly for their use in identifying patients at high risk.

Framingham scoring sheets for projecting 10-year risk for myocardial infarction + coronary death (hard CHD) for men and women and employed by ATP III are given in Tables 1 and 2 (14). Framingham investigators also have published scores for *total CHD* (stable angina, unstable angina, myocardial infarction and coronary death) (4). This expanded score sheet was employed by the 1997 European Cardiovascular Society guidelines (28) and gives projected risks for total CHD about 30% higher than those for hard CHD. Framingham scores for hard CHD were recently compared to those from other prospective studies in the United States. Comparisons showed a high correlation between scores for the Framingham population and most other population groups in the United States (231,232). However, Framingham scoring *overestimated* risk in some populations, e.g., Puerto Rican Hispanics and Hawaiian men of Japanese ancestry. The latter findings indicate that Framingham scoring is not directly applicable to all populations. To apply to some populations, calibration of scoring is required. Nonetheless, it can be employed widely in the United States. The risk factors that are included in Framingham scoring for hard CHD are cigarette smoking, total cholesterol, HDL cholesterol, blood pressure, and age. Diabetes is not included as a risk factor in this version because diabetes counts as a high-risk condition (CHD risk equivalent) in the ATP III report (14).

The PROCAM (Prospective Cardiovascular Munster study) algorithm was developed from a prospective study of company employees including a large number of individuals in the region of Westfalia, Northern Germany (74). Scoring sheets for men in the PROCAM algorithm are given in Tables 3. This score sheet was based on 325 acute coronary events occurring within a 10-year follow-up among 5,389 men 35 to 65 years of age. Risk factors included in PROCAM scoring are the following: age, smoking, LDL cholesterol, HDL cholesterol, blood pressure, diabetes, and family history of CHD. PROCAM investigators have made use of integrative techniques (neural networks) to improve risk assessment. Physicians can utilize the website of the Task Force on Prevention of Coronary Heart Disease (http://www.CHD-taskforce.com) to carry out risk assessment with the PROCAM algorithm.

Ideally risk-scoring sheets would be available for individuals in specific populations. Some reports suggest that baseline risk is lower in southern Italy than in North Europe or the United States, but in general prospective data for defining baseline risk in various populations around the world are limited. Theoretically it should be possible to "calibrate" Framingham or PROCAM algorithms to other populations (231). This would be possible if absolute rates of CHD in specific populations were known. For example, efforts are underway in Europe to define the baseline risk in different European countries. Such efforts are important for guideline development. Since clinical CVD prevention will increase healthcare costs in all nations, it is necessary that prevention strategies be as cost effective as possible. This can be done only if accurate projections of individual risk can be made. One of the necessary components of all risk algorithms for individuals is an estimate of the baseline risk of the population from which the individual derives.

*Type 2 diabetes*. This disorder is characterized by multiple risk factors, among which is categorical hyperglycemia. In the general population, most patients with diabetes have type 2 diabetes. ATP III identified diabetes occurring in the general United States population as a high-risk condition (14). This designation was based on two factors. First, absolute 10-year risk for CHD approaches or exceeds 20% in many persons with diabetes in the United States. And second, when patients with diabetes experience myocardial infarction they have a much worse survival outcome, both at time of myocardial infarction and thereafter. These two factors lead ATP III to recommend that intensive efforts be made to prevent new-onset CHD in patients with diabetes, hence the high-risk status. In the United States, this position is supported by the American Diabetes Association (259), the American Heart Association, and the American College of Cardiology.

In other populations, the presence of categorical hyperglycemia per se may not be indicative of a high-risk condition. This is especially the case for populations with a relatively low baseline risk for CHD/CVD. For example, the PROCAM observed that many patients with diabetes had a 10-year risk for CHD < 20% (74). A recent report from the U.K. also noted that many patients with diabetes have a risk for CVD events considerably below that of persons with established CHD (119-121,260). In the PROCAM algorithm hyperglycemia is included as a risk factor in PROCAM risk assessment; diabetes is not counted as a CHD risk equivalent (74).

The absolute risk for CHD in patients with diabetes thus appears to vary in different populations. In the Finnish population, the presence of type 2 diabetes carried a risk for future CHD events equivalent to that of non-diabetic patients with established CHD/CVD (108). However, in some other European countries in addition to Germany, the risk accompanying diabetes appears to be less than that imparted by established CHD. Yet in the populations of South Asia and Southeast Asia, diabetes appears to be associated with a very high risk for CHD (261-263). But conversely, in East Asian populations, the

presence of hyperglycemia raises the risk for CHD, but the absolute risk may be less than in other populations (264,265). Therefore, whether to classify patients with diabetes as high risk will depend on demographic considerations as well as on accompanying risk factors. Regardless, it is likely that diabetes conveys a worse prognosis after onset of CHD, and this fact too must be taken into consideration when assessing overall risk accompanying hyperglycemia.

Risk Stratification When 10-Year Risk CHD is < 20%

Considerable controversy exists as to the appropriate clinical management of persons whose 10-year risk for CHD is < 20%. In some countries, clinical management is largely limited to high-risk patients because of cost considerations. The costs of clinical management include time commitments of patients and health professionals, processing and scheduling in clinics, laboratory monitoring, and often medication. Although risk for CVD could undoubtedly be reduced by providing individual attention by healthcare professionals to a large portion of the population, the costs of such management are prohibitive in many societies. Moreover, when medical care is rationed because of cost considerations, choices must be made among different options for financial expenditure for health care. In the face of the need to limit healthcare costs, clinical prevention of CVD often does not achieve a high priority.

Healthcare professionals nonetheless should recognize that less expensive strategies often can be employed in lower risk persons. Advice on healthy lifestyle changes can be provided, and in some cases, risk factors can be treated with inexpensive medications. The decision to intervene with medications in lower risk populations depends in part on estimated cost effectiveness of interventions. Clinical primary prevention in lower risk persons almost always will incur incremental health costs. However, if these costs are kept within bounds that are acceptable to society, preventive therapies may be acceptable. One factor that determines cost-effectiveness of intervention is absolute risk of the patient. Consequently, the nearer absolute risk approaches the high-risk category, the more cost effective will be the intervention.

An example of use of the latter concept was applied in the ATP III report (14). The panel examined costs of cholesterol-lowering therapy in different levels of absolute risk. This report employed Framingham risk scoring to categorize risk for hard CHD into high, moderately high, moderate, and lower levels; cost estimates were made for use of cholesterol-lowering drugs according to current standards of cost effectiveness of medical interventions in the United States. This section will describe the strategy employed by ATP III. The IAS Executive Committee notes that the costs of cholesterol-lowering drugs appear to be a major limiting factor in clinical management of patients for primary prevention. Since these drugs are relatively new on the market, they also are relatively expensive. Their widespread use for primary prevention at this time could impose a high cost on society. As costs of drugs decline, their use likely will increase. But in addition, the other costs mentioned before must be taken into consideration when recommendations are being made for healthcare policy on primary prevention.

ATP III defined the next lower level in absolute risk for hard CHD below 20% per 10 years as a risk of 10-20% per 10 years (14). This range was designated *moderately high risk*. The lower end of this range was identified as that in which cholesterol-lowering drugs would be cost effective by current cost-effectiveness standards in the United States. With this level of risk, patients were found to be candidates for cholesterol-lowering drugs when LDL-cholesterol levels were ≥ 130 mg/dL (≥ 3.4 mmol/L) after therapeutic lifestyle changes. Cost-effectiveness of cholesterol-lowering drugs at a risk

for CHD at the 10% threshold was estimated to be near US$50,000 per year of quality adjusted life year (QALY) saved at current retail prices of cholesterol-lowering drugs. According to economic standards in the United States, a medical intervention or procedure is considered to "cost-effective" if QALY saved is < US$50,000. This value includes only the cost of the particular medication. Aggregate costs for management in the clinical setting will exceed those of the drug alone, and will depend on the management system employed. It has been estimated that about 6 million Americans would have a 10-year risk 10-20% and LDL cholesterol ≥130 mg/dL (≥3.4 mmol/L) on dietary therapy and hence would be candidates for cholesterol-lowering drugs. The aggregate cost of this intervention for national health care would be considerable at current prices of cholesterol-lowering drugs; this would be true even if therapy for individuals were "cost effective." The high aggregate costs likely would restrict usage to subgroups of the population. For example, in the United States, Medicare pays little for prescription drugs for older persons and a large number of older people have no alternative health-insurance policies. Many other people in the United States do not carry health-insurance policies that will cover the costs of cholesterol-lowering drugs. Therefore, in spite of accepted cost effectiveness of therapy for individuals, universal implementation of this recommendation likely will not occur in the United States. In most other countries, national healthcare systems will not pay for cholesterol-lowering drug for persons at moderately high risk; this picture however may change with declining costs of LDL-lowering drugs.

