Writing Group I of Prevention Conference V reviewed the role of medical office assessment in the detection of risk factors and estimation of total cardiovascular risk. The primary focus was on identification of known risk factors for coronary heart disease (CHD). Population screening may identify risk factors that prompt people to seek clinical consultation. Risk factors may also be identified in patients who are seeking medical treatment for other conditions. Physicians have the responsibility to evaluate cardiovascular risk in all their patients. Medical office assessment permits the identification of many high-risk patients without the need for noninvasive testing for atherosclerotic burden or subclinical myocardial ischemia. Techniques for office assessment available to clinicians include history, physical examination, laboratory testing, and electrocardiography (ECG). Routine evaluation and testing provides most of the information needed to estimate risk and make treatment decisions. The essential information required for estimating risk for CHD lies in the known risk factors for coronary disease. These risk factors must first be identified and their severity determined. The relationship between risk factors and development of CHD is strong but variable. When a risk factor is causally and independently related to disease, the physician should make recommendations to the patient about risk factor modification. When risk factors are associated with increased risk for CHD but are not directly causative, the risk factor is considered to be a marker for increased risk. In the following discussion, the major risk factors and risk markers for CHD that can be detected in medical office assessment are reviewed. The different categories of risk are then considered. Finally, the special characteristics of each risk factor in relation to global risk assessment are reviewed. Special groups, including older patients and those with diabetes, are considered, and suggestions are made for modifying the existing guidelines for risk assessment.

Categories of Risk Factors

The Framingham Heart Study has taken the lead in developing the concept of risk factors, a concept that is now widely accepted and used. Several risk factors are recognized as major independent risk factors. Abundant evidence indicates that independent risk factors are direct causes of CHD and occur commonly in the population; moreover, their modification reduces the risk for major coronary events. The major risk factors include cigarette smoking, elevated blood pressure, elevated serum total cholesterol (particularly low-density lipoprotein [LDL] cholesterol), and diabetes mellitus. Another risk factor commonly included in this category is a low level of serum high-density lipoprotein (HDL) cholesterol. The causal link between low HDL cholesterol and CHD is not as well understood as that for the other major risk factors, but epidemiological studies reveal a strong independent association between low HDL-cholesterol levels and increased incidence of CHD. In prospective epidemiological surveys, these 4 major risk factors account for ~50% of the variability in risk in high-risk populations; moreover, they can explain up to 90% of the excess risk for CHD. This latter estimate is based on risk for CHD in patients with established risk factors compared with risk in nonsmokers who have optimally low levels of blood pressure and total cholesterol, relatively high levels of HDL cholesterol, and no diabetes. The variability in risk in high-risk populations at a given level of each risk factor reveals the need to refine risk assessment through other noninvasive techniques; these
methods may permit better selection of patients for intensive preventive therapies. In contrast, the very high level of excess risk imparted by the major risk factors shows the potential for decreasing the incidence of CHD by risk factor modification.

Advancing age is another risk factor in epidemiological studies. Age itself is not causally related to CHD but reflects the length of exposure to risk factors that lead to progressively increased amounts of coronary atherosclerosis. Once a patient has acquired an appreciable amount of coronary plaque, the plaque itself becomes a risk factor because of the tendency of plaques to rupture or erode; these events produce coronary thrombosis and are responsible for most acute coronary syndromes (unstable angina or acute myocardial infarction). Other risk factors include certain historical features (eg, physical inactivity, family history of premature CHD, socioeconomic status, mental depression, ethnicity), physical findings (eg, obesity), and laboratory abnormalities (eg, elevations of serum triglycerides, small LDL particles, lipoprotein(a), impaired fasting glucose, homocysteine, certain coagulation factors, and apolipoprotein B, as well as ECG evidence of left ventricular hypertrophy [LVH]). The relation of each of these factors to CHD is more complex than that of the major independent (or causal) risk factors. Elevations of apolipoprotein B are closely linked to increased LDL cholesterol and can be considered a direct cause of coronary atherosclerosis. Elevations of triglycerides, small LDL particles, lipoprotein(a) [Lp(a)], homocysteine, and certain coagulation factors are conditional risk factors. Many studies show that these factors are associated with increased risk for CHD, but their mechanistic link to CHD has not been elucidated. Still other risk factors, eg, obesity, physical inactivity, family history of premature CHD, socioeconomic and behavioral factors, ethnicity, and male sex are predisposing risk factors; ie, they contribute to the development of causal and conditional risk factors. The presence of each of these risk factors has some significance for risk assessment as discussed below. The American Heart Association recognizes obesity and physical inactivity as major risk factors; this is because in the United States they are the leading causes of several other risk factors, particularly elevated cholesterol level, low HDL-cholesterol level, hypertension, and diabetes.

