INTERNAL MEDICINE GRAND ROUNDS

Thursday, October 14, 1999

ASSESSMENT OF RISK FOR CORONARY HEART DISEASE

by

Scott M. Grundy, M.D., Ph.D.

from

Center for Human Nutrition and the
Departments of Clinical Nutrition and Internal Medicine
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, Dallas, Texas 75235-9052
TEL: 214.648.2890 FAX: 214.648.4837

The concept that coronary heart disease (CHD) can be prevented has increasingly become a driving force in cardiovascular medicine. For many years, the field gave lip service to prevention but neglected to take it seriously. The possibility of effective prevention was met with skepticism from many quarters. Gradually, however, the tide has turned, and prevention is getting the upper hand. Widespread acceptance of the benefits of prevention came first in the area of *secondary prevention,* i.e., preventing recurrent coronary events in patients with established CHD (1). Secondary prevention stands at the boundary between *prevention* and *treatment*. Many cardiologists consider secondary prevention to be *treatment of coronary artery disease*; others see it as prevention of recurrent coronary events. There is a more uniform agreement that prevention of new onset CHD should be called *primary prevention.* This article examines some of the major issues currently under scrutiny for primary prevention of CHD. Without question, the area of primary prevention is complex and contentious; some of the issues will not be easily resolved. On the other hand, if the burden of CHD in industrialized and developing societies is going to be substantially reduced, effective strategies of primary prevention must be put in place.

Medical Prevention of Acute Coronary Syndromes

Major advances have recently been made in understanding the pathogenesis of acute coronary syndromes (unstable angina, myocardial infarction, and coronary death). Of great importance was the recognition that rupture of vulnerable plaques leading to coronary thrombosis accounts for most acute coronary syndromes (2,3). Equally important was the discovery that the risk of plaque rupture and its consequences can be substantially reduced by medical intervention. For example, cigarette smoking almost certainly predisposes to plaque rupture, and smoking cessation rapidly lowers risk for coronary thrombosis (4). Meta-analysis confirms that blood pressure lowering in hypertensive patients will reduce acute myocardial infarctions (5). Low-dose aspirin therapy likewise lowers the danger of acute coronary events (6,7). Finally, recent clinical trials (8-12) demonstrate that cholesterol-lowering therapy will reduce risk for major coronary events beyond previous expectations. Thus, preventive medical therapies are now available to intervene on coronary atherosclerotic disease before it becomes clinically manifest. Appropriate selection of patients for aggressive primary prevention thus emerges as a critical issue.

Concept and Categories of Risk

At the core of primary prevention lies the concept of risk. The general notion has evolved that the intensity of preventive efforts should be adjusted to a patient's risk for developing CHD, e.g., the higher the risk, the more aggressive should be the intervention (13). This strategy seeks to achieve a reasonable balance among three factors-- efficacy, safety, and costs of intervention. The need for this balance especially pertains in the clinical setting where professional and financial resources are constrained. The place of clinical management in primary prevention, in contrast to secondary prevention, remains to be clearly defined. Two functions of clinical involvement nonetheless can be visualized. First, by promoting healthier life habits, clinicians

link the public health strategy to individuals; and second, by instituting specific risk-reducing therapies, clinicians move secondary-prevention strategies across the boundary into high-risk primary prevention. The first step in primary prevention in the clinical setting is to estimate a patient's risk. Appropriate application of measures to reduce risk in primary prevention requires a full understanding of the categories of risk. Among these categories, three can be distinguished: *absolute risk*, *relative risk*, and *attributable risk*. Each deserves brief mention to introduce both risk assessment and treatment strategy.

Absolute risk defines the probability of developing CHD over a finite period. According to probability of CHD, risk can be qualified as *high risk* or *low risk*. According to period, it can be either *short-term* (e.g. $\leq$ 10 years) or *long-term*. Thus, high risk can be divided between *high short-term risk* and *high long-term risk*. Treatment regimens in the two high-risk categories may differ by intensity, but both categories need attention by clinicians (14). Just what *probability* of developing CHD qualifies a patient for being at high short-term risk has been a matter of some dispute (14,15). One standard could be the likelihood of suffering a major coronary event that is similar to that of patients known to be high risk, i.e., those with established CHD. The projected 10-year risk in the placebo groups of the major cholesterol-lowering trials provides one example. Patients on placebo of the Cholesterol and Recurrent Events (CARE) study (9) and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (10), who should be representative of American patients with CHD, had a projected 10-year risk for major coronary events of about 26%. A related standard could be the patient with stable angina pectoris; recent analyses (16,17) project an average risk of fatal or nonfatal myocardial infarction in patients with stable angina to be about 20% in 10 years. Thus, for primary prevention, a high short-term risk might be defined as a probability of developing a fatal or nonfatal myocardial infarction of $\geq$ 20% in the next 10 years. High risk for CHD in the short term can be identified by the presence of clinical atherosclerotic disease in other arterial beds, by the presence of subclinical atherosclerosis, or by multiple risk factors.

High risk in the long term can be defined by an elevated risk for CHD over a longer period (even over a lifetime) (18). In this document the term intermediate risk will be used to define patients whose 10-year absolute risk for fatal and nonfatal myocardial infarction is in the range of 10-20%. Several risk factors may contribute to intermediate risk, but even single risk factors if left untreated for many years can hasten the onset of CHD. Thus, patients with single or multiple categorical risk factors even if at only intermediate risk should not be ignored by their physicians; primary prevention is for the long term as well as the short term. Patients at increased risk in the long term deserve risk reduction under medical supervision.

Finally, a lower risk can be ascribed to patients who are largely devoid of risk factors. For instance, investigators of the Framingham Heart Study (19) recently defined *low-risk* individuals as being nonsmoking, nondiabetic persons who have a desirable level of LDL-cholesterol (100-129 mg/dL), an optimal blood pressure (<120/<80 mm Hg), and a relatively high HDL-cholesterol ($\geq$45 mg/dL for men and $\geq$ 55 mg/dL for women). Even low-risk persons by these criteria deserve some attention by physicians. Periodic monitoring is needed to assess whether risk status has changed. Also, because absolute risk rises with advancing age, risk-reduction messages should be conveyed to low-risk persons in accord with the public health effort to reduce risk in the general population.

Relative risk is the ratio of two levels of absolute risk. The numerator is the absolute risk of the individual under consideration; the denominator is the average absolute risk of a baseline population, e.g. either a low-risk group or an average-risk group. The low-risk state, as defined by Framingham investigators (19), makes an attractive denominator for evaluating the impact of risk factors in given individuals. Estimates of relative risk carry certain advantages in risk assessment. For instance, a high relative risk in a young adult signifies a high level of absolute risk over the long term; such may call for early, intensified risk reduction. Moreover because of a rising absolute risk with advancing age, a high relative risk after age 65 signifies a particularly high absolute risk and suggests the need for more aggressive intervention on risk factors.

Attributable risk is the *difference* in absolute risk between an individual under consideration and that of a control group. Attributable risk typically is low in young adulthood and rises with age. This rise illustrates the continuing importance risk factors in older age groups, even though relative risk declines with aging.

Coronary Endpoints

Risk estimates must be linked to specific endpoints. Previous prospective studies and clinical trials have employed a variety of endpoints. For instance, Framingham investigators (19) recently related risk factors to *total CHD.* This outcome combined several coronary endpoints—angina pectoris, coronary insufficiency (unstable angina), nonfatal myocardial infarction, and coronary death. The summation thus included both *soft* and *hard* coronary endpoints. Diagnoses of angina pectoris and coronary insufficiency however depend on clinical judgment and not on objective data; this softer endpoint is open to some question because it overestimates risk for clinically solid CHD. As mentioned before, most clinical trials (8-11) have defined outcomes in terms of hard coronary endpoints—nonfatal myocardial infarction and coronary deaths. It might be noted that joint European societies (15) recently set cutpoints for initiation of aggressive primary prevention on earlier Framingham estimates of total CHD (20); this inclusion of *soft* CHD in risk estimates seemingly sanctions aggressive medical therapies for many intermediate-risk patients.

Concept and Categories of Risk Factors

The identification of measurable correlates of CHD constitutes one of the foremost advances in cardiovascular medicine. These correlates are named *risk factors* (19,21). Coronary risk factors are important both for assessment of risk and as targets for intervention. For these two purposes, a mechanistic classification of risk factors is helpful. Four categories according to mechanism emerge: (a) causal risk factors, (b) conditional risk factors, (c) predisposing risk factors, and (d) plaque burden as a risk factor. Each category requires some explanation.

Causal risk factors. The major *causal* risk factors are cigarette smoking, high blood pressure, elevated serum cholesterol (or LDL-cholesterol), low HDL cholesterol, and high plasma glucose (19). Categorical levels of these risk factors are shown in Table 1. Although the precise mechanisms whereby these five risk factors promote atherosclerosis and predispose to

CHD are not fully understood, abundant evidence supports a directly causal role. Moreover they act independently of one another. Even so, some elevation of serum LDL cholesterol seemingly is required for atherogenesis; when LDL-cholesterol levels are very low, atherogenesis proceeds slowly even when other risk factors are present (22). Once the serum LDL cholesterol reaches a "permissive" level, the other causal risk factors come into play and independently accelerate atherogenesis. The causal factors further are called *major* risk factors because they occur commonly and act powerfully in societies that have high rates of CHD.