*Moderate risk for CHD* is defined by ATP III as a 10-year risk for CHD of < 10% in persons with multiple (2+) risk factors (exclusive of elevated LDL cholesterol). At this risk level, the addition of cholesterol-lowering drugs to therapeutic lifestyle changes was found not to be cost effective by current U.S. standards at present-day prices of cholesterol-lowering drugs (14). However, the guidelines recommended that consideration be given to using drug therapy in patients with 2+ other risk factors when LDL-cholesterol levels were ≥ 160 mg/dL (4.1 mmol/L) after therapeutic lifestyle changes. The argument was made that such persons are at high lifetime risk for CHD and society can afford to divert resources to preventing CHD in this population. The total number of patients in this category in the United States is not large and thus aggregate costs to society probably would not be excessive. Furthermore, it was anticipated that current costs of medications should not necessarily dictate health policy. In the long run, as patents expire, the costs of medications will decline progressively. Thus, preventive strategies should take into account the integrated lifetime costs of medications and not just current costs. Even in high-risk prevention, the benefits of therapy will be limited in the short term. In other words, prevention is for the long term, and societal investment in prevention now will provide dividends in later years. Moreover, it should be noted that reduction in the price of cholesterol-lowering drugs by one-half would double cost effectiveness of therapy.

Again recommendations for long-term prevention using cholesterol-lowering drugs based on guidelines from the United States likely will not be universally accepted because of the realities of considerations of healthcare costs. In many countries, national healthcare policy does not support use of cholesterol-lowering drugs for long-term, primary prevention. Although ATP III provides a scientific rationale for use of more intensive medical intervention in patients who are at relatively low risk in the short term but are at high risk for CVD over a lifetime, economic realities may stand in the way of implementation of evidence-based recommendations in some subpopulations of the United States and in many countries of the world.

*Risk associated with the metabolic syndrome*. The metabolic syndrome represents a special combination of underlying risk factors, major risk factors, and emerging risk factors. For this reason, the absolute risk associated with the metabolic syndrome has not been defined precisely. One recent

report (266) indicated that patients with the metabolic syndrome carry increased risk for CHD. Thus, it is likely that current algorithms for risk assessments based on major risk factors (e.g., Framingham risk scoring) underestimate absolute risk accompanying the metabolic syndrome. This is because both underlying risk factors and emerging risk factors likely contribute independently to risk beyond that which is imparted by the major risk factors. For example, several of the risk factors accompanying the metabolic syndrome, which are not included in risk scoring, may independently raise risk for CVD. Examples include obesity (54), physical inactivity (23,24), elevated triglycerides (148,149), insulin resistance (209-211), prothrombotic state (186-194), and a proinflammatory state (199-204). Since the quantitative, independent risk imparted by other risk factors is not known, an absolute 10-year risk cannot be estimated with accuracy in patients with the metabolic syndrome. However, in the presence of a clinical diagnosis of the metabolic syndrome, one reasonable approach would be to raise absolute risk status by one category beyond that identified by risk algorithms that employ only standard risk factors, e.g., moderate risk → moderately high risk → high risk. At present, however, such an approach is somewhat speculative and cannot be fully defended because of a lack of prospective studies that define more precisely the absolute risk in patients with the metabolic syndrome.

*Risk associated with single risk factors*. Even in the absence of other risk factors, single risk factors can lead to premature CVD. For example, heavy cigarette smoking alone can precipitate acute coronary syndromes. Severe hypertension can lead to stroke or congestive heart failure. Severe hypercholesterolemia can induce premature CHD. Type I diabetes alone can produce both microvascular and macrovascular disease. And persons with a strong family history of premature CVD likewise can develop premature CVD in the apparent absence of other risk factors. For these reasons, severe single risk factors should not be ignored in clinical practice. Appropriate clinical intervention to reduce risk with such risk factors is justified regardless of estimates of absolute, 10-year risk. Certainly there is always the question of what constitutes a "severe" risk factor that requires clinical intervention regardless of other risk factors. Examples of major risk factors that require medical intervention regardless of other risk factors according to current United States guidelines are persistent cigarette smoking (6), LDL cholesterol > 190 mg/dL (> 4.9 mmol/L) after therapeutic lifestyle changes (14), persistent hypertension after therapeutic lifestyle changes (9), type 1 diabetes (123), and body mass index $\geq 30$ kg/m$^2$ (20,21). Guidelines in different countries societies vary in recommendations for these risk factors. Guidelines that focus on single risk factors tend to place more emphasis on single, severe risk factors than do guidelines that are developed around global risk estimates. In the United States, for example, national education programs for each of the risk factors emphasize the need for management of single risk factors, whereas in other countries or regions, more emphasis is given to intervention on multiple risk factors. This difference relates in part to emphasis on short-term prevention versus long-term prevention. In these harmonized recommendations, the IAS Executive Committee seeks a balance in guidelines that allows for appropriate attention to reduction of risk both in the short term and in the long term. It is recognized that national health policies may alter this balance to some extent depending on healthcare priorities.

## Multifactorial Clinical Intervention On CVD Risk Factors

Guidelines on treatment of risk factors in patients at various risk levels have become available only in recent years. In general these have been consensus guidelines because of lack of clinical trials in patients at different risk levels, particularly those testing interventions on multiple risk factors at once. It has generally been assumed that multiple interventions that act through different mechanisms will produce additive benefit, but this assumption has not been rigorously tested. In this section, recommendations will be presented separately for patients in the high-risk category, as defined in the preceding section and for patients with 10-year risk for CHD < 20%. This section will attempt to harmonize recommendations of major cardiovascular institutions of the United States and Europe. Nonetheless, consideration will be given to recommendations of national cardiovascular societies.

Therapeutic Strategies for High Risk Patients

There is virtually universal agreement that patients at high risk for experiencing major CVD events are candidates for intensive risk-reduction therapies by healthcare professionals. The benefits of reducing risk factors in high-risk patients are well established. Moreover, they are highly cost-effective. Unfortunately, many high-risk patients are not receiving the benefits of preventive management. The IAS strongly supports worldwide efforts to institute life-saving therapies in patients of this type. The approach is multifactorial. Modification of underlying risk factors is the foundation of management, but specific attention should also be given to each of the major risk factors. And finally, several emerging risk factors are potential targets of therapy; for these clinical judgment is required in selection of therapies. Each type of risk factor can be reviewed in the context of the high-risk patient.

Underlying Risk Factors

*Atherogenic diet*. The composition of the diet can be modified in several ways to reduce its atherogenicity. First on the list of dietary changes is to reduce intakes of nutrients to lower LDL-cholesterol levels. ATP III recommendations (14) are consistent with other guidelines and include the following:

- Reduce dietary saturated fatty acids to < 7% of total energy (267-269)
- Reduce dietary cholesterol to < 200 mg/day (270-273)

A reduction in dietary saturated fatty acids is achieved by avoidance of foods high in these fatty acids: fat-rich milk products (butter, whole milk, cream, ice cream, and cheese), animal fats (lard, beef tallow), high-fat meats (hamburger, frankfurter, sausage, bologna), and tropical oils (coconut oil, palm kernel oil, and palm oil). Sources of dietary cholesterol also must be limited to reduce cholesterol intake: dairy fats, meat fats, eggs, and organ meats.

ATP III further recommends that consideration be given to adding other non-drug options for enhanced lowering of LDL-cholesterol levels:

- Plant stanol/sterols (2 g/day) (274-279)
- Viscous fiber (10 g/day) to enhance LDL-lowering (280-282)

Additional dietary recommendations that appear to further reduce the risk for CVD are the following:

- Consume at least five servings of fruits and vegetables daily (27)
- Keep intakes of *trans* fatty acids low (283-295)
- Ensure adequate intake of folic acid (400-1,000 micrograms per day) (296)
- Maintain N-3 fatty acids intake to at least 1% of total energy (2-3 g/day). (26)
  -Consider increasing N-3 fatty acids to 1 g/day for high-risk patients (43,44,297,298)
- Avoid excessive intakes of alcohol. If alcohol is consumed, limit their consumption to no more than 20-30 g of ethanol per day for men, and no more than 10-20 g of ethanol per day for women (27)
- For patients with hypertension, restrict sodium intake to no more than 100 mmol per day (2.4 g sodium or 6.0 g sodium chloride); limit alcohol intake to no more than 1-2 drinks per day; get at least 30-45 minutes of aerobic activity on most days; maintain adequate potassium intake (about 90 mmol per day); and maintain adequate intakes of calcium and magnesium (9)

*Overweight/obesity.* Because of the increased risk accompanying overweight/ obesity, the general goals for weight loss and management of high-risk patients, as outlined by the U.S. Obesity Education Initiative (20,21) are the following:

- At a minimum, to prevent further weight gain
- To reduce body weight
- To maintain lower body weight over the long term

The specific goals of weight loss and management are the following:

- The initial goal of weight loss therapy is to reduce body weight by approximately 10% from baseline.
- A reasonable time line for a 10% reduction in body weight is 6 months of therapy
- Lost weight usually will be regained unless a weight maintenance program consisting of dietary therapy, physical activity, and behavior therapy is continued indefinitely.
- After 6 months of successful weight loss treatment, efforts to maintain weight loss should be put in place. If more weight loss is needed, another attempt at weight reduction can be made.
- For patients unable to achieve significant weight reduction, prevention of further weight gain is an important goal; such patients may also need to participate in a weight maintenance program.

