Prevention Conference V

Beyond Secondary Prevention: Identifying the High-Risk Patient for Primary Prevention

Executive Summary

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Introduction

This conference, "Beyond Secondary Prevention: Identifying the High-Risk Patient for Primary Prevention," which was the fifth in a series of prevention conferences sponsored by the American Heart Association (AHA), was held October 26–28, 1998, in San Francisco, Calif. The need for this conference was precipitated by the remarkable advances in medical therapies for the prevention of coronary heart disease (CHD). The AHA has already set forth guidelines for aggressive medical therapy in patients with established CHD (secondary prevention). The major issue under consideration at this conference was the development of strategies to identify high-risk patients without established CHD who are candidates for aggressive medical therapies for primary prevention. Therefore, a central theme for the conference was the emphasis on establishing a prognosis for high-risk patients without clinical evidence of CHD. Three writing groups were established to report on the following areas: (1) medical office assessment, (2) tests for silent and inducible ischemia, and (3) noninvasive tests of atherosclerotic burden. Each working group reviewed research on existing risk-assessment strategies relevant to the prediction of risk in patients without clinical evidence of CHD.

The key findings of each working group are presented in this Executive Summary of the conference. The full conference report with references is available online at http://circ.ahajournals.org/ in the January 4/11, 2000, issue of *Circulation*. The recommended strategies will assist in expanding preventive therapies, including lipid lowering, blood pressure control, smoking cessation, diet, and exercise, to patients at high risk for developing CHD. The following briefly summarizes the major conclusions of the conference.

In the development of the Prevention V report, Writing Group I outlined a strategy for initial risk assessment of the asymptomatic patient to obtain an estimate of absolute risk. On the basis of standard risk factors and related risk correlates, the concept was set forth that asymptomatic patients can be placed into 1 of 3 risk categories: low risk, intermediate risk, and high risk (Table 1). Low-risk patients can be encouraged to adhere to healthy life habits. High-risk patients can directly enter a regimen of aggressive risk reduction through a combination of nondrug and drug regimens. Patients at intermediate risk become candidates for further risk stratification through noninvasive procedures that test for the presence of myocardial ischemia or coronary atherosclerotic burden. The purpose of the latter procedures is to assist the physician in better defining absolute risk of intermediate-risk patients. Although these noninvasive procedures have traditionally been used for diagnosis of coronary artery disease for the purpose of invasive intervention, the emphasis of Prevention Conference V was on their use to predict future major coronary events (unstable angina and myocardial infarction). This shift in emphasis from diagnosis to prognosis is illustrated by differences in terminology between the 2 activities (Table 2).

Writing Group II examined the potential of techniques for determining subclinical myocardial ischemia for risk prognostication in intermediate-risk patients. A review of the literature indicated that exercise electrocardiography (ECG) has independent predictive power beyond standard risk factors for patients of this type. Other techniques to detect subclinical ischemia may have utility for this purpose in selected patients, although literature related to this issue is sparse.

Writing Group III examined techniques used to estimate atherosclerotic burden for the purpose of risk prognostication. The ankle/brachial blood pressure index (ABI) emerged as a powerful, independent predictor of future coronary events. Several reports further indicate that measures of carotid intimal-medial thickness (IMT) by B-mode sonography provide an independent assessment of coronary risk. Finally, measures of coronary calcium by computerized tomography (CT) show a high correlation with extent of coronary atherosclerosis. Furthermore, preliminary studies suggest that coronary calcium scores provide an independent estimate of future coronary events; however, available studies are insufficient to define the magnitude of independent prediction. Overall, noninvasive procedures for assessing myocardial ischemia and atherosclerotic burden promise to improve the accuracy of risk prognostication for patients found to be at intermediate risk by office-based assessment.

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TABLE 1. Risk Stratification of Asymptomatic Persons According to Probability for Future Coronary Events

- High risk*
- Intermediate risk*
- Low risk*

*Quantitative definitions of risk categories based on probabilities of developing a disease await future analysis of efficacy, safety, and cost-effectiveness for specific risk-reduction interventions.