Categories of Risk
End Point of Risk
In defining risk for CHD, the coronary end point must be specified. The Framingham Heart Study traditionally uses total CHD, which includes angina pectoris, clinically recognized myocardial infarction, ECG evidence of previous myocardial infarction, coronary insufficiency, unstable angina, and CHD death. A recent Framingham report also provides estimates for hard CHD; this end point includes total CHD minus angina pectoris. Another potential end point can be acute coronary syndromes, ie, acute myocardial infarction, unstable angina, and CHD death; this combined end point was used in the recent AFCAPS/TexCAPS study of lovastatin therapy. Writing Group I did not specify a preferred end point but noted the need for precision and consistency in the definition and in particular the close link between causal risk factors and major coronary syndromes.

Absolute Risk
This category represents the probability of a person developing CHD in a finite period, eg, within the next decade. Absolute risk has been increasingly recognized as a critical determinant for making decisions about instituting pharmacological therapy for risk reduction in primary prevention.

Relative Risk
Relative risk is the ratio of absolute risk for CHD in a patient with risk factors compared with a person at a standard level of risk. Framingham investigators have used 1 of 2 denominators for estimating relative risk. The first is risk in a person of the same age who has none of the major risk factors; such a person is classified as being at low risk. An alternative standard level of risk could be the population average risk. A person at this level of risk could be said to be at average risk. Relative risk estimates may be useful for making clinical decisions in young adults and elderly patients. They may also be used for defining risk in various ethnic populations in which Framingham scoring for absolute risk has not been validated.

Number Needed to Treat
Another way to assess absolute risk is to identify the number of patients needed to treat (NNT) to achieve 1 desirable outcome. This number helps provide perspective, although it can be misleading too. To be meaningful, NNT must be qualified by a time frame, ie, whether the number needed to treat to achieve a favorable outcome is for 5, 10, 20, or 30 years.

Global Risk Assessment
In the past decade, one attractive concept that has evolved is that the intensity of risk factor management should be adjusted to the severity of risk. This concept was advocated in the first Adult Treatment Panel report of the National Cholesterol Education Program (NCEP) and was reconfirmed in the second report. The NCEP identifies 3 tiers of absolute risk: very high risk for patients with established CHD and other forms of atherosclerotic disease, high risk for patients with multiple risk factors, and low risk for patients with <2 risk factors. Basically the same approach was also advocated by the first joint European societies’ recommendations for coronary prevention, which were recently revised. The paradigm of matching intensity of therapy to absolute risk was further endorsed and developed in a consensus conference sponsored by the American College of Cardiology (ACC). The National High Blood Pressure Education Program Joint National Commission (JNC), which sets forth guidelines for treatment of hypertension, also adjusted intensity of antihypertensive therapy to absolute risk in its most recent guidelines. Matching intensity of preventive regimens to absolute risk is attractive because it offers a way to achieve an appropriate balance of efficacy, safety, cost of therapy, and professional time commitment. The effort to quantify each component of this balance requires an estimate of absolute risk. Because estimates of absolute risk usually
require that the contribution of each risk factor be summed, the summation has been called global risk assessment.

A quantitative estimate of risk based on the contribution of each risk factor has been made by the Framingham Heart Study, a 50-year study of the relationship between risk factors and CHD risk in the predominantly white population of Framingham, Mass. Framingham data seemingly can be used as the foundation of a risk-assessment program. In fact, Framingham data are the basis of risk-assessment schedules outlined in the NCEP and JNC guidelines. The AHA Task Force on Risk Reduction recently reviewed the Framingham scoring algorithm in detail. In addition, the AHA and the ACC have published a joint scientific statement on the use of multiple risk factor equations for global risk assessment. The foundation of this statement is the Framingham scoring algorithm.