Conditional risk factors consist of factors that are *associated* with an increased risk for CHD, but their causal link to CHD however remains to be documented with certainty. Because of uncertainty about their role in atherogenesis, the conditional risk factors are not universally accepted as being major, causal risk factors. Two reasons could account for a failure to document causality: (a) the atherogenic potential of these factors may be relatively small as compared to the major risk factors, and/or (b) their frequency in a population may not be high enough for a major, independent effect to be detected in prospective studies. The conditional risk factors include elevated concentrations of serum triglycerides, lipoprotein (a) [Lp(a)], small LDL particles, homocysteine, and coagulation factors (e.g. fibrinogen and plasminogen activator inhibitor-1 (PAI-1) (21).

Predisposing (underlying) risk factors consist of obesity (23,24), physical inactivity (25,26), family history of premature CHD (27), male sex (19), and possibly, behavioral, socioeconomic, and ethnic factors. Their association with CHD is complex. In one way or another all of them contribute to the major, causal risk factors. One view holds that their influence on CHD risk is due almost entirely to intensification of the causal risk factors. Some of the predisposing (underlying) factors also affect the conditional risk factors and potentially raise risk in this way. They also might act through *unidentified causal risk factors.* When the claim is made that predisposing risk factors are *independent risk factors*, what is meant is that their influence on CHD risk is mediated in part through unidentified but causal mechanisms.

Another predisposing risk factor appears to be *insulin resistance,* a condition in which cellular action is impaired by metabolic aberration. Many investigators (28-30) contend that insulin resistance predisposes to several of the causal (and/or conditional) risk factors. The major predisposing risk factors—obesity (31,32) and physical inactivity (33,34)--worsen insulin resistance, and their impact on causal and conditional risk factors may be mediated largely via this mechanism.

Plaque burden as a risk factor. Once an atherosclerotic plaque reaches a certain stage of development the plaque itself becomes a *risk factor* for major coronary events. This is because existing coronary plaques can undergo rupture or erosion, causing an occluding coronary thrombus (2,3). Of critical importance, the more extensive is the burden of coronary atherosclerosis, the greater is the frequency of plaque rupture. Follow-up studies (35-37) on patients undergoing coronary angiograms reveal that the probability of future coronary events relates to the extent of coronary atherosclerosis. The usual way of estimating plaque burden in the clinical setting is to use age as a surrogate marker (19). The severity of coronary atherosclerosis rises with age; hence older persons on average have a greater plaque burden than

do younger persons. This fact accounts for the well-known claim that "age is a risk factor" for CHD. Later in this article the possibility of estimating coronary plaque burden by noninvasive techniques will be examined. Introducing the concept of plaque burden as a risk factor may be "pushing the envelope" of primary prevention into the territory of secondary prevention. Many investigators believe that there is a gray zone between primary prevention and secondary prevention. Use of age as an indicator of plaque burden generally has been acceptable for primary prevention (19); however, once significant coronary atherosclerosis has been definitely identified, the patient is often designated as having *coronary artery disease*, even without anginal symptoms. In this paper, the attempt will be made to integrate plaque burden into risk assessment in asymptomatic patients. An essential hypothesis of the paper is that for purpose of primary prevention, *asymptomatic coronary artery disease (in the absence of myocardial dysfunction) can be viewed as a risk factor for coronary heart disease.* Once clinically significant myocardial dysfunction supervenes in a patient with coronary atherosclerosis, the patient must be said to have coronary heart disease, even if asymptomatic.

Risk Assessment

Identification of risk factors. The first step in the assessment of risk is to identify the major, causal risk factors. This requires taking a smoking history, recording blood pressure, estimating cholesterol in total serum, LDL, and HDL, and measuring glucose in fasting plasma. The patient's age represents a first approximation of plaque burden as a risk factor. Predisposing risk factors--overweight and obesity, physical inactivity, family history of premature CHD, and likely insulin resistance – can be detected by history and physical examination. Body habitus is assessed by body weight, body mass index, and waist circumference. Body mass index approximates total body fat, but waist circumference gives a better estimate of the degree of insulin resistance (24). A waist circumference of >102 cm (>40 in) in men and > 88 cm (>36 in) in women usually denotes the presence of significant insulin resistance (24,38). Finally, measurements of conditional risk factors--triglycerides, small LDL, Lp(a), homocysteine, and fibrinogen--may provide some information about a patient's risk beyond the causal risk factors; their presence also may modify therapeutic strategy.

Clinical assessment of risk. Exploring all classes of risk factors allows for a clinical synthesis of risk. A high-risk status will be obvious when a patient has multiple categorical risk factors. The National Cholesterol Education Program (NCEP) (14) and the National High Blood Pressure Education Program's Joint National Commission (JNC) (39) recommend the counting of categorical risk factors as the first step in clinical risk assessment. There is a growing consensus within the cardiovascular community however that more precision in absolute risk assessment is needed. Indeed, large epidemiological studies (40,41) have quantitatively defined the relation between the causal risk factors and incidence of CHD. The Framingham Heart Study (19,20) systematically creates this quantitative link and provided a scoring system derived largely from the Caucasian population of Framingham, MA. Framingham scores probably are valid for most other populations in the United States (42); population patterns of CHD incidence are similar although not identical among Americans of Caucasian, Hispanic and African origin (42). Framingham projections however may not be reliable in some ethnic groups; for example, they almost certainly *underestimate* risk in South Asians living in the United States (43-45).

The Framingham technique (19) grades the major risk factors and summates these gradations to obtain aggregate risk. Risk points are assigned according to the severity of the risk factor. The total number of points defines absolute risk. One set of scores pertains to men, another to women. The points for each grade of risk factor, for men and women, are listed in Table 2. Gradation of scoring here has been slightly modified to accord with categories of NCEP (14) and JNC (39); in addition, points here are assigned to impaired fasting glucose (110-126 mg/dL) because of evidence that it is an independent risk factor (46,47). Risk projections shown in Table 2 denote the 10-year likelihood of developing *hard* CHD. Projections for *hard* CHD are approximated from the published Framingham data (19). They equate to total CHD minus stable angina pectoris. Framingham's *hard* CHD includes some endpoints not used in most clinical trials. The latter typically list documented myocardial infarction plus coronary death as the primary endpoint (8-11); Framingham estimates for *hard* CHD go beyond these by including coronary insufficiency (unstable angina) and electrocardiographic evidence of silent myocardial infarction. Compared to absolute risk estimates for the placebo group of major clinical trials, Framingham's more liberal definition of *hard* CHD will give a somewhat higher estimate for the absolute risk for fatal and nonfatal myocardial infarction.

Framingham investigators (19) assign no quantitative scores to either predisposing risk factors or conditional risk factors. If these additional factors are independently causative, Framingham scoring will *underestimate* the true absolute risk. The Framingham team (19) contends that most of the risk associated with predisposing risk factors is mediated through the major risk factors, whereas conditional risk factors seemingly carry little independent risk. In spite of the great interest in a variety of other risk factors, the Framingham Heart Study (19) and other prospective studies (40) reveal that most of the *excess risk* for CHD occurring in high-risk societies can be explained by the known causal risk factors; according to these studies (19,40), the incidence of CHD is extremely low in the subgroup of the population that is completely devoid of the major risk factors.

One weakness of Framingham-type scoring is that age becomes the overriding risk factor in older persons. Certainly coronary plaque burden increases with age; moreover, advancing coronary disease increases the danger of plaque rupture and acute myocardial infarction. Age alone however is not a particularly good indicator of the severity of coronary atherosclerosis for *individuals*; this is so even though age predicts *average* coronary atherosclerosis in *populations*. Quantitative risk assessment for individuals thus should be improved if coronary plaque burden could be assessed more directly.

Noninvasive measures of coronary plaque burden. In recent years, noninvasive techniques for estimating the severity of atherosclerosis have been investigated. Most promising are two techniques: sonography of the carotid arteries and electron-beam computerized tomography (EBCT) of the coronary arteries. Sonography measures intimal-medial thickness of the carotid arteries, an indicator of carotid atherosclerosis. EBCT measures coronary calcium, a correlate of coronary atherosclerosis. If either method could be made practical, their measurements of atherosclerotic disease burden might replace age as a surrogate for plaque burden (48). This replacement should reduce uncertainty as to the extent of plaque burden in particular persons.

Several studies reveal that a moderately high correlation exists between severities of atherosclerosis in carotid and coronary arteries (49-52). Measurement of carotid atherosclerosis by sonography thus might be used to estimate coronary plaque burden and to replace the surrogate of age. Recent reports (53,54) further claim that measurements of intimal medial thickness by sonography predict major coronary events independently of other risk factors. These reports add support to the connection between carotid and coronary atherosclerosis. Carotid sonography however has not yet been standardized for routine clinical usage; recent studies nonetheless reveal the potential utility of this technique.