Writing Group I: Medical Office Assessment

Writing Group I examined methods for estimating total cardiovascular risk in the medical office. The emphasis of this group was on the known risk factors for CHD. For some patients, the presence of multiple risk factors is sufficient to confer a high-risk status, and additional noninvasive testing for coronary atherosclerotic burden or for subclinical myocardial ischemia will be unnecessary. In patients found to be at intermediate risk, however, additional testing may be indicated to better stratify risk. Techniques for office assessment include history, physical examination, laboratory testing, and ECG. The focus of the examination is on detection of risk factors that can either be directly modified or that will modify the overall intensity of risk-reduction therapies. Patients should be examined for the presence of risk factors listed in Table 3. The major causal risk factors—cigarette smoking, elevated blood pressure, elevated serum total cholesterol (and low-density lipoprotein [LDL] cholesterol in particular), low high-density lipoprotein (HDL) cholesterol, and diabetes—account for ≈50% of the variability in risk in high-risk populations and explain up to 90% of the excess population risk for CHD. A patient's age is a powerful indicator of absolute risk because it reflects the total burden of coronary atherosclerosis that has accumulated; the probability of suffering a major coronary event (unstable angina or myocardial infarction) is highly correlated with total plaque burden. Conditional risk factors are those that have been correlated with CHD risk, but their quantitative relation to major coronary events remains to be defined adequately in large prospective studies. The predisposing risk factors contribute to the development of the causal and conditional risk factors. Two of these, obesity and physical inactivity, have such a strong relationship with the development of cardiovascular disease (CVD) that they are designated as major risk factors by the AHA. Abnormalities in the resting ECG (nonspecific ST-segment changes and left ventricular hypertrophy) also carry predictive power and can be called risk factors.

TABLE 2. Two Approaches to Cardiovascular Evaluation

I. Diagnosis of existing disease
- A. Diagnostic sensitivity: percentage of patients with disease who have an abnormal test result
- B. Diagnostic specificity: percentage of patients without disease who have a normal test result
- C. Diagnostic value of abnormal test: percentage of patients with an abnormal test result who have existing disease
- D. Diagnostic value of normal test: percentage of patients with a normal test result who do not have existing disease

II. Prognosis for future coronary events
- A. Absolute risk: probability of developing events in a finite period
- B. Relative risk: absolute risk of high-risk group/absolute risk of low-risk group

TABLE 3. Categories of Risk Factors

- Causative risk factors
  - Cigarette smoking
  - Elevated blood pressure
  - Elevated serum cholesterol (or LDL cholesterol)
    - Alternative: elevated apolipoprotein B
  - Low HDL cholesterol
  - Diabetes mellitus
- Coronary plaque burden as a risk factor
  - Age
  - Nonspecific ST-segment changes on resting ECG
- Conditional risk factors
  - Triglycerides*
  - Small LDL particles*
  - Lp(a)*
  - Homocysteine*
  - Coagulation factors*
    - Plasminogen activating factor inhibitor-1
    - Fibrinogen
  - C-reactive protein
- Predisposing risk factors
  - Overweight and obesity (especially abdominal obesity)†
  - Physical inactivity†
  - Male sex
  - Family history of premature CHD
  - Socioeconomic factors
  - Behavioral factors (eg, mental depression)
  - Insulin resistance
- Susceptibility risk factor
  - Left ventricular hypertrophy

*These factors are considered conditional risk factors when serum levels are abnormally high.

†Obesity and physical inactivity are counted as major risk factors by the AHA.

Categories of Risk

To determine the risk for CHD, the coronary end point must be specified. The Framingham Heart Study traditionally identifies total CHD as its end point; this includes stable angina pectoris, major coronary events (unstable angina and myocardial infarction), and coronary death. Recently, Framingham investigators have distinguished between total CHD and hard CHD, the latter consisting of major coronary events and coronary death. Hard CHD typically is the primary end point in clinical trials of risk factor reduction. Risk estimates essentially are of 2 types, absolute risk and relative risk. Absolute risk is the probability of developing CHD in a finite period, whereas relative risk is the ratio of absolute risk for a patient over a standard risk. The latter can be either the average risk or the low risk associated with an absence of risk factors.