Despite the adoption of Framingham estimates for risk assessment by the AHA and ACC, a systematic study of their applicability to a series of other populations needs to be checked. In January 1999, the National Heart, Lung, and Blood Institute (NHLBI) sponsored a workshop to compare risk estimates derived from the Framingham population with those of other populations. The publication of the proceedings of this workshop should better define the transportability of Framingham estimates.

The NCEP and JNC assess global risk by counting categorical risk factors. The presence of categorical levels of any 3 major risk factors essentially confers a high-risk status. Framingham investigators have proposed an alternative approach to global risk assessment. Because of the continuous relationship between intensity of risk factors and risk for CHD, Framingham researchers have delineated a risk-scoring technique founded on the summation of graded risk factors. This technique is based on the theory that the relation between risk factors and the likelihood of developing CHD is continuous rather than threshold, as might be suggested by the use of categorical risk factors. The recent Framingham scoring system merges the continuous relationship with the graded categories defined by the NCEP and JNC. The continuous model has been adopted by the joint European cardiovascular societies; their guidelines in fact adhere more strictly to a continuous model than that used in the recent Framingham proposal of stepwise increments in risk factors. The advantage of continuous (or graded) risk factors over the use of categorical risk factors is that the former should provide more quantitative estimates of global risk. For example, by combining multiple marginal risk factors, the estimate of total risk should be more accurate in circumstances in which categorical risk factors are absent but multiple marginal risk factors are present.

Writing Group I recognized that as future guidelines for risk assessment are developed, strong consideration should be given to incorporating a graded scoring technique similar to that proposed by the Framingham researchers. The potential advantages of combining multiple marginal risk factors over the NCEP and JNC method, in which only categorical risk factors are added, deserves review and evaluation by future guidelines committees. The writing group recognized that the current NCEP and JNC guidelines have the advantage of simplicity in practice; therefore, if Framingham scoring were to replace these guidelines, special attention must be given to simplifying the Framingham approach. The writing group did not question the reliability of Framingham estimates but recognized the need to make them “user friendly.” Suggestions include development of computer disks, hand-held calculators, and/or Internet Web pages to facilitate application. The colored charts published by the European societies are visually appealing and might be attractive to healthcare professionals and patients. Construction of the optimal presentation of Framingham scoring will require some research, and different methods of presentation should be compared. Despite the writing group’s enthusiasm for Framingham scoring, the need to develop and evaluate practical methods for its use is recognized.

Short- Versus Long-Term Risk

A high-risk state for primary prevention has been widely defined in terms of short-term risk, eg, the likelihood of developing CHD in the next decade. This definition is influenced in large part by the view that high-risk primary prevention equates with pharmacological therapy, which can be expensive and may have side effects. Thus, the heart of the definition of high risk is the question of whether absolute risk is high enough in the short term to justify the side effects and cost of pharmacological therapy. Recent European guidelines have argued that when risk for developing CHD reaches 20% per decade, a patient can be categorized as high risk, and implementation of guidelines for risk factor reduction similar to those advocated for secondary prevention is justified. However, one difference between the European guidelines for high-risk primary and secondary prevention is that a more conservative stance is taken toward the use of aspirin in primary prevention. In the European guidelines, the definition of high risk extends to age 65; at older ages, clinical judgment must be used in implementing secondary prevention guidelines for primary prevention. The critical risk level of 20% per decade was presumably derived through an attempt to balance the efficacy, safety, and cost of pharmacological therapy. Nonetheless, it might be noted that the coronary end point used in European guidelines is total CHD, not hard CHD. The use of these less-strict criteria for the high-risk state will open the door to pharmacological therapy to approximately one third more patients than would be subsumed under the end point of hard CHD.