Even more promising is the direct measurement of coronary plaque burden by quantifying the calcium content of coronary arteries. Coronary artery calcium measured by EBCT correlates positively with the extent of coronary atherosclerosis, whether the latter is determined by autopsy or coronary angiography (55-60). Coronary scores therefore promise to yield a reliable measure of coronary plaque burden. Coronary calcium scores likewise could replace age as a risk factor (48). Use of calcium scores for this purpose will require the wide availability of reproducible and standardized techniques for measuring coronary calcium; in addition clinicians must have access to population-based cutpoints for calcium scores according to age and sex. Neither of these needs has been met, but they should be soon. The first requirement for employing either calcium scores or sonographic measures is a set of distributions of scoring in the general population as a function of age and sex. Such distributions have not been published.

Detection of subclinical myocardial ischemia in risk assessment. The discovery of myocardial ischemia during exercise testing in asymptomatic patients is another indicator of plaque burden. Several large studies (63-67) found that a "positive" exercise tolerance test predicts an increased risk for acute coronary events. A review of previous studies by Froelicher et al. (68) indicate that a positive versus negative exercise test imparts a risk ratio for *total CHD* (including angina pectoris) of about twelve, whereas for *hard CHD,* the ratio is at least four. According to Froelicher et al. (68), the major studies show that a positive exercise test remains a powerful predictor for myocardial infarction even after correcting for the standard risk factors. Exercise testing in asymptomatic people currently is not recommended for diagnosis of "subclinical coronary artery disease" (68). One concern is that "false positive" tests will lead to many unnecessary invasive evaluation (e.g. coronary angiography); the undeniable possibility exists that inappropriate invasive procedures would proliferate because of indiscriminate screening. Therefore, any use of exercise testing as a part of risk assessment as a guide to primary prevention carries an important caveat: *most asymptomatic patients having a positive test should not be referred for further diagnostic procedures for "subclinical coronary atherosclerotic disease"*, because no evidence indicates that invasive intervention in asymptomatic patients with a positive exercise test causes a reduction in major coronary events. Nonetheless, the potential utility of exercise testing for risk assessment and institution of preventive medical therapies for primary prevention should not be ruled out. If exercise testing is done in middle-aged to older people who have risk factors, a positive test probably justifies adding at least two points beyond age to the Framingham risk score. Again this is a conservative estimate.

Therapeutic Approaches to Risk Factors

Causal risk factors. These risk factors are the primary targets of preventive therapy. A fundamental tenant of primary prevention is that *all causal risk factors must be treated*, once they reach a categorical level (Table 1). Any single categorical risk factor if left untreated for long periods can produce major cardiovascular events. Treatment of the causal risk factors is best carried out by physicians. Examples of the dangers of unattended risk factors abound. Many years of cigarette smoking predispose to chronic lung disease and lung cancer, as well as to atherosclerotic cardiovascular disease (69). Cigarette smokers therefore must be encouraged to by their physicians to quit the habit (70). Untreated hypertension can cause stroke, CHD, renal failure, and hypertension; categorical hypertension therefore must be treated, with drugs if necessary (39). Persistent hypercholesterolemia raises the long-term risk for CHD (71,72); an elevated LDL cholesterol needs to be lowered, the extent to which and by what means depends on a patient's risk status (14). Categorical hyperglycemia (diabetes mellitus) predisposes to both microvascular and macrovascular disease; thus hyperglycemia in patients with diabetes should be treated adequately to achieve near normal concentrations of hemoglobin A1c (73). Finally, low HDL levels are a powerful risk factor (19); and if possible, HDL levels should be raised--preferably by changes in life habits (14). Global risk assessment, with its emphasis on short-term dangers of multiple risk factors, must not be allowed to obscure the long-term dangers of single risk factors.

Predisposing risk factors. The foremost modifiable risk factors of this type are overweight (and obesity) and physical inactivity. These conditions occur commonly in our society and predispose to multiple risk factors, both causal and conditional. Because the latter risk factors accompanying obesity and physical inactivity result from metabolic aberration and often cluster in individuals, their clustering has been called the *metabolic syndrome.* Many investigators (28-30) believe that the risk factors that constitute the metabolic syndrome derive largely from *insulin resistance*. Certainly obesity (31,32) and physical inactivity (33,34) are the dominant causes of insulin resistance, although genetic factors undoubtedly affect its severity. The most effective therapies for insulin resistance are weight loss and increased physical activity (74,75). Efforts to achieve a desirable body weight and to enhance physical activity are essential components of primary prevention--both in public health and clinical arenas. Pharmacological treatment of insulin resistance also may become a reality before long. Metformin (76) and thiazolidenediones (77) are first-generation agents for reducing insulin resistance; however they are not ideal agents and their use in insulin-resistant patients without diabetes is problematic. Undoubtedly improved agents will be developed in the future.

Conditional risk factors. Since the atherogenicity of the conditional of risk factors remains uncertain, the benefit of their modification is open to question. Limited evidence nonetheless suggests some benefit from intervention. For instance, treatment of hypertriglyceridemia with fibrates and/or nicotinic acid appears to reduce the risk for major coronary events (78,79). Dietary folic acid lowers an elevated homocysteine, and in this way may reduce CHD risk (80,81). Low-dose aspirin should mitigate a prothrombotic state; in accord, clinical trials demonstrate efficacy in primary prevention of CHD (6,7). Use of low-dose aspirin in high-risk patients having a prothrombotic state thus seems reasonable. High Lp(a)

concentrations resist currently available lipid-lowering drugs; a high level of Lp(a) nonetheless may justify more aggressive modification of other lipid risk factors.

HIGH-RISK PRIMARY PREVENTION (CONCEPT OF CHD RISK EQUIVALENTS)

Patients are at high risk in the short term when their likelihood of experiencing a major coronary event is similar to that of patients with established CHD. As previously noted, risk in patients with established CHD is at least > 20% per decade (9,10,16,17). The concept has previously been set forth by NCEP (14) of *CHD risk equivalents*. Patients with CHD risk equivalents are those without symptomatic coronary disease in whom absolute risk for new major coronary syndromes is equivalent to that for recurrent major coronary events of patients with established CHD. The following proposes three categories of patients who qualify as having a CHD risk equivalent: (a) patients with non-coronary forms of clinical atherosclerotic disease, (b) asymptompatic patients with type 2 diabetes, and (c) non-coronary patients who have multiple risk factors and an absolute risk for hard CHD of > 20% per decade. Each of these categories can be examined briefly.

Patients with Clinical Atherosclerotic Disease (Other Than Coronary Disease)

In patients with clinical atherosclerosis in non-coronary arteries, absolute risk for major coronary events approximates that of patients with established CHD. Three diseases in this category include symptomatic peripheral arterial disease, symptomatic carotid artery disease, and abdominal aortic aneurysm (14). The most common cause of death in patients with each of these disorders is CHD. Thus, patients having these other forms of atherosclerotic disease can be said to have an absolute risk equivalent to that of CHD patients. For such patients, the general approach advocated in secondary prevention can be employed.

There is growing evidence that subclinical peripheral arterial disease also carries a high risk for CHD, and if detected, it can elevate a patient to the category of a CHD risk equivalent (82-86) . One method for detecting high-risk, subclinical peripheral atherosclerosis is by measurement of blood pressure in the arms and legs. This measurement is called the ankle-brachial blood pressure index (ABI). This test detects a discrepancy in blood pressure between upper and lower extremities. The usual cause of such a discrepancy is advanced atherosclerosis in arteries of the lower extremities. The ABI can be determined with an ordinary blood pressure cuff and a Doppler ultrasonic velocity detector. The Doppler probe reads the blood pressures in the anticubital fossa and over the posterior tibial and dorsalis pedis arteries. The ABI is calculated for each leg. A value of < 0.90 in either leg can be considered abnormal and equates to significant peripheral arterial disease. If the test is abnormal, a CHD risk equivalent is established.

The inclusion of atherosclerotic disease of the peripheral arteries and symptomatic disease of the carotid arteries among CHD risk equivalents will require increased attention on the part of vascular surgeons and neurologists to the primary prevention of CHD. These specialists may be inclined to focus on the diseases of their primary interest; in so doing however they may

overlook the opportunity to reduce the risk for CHD through aggressive medical intervention. For example, the observation that cholesterol-lowering drugs will reduce the risk for stroke as well as CHD offers a new opportunity for prevention of stroke (8,10). Nonetheless, a lack of clinical trials of cholesterol-lowering therapy specifically designed for test for stroke reduction makes many neurologists reticent to adopt cholesterol-lowering drugs in patients with symptomatic carotid artery disease for the express purpose of preventing stroke; it must not be forgotten nonetheless that these same patients deserve aggressive cholesterol-lowering therapy to reduce risk for new coronary events as well. This same justification for cholesterol control in various forms of atherosclerotic disease extends to the treatment of other risk factors for CHD as well.