Specific strategies for weight loss and weight maintenance include this list.

- *Dietary therapy.* To achieve a 10% reduction in weight from baseline in 6 months, energy intake should be reduced by 500-1,000 kcal per day.
- *Physical activity therapy.* Physical activity will facilitate weight reduction, and importantly, will assist in maintaining weight loss in the long term. Under advice of a physician, a high-risk patient who is overweight/obese should start walking 30 minutes for 3 days per week. Ideally, exercise should build up to 45 minutes of more intense walking at

least 5 days a week. Patients also should be encouraged to modify daily activities, (e.g., walking instead of driving and climbing stairs instead of using the elevator)

- *Behavior therapy*. Strategies, based on learning principles such as reinforcement, that provide tools for overcoming barriers to comply with dietary therapy and/or increased physical activity are helpful in achieving weight loss and weight maintenance. Specific strategies of behavior therapy include self-monitoring of eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring, and social support.
- *Combined therapy***.** A combined intervention of a low-calorie diet, increased physical activity, and behavioral therapy provides the most successful therapy for weight loss and weight maintenance.
- *Pharmacotherapy and weight loss surgery***.** These adjuncts to weight loss are an option for some patients who are severely obese or who have multiple medical complications of obesity. They should be employed only after conventional means of weight loss have failed. Their use should be carried out by specialists who are fully aware of the potential side effects of therapy.

*Physical activity*

Regular physical activity should be an integral part of risk reduction of the high-risk patient. Special considerations nevertheless may be necessary for some patients with functional impairment. For patients with established CHD or other vascular diseases, the American Heart Association (33) recommends a minimum goal of physical activity of 30 minutes, 3 to 4 days per week of dedicated exercise, with an optimal goal of daily activity. Before starting an exercise program, an exercise tolerance test is valuable to guide the prescription. Examples of exercise activities including walking breaks at work, gardening, and household work. High-risk patients ideally should be involved in medically supervised programs.

<u>Major, independent risk factors</u>

*Cigarette smoking.* Since smoking is a major cause of CVD, smoking cessation efforts are essential for high-risk patients. Health professionals should consider the following findings and recommendations of the U.S. Surgeon General's updated smoking-cessation guideline, *Treating Tobacco Use and Dependence* (6)*.*

- *Tobacco dependence is a chronic condition that often requires repeated intervention.* However, effective treatments exist that can produce long-term or even permanent abstinence.

- *Because effective tobacco dependence treatments are available, every patient who uses tobacco should be offered at least one of these treatments.* Patients *willing* to try to quit tobacco use should be provided treatments identified as effective in this guideline. Patients *unwilling* to try to quit tobacco use should be provided a brief intervention designed to increase their motivation to quit. Moreover, these patients should be objectively and reliably informed of the dangers of persistent smoking.

- *It is essential that clinicians and healthcare delivery systems (including administrators, insurers, and purchasers) institutionalize the consistent identification, documentation, and treatment of every tobacco user seen in a healthcare setting.*

- *Brief tobacco dependence treatment is effective, and every patient who uses tobacco should be offered at least brief treatment.*

- *There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness.* Treatments involving person-to-person contact (via individual, group, or proactive telephone counseling) are consistently effective, and their effectiveness increases with treatment intensity (e.g., minutes of contact).

- *Three types of counseling and behavioral therapies were found to be especially effective and should be used with all patients attempting tobacco cessation:* (a) Provision of practical counseling (problem solving/skills training), (b) Provision of social support as part of treatment (intra-treatment social support), (c) Help in securing social support outside of treatment (extra-treatment social support).

- *Numerous effective pharmacotherapies for smoking cessation now exist. Except in the presence of contraindications, these should be used with all patients attempting to quit smoking.* Five *first-line* pharmacotherapies were identified that reliably increase long-term smoking abstinence rates: (a) Bupropion SR, (b) Nicotine gum, (c) Nicotine inhaler, (d) Nicotine nasal spray. (e) Nicotine patch. Two *second-line* pharmacotherapies were identified as efficacious and may be considered by clinicians if first-line pharmacotherapies are not effective: (a) Clonidine (b) Nortriptyline. *Finally,* over-the-counter nicotine patches are effective relative to placebo, and their use should be encouraged.

- *Tobacco dependence treatments are both clinically effective and cost-effective relative to other medical and disease prevention interventions.* As such, insurers and purchasers should ensure that: All insurance plans include as a reimbursed benefit the counseling and pharmacotherapeutic treatments identified as effective in this guideline. Clinicians are reimbursed for providing tobacco dependence treatment just as they are reimbursed for treating other chronic conditions.

*Hypertension.* In high-risk patients with target organ damage/clinical cardiovascular disease (left ventricular hypertrophy, angina/prior myocardial infarction, prior coronary revascularization, heart failure), stroke or transient ischemic attack, nephropathy, peripheral arterial disease, retinopathy), the goal of treatment is to reduce blood pressure to < 130/85 mmHg). For high-risk patients, drug treatment should be instituted within a few days as soon as repeated measurements have confirmed the patient's blood pressure. For those patients who have diabetes and/or renal insufficiency, drug treatment should be initiated for patients with high-normal blood pressure (130-139/85-89 mmHg) or higher. In these patients, early and active drug treatment has been shown to reduce the rate of loss of renal function.

The 1999 WHO recommendations for treatment of hypertension have provided guidelines for selecting drugs treatment of hypertension (10) (Table 4). Beta-blockers and ACE inhibitors are given

priority for high-risk patients with previous myocardial infarction. ACE inhibitors are favored by many investigators for patients with diabetes.

*Elevated LDL cholesterol*. Four large clinical trials (47,69-71) and other smaller trials (299) of LDL-lowering therapy provide strong evidence that LDL-lowering therapy will reduce risk for major cardiovascular events, including acute coronary syndromes, stroke, and coronary procedures in high-risk patients. This therapy further reduces total mortality in high-risk patients, and adverse effects of therapy are rare. Clinical trials show that reduction of LDL-cholesterol levels with HMG CoA reductase inhibitors (statins) of > 30% will lower relative risk for major coronary events by about one third. The optimal goal for LDL cholesterol in high-risk patients has not been determined with certainty. According to the National Cholesterol Education Program (14), evidence from epidemiology and clinical trials support a goal for LDL cholesterol of < 100 mg/dL (< 2.6 mmol/L). European Cardiovascular Societies (28) propose a similar LDL-cholesterol goal, namely, ≤3.0 mmol/L (≤ 115 mg/dL). The possibility that even lower concentrations of LDL cholesterol will confer additional benefit is currently under study in on-going clinical trials. The recent Heart Protection Study (47) found that all categories of high-risk patients would benefit from LDL-lowering therapy with statins, regardless of LDL-cholesterol concentrations. Those patients who had baseline LDL-cholesterol concentrations < 100 mg/dL (< 2.6 mmol/L) obtained significant risk reduction when treated with a statin; thus, an LDL-cholesterol concentrations of 100 mg/dL (2.6 mmol/L) does not represent a threshold level below which no further risk reduction occurs. IAS adopts the following recommendations for LDL-lowering therapy, based on ATP III guidelines and modified by recent Heart Protection Study results.

- For high-risk patients, LDL-lowering drugs should be considered for use simultaneously with therapeutic lifestyle changes regardless of LDL-cholesterol levels.
- As a first step of therapy, the LDL cholesterol should be reduced to at least 30% below baseline.
- If the baseline LDL cholesterol is ≥ 100 mg/dL (≥ 2.6 mmol/L), the goal for LDL-lowering should be a level < 100 mg/dL (< 2.6 mmol/L).

Clinical judgment must be employed when applying LDL-lowering therapy to high-risk patients. For example, standard doses of statins, such as those employed in the major clinical trials, confer substantial risk reduction. Although it is probable that reductions of LDL cholesterol beyond that produced by standard doses will confer additional benefit, such has yet to be proven through controlled clinical trials. In high-risk patients, efforts to attain greater LDL-lowering by higher doses of statins or by combining statins with other cholesterol-lowering drugs are justified for those patients who have not attained recommended LDL goals, but therapies should not be intensified to the point that confer undue costs or risk for side effects.