TABLE 4. Categorical Risk Factors

- Cigarette smoking (any current smoking)
- Hypertension (blood pressure ≥140/90 mm Hg)
- Elevated LDL cholesterol (≥160 mg/dL)
- Low HDL cholesterol (<35 mg/dL)
- Diabetes mellitus (plasma glucose ≥126 mg/dL)

Global Risk Assessment

In the past decade, the concept has evolved that the intensity of risk factor management should be adjusted by the severity of risk. This concept has been adopted in the guidelines of the National Cholesterol Education Program, the joint European societies, and other organizations. Global risk assessment is the estimation of absolute risk based on the summation of risks contributed by each risk factor. Several methods have been used to sum risks. Writing Group I favored a method recently proposed by Framingham researchers in which the continuous relationship between risk factor intensity and coronary risk is used. Framingham scoring uses only the "standard" risk factors (smoking, blood pressure, serum cholesterol, HDL cholesterol, blood glucose, and age). Conditional and predisposing risk factors are not used in the Framingham risk equation because of lack of evidence of a strong, independent contribution to CHD risk. The writing group nonetheless stressed that several of the conditional and predisposing risk factors undoubtedly contribute to the development of CHD. Thus, the detection and even therapeutic modification of these risk factors may be appropriate in some patients.

Short-Term Versus Long-Term Risk

Global assessment for short-term (≤10 years) risk is the foundation of guidelines of the joint European societies. European recommendations defined a high-risk state as a 10-year absolute risk for developing CHD of ≥20%. This level of risk was identified as one that justifies management of risk factors in the clinical setting, particularly for the pharmacological control of elevated blood pressure and cholesterol. Writing Group I was attracted to the European concept of applying increased intensity of therapy to a category of patients at high short-term risk. However, the writing group was reluctant to embrace the specific European definition of high risk. This arbitrary definition derives from 3 factors: efficacy, safety, and cost of therapy. Because efficacy and safety of pharmacological therapy have improved progressively, the dominant factor in the definition becomes cost-effectiveness. The writing group hesitated to adopt a general definition of high risk without the availability of extensive cost-effectiveness analyses.

Moreover, the writing group also expressed reluctance to allow short-term risk estimates to drive all treatment decisions. Patients who have intermediate risk in the short term may still be at high risk in the long term. To exclude such patients from clinical management of risk factors may not be prudent. For example, any single risk factor can produce cumulative damage and thus lead to premature clinical syndromes if left untreated for many years. Therefore, most members of the writing group expressed the opinion that every causative risk factor deserves modification under physician supervision once it has reached a categorical level (Table 4). Clinical judgment is required as to whether risk-factor reduction is best carried out with nondrug or drug therapies.

Finally, Writing Group I emphasized that risk assessment in the medical office is the backbone of global risk assessment. Even if risk estimates can be improved by noninvasive measures of coronary atherosclerosis, the selection of patients for noninvasive testing should issue from office-based risk assessment. Patients found to be at high risk through office-based assessment need not proceed to noninvasive testing. On the other hand, some asymptomatic patients who appear to be at intermediate risk on the basis of office assessment could be elevated to the high-risk category by the finding of advanced subclinical atherosclerosis or myocardial ischemia.