Patients with Type 2 Diabetes

There is a growing recognition that patients with type 2 diabetes who do not yet have clinical CHD carry a risk for major coronary events roughly equivalent to that for recurrent events in non-diabetic patients without CHD (87,88). This is particularly the case for patients with diabetes who are from ethnic groups at high baseline risk for CHD (87,88). High-risk populations living in the United States seemingly include nonHispanic whites, Hispanics, blacks and South Asians. The excessively high risk for development of CHD in patients with type 2 diabetes derives from an aggregation of metabolic risk factors that together are called the *metabolic syndrome* (89). This syndrome consists of the following risk factors: atherogenic dyslipidemia, hypertension, glucose intolerance, and a prothrombotic state (90). Atherogenic dyslipidemia consists of raised serum triglycerides (>150 mg/dL), small, dense LDL particles, and low HDL cholesterol (< 35 mg/dL). The root of the metabolic syndrome appears to reside in a state of insulin resistance, which almost is always present in patients with type 2 diabetes (91,92). Not only do patients with type 2 diabetes carry a high-risk for CHD (87,88), once they develop overt CHD, their prognosis for survival is much worse than that for CHD patients without diabetes (93,94). All of these factors have led the American Diabetes Association to position type 2 diabetes as a CHD risk equivalent (95).

High-Risk Middle-Aged Patients with Multiple Risk Factors

Recent guidelines of the European cardiovascular societies (15) have classified another group of patients under the category of a CHD risk equivalent. These patients do not have clinically manifest atherosclerotic disease, nor do they have diabetes; instead, they manifest multiple risk factors that raise their risk to the level of a CHD risk equivalent. A high absolute risk for major coronary events can be identified from Framingham risk scores (19). This scoring can be recommended up to age 65. A modified version of published Framingham scoring is given in Table 2. Risk scoring should not be carried out at the first encounter with the patient. A stable baseline of risk factors should be achieved before absolute risk is projected. To this aim, the LDL cholesterol level should be scored after 3 months of maximal dietary therapy (14); scoring for blood pressure should be done after 3 months of appropriate blood-pressure therapy (39). According to the European guidelines (15), a CHD risk equivalent is defined as an absolute risk for developing CHD of $\geq$ 20% per 10 years. Although European guidelines identify a combined CHD end point including stable angina, major coronary events, and CHD death as the

definition of CHD, a preferred definition may be one limited to nonfatal and fatal myocardial infarction alone. This latter definition has been employed as the major endpoint in secondary prevention trials of cholesterol-lowering therapy (8-10). Thus, an absolute 10-year risk of $\geq$ 20% for a major coronary event (nonfatal and fatal myocardial infarction) will define a CHD risk equivalent in the current document. The European guidelines apply up to age 65. It was recognized by European investigators that risk assessment in older patients is more complex and requires special considerations. This is a prudent approach. The issue of primary prevention of CHD in older patients will be considered separately in a later section.

Risk Reduction Therapies in CHD Risk Equivalents

For asymptomatic patients with a CHD risk equivalent, general therapeutic recommendations for secondary prevention can be employed (1) (Table 3). Smoking cessation has a high priority. Blood pressure should be normalized, by medication if necessary (39). Low-dose aspirin is warranted in high short-term risk, and its use is supported by primary prevention trials (6,7). Glucose levels and hemoglobin A1c levels should be reduced to near normal in patients with type 2 diabetes (73). Life habits should be modified to minimize risk (1). Finally, the LDL-cholesterol goal is a level $\geq$ 100 mg/dL (1,14); this is the goal designated by NCEP (14) for patients with established CHD. This goal was equated to NCEP's assessment of the *optimal LDL-cholesterol level* as it relates to CHD risk. This assessment was based on evidence derived from epidemiological studies, coronary angiographic studies, and randomized clinical trials (14). Most patients with baseline LDL-cholesterol levels > 130 mg/dL will require cholesterol-lowering drugs to achieve the optimal LDL cholesterol (85). The favored drugs are the statins; the utility of stains has been demonstrated both for patients with established CHD (8-10) and for those at high short-term risk without CHD (11). When LDL-cholesterol levels have been reduced in the range of 100 to 129 mg/dL on standard doses of statins, several clinical options are open: to increase the statin dose (or to add a different cholesterol-lowering drug) to achieve an LDL-cholesterol $\leq$ 100 mg/dL, to add another lipid-lowering drug (e.g. nicotinic acid or fibrate) to reduce triglycerides and to raise HDL-cholesterol levels, or aggressively modify the nonlipid risk factors. NCEP (14) favors the first option; some investigators opt for the latter two.

INTERMEDIATE-RISK PRIMARY PREVENTION

Middle-Aged Men

Many men between ages 45 and 65 will be found to be at intermediate risk by Framingham scoring, i.e., their 10-year absolute risk for major coronary events will be in the range of 10 to 19%. In truth, some of these men will be at higher risk than estimated by standard risk factors (Table 2); this is because of undetected but advanced coronary atherosclerosis. Therefore, if such atherosclerosis can be identified by noninvasive methods, its presence would elevate an intermediate-risk patient to a high-risk category. Such patients could then be classified as having a CHD risk equivalent and thus would be good candidates for aggressive risk-reduction therapies.

Noninvasive testing for subclinical atherosclerosis has been a contentious area. Many investigators are concerned that a diagnosis of subclinical "coronary artery disease" will be used inappropriately. For instance, its finding may provide a temptation for some cardiologists to perform invasive coronary procedures on patients found to have advanced subclinical coronary atherosclerosis. Such patients could be subjected to coronary catheterization and even to coronary angioplasty despite their being are asymptomatic. Those who fear this consequence believe it would be better not to do perform noninvasive testing in the first place, i.e. better to let sleeping dogs lie. On the other hand, if patients at high risk can be identified by such testing, they could benefit from aggressive risk-factor reduction with medical therapy. If noninvasive testing were to be made acceptable to the cardiovascular community, the preventive cardiologist could be the "gatekeeper" for noninvasive procedures. This role would put the preventive cardiologist at the center of high-risk primary prevention. Thus, the potential utility of different modalities of noninvasive testing for subclinical atherosclerosis can be reviewed. Figure 1 suggests a strategy for the work up of a patient in this category.

Ankle-brachial blood pressure index (ABI). The first noninvasive test to perform in middle-aged men found to be at intermediate risk by standard risk factors is the ABI. Most patients will have a negative test. However, if the test is positive, the patient's risk will be elevated to the category of CHD risk equivalency and high-risk prevention can be instituted.

Exercise ECG. Patients at intermediate risk who have a negative ABI are candidates for an exercise ECG. Several prospective studies (63-68) indicate that an abnormal exercise ECG provides an independent estimate of CHD risk in middle-aged men with risk factors. In middle aged men with standard risk factors, an abnormality is strongly suggestive of advanced coronary atherosclerosis. Therefore, a positive exercise ECG in a middle-aged man with standard risk factors will elevate the patient to a category of a CHD risk equivalent. Aggressive risk reduction therapy can be instituted.

Noninvasive estimates of coronary plaque burden. If the ABI and exercise ECG are negative in a middle-aged man of intermediate risk, the option is available to further stratify risk by noninvasive testing for coronary plaque burden. Two methods are options for such testing: B-mode ultrasound of the carotid arteries and electron beam computerized tomography (EBCT) of the coronary arteries. Use of ultrasound of the carotid arteries is based on evidence that severity of atherosclerosis in the carotid arteries correlates positively with that in the coronary arteries. Carotid sonography thus is an indirect measure of coronary atherosclerosis. EBCT in contrast is a direct measure; it determines the calcium content of coronary arteries, which correlates highly with the severity of coronary atherosclerosis.

As mentioned before, several studies (49-52) show that IMT scores correlate positively with severity of coronary atherosclerosis. In addition, recent reports (53,54) indicate that IMT scores predict major coronary events independently of other risk factors. Thus, if B-mode ultrasonography could be established routinely in vascular laboratories, it should better define the absolute risk of a patient found to be at intermediate risk by standard risk factors. For example, an IMT score between the 50^{th} and 74^{th} percentile for age and sex justifies adding one point to the Framingham score for age; likewise, between the 75^{th} and 89^{th} percentile, two points can be

added, and above the 90th percentile, three points. By the same token, percentiles of IMT below the 50th percentile justifies a subtraction of points (Figure 1).

EBCT provides a direct measure of coronary atherosclerosis, using coronary calcium as the indicator. As discussed before, coronary calcium correlates positively with the extent of coronary atherosclerosis, as shown by both autopsy studies and coronary angiography (55-60). Preliminary studies (61-62) further suggest that coronary calcium scores carry independent predictive power for estimating absolute coronary risk. The coronary calcium score thus should refine the estimate of coronary plaque burden according to age. The literature does not report coronary calcium scores according to age and sex. However, one large data base is available on the internet (Harbor-UCLA Medical Center Website: http://heartct.humc.edu). For a calcium score between the 50th and 75th percentile for age and sex, one point can conservatively be added to the age score, whereas two points can be applied between the 75 and 90th percentile; higher calcium scores warrant three points (Figure 1) (48). Below the 50th percentile for calcium scores, points can be subtracted (Figure 1).