*Low HDL Cholesterol*. For high-risk patients with low HDL-cholesterol levels, primary therapy is directed towards LDL-lowering. The goals for LDL cholesterol, as described above, should be attained. In many persons, a low HDL-cholesterol level is secondary to elevated serum triglyceride. When this occurs, secondary attention should be given to management of hypertriglyceridemia (see section on elevated triglycerides under Special Issues). Finally, if low serum HDL cholesterol occurs in patients without elevated triglyceride or persists after treatment of hypertriglyceridemia, consideration can be given to directly raising HDL levels. Primary therapy includes lifestyle changes

(weight reduction and increased physical activity), but secondarily, consideration can be given to the use of a fibrate or nicotinic acid. Often it will be necessary to employ one of these drugs in combination with a cholesterol-lowering drug. ATP III did not define a specific HDL-cholesterol goal of therapy, but noted the potential benefits of raising HDL levels.

*Prothrombotic state*. For patients with established CHD or other high-risk conditions, anti-platelet drugs should be employed unless contraindicated. Primary anti-platelet therapy is aspirin 75 to 325 mg/day unless contraindicated (33). When aspirin is contraindicated in patients with established CHD or other clinical form of atherosclerotic disease, consideration should be given to using either clopidogrel or warfarin. A dose of clopidogrel of 75 mg/day can be used, or if warfarin is needed, an international normalized ratio of 2.0-3.0 is indicated for patients after myocardial infarction (33).

*Diabetes (hyperglycemia)*. For patients with diabetes, the primary goal for glycemic control is to reduce glycohemoglobin (HbA1c) to ≤ 7% (301). This percentage of glycohemoglobin should be achieved with standard hypoglycemic therapy. In addition, the benefits of smoking cessation, blood pressure control, and LDL-lowering therapy are well established for patients with diabetes. Current recommendations for blood pressure management were discussed. JNC VI (9) recommends a blood pressure goal of < 130/85 mmHg, whereas the American Diabetes Association recommends an even lower goal, namely, < 130/80 mmHg (125).

According to ATP III guidelines, diabetes counts as a CHD risk equivalent, and thus places patients with diabetes in the high-risk category with an LDL-cholesterol goal of < 100 mg/dL (< 2.6 mmol/L) (14). It was recognized that not all patients with diabetes will have a 10-year risk for developing CHD of > 20%. Both PROCAM and Framingham Studies have shown that a portion of patients with diabetes have < 20% risk. However, ATP III justified elevation of diabetes to a CHD risk equivalent based in part on the poor prognosis in patients with diabetes both at time of acute myocardial infarction and afterwards. Moreover, ATP III guidelines supports use of cholesterol-lowering drugs in patients who are at moderately high risk (10-20% risk for 10 years). Most patients with diabetes who do not have a 10-year risk > 20% will have a risk of 10-20%. This latter risk also would warrant cholesterol-lowering drugs. The Heart Protection Study (47) showed a broad benefit of statin therapy in patients with diabetes.

In countries in which a 10-year risk of > 20% is required before payment can be made for cholesterol-lowering drugs, absolute risk estimates for patients with diabetes have become crucial. There is no question that absolute risk varies considerably among persons with diabetes, as shown by several prospective studies. For example, both PROCAM investigators (74) and previous Framingham reports (4) have incorporated diabetes into the risk algorithms. For ATP III guidelines (14), diabetes was removed as a risk factor from the risk algorithm because diabetes was designated a CHD risk equivalent. However, the Framingham algorithm for hard CHD could be modified to include diabetes as a categorical risk factor. If a cholesterol-lowering drug is avoided in patients with diabetes who are at moderately high risk (10-year risk 10-20%), the price to pay for a cost-saving on drugs is a worse prognosis should the patient suffer myocardial infarction.

*Cardioprotection therapies in patients with established CVD*. For patients with anterior myocardial infarction, previous myocardial infarction, or congestive heart failure (Killip Class II), employ ACE inhibitors (33). Also, for patients who have a history of myocardial infarction, consider long-term use of ACE inhibitors. Finally, for all patients with myocardial infarction or other acute coronary syndromes, start beta-blockers. Consider indefinite use of beta-blockers, but monitor patients for side effects or possible contraindications.

Strategies for Primary Prevention (10-year risk for CHD < 20%)

*Underlying Risk Factors*. Clinical primary prevention (10-year risk for CHD < 20%) represents an extension of the public health approach for prevention of CVD. The goal of public health prevention is to slow the initiation and progression of atherosclerotic disease. This goal is best achieved through prevention and modification of the underlying risk factors. It is attained by national public health policy and population education. However, in a subgroup of the population at higher risk, clinical intervention on underlying risk factors is warranted. The allocation of national resources towards clinical intervention on underlying risk factors varies according to national health care policy. However, an important principle is that health care professionals have a responsibility to the public health arena. Professional intervention on underlying risk factors is appropriately carried out in the *case-finding* mode. When patients enter the health care system for whatever reason and are identified to have these risk factors, professionals have the opportunity to intervene. The intensity of intervention can vary from providing information and advice, through further testing for other risk factors, to intervention with allied health professionals (e.g., dietitians and kinesiologists), and to long-term follow-up. The IAS encourages healthcare professionals worldwide to assume their responsibilities for extending primary prevention of CVD to assisting in modification of underlying risk factors in the clinical setting. On the other hand, it is recognized that this effort must to some extent accord with national health care resources and policies. The following provides guidelines for professional intervention on underlying risk factors for the purpose of primary prevention in persons whose 10-year risk for CHD is < 20%.

*Atherogenic diet*. At the least, physicians should provide any person at potential long-term risk for CVD with basic information on healthy dietary modifications (14). First it is necessary to briefly assess dietary intake of saturated fat and cholesterol. Then provide pamphlets and handouts from cardiovascular organizations that promote heart-healthy diets. For patients at higher risk (e.g., 10-year risk for CHD 5-20%), physicians can promote dietary modification in several ways. These include individualized diet counseling that provides acceptable substitutions for favorite foods contributing CVD risk factors. Counseling often is best performed by a professional dietitian or nutritionist. Adoption of dietary principles can be reinforced by follow-up visits that examine the response in risk factors. Readiness to change and level of motivation should be considered in recommending dietary modification. The specific dietary changes to an atherogenic diet that are appropriate to employ are those outlined above under the high-risk strategy. *Overweight/obesity.* The physician should attempt to identify the presence of overweight or obesity in all patients coming under his/her care. It is important to ensure that weight, height, and waist circumference are measured at every visit. At the least, it is important to prevent weight gain, and if possible to promote weight reduction. Consideration should be given to providing tables in waiting room or exam room identifying height/weight categories for BMI and providing literature relating BMI to health outcomes and literature explaining the use of nutrition labeling to identify calorie content and recommended portion sizes of foods.

The general approach to overweight/obesity outlined under the high-risk strategy can be applied according to available resources for primary prevention. To prevent weight gain, physicians should calculate BMI for every patient at every visit and anticipate high-risk times for weight gain (peri-menopausal years, times of significant life stress) and counsel patient on ways to prevent weight gain. For weight reduction, the professional should discuss 10% weight loss goals for persons who are overweight, discuss lifestyle patterns that promote weight loss, emphasize the importance of portion

control, and review daily physical activity. At follow-up visits, the patient's progress with weight/BMI measurement should be monitored and barriers to adherence should be reviewed.

*Physical inactivity*. Physicians in general should routinely promote regular physical activity by taking a physical activity habit history, provide pamphlets/advice regarding general principles of physical activity and recommend 30 minutes/day of regular, moderate-intensity physical activity. Promotion of regular physical activity for individuals should be based on a patient's cardiac status, age, and other factors; also specific advice can be given on how physical activity can be integrated into specific lifestyles of the patient. At follow-up visits, the physical activity level should be monitored, and follow-up counseling should be provided regarding barriers to daily physical activity.

The American Heart Association (23) has outlined a general program of physical activity that will benefit most persons of all ages. To the extent possible these guidelines can be applied to high-risk patients. Exercise should be part of a comprehensive program of health promotion and disease prevention. It is recommended that persons increase their habitual physical activity to a level appropriate to their capacities, needs, and interest. For healthy people, dynamic exercise of the large muscles for 30 to 60 minutes, three to six times weekly is recommended. Preferably, an exercise regimen should include short periods of moderate intensity (60- 75% of maximal capacity) activity (approximately 5 to 10 minutes) as part of the 30-minute routine. Moderate resistance training is also valuable. This can employ 8 to 10 different exercise sets with 10 to 15 repetitions with 10 to 15 pounds of free weight to arms, shoulders, chest, trunk, back, hips, and legs performed at a moderate to high intensity for at least 2 days per week.