Writing Group I recognized the simplicity of the European definition of a high-risk state. At the same time, the view was expressed that this definition is arbitrary and may be subject to change. Many investigators have been impressed with recent primary prevention trials in which 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) were found to be highly efficacious and safe. Indeed, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), statin therapy was used for patients whose average absolute risk at baseline was well below the level of 20% per decade; risk for acute coronary events was safely reduced by ~40%. Some investigators believe that treatment of patients like those recruited into AFCAPS/TexCAPS is not cost-effective. Nonetheless, as
the cost of statins declines, it may become increasingly cost-effective to use drug therapy for patients whose absolute risk is <20% per decade. Without question, the concept of cost-effectiveness is itself a contentious issue, and there are no established guidelines for defining it. The issue revolves largely around decisions on the allocation of scarce resources. The writing group was therefore reluctant to recommend a specific absolute risk that confers a high-risk state, particularly as a cutoff point for use of cholesterol-lowering drugs in primary prevention. To develop such a cut point for drug therapy in the United States will require considerable discussion among interested groups, as well as emergence of a consensus. Relevant practice and managed care groups are just beginning to address the balance of risk versus cost of cholesterol-lowering drugs. Undoubtedly, at lower levels of absolute risk, the issue of cost-effectiveness increasingly enters the equation.

The writing group was also reluctant to place exclusive emphasis on using an estimate of short-term absolute risk to make treatment decisions. Long-term risk cannot be ignored. The Framingham Heart Study and other prospective studies clearly show that any single risk factor can produce cumulative damage and high risk if left untreated for many years. Indeed, the Framingham investigators have introduced the concept of lifetime risk to contrast with short-term risk. The long-term dangers of several untreated risk factors—cigarette smoking, hypertension, and elevated serum cholesterol levels—are well established. Writing Group I thus recommended that during the formulation of future guidelines, appropriate emphasis should be given to intervention in long-term risk that accompanies single categorical risk factors and multiple marginal risk factors. Long-term risk assessment is particularly relevant for younger candidates for coronary disease.

In the same vein, Writing Group I affirmed that exclusive attention should not be given to absolute risk in global risk assessment. Relative risk estimates also deserve consideration. For example, a high relative risk in young adulthood carries a high absolute risk in the long term. Thus, in adolescents and young adults, the relative risk estimate may be a better guide to risk factor management than absolute risk. Relative risk estimates may also be useful for deciding when to begin risk factor interventions in elderly patients. Although absolute risk may be a useful guide for starting pharmacological therapy in some patients, it may be insufficient for complete management of risk factors in many patients. Still, in general, absolute risk is at the heart of global risk assessment and has a broad utility for identification of patients for various forms of risk management. In this regard, some have argued in favor of defining “a number needed to treat” ( . . . to prevent an event) as a clinically useful way to expand the absolute risk estimate when considering the benefits of therapies.

Special Considerations for Specific Risk Factors

Diabetes Mellitus

There is growing evidence that diabetes mellitus, particularly type 2 diabetes, confers a very high risk for CHD and its complications. Although hyperglycemia in patients with diabetes may increase risk in the same manner as other major risk factors, patients with type 2 diabetes are often overweight and sedentary and carry multiple metabolic risk factors; the latter together constitute the metabolic syndrome: insulin resistance, mild hypertension, elevated triglyceride level, low HDL-cholesterol level, and a prothrombotic state. Thus, in many patients with type 2 diabetes, the presence of hyperglycemia combined with a constellation of metabolic risk factors elevates absolute risk to a degree comparable to that of patients with established CHD. For this reason, Writing Group I recommended that type 2 diabetes be described as “CHD risk equivalent” in terms of risk factor management, meaning that the current AHA guidelines for risk factor management of patients with established CHD should probably be extended to patients with type 2 diabetes who do not have CHD. Some physicians may use the same reasoning for patients with type 1 diabetes, but a solid recommendation cannot be made because such patients do not always have the concomitant risk factors that are common in type 2 diabetes. The AHA recently published a scientific statement to draw more attention to diabetes as a risk factor for cardiovascular disease. This statement has been reinforced by a joint affirmation of the importance of diabetes as a cause of cardiovascular disease by the American Diabetes Association, the Juvenile Diabetes Foundation International, the National Institute of Diabetes and Digestive and Kidney Diseases, and the AHA.