Writing Group II: Tests for Silent and Inducible Ischemia

Writing Group II addressed the question of whether tests that assess silent ischemia or inducible ischemia add to prognostic information gained from standard risk factors in asymptomatic patients without known coronary disease. The tests reviewed included exercise ECG, exercise and pharmacological (stress) echocardiogram (echo), exercise and pharmacological myocardial perfusion imaging, ambulatory ECG monitoring, and positron emission tomography (PET). These noninvasive tests detect myocardial ischemia associated with obstructive coronary artery disease. Their greatest application to date has been diagnostic, in the evaluation of patients with symptoms of angina or a previous clinical manifestation of CHD. A limitation of all methods used to detect stress (exercise or pharmacologically induced) myocardial ischemia is their dependence on the presence of flow-limiting coronary stenosis. As with all diagnostic studies, their predictive value is dependent on the prevalence of disease in the population tested. Also central to the Writing Group II discussions was the recognition that the majority of future events among patients with CHD are related to severity of obstruction, plaque instability, and total atherosclerotic burden. The group was specifically concerned with delineating the prognostic information available from these tests that could contribute toward identifying patients at higher risk for major CHD-related events.

Exercise ECG Testing

Among asymptomatic individuals, there is evidence that the development of an ischemic ECG response at low workloads of exercise testing is associated with a higher incidence of future events such as angina pectoris, myocardial infarction, and sudden death. However, the absolute risk of cardiac events in these populations remains low.

The Multiple Risk Factor Intervention Trial (MRFIT) reported a nearly 4-fold increase in 7-year coronary mortality (7.6 versus 2.0 per 1000 person-years of risk) among middle-aged men with an abnormal exercise ECG versus those with a normal exercise ECG and suggested that the exercise ECG might serve to identify high-risk men who could benefit from risk factor reduction. There is a paucity of similar data

regarding the use of the exercise ECG in women and the elderly (age >75 years).

In the Lipid Research Clinics Coronary Primary Prevention Trial, of 3775 asymptomatic hypercholesterolemic men, half of whom were taking cholestyramine and half of whom were taking placebo, there was a 5.7 times greater risk of death due to coronary heart disease in the placebo group among those with a positive exercise test result (≥1-mm ST-segment depression or elevation on exercise testing) than among those with a negative test result. Overall, during a mean follow-up period of 7.4 years, there was a 6.7% mortality rate in the group with a positive test result versus 1.3% in the group with a negative test result.

The routine use of exercise ECG testing in completely unselected asymptomatic populations before office screening for risk cannot be recommended. In asymptomatic men >40 years of age with ≥1 risk factor, exercise testing may provide useful information as a guide to aggressive risk factor intervention or the need to evaluate further the cause of myocardial ischemia. The role of exercise testing in women and among the elderly (age >75 years) as a guide to identifying the high-risk patient for primary prevention requires additional study.

Exercise and Pharmacological Stress Echocardiography

Stress echocardiography (SE) is based on the premise that myocardial ischemia leads to left ventricular dyssynergy that can be detected with 2-dimensional echo. Only limited data exist to support the use of SE as a tool to elevate the intermediate-risk, asymptomatic patient to a higher risk category. Also, the addition of echocardiographic imaging to exercise ECG in intermediate-risk patients increases the cost and complexity of the examination. On the other hand, SE could be of value in the assessment of women and elderly patients who fall into the intermediate-risk category; nevertheless, additional studies are needed to define its role for elevating such patients to the high-risk category for primary prevention.

Exercise and Pharmacological Myocardial Perfusion Imaging

Myocardial perfusion imaging has evolved as an important clinical tool in the evaluation of patients with symptoms suggestive of angina pectoris or its equivalents. An important question is whether stress thallium scintigraphy can be a useful addition to exercise ECG for determining risk for major coronary events in intermediate-risk asymptomatic patients. Limited data suggest incremental value for this purpose in some populations. Such populations might include postmenopausal women and elderly men (age >75 years), in whom the use of exercise ECG testing is problematic.

Ambulatory ECG Monitoring

Because of the low sensitivity and specificity of ambulatory ECG monitoring for the diagnosis of multiple coronary arteries with >50% occlusion, published recommendations suggest that it is an inaccurate modality for use as a guide in the selection of patients for invasive procedures. The guidelines for use of ambulatory ECG generated by the American College of Cardiology/AHA Task Force consider that its use for detecting myocardial ischemia in the asymptomatic individual is a class III indication, ie, there is general agreement that it is not a useful test in these circumstances. The value of ambulatory ECG monitoring as a prognostic indicator of major coronary events in intermediate-risk patients has not been adequately evaluated. Whether it provides incremental information over that obtained from a resting ECG is unknown.