American Heart Association-suggested activities include brisk walking, hiking, stair-climbing, aerobic exercise, calisthenics, resistance training, jogging, running, bicycling, rowing, swimming, and sports such as tennis, racquetball, soccer, and basketball. These are especially beneficial when performed regularly. Such activities are most beneficial for cardiac fitness when exercise intensities exceed 40-50% of exercise capacity. (Exercise capacity is the point of maximum ventilatory oxygen uptake or the highest work intensity that can be achieved.) However, even low- to moderate-intensity activities performed daily apparently have long-term health benefits including lowering the risk of cardiovascular disease. These latter activities include walking for pleasure, gardening, yard work, housework, dancing, and prescribed home exercise.

## Major Risk Factors

*Cigarette smoking*. Smoking cessation in smokers heads the list of measures to prevent both cardiovascular and non-cardiovascular diseases. All patients who smoke and who come under medical care for whatever reason should receive appropriate counseling for smoking cessation. Nicotine replacement therapy should also be considered, since it appears to augment other interventions for smoking cessation. The principles for smoking cessation outlined for high-risk patients are applicable in primary prevention of CVD.

*Hypertension.* The efficacy for reducing both CHD and stroke has been documented in primary prevention trials for hypertension. JNC VI (9) identified three stages of blood pressure elevation in persons not considered to be at high risk (e.g., 10-year risk for CHD $\leq$ 20%):

- High-normal blood pressure: BP 130-139/85-89 mmHg

- State 1 hypertension: BP 140-159/90-99 mmHg
- Stages 2/3 hypertension: BP ≥160/≥100 mmHg

WHO guidelines for blood pressure control for primary prevention are largely congruent with those of JNC VI (9). British hypertension guidelines (11) also are similar, although they do not provide as strong a recommendation for pharmacological therapy for stage 1 hypertension as does JNC VI (9).

For persons not at high risk, the blood pressure goal is a level < 140/90 mmHg. First line of management is therapeutic lifestyle change: quit smoking; lose weight, if needed; restrict sodium intake to no more than 100 mmol (2.4 g) per day; limit alcohol intake to no more than 1-2 drinks per day; get at least 30-45 minutes of aerobic activity on most days; maintain adequate potassium intake--about 90 mmol per day; and maintain adequate intakes of calcium and magnesium.

If the goal of therapy is not achieved, the physician should consider adding pharmacological therapy. JNC (9) and WHO guidelines (10) opt for initiation of drug therapy for Stage 1 hypertension more readily than do British guidelines (11). Six major classes of blood pressure-lowering drugs are: diuretics, beta-blockers, calcium antagonists, ACE inhibitors, angiotensin II antagonists, and alpha-adrenergic blockers. Other less commonly used drugs are reserpine and methyldopa. Although all of these agents similarly lower blood pressure, they differ in side-effect profiles. In addition, there is a large body of data demonstrating the benefits of the older agents such as diuretics and beta-blockers. Fewer data are available about calcium antagonists, ACE inhibitors, angiotensin II antagonists, although clinical-trial evidence of benefit for these agents is growing.

JNC VI (9) and British guidelines favor initial therapy with a diuretic or beta-blocker unless there is a compelling reason to use other agents. WHO guidelines (10) are more flexible in choice of initial drugs. Therapy should be started in low doses with upward titration as needed. If blood pressure is not adequately controlled with initial drug therapy, consideration should be given to using a drug from another class, or if necessary, a second agent from a different class.

*LDL cholesterol*. Clinical trials have shown that LDL-lowering therapy will reduce risk for major coronary events in persons with 10-year risk < 20% (72,73). There is general agreement that persons with elevated LDL cholesterol deserve cholesterol-lowering therapy carried out with therapeutic lifestyle changes (28). Whether to employ LDL-lowering drugs in persons whose 10-year risk is < 20% is a matter for national health policy. Table 5 outlines ATP III recommendations for initiation of therapeutic lifestyle changes and consideration of LDL-lowering drugs in persons with 10-year risk < 20%, depending on whether they have 2+ risk factors or 0-1 risk factor (14).

According to ATP III, for persons with multiple (2+) risk factors and 10-year risk ≤ 20%, intensity of therapy is adjusted according to 10-year risk and LDL-cholesterol level.

- *Multiple (2+) risk factors and a 10-year risk of 10-20%.* In this category, the goal for LDL cholesterol is < 130 mg/dL (< 3.4 mmol/L). The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥ 130 mg/dL (≥ 3.4 mmol/L), therapeutic lifestyle changes is initiated and maintained for 3 months. If LDL remains ≥130 mg/dL (≥ 3.4 mmol/L) after 3 months of therapeutic lifestyle changes, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal of < 130 mg/dL (< 3.4 mmol/L). Use of LDL-lowering drugs at this risk level reduces CHD risk and is cost-effective.

Should the LDL fall to less than 130 mg/dL (< 3.4 mmol/L) on dietary therapy alone, the latter can be continued without adding drugs. In older persons (≥65 years), clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

- *Multiple (2+) risk factors and a 10-year risk of < 10%*. Here the goal for LDL cholesterol also is < 130 mg/dL (< 3.4 mmol/L). The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL (≥3.4 mmol/L), persons are started on the therapeutic lifestyle changes (diet) for reducing LDL cholesterol. If LDL is < 160 mg/dL (< 4.1 mmol/L) on therapeutic lifestyle changes alone, it should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if LDL cholesterol is ≥160 mg/dL (≥ 4.1mmol/L), drug therapy can be considered to achieve an LDL-cholesterol level of < 130 mg/dL (< 3.4 mmol/L); the primary aim is to reduce long-term risk. Cost-effectiveness is marginal, but drug therapy can be justified to slow development of coronary atherosclerosis and to reduce long-term risk for CHD.

For persons with 0-1 risk factor, the goal for LDL cholesterol is < 160 mg/dL (< 4.1 mmol/L). The primary aim of therapy is to reduce long-term risk. First-line therapy is to implement therapeutic lifestyle changes. If after 3 months of therapeutic lifestyle changes, LDL cholesterol is < 160 mg/dL (< 4.1 mmol/L), therapeutic lifestyle changes are to be continued. However, if LDL cholesterol is 160-189 mg/dL (4.1-4.9 mmol/L) after an adequate trial of therapeutic lifestyle changes, drug therapy is *optional* depending on clinical judgment; factors favoring use of drugs include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol)
- Multiplicity of life-habit risk factors and emerging risk factors (if measured)
- 10-year risk approaching 10%

If LDL cholesterol is ≥ 190 mg/dL (≥ 4.9 mmol/L) in spite of therapeutic lifestyle changes, drug therapy should be considered to achieve the LDL goal of <160 mg/dL (< 4.1 mmol/L).

The purpose of using LDL-lowering drugs in persons with 0-1 risk factor and elevated LDL cholesterol [≥ 160 mg/dL (≥ 4.1 mmol/L)] is to slow the development of coronary atherosclerosis, which will reduce long-term risk. This aim may conflict with cost-effectiveness considerations; thus clinical judgment is required in selection of persons for drug therapy, although a strong case can be made for using drugs when LDL cholesterol is ≥ 190 mg/dL (≥ 4.9 mmol/L) after therapeutic lifestyle changes.

For persons whose LDL-cholesterol levels are already below goal levels upon first encounter, instructions for appropriate changes in life habits, periodic follow-up, and control of other risk factors are needed.

U.S. guidelines for LDL-cholesterol lowering for primary prevention are more explicit in use of cholesterol-lowering drugs than those allowed by other nations in which costs of drugs must be integrated into overall national healthcare programs. For example, several countries have restricted use of cholesterol-lowering drugs to high-risk patients, i.e., to patients with a projected 10-year risk of > 20%. An exception usually is made for patients who have severe hypercholesterolemia. The priority for use of cholesterol-lowering drugs in these countries is not high enough to compete with other

priorities in the financing of national health care. U.S. guidelines are more liberal with use of cholesterol-lowering drugs for three reasons. First, drug costs are not restricted by government fiat; second, recommendations are largely consistent with accepted cost-effectiveness analysis in the United States; and third, one goal of cholesterol-lowering therapy is to reduce long-term risk of CHD in patients who are at moderately high or moderate risk. The use of cholesterol-lowering drugs in primary prevention depends in large part on their costs.