Cigarette Smoking

Patients who smoke cigarettes deserve special attention in primary prevention. Not only are they at higher risk for CHD, peripheral arterial disease, and stroke, but they are likely to develop emphysema, lung cancer, and other forms of cancer. Writing Group I thus recommended that the AHA place increased emphasis on developing tools to guide healthcare professionals in helping patients quit smoking. Cigarette smoking is justifiably classified as a risk factor to be included in the assessment of absolute risk for the purpose of adjusting intensity of efforts to control other risk factors, eg, elevated LDL-cholesterol levels. But the independent dangers that accompany habitual smoking deserve special consideration and make smoking itself a primary target for treatment. Appropriate measures therefore should be taken to encourage and help patients quit smoking. The AHA recently issued a statement to guide physicians in smoking-cessation efforts.

Hypertension

In comparison with previous JNC reports, the most recent JNC guideline places greater emphasis on global risk assessment in establishing treatment goals for blood pressure for patients with hypertension. For most patients, an acceptable minimal goal of therapy is a blood pressure <140/90 mm Hg; this goal routinely holds even when pharmacological therapy is required to achieve it. The need to achieve this goal derives from the recognition that lack of treatment of even milder forms of hypertension over the long term can cause cardiovascular complications. Writing Group I confirmed the need for intensive management of established
hypertension and urged the AHA to continue to endorse the guidelines developed by the JNC.\textsuperscript{20} Writing Group I also supported the JNC’s admonition\textsuperscript{20} to reduce blood pressure to still lower, or optimal, blood pressures for patients with end-organ damage or diabetes.

**Elevated LDL Cholesterol**

The NCEP\textsuperscript{15} has identified several cut points for LDL cholesterol. An LDL cholesterol level <130 mg/dL is described as desirable; a level of 130 to 159 mg/dL is considered borderline high risk; and a level \( \geq 160 \) mg/dL is designated high risk. According to the NCEP, in general, pharmacological therapy should be considered for an LDL-cholesterol level \( \geq 190 \) mg/dL, even in the absence of other risk factors. Possible exceptions are young men (<35 years) and premenopausal women in whom pharmacological therapy can be delayed; nonetheless, drug therapy is almost always necessary when LDL cholesterol is \( >220 \) mg/dL.

These recommendations are based in part on the long-term dangers accompanying elevated LDL-cholesterol concentrations, even in the absence of other risk factors. Writing Group I recommended that the AHA continue to endorse the NCEP guidelines for management of LDL-cholesterol concentrations. Global risk assessment is not required for making decisions about pharmacological therapy in middle-aged or elderly patients whose LDL-cholesterol levels are \( \geq 190 \) mg/dL.

The NCEP guidelines\textsuperscript{15} additionally indicate that the use of cholesterol-lowering drugs should be considered for LDL-cholesterol concentrations of 160 to 189 mg/dL, provided that \( \geq 2 \) risk factors are present. In essence, the NCEP defines a high-risk patient as one with 3 risk factors (a high-risk LDL-cholesterol level plus 2 other risk factors). For example, in a 55-year-old man, 3 categorical risk factors, one of which is an LDL-cholesterol level of 160 to 189 mg/dL, confers an absolute risk of \( \approx 15\% \) per decade for a major coronary event. This value is less than the 20\% per decade advocated in the European guidelines.\textsuperscript{17,18} In general, Writing Group I supported the current NCEP guidelines for patients with LDL-cholesterol levels of 160 to 189 mg/dL. Nonetheless, the view was frequently expressed that Framingham scoring might be a better means of identifying those patients who should receive cholesterol-lowering drugs than risk assessment, based on methods currently used by the NCEP. At the same time, it was noted that the relative risk associated with an elevated LDL-cholesterol level declines with age; for this reason, the LDL-cholesterol value has less power to discriminate between high and low risk in older persons. This fact contributes to the need for other approaches to risk assessment in older patients, eg, for the detection of advanced subclinical coronary atherosclerosis or myocardial ischemia (see the sections by Writing Groups II and III). Noninvasive assessment could facilitate identification of high-risk patients among the older population.