A recent study by Detrano et al. (96) compared the standard risk factors to coronary calcium scores as predictors of major coronary events. This report has received considerable attention, and its apparently *negative* results have been put forth as an argument against use of EBCT in noninvasive testing (97). However, even this small, short-term study (96) suggested that coronary plaque burden estimated by EBCT alone predicts coronary events as well as do all of the standard risk factors combined. EBCT and risk factors combined seemingly did not predict CHD events independently of one another. Because this was a small study (96), it almost certainly underestimated the independence of the two types of risk factors--the standard risk factors versus plaque burden. With little doubt, age (as a surrogate for plaque burden) contributes to risk estimation independently of the other risk factors; plaque burden undoubtedly will do the same. However, even if we take the study (69) at face value, the power of coronary calcium as a single measure of risk becomes apparent. In addition, the coronary calcium score has an advantage over risk factors that should not be overlooked. The calcium score is a "hard" risk factor, whereas the standard risk factors are soft "risk factors". The calcium score should be an unchanging number for a particular individual. To obtain reliable baseline values for the standard risk factors, multiple measures will be required; generally "average" baseline values are difficult to obtain in clinical practice. Thus, a similarity in predictive powers of standard risk factors and calcium scores for a group will not necessarily hold for individuals in whom measures of risk factors can vary from day to day. One way to view the calcium score is that it represents a summation of the impact of <u>all</u> the risk factors over a lifetime. An analogy might be the relation between glucose levels and hemoglobin A1C. In prospective studies on groups, the plasma glucose level predicts diabetic complications as well as hemoglobin A1C; but for individuals, the hemoglobin A1C measure has utility over glucose testing because it integrates multiple glucose levels. For the same reasons, calcium scores should provide a more reliable estimate of risk in the clinical setting than can be obtained from the standard risk factors.

Some investigators have speculated that use of EBCT to determine plaque burden in intermediate-risk patients is not "cost effective". Before this hypothesis can be accepted, however, several points must be kept in mind. First, the cost of testing must be weighed against

the costs of life-time therapy with medication for patients in whom testing would proscribe therapy. Second, the test is used to define risk with respect to a life-threatening condition, i.e., coronary atherosclerosis. And third, if EBCT were to be widely accepted for global risk assessment, the cost per individual measurement would decline. Regardless, if coronary calcium scores offer a definite advance in global risk assessment, it undoubtedly will become increasingly used. Certainly concerns about cost should not stand in the way of further development and evaluation of this technique.

Once patients are assigned a risk equivalent to that of CHD patients, they become candidates for aggressive risk-reduction therapies. Not only should appropriate efforts be made to achieve smoking cessation in smokers and blood pressure control in hypertensive patients, but low-dose aspirin and cholesterol-lowering drugs can be considered. Just as in CHD patients, those with a CHD risk equivalent are candidates for a goal for LDL cholesterol in the optimal range, i.e. $\leq$ 100 mg/dL.

Elderly Patients

The predictive power of standard risk factors is lessened in older patients (> 65 years); there are two reasons for this. First, relative risk imparted by the major risk factors declines with aging; and second, age becomes the dominant risk factor in older persons. There is no question that advancing age becomes the most powerful "risk factor" in older people. As people age, atherosclerosis progressively accumulates in the coronary arteries; further, the risk for having a major coronary event increases with increasing severity of coronary atherosclerosis. As mentioned before, patients having a heavy burden of coronary plaques also have an increased number of plaques that are prone to rupture. Thus, in older persons, coronary plaque burden becomes the predominant risk factor. However, the severity of coronary atherosclerosis varies greatly in the older population. To define more precisely the absolute risk in older persons, a direct measure of plaque burden could be helpful. Preventive cardiologists have an opportunity to participate importantly in risk assessment in the older population by making use of noninvasive testing for subclinical atherosclerosis. For practical purposes, it may be prudent to divide older patients into younger elderly (65-75 years) and older elderly (> 75 years).

For any old patient found to be a high-or-intermediate risk by standard risk factors (Table 4), consideration should be given to testing for subclinical atherosclerosis. Such testing could prove valuable in the selection of risk-reduction therapy. As a first step, patients in the age range of 65 to 75 years should receive periodic measurements of ABI (Figure 1). An abnormal ABI in a person in this age range justifies aggressive risk-reduction therapy. If the ABI is negative in men up to age 75, exercise ECG can be used to identify subclinical myocardial ischemia and hence advanced subclinical atherosclerosis. The utility of this test in men > 75 years and postmenopausal women has not been determined. A positive exercise ECG in men 65-75 years almost certainly warrants the designation of a CHD risk equivalent. Noninvasive assessment of coronary plaque burden by either carotid sonography or EBCT provides a third level of testing for the elderly patient. Extra points for plaque burden can be added or subtracted to Framingham age scores according to the scheme outlined in Figure 1. If the results of IMT or EBCT places

the patient in the category of a CHD risk equivalent, aggressive risk reduction therapy is indicated.

For patients in the age range of 65-75 years who are found to be at intermediate risk (10-year risk for hard CHD = 10-20%), by combined risk scoring and non-invasive assessment, risk factor management is still prudent. Smoking cessation and blood pressure control receive high priority. Weight reduction and regular physical activity may delay the onset of type 2 diabetes. LDL-cholesterol levels should be lowered to below 130 mg/dL. Cholesterol-lowering drugs can be considered if life-habit changes are insufficient to achieve this goal. Some authorities consider aspirin therapy to be appropriate in intermediate-risk patients in this age group. In patients over age 75 who do not have established atherosclerotic disease, maximal non-drug therapy within the bounds of safety is indicated (Table 1). This includes an effort to eliminate cigarette smoking if present. Blood pressure must be controlled appropriately in accord with the patient's general health status. A reduction in both CHD and stroke has been documented from treatment of hypertension in older patients. If the projected 10-year risk is >20%, low-dose aspirin and cholesterol-lowering therapy probably are indicated. However, a reasonable target for LDL cholesterol in patients in this age range is a level of < 130 mg/dL.

Implications for Preventive Cardiology

If noninvasive testing for subclinical atherosclerosis and coronary plaque burden become an integral part of global risk assessment, a new expertise must be developed. This expertise could come largely from physicians with training in preventive cardiology. Interpretation of results of noninvasive testing and integrating the findings into global risk assessment requires an understanding of the principles of risk analysis. One argument against the introduction of noninvasive testing is the potential for misuse of the results. Well-informed preventive cardiologists can serve as arbiters of whether patients should undergo intensive medical therapies or require invasive testing. This arrangement appears preferable to leaving interpretation of noninvasive testing in the hands of busy primary-care physicians. Further, if the patient with an abnormal noninvasive test is referred directly to an invasive cardiologist, the chances of undergoing invasive procedures may will be increased. The danger of inappropriate procedures will be diminished by allowing the preventive cardiologist to be the link between the primary care physician and the invasive cardiologist by providing an interpretation of noninvasive testing. The preventive cardiologist also can play a vital role in the institution of appropriate medical therapies in high-risk patients.

References

1. Smith, S.C.Jr., S.N. Blair, M.H. Criqui, G.F. Fletcher, V. Fuster, B.J. Gersh, A.M. Gotto, L. Gould, P. Greenland, S.M. Grundy, M.N. Hill, M.A. Hlatky, N. Houston-Miller, R.M. Krauss, J. LaRosa, I.S. Ockene, S. Oparil, T.A. Pearson, E. Rapaport, R. Starke, and Secondary Prevention Panel. 1995. Preventing heart attack and death in patients with coronary disease. *Circulation* 92: 2-4.

2. Constantinides, P. 1990. Plaque hemorrhages, their genesis and their role in supraplaque thrombosis and atherogenesis. InPathobiology of the Human Atherosclerotic Plaque. S. Glagov, W.P. Newman, and S.A. Schaffer, editors. Springer-Verlag, New York, 393-411.

3. Davies, M.J. 1990. A macro and micro view of coronary vascular insult in ischemic heart disease. *Circulation* 82(suppl II): II-38-II-46.

4. Ockene, J.K., L.H. Kuller, K.H. Svendsen, and E. Meilahn. 1990. The relationship of smoking cessation to coronary heart disease and lung cancer in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Public Health* 80: 954-958.

5. Cutler, J.A., B.m. Psaty, S. MacMahon, and C.D. Furberg. 1995. Public health issues in hypertension control: what has been learned from clinical trials. InHypertension: Pathophysiology, Diagnosis and Management. 2nd ed. J.H. Laragh and B.M. Brenner, editors. Raven Press, Ltd, New York,

6. Steering Committee of the Physicians' Health Study Research Group, 1989. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 321: 129-135.

7. The Medical Research Council's General Practice Research Framework, 1998. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 351: 233-241.