*HDL cholesterol*. Although clinical trial results suggest that raising HDL will reduce risk, the IAS accords with ATP III that the evidence is insufficient to specify a goal of therapy. Further, currently available drugs do not robustly raise HDL cholesterol. Nonetheless, a low HDL should receive clinical attention and management according to the following sequence. In all persons with low HDL cholesterol, the primary target of therapy is LDL cholesterol; recommended guidelines should be followed to achieve the LDL-cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low HDL-cholesterol level is associated with high triglycerides [200-499 mg/dL (2.24-5.63 mmol/L)], secondary priority goes to achieving the non-HDL-cholesterol goal, as outlined before. (Some guidelines favor using the total cholesterol/HDL cholesterol ratio as the secondary target in preference to non-HDL cholesterol.) Finally, if triglycerides are < 200 mg/dL (< 2.24 mmol/L) (isolated low HDL cholesterol), drugs for HDL raising (fibrates or nicotinic acid) can be considered; however, treatment for isolated low HDL is mostly reserved for persons with CHD and CHD risk equivalents.

*Emerging Risk Factors and the Metabolic Syndrome*

The emerging risk factors usually manifest as components of the metabolic syndrome. Primary therapy for these risk factors is lifestyle change (weight reduction and increased physical activity). However, for patients in whom metabolic risk factors persist after lifestyle change, consideration can be given to use of drug therapy to treat specific risk factors. Treatment of elevated blood pressure is described above. Specific management of dyslipidemia is considered under special issues. Consideration can be given to chronic use of aspirin for treatment of the prothrombotic state when patients manifest the metabolic syndrome. Insulin resistance is best treated with weight reduction and increased physical activity. The benefits of treatment of insulin resistance without categorical hyperglycemia with insulin sensitizing agents is under investigation, but cannot be specifically recommended at this time.

Testing for other emerging risk factors is optional. For example, if elevated homocysteine levels are found, adequate intakes of folic acid are indicated. There are no specific therapies for elevated lipoprotein (a). Imaging for subclinical atherosclerosis is not specifically recommended, but imaging to detect higher risk patients for primary prevention can be considered an option. The finding of advanced subclinical atherosclerosis in a person without clinical atherosclerotic disease can be considered a "risk factor" for future CVD events; in such persons, appropriate control of all major risk factors and the metabolic syndrome is recommended.

## Special Issues

Special Considerations on Management of Cardiovascular Risk Factors

Cardiovascular risk factors are common in many populations. In the majority of people they occur in mild-to-moderate forms. However, long-term exposure to moderate single risk factors or a combination of moderate risk factors (e.g., smoking, hypertension, metabolic syndrome) can lead to cardiovascular disease. This document generally describes 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, a brief description will be given of approaches to disorders of lipid and lipoprotein metabolism, as described in recent U.S. guidelines on cholesterol management (14). In addition, consideration will be given to special issues that arise in different gender and age groups as well as in ethnic differences in susceptibility to cardiovascular disease.

Management of Specific Dyslipidemias

*Very high LDL cholesterol* [*≥ 190 mg/dL(≥ 4.9 mmol/L)]*. Persons with very high LDL cholesterol usually have genetic forms of hypercholesterolemia: monogenic familial hypercholesterolemia (302), familial defective apolipoprotein B (303,304), and polygenic hypercholesterolemia (305). Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature CHD. Family testing is important to identify similarly affected relatives. These disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of LDL-lowering therapy (306-308).

*Elevated serum triglycerides*. Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for CHD (148,149,309). Factors contributing to elevated (higher than normal) triglycerides in the general population include: obesity and overweight, physical inactivity, cigarette smoking, excessive alcohol intake, high carbohydrates diets (> 60% of energy intake), several diseases (e.g., type 2 diabetes, chronic renal failure, nephrotic syndrome), certain drugs (e.g., corticosteroids, estrogens, retinoids, higher doses of beta-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia) (14). In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. ATP III (14) adopted the following classification of serum triglycerides:

- Normal triglycerides: < 150 mg/dL (< 1.69 mmol/L)
- Borderline-high triglycerides: 150-199 mg/dL (1.69-2.24 mmol/L)
- High triglycerides: 200-499 mg/dL (2.24-5.63 mmol/L)
- Very high triglycerides: ≥ 500 mg/dL (≥ 5.63 mmol/L)

The finding that elevated triglycerides are an independent CHD risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded VLDL, commonly called remnant lipoproteins. In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, VLDL cholesterol can be a target of cholesterol-lowering therapy. ATP III identifies the sum of LDL + VLDL cholesterol [termed non-HDL cholesterol (total cholesterol – HDL cholesterol)] as a secondary target of therapy in persons with high triglycerides [≥ 200 mg/dL (≥ 2.24 mmol/L)] (14). The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL (0.8 mmol/L) higher than that for LDL cholesterol on

the premise that a VLDL-cholesterol level ≤30 mg/dL (≤ 0.8 mmol/L) is normal. For example, if the LDL-cholesterol goal is < 100 mg/dL (< 2.6 mmol/L), the non-HDL-cholesterol goal would be< 130 mg/dL (< 3.4 mmol/L).

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons with elevated triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are *borderline high* [150-199 mg/dL (1.69-2.24 mmol/L)], emphasis should also be placed on weight reduction and increased physical activity. According to ATP III, for *high triglycerides* [200-499 mg/dL (2.24-5.63 mmol/L)], non-HDL cholesterol becomes a secondary target of therapy. Besides weight reduction and increased physical activity, drug therapy can be considered in high-risk persons to achieve the non-HDL-cholesterol goal. There are two approaches to drug therapy. First, the non-HDL cholesterol goal can be achieved by intensifying therapy with an LDL-lowering drug; or second, nicotinic acid or fibrate can be added to achieve the non-HDL-cholesterol goal by further lowering of VLDL cholesterol. Some guidelines have not adopted the non-HDL-cholesterol approach and focus more closely on triglyceride levels (74). There is widespread agreement that borderline-high triglycerides should be treated largely by therapeutic lifestyle changes. However, a focus on triglycerides (and not on non-HDL cholesterol) for high triglycerides, would lead to a strategy that favors fibrates or nicotinic acid as secondary lipid-lowering therapy.

In rare persons in whom triglycerides are *very high* [>500 mg/dL (5.63 mmol/L)], the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low fat diets (≤ 15% of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to < 500 mg/dL (< 5.63 mmol/L) should attention turn to LDL lowering to reduce risk for CHD.

*Diabetic dyslipidemia*. This disorder is essentially atherogenic dyslipidemia in persons with type 2 diabetes, i.e., elevated triglyceride, small LDL particles, and low HDL cholesterol. Although elevated triglycerides and/or low HDL cholesterol are common in persons with diabetes, clinical trial results support the identification of LDL cholesterol as the primary target of therapy, as it is in non-diabetic subjects (47,126-128). Since diabetes is designated a CHD risk equivalent in ATP III, the LDL-cholesterol goal of therapy for most diabetics will be < 100 mg/dL (< 2.6 mol.L). Accordingly, according to ATP III, when LDL cholesterol is ≥ 130 mg/dL (≥ 3.4 mmol/L), most persons with diabetes will require initiation of LDL-lowering drugs simultaneously with therapeutic lifestyle changes to achieve the LDL goal. Still, when LDL-cholesterol levels are in the range of 100-129 mg/dL (2.6-3.4 mmol/L) at baseline or on treatment, several therapeutic options are available: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia. The results of the recent Heart Protection Study (47), however, favor the use of LDL-lowering drug therapy when baseline LDL cholesterol is in this range [100-129 mg/dL (2.6-3.4 mmol/L)]. In older persons (≥ 65 years of age) with diabetes, who have no additional CHD risk factors other than age, clinical judgment is required for when and how intensely to use cholesterol-lowering drugs. Certain a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

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

*Middle-aged men (35-65 years).* In general, men have a higher risk for CHD than do women (4). Middle-aged men in particular have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. A sizable fraction of all CHD in men occurs in middle age. Thus, many middle-aged men carry a relatively high risk for CHD, and for those who do, intensive LDL-lowering therapy is needed.

*Women (45-75 years).* In women, onset of CHD generally is delayed by some 10-15 years compared to men; thus most CHD in women occurs after age 65 (310). All risk factors contribute to CHD in women, and most premature CHD in women (< 65 years) occurs in those with multiple risk factors and the metabolic syndrome. Elevated triglycerides appear to be a particularly powerful risk factor in women (311-315); this finding reflects the importance of the metabolic syndrome as a risk factor in women. In spite of a widely held belief that the gender difference in risk for CHD reflects a protective effect of estrogen in women, this remains an unresolved issue (14). On the other hand, clinical trials of cholesterol-lowering therapy reveal similar relative benefit for men and women (47,69-73). Therefore, for both primary and secondary prevention of CHD, the same principles should be applied for both middle-aged women and men. Even so, 10-year risk assessment generally will reveal a lower risk in women, which implies that intensity of LDL-cholesterol lowering therapy will be less for most women than for men. In other words, the later onset of CHD for women in general should be factored into clinical decisions about use of cholesterol-lowering drugs. Since women are more similar to men in likelihood of suffering a stroke, the goals for hypertension therapy should be the same for the two sexes. Moreover, for women who develop diabetes, the difference in the age of onset of CVD between men and women generally is reduced. Consequently women with diabetes deserve the same guidelines for strategies for prevention of CVD.