The NCEP\textsuperscript{15} does not recommend starting a regimen of cholesterol-lowering drugs when LDL-cholesterol levels are in the borderline–high risk range (130 to 159 mg/dL). Instead, emphasis is placed on diet modification, increased exercise, and reduction of excess weight. In contrast, the current European guidelines\textsuperscript{17,18} recommend the initiation of a cholesterol-lowering drug regimen when absolute risk is \( \geq 20\% \) per decade, even when the LDL-cholesterol level is in the borderline–high risk range. Writing Group I found the European recommendation attractive and suggested that as US cholesterol guidelines are updated, consideration should be given to recommending the use of cholesterol-lowering drugs for LDL-cholesterol levels of 130 to 159 mg/dL in patients defined as being at high risk. The recent AFCAPS/TexCAPS study\textsuperscript{13} demonstrated the efficacy of cholesterol-lowering therapy in patients with LDL-cholesterol levels in this range. Although many patients in AFCAPS/TexCAPS were not at high risk, the study showed that lowering LDL levels in persons at moderate risk decreases their risk even more.

**HDL Cholesterol**

The NCEP defines an HDL-cholesterol level of <35 mg/dL as a major risk factor.\textsuperscript{15} In epidemiological studies,\textsuperscript{4–6} HDL-cholesterol concentrations are inversely and independently correlated with risk for CHD. Some investigators believe that HDL is directly protective against the development of coronary atherosclerosis; ie, it directly counteracts the effects of an elevated LDL-cholesterol level. In addition, growing evidence points to the inverse relation of HDL cholesterol to CHD risk, owing in part to the association of low HDL with insulin resistance and other components of the metabolic syndrome.\textsuperscript{30} The NCEP recommendations were based largely on the concept that a high HDL level is directly protective against development of CHD; in accord with this view, the NCEP recommendations do not take into account the common association of a low HDL level with the metabolic syndrome. To avoid the complexity that would be created by sex-specific cut points, the NCEP guidelines categorically defined an HDL-cholesterol level of <35 mg/dL as being a risk factor for both men and women. Writing Group I suggested that future cholesterol guidelines take into account the importance of a low HDL-cholesterol level in overall CHD risk. Because average HDL-cholesterol concentrations differ between men and women, different criteria might be used for defining a low level of HDL-cholesterol for each of the sexes, as was done in recent Framingham scoring.\textsuperscript{7} At the same time, the implications of introducing a greater degree of complexity by using different cut points for men and women will need to be weighed in future deliberations.

**Age as a Risk Factor**

Framingham risk scoring counts age as an independent risk factor. Moreover, the risk score assigned to age increases with advancing years. The increase in risk with advancing age reflects a progressive accumulation of coronary atherosclerosis. The presence of advanced coronary atherosclerosis as such poses the threat of plaque rupture and major coronary events. This threat is independent of concurrent risk factors, which act by promoting coronary atherosclerosis. A person’s age becomes a surrogate for coronary plaque burden. Herein lies a major problem with global risk assessment in older people. The average risk scores for age fail to account for individual variability of plaque burden in the older popul-
tion. This fact explains the decline in reliability of prediction of risk factors, especially serum cholesterol levels, with advancing age.

The attenuation of the predictive power of standard risk factors in the older population enhances the difficulty in selecting appropriate patients for aggressive risk-reduction therapies. It implies the need for alternative methods to select patients for medical intervention in risk factors. The standard risk factors still carry some predictive power in older patients, and a high relative risk based on these risk factors can be helpful in selecting patients for medical intervention. A potential way to improve risk assessment in elderly patients is direct determination of coronary plaque burden by noninvasive methods. There is a strong positive association between the extent of coronary atherosclerosis and the likelihood of a major coronary event occurring; if the coronary plaque burden could be estimated noninvasively, this estimate could replace age as a risk factor. One of the major goals of the Prevention Conference V was to evaluate the status of noninvasive methods for estimating coronary plaque burden and predicting major coronary events. Patients with a heavy burden of coronary atherosclerosis seemingly are those at highest risk and represent the best candidates for aggressive medical intervention in risk factors. This approach could be particularly applicable for the elderly population.

Obesity as a Risk Factor
The AHA lists obesity as a major risk factor for cardiovascular disease. Obese predisposes an individual to elevated blood pressure; elevated serum cholesterol and triglyceride levels; a lower HDL-cholesterol level; small, dense LDL particles; a prothrombotic state; and type 2 diabetes. The clustering of these CHD risk factors, as commonly occurs in overweight and obese patients, has been called the metabolic syndrome. This syndrome appears to be closely linked to the metabolic disorder called insulin resistance. Although earlier Framingham studies found a positive relationship between obesity and CHD risk, Framingham risk scoring does not include increased body weight as an independent risk factor because of the strong association between obesity and other risk factors. Obesity is a cause of the independent risk factors, but it may not be a direct cause of coronary atherosclerosis. Nonetheless, from a clinical point of view, obesity must be carefully tested for coexisting metabolic risk factors and should be encouraged to lose weight.