Positron Emission Tomography

The basis for detecting myocardial ischemia by PET is the detection of flow heterogeneity during maximal coronary hyperemia, and significant ischemia is only detectable if coronary stenosis is hemodynamically significant. Because PET is insensitive for the detection of <50% coronary stenoses, its incremental prognostic power over exercise ECG is doubtful. Moreover, the test is expensive. Therefore, it was not considered to provide additional quantitative risk prediction over exercise ECG in middle-aged asymptomatic men in the intermediate-risk category. Whether it would be more useful than exercise ECG in women or elderly men (>75 years) remains to be determined. Although significant issues exist surrounding the cost-effectiveness of PET in the evaluation of asymptomatic patients at risk for CHD, preliminary research suggests there may be future applications of this technique in the detection of coronary endothelial dysfunction and the noninvasive monitoring of aggressive medical therapy and risk factor modification.

Conclusions

Data are quite limited regarding the prognostic utility of noninvasive measures of inducing myocardial ischemia in apparently asymptomatic people. Very few prognostic studies have included adequate numbers of asymptomatic people. With the exception of exercise ECG testing in asymptomatic men with increased cardiovascular risk profiles, few data exist to support the use of the noninvasive testing modalities discussed by Writing Group II to screen asymptomatic populations for high-risk subclinical CHD. Future research should investigate the role of these techniques in association with global risk assessment to further define prognosis, guide intensity of therapy, and monitor the effectiveness of risk-intervention strategies.

Summary

The purpose of noninvasive testing for subclinical myocardial ischemia is to detect patients who have been found to be at intermediate risk by office-based risk assessment and identify those who are candidates for more aggressive risk-reduction therapies. Several studies in middle-aged men in this category have documented that exercise ECG has independent power for predicting major coronary events and may be a useful adjunct in identifying high-risk patients who otherwise would be classified as being at intermediate risk. On the other hand, exercise ECG has little use in the routine screening of young adults who as a group are at low risk for developing CHD in the next decade. Furthermore, its predictive power in older men (>75 years) and women is uncertain. Ambulatory ECG apparently is less sensitive than exercise ECG for detecting myocardial ischemia, and its use for risk adjustment cannot

be recommended at this time. SE appears to add little prognostic/diagnostic information to exercise ECG in middle-aged men but may have utility for adjusting risk assessment in women and older men (>75 years), in whom the predictive power of exercise ECG is uncertain. The same can be said regarding myocardial perfusion imaging. PET scanning may detect myocardial ischemia in the presence of less severe degrees of coronary atherosclerosis than can be detected by exercise ECG; however, its lack of availability and high cost seemingly do not justify PET scanning of intermediate-risk patients whose exercise ECGs are normal.

Writing Group III: Noninvasive Tests of Atherosclerotic Burden

Writing Group I considered the role of routine office-based measures for assessment of global risk in asymptomatic people. With the physician-directed office risk assessment as a foundation, further risk stratification may be valuable, especially when the risk estimate is neither clearly low risk nor high risk (intermediate risk). For the intermediate-risk patient, additional testing might include one or more noninvasive measures of atherosclerotic burden.

Pathology studies document that the levels of "traditional" risk factors are associated with the extent and severity of atherosclerosis. However, at every level of risk factor exposure, there is substantial variation in the amount of the atherosclerosis. Thus, subclinical disease measurements, representing the end result of risk exposures, may be useful in improving CHD risk prediction.