*Older adults (men ≥ 65 years and women ≥ 75 years).* Overall, most new CHD events and most coronary deaths occur in older persons (≥ 65 years). Cigarette smoking, hypertension, and diabetes remain powerful risk factors in older persons. For older persons, the relative risk conferred by cigarette smoking and diabetes, although not hypertension, decline somewhat in older people, but absolute (and attributable) risk remains high. A high level of LDL cholesterol and low HDL cholesterol still carry predictive power for the development of CHD in older persons. Secondary prevention trials with statins that have included persons over age 65 have shown significant risk reduction with statin therapy (47,69-71). Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established CHD for LDL-lowering therapy. For primary prevention through LDL-lowering, therapeutic changes in lifestyle are the first line of therapy for older persons. However, LDL-lowering drugs can also be considered when older persons are at higher risk because of multiple risk factors or advanced subclinical atherosclerosis.

Since older persons have a high absolute risk for CVD, cardiovascular prevention questions open many healthcare policy issues. The ability to reduce CVD events and total mortality through use of multiple risk-reducing drugs now exists. However, the costs of such therapies confer a major financial burden on both societies and individuals. Therefore, issues of healthcare finances, medical ethics, social attitudes, and confounding illnesses must come into play in the development of a national policy on CVD prevention in the older population. Different nations undoubtedly will develop different policies based on national resources and priorities (28). These differences in policy will affect prevention guidelines, and it is not possible to set forth unified recommendations for all nations on prevention of CVD in the older population.

*Younger adults (men 20-35 years; women 20-45 years).* CHD is rare except in those younger adults with severe risk factors, e.g., familial hypercholesterolemia, heavy cigarette smoking, or diabetes. Even though clinical CHD is relatively rare in young adults, coronary atherosclerosis in its early stages may progress rapidly. The rate of development of coronary atherosclerosis earlier in life correlates with the major risk factors. In particular, long-term prospective studies reveal that elevated serum cholesterol detected in young adulthood predicts a higher rate of premature CHD in middle age (316-318). Thus, risk factor identification in young adults is an important aim for long-term prevention. As populations are becoming more urbanized, with a growing prevalence of overweight/obesity and sedentary life habits, the risk factors of the metabolic syndrome are on the rise. Early detection of hypertension is particularly important. Further, efforts to achieve smoking cessation in young adults must receive high national priority. There has been some dispute as to when to begin cholesterol testing for cholesterol disorders. According to the principles outlined in United States cholesterol guidelines (319-320), the combination of early detection and early intervention on elevated LDL cholesterol with life-habit changes offers the opportunity for delaying or preventing onset of CHD later in life. For young adults with LDL-cholesterol levels ≥130 mg/dL (≥ 3.4 mmol/L), lifestyle changes should be instituted and emphasized. Particular attention should be given to young men who smoke and have high LDL cholesterol [160-189 mg/dL (4.2-5.0 mmol/L]); according to U.S. guidelines, they may be candidates for LDL-lowering drugs. When young adults have very high LDL-cholesterol levels [≥190 mg/dL (≥ 5.0 mmol/L)], drug therapy should be considered, as in other adults. This "more aggressive" approach to cholesterol disorders in young adults is not accepted in all nations. Questions of "cost effectiveness" and long-term efficacy have been raised. Nonetheless, healthcare policy should carefully study the issue of when to begin cholesterol testing in young adults. A rational policy should be developed. Nonetheless, the long-term dangers of untreated hypercholesterolemia should be kept in mind (316-318).

*Racial and ethnic groups*. Susceptibility to CVD differs in different populations. Lifestyle risk factors—atherogenic diet, overweight/obesity, physical inactivity, and smoking habits—vary in different populations and influence population risk. In addition, genetic/racial factors undoubtedly contribute to differences in susceptibility for CVD. Ideally, prevention guidelines should be modified according to the genetic/racial susceptibility in different populations. Several general principles nonetheless seem universal. First, efforts should be made to modify lifestyle risk factors, both at a public health and clinical level. To stem the rising tide of CVD worldwide, national resources should be reallocated for this purpose. Second, the major risk factors—smoking, hypertension, cholesterol disorders, and diabetes—deserve clinical attention in all societies; these factors universally increase risk in all populations. However, the intensity of clinical intervention on the major risk factors will necessarily vary depending on national healthcare policy including resource availability and allocation.

It must be noted that some populations are particularly susceptible to particular risk factors. These are well known. Blacks of African origin are prone to hypertension (321-322). 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 (323-324). 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 325). Japanese appear to have a low baseline risk for CHD (326), but have a relatively high prevalence of hypertension and stroke (327). These different populations vary in their susceptibility to cardiovascular risk factors and disease patterns. This variability in susceptibility will be yet another factor that may modify national adaptation of IAS guidelines for CVD prevention.

<u>Special Considerations for Differences in National and Regional Venues</u>

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 the 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 blue print for clinical CVD prevention will serve as a resource for development of national and regional strategies at all levels for preventing CVD worldwide.

## Adherence to Risk Reduction Therapies

Adherence to the IAS guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed in order to attain the highest possible levels of CHD risk reduction. JCN VI and the IAS have provided summaries of state-of-the-art multidisciplinary methods for targeting the patient, providers, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention (see Table 6).

**Table 1. Estimate of 10-Year Risk for Men (Framingham Point Scores)**

| Age | Points | Age | Points | Age | Points | Age | Points | Age | Points |
|---|---|---|---|---|---|---|---|---|---|
| 20-34 | -9 | 40-44 | 0 | 50-54 | 6 | 60-64 | 10 | 70-74 | 12 |
| 35-39 | -4 | 45-49 | 3 | 55-59 | 8 | 65-69 | 11 | 75-79 | 13 |

| Total Cholesterol | Points at Age 20-39 | Points at Age 40-49 | Points at Age 50-59 | Points at Age 60-69 | Points at Age 70-79 |
|---|---|---|---|---|---|
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 0 |
| 200-239 | 7 | 5 | 3 | 1 | 0 |
| 240-279 | 9 | 6 | 4 | 2 | 1 |
| 280+ | 11 | 8 | 5 | 3 | 1 |

| | Points at Age 20-39 | Points at Age 40-49 | Points at Age 50-59 | Points at Age 60-69 | Points at Age 70-79 |
|---|---|---|---|---|---|
| Nonsmoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 8 | 5 | 3 | 1 | 1 |

| HDL | Points | HDL | Points | HDL | Points | HDL | Points |
|---|---|---|---|---|---|---|---|
| 60+ | -1 | 50-59 | 0 | 40-49 | 1 | <40 | 2 |

| Systolic BP | If Untreated | If Treated |
|---|---|---|
| <120 | 0 | 0 |
| 120-129 | 0 | 1 |
| 130-139 | 1 | 2 |
| 140-159 | 1 | 2 |
| 160+ | 2 | 3 |

| Point Total | 10-Year Risk | Point Total | 10-Year Risk | Point Total | 10-Year Risk |
|---|---|---|---|---|---|
| <0 | <1% | 5 | 2% | 11 | 8% |
| 0 | 1% | 6 | 2% | 12 | 10% |
| 1 | 1% | 7 | 3% | 13 | 12% |
| 2 | 1% | 8 | 4% | 14 | 16% |
| 3 | 1% | 9 | 5% | 15 | 20% |
| 4 | 1% | 10 | 6% | 16 | 25% |
| | | | | 17 or more | ≥30 |