8. Scandinavian Simvastatin Survival Study Group, 1994. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344: 1383-1389.

9. Sacks, F.M., M.A. Pfeffer, L.A. Moye, J.L. Rouleau, J.D. Rutherford, T.G. Cole, L. Brown, J.W. Warnica, J.M.O. Arnold, C-C. Wun, B.R. Davis, E. Braunwald, and for the Cholesterol and Recurrent Events Trial Investigators. 1996. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 335: 1001-1009.

10. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339: 1349-1357.

11. Shepherd, J., S.M. Cobbe, I. Ford, C.G. Isles, A.R. Lorimer, P.W. Macfarlane, J.H. McKillop, C.J. Packard, and for the West of Scotland Coronary Prevention Study Group. 1995. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 333: 1301-1307.

12. Downs, J.R., M. Clearfield, E. Whitney, D. Shapiro, P.A. Beere, and A.M. Gotto. 1998. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. *JAMA* 279: 1615-1622.

13. Bethesda Conference Report, 1996. 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. *J Am Coll Cardiol* 27: 957-1047.

14. Expert Panel on Detection, Evaluation,and Treatment of High Blood Cholesterol in Adults 1994. National Cholesterol Education Program: second report of the Expert Panel on Detection, Evaluation, and Treatment of high blood cholesterol (Adult Treatment Panel II). *Circulation* 89: 1329-1445.

15. Wood, D., G. De Backer, O. Faergemann, I. Graham, G. Mancia, and K. Pyorala. 1998. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other societies on coronary prevention. *J Hypertension* 16: 1407-1414.

16. Cleland, J.G. 1996. Can improved quality of care reduce the costs of managing angina pectoris? *Eur Heart J* 17: A29-A40.

17. Juul-Moller, S., N. Edvardsson, B. Jahnmatz, A. Rosen, S. Sorensen, and R. Omblus. 1992. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet* 340: 1421- 425.

18. Lloyd-Jones, D.M., M.G. Larson, A. Beiser, and D. Levy. 1999. Lifetime risk of developing coronary heart disease. *Lancet* 353: 89-92.

19. Wilson, P.W.F., R.B. D'Agostino, D. Levy, A.M. Belanger, H. Silbershatz, and W.B. Kannel. 1998. Prediction of coronary heart disease using risk factor categories. *Circulation* 97: 1837-1847.

20. Anderson, K.M., P.W.F. Wilson, P.M. Odell, and W.B. Kannel. 1991. An updated coronary risk profile: A statement for health professionals. *Circulation* 83: 356-362.

21. Grundy, S.M., G.J. Balady, M.H. Criqui, G. Fletcher, P. Greenland, L.F. Hiratzka, N. Houston-Miller, P. Kris-Etherton, H.M. Krumholz, J. LaRosa, I.S. Ockene, T.A. Pearson, J. Reed, R. Washington, and S.C.Jr. Smith. 1998. Primary prevention of coronary heart disease: Guidance from Framingham. A statement for healthcare professionals from the American Heart Association's Task Force on Risk Reduction. *Circulation* 97: 1876-1887.

22. Grundy, S.M., L. Wilhelmsen, R. Rose, R.W.F. Campbell, and G. Assman. 1990. Coronary heart disease in high-risk populations: Lessons from Finland. *Eur Heart J* 11: 462-471.

23. Eckel, R.H. 1997. Obesity in heart disease. A statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation* 96: 3248-3250.

24. NHLBI Obesity Education Initiative Expert Panel, 1998. Clincal Guidelines on Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report. In. National Institutes of Health. National Heart, Lung, and Blood Institute, Bethesda, MD.

25. Fletcher, G.F., G. Balady, S.N. Blair, J. Blumenthal, C. Caspersen, B. Chaitman, S. Epstein, E.S.S. Froelicher, V.F. Froelicher, I.L. Pina, and M.L. Pollock. 1996. Statement on exercise: Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation* 94: 857-862.

26. US Department of Health and Human Services, 1996. Physical activity and health: A report of the Surgeon General. Department of Health and Human Services, Centers for Disease Control and Prevention. National Center for Disease Prevention and Health Promotion, Atlanta, GA.

27. Myers, R.H., D.K. Kiely, L.A. Cupples, and W.B. Kannel. 1990. Parental history is an independent risk factor for coronary artery disease. The Framingham Study. *Am Heart J* 120: 963-969.

28. Reaven, G.M. 1991. Insulin resistance and compensatory hyperinsulinemia: Role in hypertension, dyslipidemia, and coronary heart disease. *Am Heart J* 121: 1283-1288.

29. DeFronzo, R.A. and E. Ferrannini. 1991. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* 14: 173-194.

30. Mostaza, J.M., G.L. Vega, P. Snell, and S.M. Grundy. 1998. Abnormal metabolism of free fatty acids in hypertriglyceridaemic men: apparent insulin resistance of adipose tissue. *J Intern Med* 243: 265- 74.

31. Bogardus, C., S. Lillioja, and D. Mott. 1984. Relationship between obesity and maximal insulin-stimulated glucose uptake in vivo and in vitro in Pima Indians. *J Clin Invest* 73: 800.

32. Abate, N., A. Garg, R.M. Peshock, J. Stray-Gundersen, and S.M. Grundy. 1995. Relationship of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 96: 88-98.

33. Sinacore, D.R. and E.A. Gulve. 1993. The role of skeletal muscle in glucose transport, glucose homeostasis, and insulin resistance: implications for physical therapy. *Phys Ther* 73: 878-891.

34. Rogers, M.A., D.S. King, J.M. Hagberg, A.A. Ehsani, and J.O. Holloszy. 1990. Effect of 10 days of physical inactivity on glucose tolerance in master athletes. *J Appl Physiol* 68: 1833-1837.

35. Ringqvist, I., L.D. Fisher, M. Mock, K.B. Davis, H. Wedel, B.R. Chaitman, E. Passamani, R.O.Jr. Rusell, E.L. Alderman, N.T. Kouchoukas, G.C. Kaiser, T.J. Ryan, T. Killip, and D. Fray. 1983. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). *J Clin Invest* 71: 1854-1866.

36. Emond, M., M.B. Mock, K.B. Davis, L.D. Fisher, D.R.Jr. Holmes, B.R. Chaitman, G.C. Kaiser, E. Alderman, and T.3rd Killip. 1994. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 90: 2645-2657.

37. Storstein, O., I. Engel, E.J. Erikssen, and E. Thaulow. 1981. Natural history of coronary artery disease studied by coronary arteriography. A seven-year study of 795 patients. *Acta Med Scand* 210: 53- 58.

38. Despres, J.P. 1998. The insulin resistance-dyslipidemic syndrome of visceral obesity: effect of patients' risk. *Obes Res* 6(Suppl 1): 8S-17S.

39. The Sixth Report of the Joint National Committee on Prevention, Detection,Evaluation,and Treatment of High Blood Pressure 1997. National Institutes of Health, National Heart, Lung, and Blood Institute. National High Blood Pressure Education Program. *NIH Publication* 98-4080, Bethesda, MD.

40. Stamler, J., D. Wentworth, and J.D. Neaton. 1986. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 256: 2823-2828.

41. Law, M.R., N.J. Wald, T. Wu, A. Hackshaw, and A. Bailey. 1994. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *Br Med J* 308: 363-366.

42. Karter, A.J., J.M. Gazzaniga, R.D. Cohen, M.L. Casper, B.D. Davis, and G.A. Kaplan. 1998. Ischemic heart disease and stroke mortality in African-American, Hispanic, and non-Hispanic white men and women, 1985-1991. *West J Med* 169(3): 139-145.

43. Williams, R., R. Bhopal, and K. Hunt. 1994. Coronary risk in a British Punjabi population: a comparative profile of non-biochemical factors. *Int J Epidemiol* 23(1): 28-37.

44. Pugh, R.N., M.M. Hossain, M. Malik, I.T. el Mugamer, and M.A. White. 1998. Arabian Peninsula men tend to insulin resistance and cardiovascular risk seen in South Asians. *Trop Med Int Health* 3(2): 89-94.

45. Seedat, Y.K. and F.G. Mayet. 1996. Risk factors leading to coronary heart disease among the black, Indian and white peoples of Durban. *J Hum Hypertens* 10(Suppl 3): S93-S94.

46. Balkau, B., M. Shipley, R.J. Jarrett, K. Pyorala, M. Pyorala, A. Forhan, and E. Eschwege. 1998. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21: 360-367.

47. Kannel, W.B. and D.L. McGee. 1979. Diabetes and glucose tolerance as risk factors for cardiovascular disease: The Framingham Study. *Diabetes Care* 2: 120-126.

48. Grundy, S.M. 1999. Age as a risk factor: you are as old as your arteries. *Am J Cardiol* 83:1455-1457.

49. Crouse, J.R. III. 1991. Carotid and coronary atherosclerosis. What are the connections? *Post Grad* 90:175-179.

50. Wofford, J.L., F.R. Kahl, G.R. Howard, W.M. McKinney, J.F. Toole, and J.R.3rd Crouse. 1991. Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. *Arterioscler Thromb* 11: 1786-1794.