Noninvasive tests such as carotid artery duplex scanning, electron beam CT (EBCT), ultrasound-based endothelial function studies, ankle/brachial blood pressure ratios, and magnetic resonance imaging (MRI) techniques offer the potential for directly or indirectly measuring and monitoring atherosclerosis in asymptomatic people. High-sensitivity testing for C-reactive protein (hs-CRP) may also represent a measure of atherosclerosis "burden" and may therefore be considered another potential marker of atherosclerotic disease risk.

Ankle/Brachial Blood Pressure Index

The ABI is a simple diagnostic test for lower-extremity peripheral arterial disease (PAD). Among well-trained operators, test-retest reliability is excellent, and the validity of the test for ≥50% stenosis in leg arteries is high (sensitivity ≈90% and specificity ≈98%).

In population studies, people with a low ABI have been found to have a considerably higher prevalence of CVD (defined as history of myocardial infarction, coronary artery bypass graft, stroke, or stroke surgery or other measures of clinical CVD, such as angina or congestive heart failure) than those individuals with a normal ABI. These data confirm that atherosclerosis is a diffuse (ie, systemic) disease and that an abnormal ABI test (ie, low ratio) will often be indicative of significant atherosclerosis in other vascular beds. At least 3 studies have reported an increased combined incidence of CVD morbidity and CVD mortality in persons with PAD detected by ABI.

Conclusions

The ABI is a simple, inexpensive, noninvasive measure of PAD. Many asymptomatic people ≥50 years of age will have abnormal ABI values. Follow-up studies have shown that an abnormal ABI provides incremental coronary and all-CVD risk-assessment information over and above that provided by traditional risk factors. The writing group concluded that the ABI might be a useful addition to the assessment of CHD risk in selected populations, especially in people aged 50 years and older or those who appear to be at intermediate or higher risk for CVD on the basis of traditional risk factor assessment, such as cigarette smokers or individuals with diabetes mellitus, who have a particularly high risk for PAD. If a patient is found to have an abnormal ABI, this patient can be elevated to a higher risk category. The high relative risk in patients with abnormal ABIs is similar to that of patients who qualify for the AHA secondary-prevention regimen.

B-Mode Ultrasound

B-mode ultrasound is a relatively inexpensive and safe technique that can noninvasively visualize the lumen and walls of selected arteries, including carotid, aorta, and femoral arteries. B-mode ultrasound has been validated for the measurement of IMT. Cross-sectional associations between common carotid artery IMT and cardiovascular risk factors have been demonstrated in several studies. Similarly, common carotid IMT has been associated with prevalent CVD in cross-sectional studies. Furthermore, at least 4 published studies found that carotid IMT measurement was a viable predictor of the presence of coronary atherosclerosis and its clinical sequelae. Thus, carotid IMT defined by noninvasive B-mode ultrasound has been shown to be an independent risk factor for CHD events and stroke.

Conclusions

Carotid artery B-mode ultrasound imaging is a safe, noninvasive, and relatively inexpensive means of assessing subclinical atherosclerosis. The technique can measure IMT, an operational measure of atherosclerosis, in a valid and reliable manner. The severity of carotid IMT is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as myocardial infarction. The writing group concluded that in asymptomatic individuals older than 45 years of age, carefully performed carotid ultrasound examination with IMT measurement can add incremental information to traditional risk factor assessment. In experienced laboratories, this test can now be considered for further clarification of CHD risk assessment at the request of a physician.

Coronary Calcium Scores in CAD Risk Assessment

Calcification within the coronary arterial wall is a recognized marker of atherosclerosis. EBCT and helical CT are highly sensitive means of detecting coronary calcium and are being intensively evaluated as noninvasive means of defining coronary atherosclerotic disease and identifying the asymptomatic but high-risk CAD patient. There are, however, relatively few prospective data linking coronary calcium scores with risk of subsequent CHD events. Data concerning risk prediction with EBCT in asymptomatic people (the primary focus of the Prevention V conference) are sparse.