**Table 2. Estimate of 10-Year Risk for Women (Framingham Point Scores)**

| Age | Points | Age | Points | Age | Points | Age | Points | Age | Points |
|---|---|---|---|---|---|---|---|---|---|
| 20-34 | -7 | 40-44 | 0 | 50-54 | 6 | 60-64 | 10 | 70-74 | 14 |
| 35-39 | -3 | 45-49 | 3 | 55-59 | 8 | 65-69 | 12 | 75-79 | 16 |

| Total Cholesterol | Points at Age 20-39 | Points at Age 40-49 | Points at Age 50-59 | Points at Age 60-69 | Points at Age 70-79 |
|---|---|---|---|---|---|
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 1 |
| 200-239 | 8 | 6 | 4 | 2 | 1 |
| 240-279 | 11 | 8 | 5 | 3 | 2 |
| 280+ | 13 | 10 | 7 | 4 | 2 |

| | Points at Age 20-39 | Points at Age 40-49 | Points at Age 50-59 | Points at Age 60-69 | Points at Age 70-79 |
|---|---|---|---|---|---|
| Nonsmoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 9 | 7 | 4 | 2 | 1 |

| HDL | Points | HDL | Points | HDL | Points | HDL | Points |
|---|---|---|---|---|---|---|---|
| 60+ | -1 | 50-59 | 0 | 40-49 | 1 | <40 | 2 |

| Systolic BP | If Untreated | If Treated |
|---|---|---|
| <120 | 0 | 0 |
| 120-129 | 1 | 3 |
| 130-139 | 2 | 4 |
| 140-159 | 3 | 5 |
| 160+ | 4 | 6 |

| Point Total | 10-Year Risk | Point Total | 10-Year Risk | Point Total | 10-Year Risk |
|---|---|---|---|---|---|
| <9 | <1% | 14 | 2% | 20 | 11% |
| 9 | 1% | 15 | 3% | 21 | 14% |
| 10 | 1% | 16 | 4% | 22 | 17% |
| 11 | 1% | 17 | 5% | 23 | 22% |
| 12 | 1% | 18 | 6% | 24 | 27% |
| 13 | 2% | 19 | 8% | 25 or more | ≥30% |

**Table 3. Estimate of 10-Year Risk (PROCAM Point Scores)**

| Age | Points | Age | Points | Age | Points | Age | Points | Age | Points | Age | Points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 35-39 | 0 | 40-44 | 6 | 45-49 | 11 | 50-54 | 16 | 55-59 | 21 | 60-65 | 26 |

| LDL-C mg/dL | LDL-C mmol/L | Points |
|---|---|---|
| <100 | <2.59 | 0 |
| 100-129 | 2.59-3.36 | 5 |
| 130-159 | 3.37-4.13 | 10 |
| 160-189 | 4.14-4.91 | 14 |
| ≥190 | ≥4.92 | 20 |

| HDL-C mg/dL | HDL-C mmol/L | Points |
|---|---|---|
| <35 | <0.91 | 11 |
| 35-44 | 0.91-1.16 | 8 |
| 45-54 | 1.17-1.41 | 5 |
| ≥55 | ≥1.42 | 0 |

| TG mg/dL | TG mmol/L | Points |
|---|---|---|
| <100 | <1.14 | 0 |
| 100-149 | 1.14-1.70 | 2 |
| 150-199 | 1.71-2.27 | 3 |
| ≥200 | ≥2.28 | 4 |

| **Cigarette Smoking** (during past 12 months) | Points |
|---|---|
| Yes | 8 |
| No | 0 |

| **Diabetes Mellitus** [Known diabetes or fasting blood glucose levels ≥ 120 mg/dL (6.66 mmol/L)] | Points |
|---|---|
| Yes | 6 |
| No | 0 |

| **Myocardial Infarction** (before age 60y in 1st degree relative) | Points |
|---|---|
| Yes | 4 |
| No | 0 |

| **Systolic BP** | Points |
|---|---|
| <120 | 0 |
| 120-129 | 2 |
| 130-139 | 3 |
| 140-159 | 5 |
| ≥160 | 8 |

**PROCAM Score: 10-Year Risk of Acute Coronary Event**

| Total score | 10y risk | Total score | 10y risk | Total score | 10y risk | Total score | 10y risk | Total score | 10y risk | Total score | 10y risk |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ≤20 | <1.0 | 27 | 1.8 | 34 | 3.5 | 41 | 7.0 | 48 | 12.8 | 55 | 22.2 |
| 21 | 1.1 | 28 | 1.9 | 35 | 4.0 | 42 | 7.4 | 49 | 13.2 | 56 | 23.8 |
| 22 | 1.2 | 29 | 2.3 | 36 | 4.2 | 43 | 8.0 | 50 | 15.5 | 57 | 25.1 |
| 23 | 1.3 | 30 | 2.4 | 37 | 4.8 | 44 | 8.8 | 51 | 16.8 | 58 | 28.0 |
| 24 | 1.4 | 31 | 2.8 | 38 | 5.1 | 45 | 10.2 | 52 | 17.5 | 59 | 29.4 |
| 25 | 1.6 | 32 | 2.9 | 39 | 5.7 | 46 | 10.5 | 53 | 19.6 | ≥60 | ≥30.0 |
| 26 | 1.7 | 33 | 3.3 | 40 | 6.1 | 47 | 10.7 | 54 | 21.7 | | |

## Table 4. Guidelines for Selecting Drug Treatment of Hypertension

| Class of Drug | Compelling Indications | Possible Indications | Compelling Contraindications | Possible Contraindications |
|---|---|---|---|---|
| Diuretics | Heart failure<br>Elderly patients<br>Systolic hypertension | Diabetes | Gout | Dyslipidaemia<br>Sexually active males |
| Beta-Blockers | Angina<br>After myocardial infarct<br>Tachyarrhythmias | Heart failure<br>Pregnancy<br>Diabetes | Asthma and chronic obstructive pulmonary disease<br>Heart block[a] | Dyslipidaemia<br>Athletes and physically active patients<br>Peripheral vascular disease |
| ACE Inhibitors | Heart failure<br>Left ventricular dysfunction<br>After myocardial infarct<br>Diabetic nephropathy | | Pregnancy<br>Hyperkalaemia | Bilateral renal artery stenosis |
| Calcium Antagonists | Angina<br>Elderly patients<br>Systolic hypertension | Peripheral vascular disease | Heart block[b] | Congestive heart failure[c] |
| Alpha-Blockers | Prostatic hypertrophy | Glucose intolerance<br>Dyslipidaemia | | Orthostatic hypotension |
| Angiotensin II Antagonists | ACE Inhibitor cough | Heart failure | Pregnancy<br>Bilateral renal artery stenosis<br>Hyperkalaemia | |

[a] Grade 2 or 3 atrioventricular block

[b] Grade 2 or 3 atrioventricular block with verapamil or diltiazem

[c] Verapamil or diltiazem

**Table 5. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Patients with 10-Year Risk for CHD < 20%.**

| Risk Category* | LDL-C Goal | Initiate Therapeutic Lifestyle Changes | Consider Drug Therapy (after lifestyle changes) |
|---|---|---|---|
| 2+ Risk Factors (10-year risk ≤20%) | < 130 mg/dL (< 3.4 mmol/L) | ≥130 mg/dL ≥ 3.4 mmol/L) | 10-year risk 10-20%: < 130 mg/dL (< 3.4 mmol/L) |
| | | | 10-year risk <10%: < 160 mg/dL < 4.1 mmol/L) |
| 0-1 Risk Factor° | <160 mg/dL (< 4.1 mmol/L) | ≥160 mg/dL (≥ 4.1 mmol/L) | < 190 mg/dL (< 4.9 mmol/L) (160-189 mg/dL (4.1-4.9 mmol/L: LDL-lowering drug optional) |

* Major risk factors that define risk category include: cigarette smoking, hypertension (BP ≥140/90 mmHg or on anti-hypertensive medication), low HDL cholesterol [< 40 mg/dL (< 1.0 mmol/L), family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years), and age (men ≥ 45 years; women ≥55 years)

° Most persons with 0-1 risk factor from the list above has a 10-year risk for CHD < 10%, so 10-year risk assessment by risk algorithm is optional.

## Table 6. Interventions to Improve Adherence

**Focus on the Patient**

- Simplify medication regimens; keep care inexpensive and simple.
- Encourage lifestyle modifications.
- Encourage a positive attitude about achieving therapeutic goals.
- Educate patients about risk factors and cardiovascular disease; involve them and their families in treatment. For blood pressure control, have patients measure blood pressure at home.
- Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment.
- Integrate pill-taking into routine activities of daily living.
- Encourage the use of prompts to help persons remember treatment regimens
- When using drugs, anticipate adverse effects, and adjust therapy to prevent, minimize, or ameliorate side effects.
- Use systems to reinforce adherence and maintain contact with the patient
- Encourage the support of family and friends
- Reinforce and reward adherence
- Increase patient visits for persons unable to achieve treatment goal
- Increase the convenience and access to care
- Involve persons in their care through self-monitoring

**Focus on the Physician and Medical Office**

- Teach physicians to implement lipid-treatment guidelines
- Use reminders to prompt physicians to attend to lipid management
- Identify a patient advocate in the office to help deliver or prompt care
- Use patients to prompt preventive care
- Develop a standardized treatment plan to structure care
- Use feedback from past performance to foster change in future care
- Maintain contact with patients; consider telecommunication. Remind patients of appointments and follow-up missed appointments

**Focus on the Health Delivery System**

- Provide lipid management through a lipid clinic
- Utilize case management by nurses; consider using nurse case management
- Deploy telemedicine
- Utilize the collaborative care of pharmacists
- Execute critical care pathways in hospitals

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