Physical Inactivity as a Risk Factor
The AHA also counts physical inactivity as a major risk factor. This judgment is based on a well-established association between physical inactivity and CVD risk, as shown by the Framingham Heart Study and others. As with obesity, physical inactivity contributes to several metabolic risk factors. Some investigators contend that physical inactivity is an independent risk factor for CHD, although the Framingham study failed to identify a strong independent predictive power. Nonetheless, physical inactivity should be identified in risk assessment, and it is an independent target for risk-reduction intervention. The AHA has published practical recommendations to guide patients in adopting a safe and effective exercise program.

Lipoprotein(a)
Most epidemiological studies show a positive correlation between Lp(a) concentrations and risk for CHD. However, this relationship has not been demonstrated in all studies. Moreover, laboratory measurements of Lp(a) have not been standardized. Thus, Writing Group I suggested that more research is needed to better define the relation between Lp(a) concentrations and CHD risk and that improved methods for measuring Lp(a) are needed. Routine Lp(a) screening was not recommended.

Triglycerides
Numerous studies have established a relationship between elevated plasma triglyceride levels and risk for CHD. Abundant evidence points to the atherogenicity of triglyceride-rich lipoproteins, most notably lipolytic remnants formed during chylomicron and very-low-density (VLDL) metabolism. In addition, multiple metabolic disturbances that accompany elevated plasma triglycerides may promote atherogenesis and predispose the patient to CHD. These include reduced concentrations of HDL cholesterol; increased small, dense LDL; insulin resistance; and increases in plasminogen activator inhibitor-1 (PAI-1). Because of these interrelationships, the independent risk specifically imparted by elevated plasma triglyceride concentrations has been uncertain. Statistical analyses of observational studies and lipid-lowering trials are confounded by multiple collinearity (particularly with regard to the inverse relation between triglycerides and HDL), although a recent meta-analysis strongly suggests that the relation of triglyceride level to CHD is independent of other risk factors. This independent risk appears to be stronger for intermediate triglyceride elevations (eg, 200 to 800 mg/dL) than for higher levels. Some recent analyses have found that elevated plasma triglyceride (eg, >200 mg/dL) interacts with other risk factors (eg, elevated LDL cholesterol or total/HDL cholesterol) in a nonlinear manner. Thus, combined elevations of triglyceride and LDL cholesterol may carry a greater risk than isolated increases of either. The notion of enhanced atherogenicity of this combined lipid phenotype is compatible with the observation that familial combined hyperlipidemia is the most prevalent genetic dyslipidemia encountered in patients with premature CHD.

The epidemiological and clinical data, including the apparent nonlinear relation of plasma triglyceride levels to CHD risk, have raised the question of whether an elevated plasma triglyceride level should be classified as a categorical risk
factor. There is little basis, however, for selecting a cut point for triglyceride concentrations that should be used to define this risk category. A recent longitudinal trial has suggested that in patients with existing CHD, triglyceride levels >100 mg/dL are associated with a significant increase in recurrent clinical events.\(^{46}\) Another possible cut point is 150 mg/dL, a level that would exclude a greater proportion of low-risk persons and above which there is a substantial increase in prevalence of atherogenic dyslipidemia characterized by increased small, dense LDL particles.\(^{34,41,42}\) Triglyceride levels in the range of 150 to 200 mg/dL thus may indicate increased risk due to other risk factors, whereas levels of 200 to 600 mg/dL may signify significantly increased concentrations of atherogenic triglyceride-rich lipoproteins in addition. Writing Group I proposed that increased attention be given to the role of elevated triglyceride levels in risk management when the cholesterol guidelines are updated. Nonetheless, it was noted that the relative risk accompanying an elevated LDL-cholesterol level declines with age; for this reason, the LDL-cholesterol value has less power to discriminate between high and low risk in older persons. This fact highlights the need for other approaches to risk assessment in older patients, eg, for the detection of advanced subclinical coronary atherosclerosis or myocardial ischemia (see sections by Writing Groups II and III).