Conclusions

The presence of coronary calcium correlates strongly with coronary atherosclerosis. Because the severity of coronary atherosclerosis (from pathological or angiographic studies) is well known to be associated with risk of coronary events, coronary calcium scores likewise should correlate with risk for coronary events. However, the extent to which coronary calcium scores predict coronary events independently of the traditional coronary risk factors needs additional study. This latter uncertainty must be weighed against the costs of measurement and the risk that the results of the tests may create enough concern for patients and their physicians to lead to inappropriate and invasive coronary evaluation. Because of these uncertainties and concerns, the writing group was reluctant to advocate the use of EBCT for routine risk assessment in spite of the promise of the technique. The greatest potential for coronary calcium scores would appear to be in the detection of advanced coronary atherosclerosis in patients at apparently intermediate risk. Conversely, low or absent coronary calcium scores may prove valuable in determining a low CAD event risk. Some clinicians and researchers currently recommend use of the coronary calcium score in risk assessment in these ways. However, the majority opinion of the writing group was that until there is more definitive information about the additive value of calcium scores in the asymptomatic individual, coronary calcium measurement should not be recommended for routine risk assessment in asymptomatic populations. Selected use of coronary calcium scores when a physician is faced with a patient with intermediate coronary disease risk may be appropriate.

MRI and Atherosclerotic Disease

There has been increasing awareness of the importance of composition of atherosclerotic plaque as a major risk factor for acute coronary syndromes. MRI has been shown to characterize tissue noninvasively in many different study systems. Therefore, research has begun to focus on the use of in vivo MRI to evaluate the vessel wall in several animal models and in humans.

Conclusions

MRI is a promising research tool, but its use appears limited to only a small number of research laboratories at this time. The writing group concluded that MRI is not ready for application in the identification of patients at high risk for CAD.

Endothelial Function Studies and CAD Risk

The most frequently used endothelium-directed vasodilator stimulus is an increase in blood flow. Investigators are still seeking to improve the methods for ultrasonographic analysis of brachial artery vasomotion. To achieve optimal results, careful attention must be paid to details such as minimization of patient stress or discomfort, recent fat intake, and cigarette smoking and other transient exposures that may alter sympathetic tone. The technique is skill and labor intensive and is not yet easily applied to the routine clinical domain.

Conclusions

Although the assessment of endothelial function, as measured most typically by flow-mediated brachial artery vasodilation, is a promising technique that may reflect an independent measure of CVD risk, additional prospective research is needed to demonstrate that this technique can truly add to standard CVD risk prediction. In addition, standardization and improvement of the measurement technique are needed before this modality can become a part of routine clinical assessment of CVD risk.

hs-CRP as a Marker of CAD Risk

A number of blood factors have received attention as potential new markers of CAD and all-CVD risk. The list of potential candidates includes total plasma homocysteine (tHcy), lipoprotein(a) [Lp(a)], fibrinolytic function (as assessed by tissue plasminogen activator and plasminogen activator inhibitor-1 antigens), and inflammatory parameters such as fibrinogen and CRP. Many of these markers are not yet considered applicable for routine clinical CVD risk assessment because of (1) lack of measurement standardization [eg, Lp(a) testing, fibrinogen, and tHcy], (2) lack of consistency in epidemiological findings from prospective studies with CVD end points [eg, data for Lp(a) and tHcy are inconsistent], and (3) lack of evidence that the novel marker adds to risk prediction over and above that already achievable through the use of established cardiovascular risk factors. Laboratory evidence and findings from pathological studies suggest that the inflammatory process plays an important part in the atherosclerotic process. CRP is a sensitive marker for vascular inflammation, and it has been suggested that hs-CRP may provide a novel method to assess CVD risk that is additive to the assessment of traditional CVD risk factors.

Conclusions

hs-CRP has been shown to predict future coronary events in several prospective studies and may add to the predictive value of lipid testing alone. hs-CRP testing may become commercially available in the near future. The writing group concluded that additional studies of this approach to risk prediction are warranted and should be undertaken before this measurement can be advised for addition to the routine assessment of coronary risk.

Appendix

Prevention V Conference Writing Group Members

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