51. Crouse, J.R.3rd, T.E. Craven, A.P. Hagaman, and M.G. Bond. 1995. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. *Circulation* 92: 1141- 1147.

52. Visona, A., R. Pesavento, L. Lusiani, A. Bonanome, C. Cernetti, M. Rossi, P. Maiolino, and A. Pagnan. 1996. Intimal medial thickening of common carotid artery as indicator of coronary artery disease. *Angiology* 47: 61-66.

53. Hodis, H.N., W.J. Mack, L. LaBree, R.H. Selzer, C.R. Liu, C.H. Liu, and S.P. Azen. 1998. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 128: 262-269.

54. O'Leary, D.H., J.F. Polak, R.A. Kronmal, T.A. Manolio, G.L. Burke, S.K.Jr. Wolfson, and for the Cardiovascular Health Study Collaborative Research Group. 1999. Carotid-artery intima and medial thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 340: 14-22.

55. Rumberger, J.A., R.S. Schwartz, D.B. Simons, P.F.3rd Sheedy, W.D. Edwards, and L.A. Fitzpatrick. 1994. Relation of coronary calcium determined by electron beam computed tomography and lumen narrowing determined by autopsy. *Am J Cardiol* 73: 1169-1173.

56. Rumberger, J.A., D.B. Simons, L.A. Fitzpatrick, P.F. Sheedy, and R.S. Schwartz. 1995. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 92: 2157-2162.

57. Rumberger, J.A., P.F.2nd Sheedy, J.F. Breen, L.A. Fitzpatrick, and R.S. Schwartz. 1996. Electron beam computed tomography and coronary artery disease: scanning for coronary artery calcification. *Mayo Clin Proc* 71: 369-377.

58. Budoff, M.J., D. Georgiou, A. Brody, A.S. Agatston, J. Kennedy, C. Wolfkiel, W. Stanford, P. Shields, R.J. Lewis, W.R. Janowitz, S. Rich, and B.H. Brundage. 1996. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation* 93: 898-904.

59. Guerci, A.D., L.A. Spadaro, J.J. Popma, K.J. Goodman, B.H. Brundage, M. Budoff, G. Lerner, and R.F. Vizza. 1997. Relation of coronary calcium score by electron beam computed tomography to arteriographic findings in asymptomatic and symptomatic adults. *Am J Cardiol* 79: 128-133.

60. Schmermund, A., D. Baumgart, G. Gorge, D. Gronemeyer, R. Seibel, K.R. Bailey, J.A. Rumberger, D. Paar, and R. Erbel. 1998. Measuring the effect of risk factors on coronary atherosclerosis: coronary calcium score versus angiographic disease severity. *J Am Coll Cardiol* 31: 1267-1273.

61. Arad, Y., L.A. Spadara, K. Goodman, A. Lledo-Perez, S. Sherman, G. Lerner, and A.D. Guerci. 1996. Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects. *Circulation* 93: 1951-1953.

62. Guerci, A.D., L.A. Spadaro, K.J. Goodman, A. Lledo-Perez, D. Newstein, G. Lerner, and Y. Arad. 1998. Comparison of electron beam computed tomography scanning and conventional risk factor assessment for the prediction of angiographic coronary artery disease. *J Am Coll Cardiol* 32: 673-679.

63. Bruce, R.A., L.D. Fisher, and K.F. Hossack. 1985. Validation of exercise-enhanced risk assessment of coronary heart disease events: longitudinal changes in incidence in Seattle community practice. *J Am Coll Cardiol* 5: 875-881.

64. Multiple Risk Factor Intervention Trial Research Group, 1985. Exercise electrocardiogram and coronary heart disease mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Cardiol* 55: 16-24.

65. Gordon, D.J., L.G. Ekelund, J.M. Karon, J.L. Probstfield, C. Rubenstein, L.T. Sheffield, and L. Weissfeld. 1986. Predictive value of the exercise tolerance test for mortality in North American men: the Lipid Research Clinics Mortality Follow-up Study. *Circulation* 74: 252-261.

66. Ekelund, L.G., C.M. Suchindran, R.P. McMahon, G. Heiss, A.S. Leon, D.W. Romhilt, C.L. Rubenstein, J.L. Probstfield, and J.F. Ruwitch. 1989. Coronary heart disease morbidity and mortality in hypercholesterolemic men predicted from an exercise test: the Lipid Research Clinics Coronary Primary Prevention Trial. *J Am Coll Cardiol* 14: 556-563.

67. Rautaharju, P.M., R.J. Prineas, W.J. Eifler, C.D. Furberg, J.D. Neaton, R.S. Crow, J. Stamler, and J.A. Cutler. 1986. Prognostic value of exercise electrocardiogram in men at high risk of future coronary heart disease: Multiple Risk Factor Intervention Trial experience. *J Am Coll Cardiol* 8: 1-10.

68. Froelicher, V.F., W.P. Follansbee, A.J. Labovitz and J Myers. 1993. Special Application: Screening apparently healthy individuals. In Exercise and the Heart. V.F. Froelicher, W.P. Follansbee, A.J. Labovitz, and J. Myers, editors. Mosby, Boston, MA, 208-229.

69. 1990. The Surgeon General's 1990 Report on the health benefits of smoking cessation. Executive Summary. *MMWR Morb Mortal Wkly Rep* 39: 1-12.

70. Ockene, I.S. and N.H. Miller. 1998. Cigarette smoking, cardiovascular disease, and stroke. A statement for Healthcare Professionals from the American Heart Association. *Circulation* 96: 3243-3247.

71. Anderson, K.M., W.P. Castelli, and D.L. Levy. 1987. Cholesterol and mortality: 30 years of follow-up from the Framingham study. *JAMA* 257: 2176-2180.

72. Klag, M.J., D.E. Ford, L.A. Mead, J. He, P.K. Whelton, K-Y. Liang, and D.M. Levine. 1993. Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med* 328: 313-318.

73. American Diabetes Association, 1997. Standards of medical care for patients with diabetes mellitus (position statement). *Diabetes Care* 20: 518-520.

74. Weinstock, R.S., H. Dai, and T.A. Wadden. 1998. Diet and exercise in the treatment of obesity: effects of 3 interventions on insulin resistance. *Arch Intern Med* 158: 2477-2483.

75. Perseghin, G., T.B. Price, K.F. Petersen, M. Roden, G.W. Cline, K. Gerow, D.L. Rothman, and G.I. Shulman. 1996. Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subject. *N Engl J Med* 335: 1357-1362.

76. Bailey, C.J. 1993. Metformin--an update. *Gen Pharmacol* 24: 1299-1309.

77. Granberry, M.C., E.F. Schneider, and V.A. Fonseca. 1998. The role of troglitazone in treating the insulin resistance syndrome. *Pharmacotherapy* 18: 973-987.

78. Carlson, L.A. and G. Rosenhamer. 1988. Reduction of mortality in the Stockholm ischaemic heart disease secondary prevention study to combined treatment with clofibrate and nicotinic acid. *Acta Med Scand* 223: 405-418.

79. Manninen, V., J.K. Huttunen, O.P. Heinonen, L. Tenkanen, and M.H. Frick. 1989. Relation between baseline lipid and lipoprotein values and the incidence of coronary heart disease in the Helsinki Heart Study. *Am J Cardiol* 63: 42H-47H.

80. Beresford, S.A. and C.J. Boushey. 1997. Homocysteine, folic acid, and cardiovascular disease risk. In Preventive Nutrition: The Comprehensive Guide for Health Professionals. A. Benedict and R.J. Deckelbaum, editors. Humana Press, Totowa, NJ.

81. Malinow, M.R., A.G. Bostom, and R.M. Krauss. 1999. Homocyst(e)ine, diet and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation* 99: 178-182.

82. Criqui, M.H., S.S. Coughlin, and A. Fronek. 1985. Noninvasively diagnosed peripheral arterial disease as a predictor of mortality: results from a prospective study. *Circulation* 72: 768-773.

83. Criqui, M.H., R.D. Langer, A. Fronek, H.S. Feigelson, M.R. Klauber, T.J. McCann, and D. Browner. 1992. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 326: 381-386.

84. McDermott, M.M., J. Feinglass, R. Slavensky, and W.H. Pearce. 1994. The ankle-brachial index as a predictor of survival in patients with peripheral vascular disease. *J Gen Intern Med* 9: 445-449.

85. Sikkink, C.J., W.N. van Asten, M.A. van 't Hof, H. van Langen, and J.A. van der Vliet. 1997. Decreased ankle/brachial indices in relation to morbidity and mortality in patients with peripheral arterial disease. *Vasc Med* 2: 169-173.

86. Leng, G.C., F.G Fowkes, A.J. Lee, J. Dunbar, E. Housley, and C.V. Ruckley. 1996. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *Br Med J* 313: 1440-1444.

87. Stamler, J., O. Vaccaro, and D.J. Neaton. 1993. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial (MRFIT). *Diabetes Care* 16: 434-444.