**Small, Dense LDL**

Many studies show that elevations in small, dense LDL are positively associated with increased risk for CHD.\(^{34,41}\) Some studies suggest that small, dense LDL are independently atherogenic. Nonetheless, Writing Group I recognized that small, dense LDL are also strongly associated with other risk factors in the metabolic syndrome. Moreover, the group noted that reliable methods for estimating concentrations of small dense LDL are not widely available. Writing Group I therefore did not recommend measurement of small, dense LDL as a part of routine lipoprotein analysis. However, the group urged the AHA to encourage more investigation of this promising measurement.

**Apolipoprotein B**

The concentration of total apolipoprotein B (apo B) is a measure of the total number of apo B–containing lipoproteins in serum. This measurement includes both LDL and VLDL particles. Some investigators\(^{43}\) have proposed that total apo B may be a better indicator than LDL cholesterol of the atherogenic potential of lipoproteins. This may be particularly true for patients with hypertriglyceridemia and/or small, dense LDL. However, accurate laboratory measurements of total apo B are not widely available. In addition, replacing LDL cholesterol with apo B in treatment algorithms would require a major educational program. Consequently, although the writing group recognized the potential utility of apo B measurement in risk assessment, it did not recommend that these measurements become a part of routine lipoprotein analysis.

**Homocysteine**

Cross-sectional studies have shown that homocysteine levels are positively correlated with CHD risk, but in prospective studies, this finding has been inconsistent.\(^{44}\) For this reason, routine screening for homocysteine levels was not recommended. Conversely, Writing Group I suggested that consideration be given to testing for homocysteine in CHD patients without other risk factors and in patients with a strong family history of premature CHD in whom established risk factors cannot be identified. If elevated homocysteine levels are found, patients should be advised to consume the recommended dietary allowance of folic acid.

**ECG Abnormalities**

Although the AHA does not currently recommend routine, repeated ECGs for risk assessment, various ECG abnormalities have been reported to have predictive power. For example, ST-segment depression, nonspecific T-wave abnormalities, LVH, bundle-branch blocks, and ischemic findings on the resting ECG have each been found to have independent predictive power for both coronary mortality and total cardiovascular mortality. In some studies, ≥1 of these abnormalities was associated with multivariate-adjusted relative risks between 2.0 and 4.0, suggesting that these findings alone might signify intermediate to high risk deserving intensive further investigation or risk reduction.\(^{45,46}\) Abnormalities on the resting ECG on serial tracings are associated with higher risk than transient findings alone.\(^{46}\) The Framingham Heart Study\(^{12}\) has long reported that ECG LVH has strong independent predictive power. It is well known that hypertension is the predominant risk factor for LVH, and according to Framingham investigators, ECG evidence of LVH carries predictive power beyond blood pressure. Resting ECG abnormalities, such as those listed above, may signify at least an intermediate risk deserving further preventive intervention or assessment.

**Recommendations for AHA Programs**

Writing Group I made the following recommendations for AHA programs:

- Expand AHA research support in the areas of patient care and outcomes research.
- Cooperate with other agencies (the NHLBI, ACC, Health Care Financing Administration, National Committee for Quality Assurance, Centers for Disease Control and Prevention, Agency for Health Care Policy and Research, and managed care organizations) to expand risk-assessment efforts. Work with these organizations to expand risk-assessment efforts by evaluating the efficacy and utility of different approaches.
- Produce AHA materials that will help educate physicians and other health professionals about how to conduct global risk assessment and how to integrate this information into existing guidelines for risk factor management.
- Develop risk-assessment sheets that can be added to all patients’ charts.
- Develop new strategies to educate patients and the general public. Use clear, simple, consistent messages, eg, “know your numbers (cholesterol, blood pressure),” “know your risk for heart attack in the next 10 years,” “talk with your doctor,” and “reach your goals.”
References


31. Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease: II: genetic analysis of lipid...


KEY WORDS: AHA Conference Proceedings ■ prevention ■ risk factors ■ risk assessment