88. Haffner, S.M., S. Lehto, T. Ronnemaa, K. Pyorala, and M. Laakso. 1998. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339: 229-234.

89. Grundy, S.M., I.J. Benjamin, G.L. Burke, A. Chait, R.H. Eckel, B.V. Howard, W. Mitch, S.C.Jr. Smith, and J.R. Sowers. 1999. Diabetes and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* 100: 1134-1146.

90. Grundy, S.M. 1999. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol* 83(9B): 25F-29F.

91. Reaven, G.M. 1996. Insulin resistance and its consequences: non-insulin-dependent diabetes mellitus and coronary heart disease. InDiabetes Mellitus. LeFoith_, S.I. Taylor, and J.M. Olefsky, editors. Lippincott-Raven Publishers, Philadelphia, PA, 509-519.

92. DeFronzo, R.A. and E. Ferrannini. 1991. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* 14: 173-194.

93. Stone, P.H., J.E. Muller, T. Hartwell, B.J. York, J.D. Rutherford, C.B. Parker, Z.G. Turi, H.W. Strauss, J.T. Willerson, and T. Robertson. 1989. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. *J Am Coll Cardiol* 14: 49-57.

94. Smith, J.W., F.I. Marcus, and R. Serokman. 1984. Prognosis of patients with diabetes mellitus after acute myocardial infarction. *Am J Cardiol* 54: 718-721.

95. American Diabetes Association, 1999. Management of dyslipidemia in adults with diabetes. American Diabetes Association: Clinical Practice Recommendations 1999. *Diabetes Care* 22: 556-559.

96. Detrano, R.C., N.D. Wong, T.M Doherty, R.M. Shavelle, W. Tang, L.E. Ginzton, M.J. Budoff, and K.A. Narahara. 1999. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. *Circulation* 99: 2633-2638.

97. Pitt, B. and M. Rubenfire. 1999. Risk stratification for the detection of preclinical coronary artery disease. *Circulation* 99: 2610-2612.

Grand Rounds 5 Oct 1999

Table 1

Categorical Levels of Major,
Causal Risk Factors

Risk Factor	Categorical Level
Cigarette smoking	Any current
Blood pressure	$\geq$ 140 mm Hg systolic $\geq$ 90 mm Hg diastolic
LDL cholesterol	$\geq$ 160 mg/dL
HDL cholesterol	< 35 mg/dL
Plasma glucose	> 126 mg/dL (fasting)

Table 2

Scoring for Global Risk Assessment

(Modified Framingham Scoring)

Risk Factor	Risk Points	
Age	Men	Women
40-44	1	0
45-49	2	3
50-54	3	6
55-59	4	7
60-64	5	8
65-69	6	9
70-74	7	10
LDL cholesterol (mg/dL) (on dietary therapy)*		
130-159		
160-189	2	2
≥ 190	3	3
HDL cholesterol (mg/dL)		
35-44	1	2
< 35	2	5
Blood Pressure (mmHg) (on treatment)†		
130-139/85-89	1	1
≥ 140/90	2	2
Baseline Fasting Plasma Glucose (mg/dL)		
110-126	1	2
Current Smoker‡		
No	0	0
Yes	2	2

Adding up the Points

Age _____ Cholesterol _____

Diabetes ____ HDL Cholesterol _____

Smoker _____ Blood Pressure _____

Total _____

Risk Points	Absolute Risk (Hard CHD)	
	Men	Women
1	2%	1%
2	3%	2%
3	4%	2%
4	5%	2%
5	6%	2%
6	7%	2%
7	9%	3%
8	13%	3%
9	16%	3%
10	20%	4%
11	25%	7%
12	30%	8%
13	35%	11%
14	45%	13%
15		15%
16		18%
17		20%
18		20%

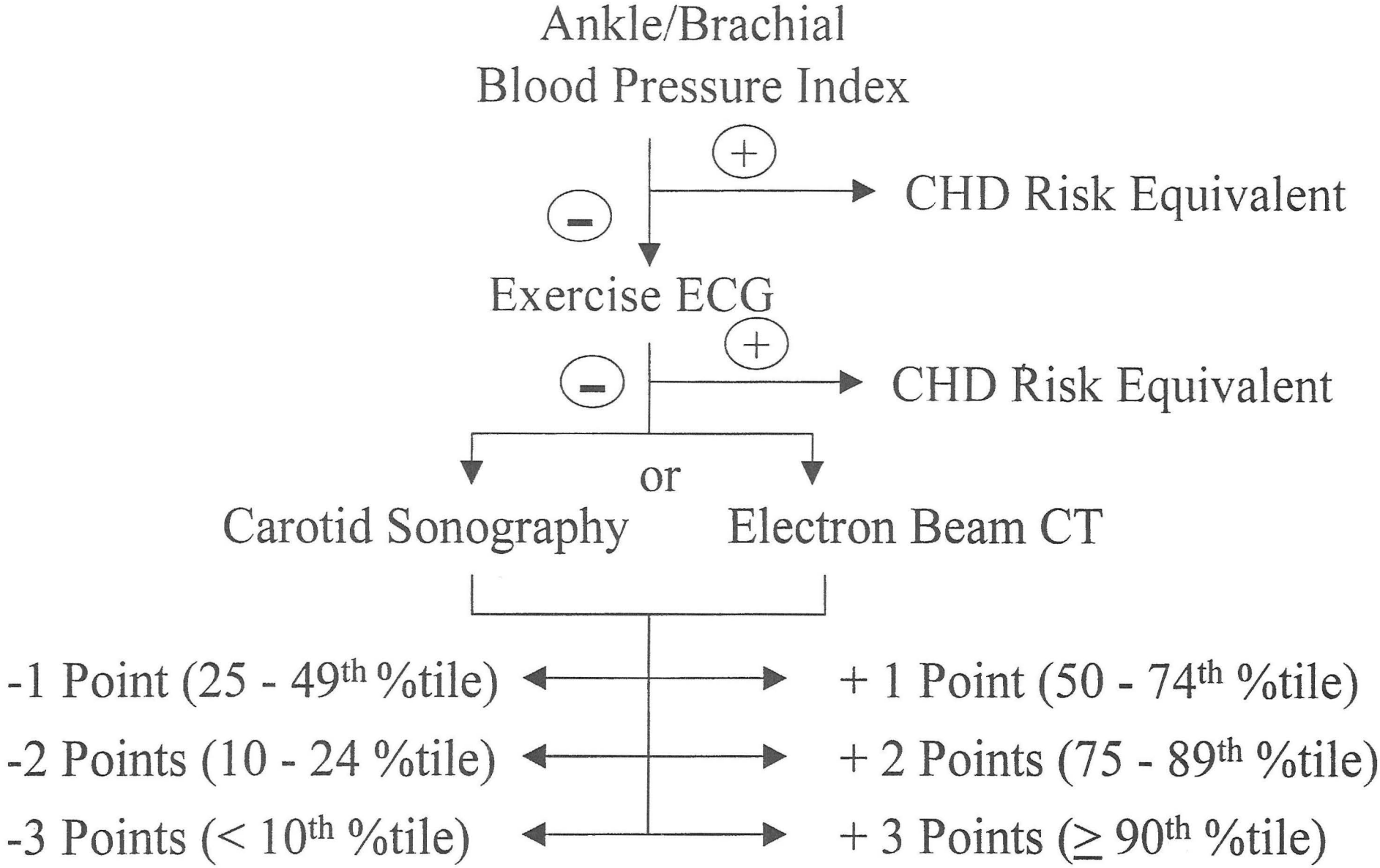
* Patient should be on maximal dietary therapy for 3 months before risk scoring (LDL-cholesterol should be average of 3 values)

† Patient should be on appropriate blood pressure therapy for 3 months before scoring. Blood pressure reading should be the average of 3 measurements.

‡ Current smoking means any cigarette smoking in last year.

Figures

Figure 1. Strategies for non-invasive assessment of subclinical atherosclerosis. The first test in this approach is the measurement of the ankle/brachial blood pressure index. If positive, the patient is designated to have a CHD risk equivalent; if negative, the patient proceeds to an exercise ECG. If the latter is abnormal, the patient has a CHD risk equivalent; if normal, consideration can be given to either carotid sonography or electron beam computerized tomography (EBCT). The patient's age score from Table 4 is adjusted according to the results of either test. Points are subtracted from the age score when age and sex adjusted scores are less than the 50^{th} percentile, whereas points are added for scores greater than the 50^{th} percentile, as shown in the figure.


Ankle/Brachial
Blood Pressure Index
+
CHD Risk Equivalent
-
Exercise ECG
+
CHD Risk Equivalent
-
or
Carotid Sonography
Electron Beam CT
-1 Point (25 - 49th %tile)
+ 1 Point (50 - 74th %tile)
-2 Points (10 - 24 %tile)
+ 2 Points (75 - 89th %tile)
-3 Points (< 10th %tile)
+ 3 Points (≥ 90th %tile)