Prevention Conference V : Beyond Secondary Prevention : Identifying the High-Risk Patient for Primary Prevention : Noninvasive Tests of Atherosclerotic Burden : Writing Group III

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Circulation 2000;101;e16-e22
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Prevention Conference V

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

Noninvasive Tests of Atherosclerotic Burden

Writing Group III

Philip Greenland, MD, Chair; Jonathan Abrams, MD; Gerard P. Aurigemma, MD; M. Gene Bond, PhD; Luther T. Clark, MD; Michael H. Criqui, MD; John R. Crouse III, MD; Lawrence Friedman, MD; Valentin Fuster, MD, PhD; David M. Herrington, MD, MHS; Lewis H. Kuller, MD, DrPH; Paul M. Ridker, MD, MPH; William C. Roberts, MD; William Stanford, MD; Neil Stone, MD; H. Jeremy Swan, MD, PhD; Kathryn A. Taubert, PhD; Lewis Wexler, MD

Writing Group I of Prevention Conference V considered the role of routine office-based measures for assessing global risk in asymptomatic persons. 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, further testing might include ≥1 noninvasive measure of atherosclerotic burden.

Pathology studies have documented that 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 atherosclerosis. This variation in disease is probably due to genetic susceptibility; combinations and interactions with other risk factors, including life habits; duration of exposure to the specific level of the risk factors; and such factors as biological and laboratory variability. Thus, subclinical disease measurements, representing the end result of risk exposures, may be useful for improving coronary heart disease (CHD) risk prediction.

Noninvasive tests such as carotid artery duplex scanning, electron beam–computed tomography (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 persons. 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 atherosclerosis disease risk. The Prevention Conference V participants considered the status of several measures of subclinical disease in CHD risk assessment. The discussion that follows is a summary of the data reviewed and discussed at Prevention Conference V.

Ankle-Brachial Blood Pressure Index

During the discussion groups at Prevention Conference V, the ankle-brachial blood pressure index (ABI) was considered as a means of predicting CHD events. The ABI is a simple, inexpensive 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 stenosis ≥50% in leg arteries is high (sensitivity ≈90% and specificity ≈98%).[1,2]

The ABI can be measured in a vascular laboratory or physician's office with inexpensive equipment, which consists of an ordinary blood pressure cuff and a Doppler ultrasonic sensor.[3] The blood pressure cuff is used to measure systolic blood pressure in the brachial artery in both arms by use of the Doppler detector in the antecubital fossa. The blood pressure cuff is then applied to the ankle, and the Doppler probe is used to determine systolic blood pressure at the left and right posterior tibial arteries and dorsalis pedis arteries. The ABI for each leg equals the ratio of the higher of the 2 systolic pressures (posterior tibial or dorsalis pedis) in the leg and the average of the right and left brachial artery pressures, unless there is a discrepancy ≥10 mm Hg in blood pressure values between the 2 arms. In such a case, the higher reading is used for the ABI. Pressures in each leg should also be measured and ABI calculated separately for each leg. An ABI <0.90 in either leg is considered evidence of PAD, and

In connection with Prevention Conference V, Writing Group I has published a complete report on "Medical Office Assessment" (*Circulation*. 2000;101:e3–e11), and Writing Group II has published a complete report on "Tests for Silent and Inducible Ischemia" *(Circulation*. 2000;101:e12–e15). In addition, the Executive Summary of "Prevention Conference V: Beyond Secondary Prevention: Identifying the High-Risk Patient for Primary Prevention" has been published in *Circulation (Circulation*. 2000;101:111–116).

(*Circulation*. 2000;101:e16–e22.)

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progressively lower ABI values indicate more severe obstruction.

There is a considerable overlap of persons with ABI-detectable PAD and clinical cardiovascular disease. In population studies, persons with a low ABI have been found to have considerably higher prevalence of cardiovascular disease (CVD) (defined as history of myocardial infarction [MI], coronary artery bypass graft, stroke, or stroke surgery, or other measures of clinical CVD such as angina or congestive heart failure) than persons with a normal ABI.[4] These data confirm that atherosclerosis is a diffuse (ie, systemic) disease and that an abnormal ABI test (ie, low ratio) will often indicate significant atherosclerosis in other vascular beds.

At least 3 studies[5–7] have reported a combined incidence of CVD morbidity and mortality in persons with PAD detected by ABI. Several other studies have reported on the ability of ABI to predict future coronary, total CVD, and all-cause mortality.[8–10] In 1 study, Criqui et al[9] found that ABI-detected PAD in men and women with an average age of 66 years had a markedly increased risk of CVD mortality (relative risk [RR] 6.3), CHD mortality (RR 4.8), and all-cause mortality (RR 3.1). High relative risks were found even after excluding persons with known CVD at baseline and after adjustment for other CVD risk factors such as cholesterol, age, sex, smoking, glucose level, and high body mass index. An abnormal ABI is generally, but not exclusively, found in men and women >50 years of age[11]; therefore, consideration of ABI for risk assessment should be restricted to persons ≥50 years old.

Conclusions

The ABI is a simple, inexpensive, noninvasive measure of PAD. Many asymptomatic persons ≥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 persons ≥50 years old or those who appear to be at intermediate or higher risk of CVD on the basis of traditional risk factor assessment, such as smokers or persons with diabetes, who have a particularly high risk of PAD. If a patient is found to have an abnormal ABI, he or she can be elevated to a higher risk category. The high relative risk in patients with an abnormal ABI is similar to that of patients qualifying for the AHA Secondary Prevention regimen.[12]

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 the carotid, aorta, and femoral. B-mode ultrasound has been validated for measuring intima-media thickness (IMT) in several independent laboratories, and its reliability has been established in single- and multicenter studies.[13] Current ultrasound instrumentation with transducers ≥8 MHz are most capable of identifying the 2 arterial interfaces (lumen-intima and media-adventitia) necessary for measuring IMT. The screening examination is performed bilaterally on the extracranial carotid artery segments. These segments are the distal straight 1 cm of the common carotid arteries, the carotid bifurcations, and the proximal 1 cm of the internal carotid arteries. Circumferential longitudinal scans can identify IMTs that are >1.3 mm on the near and far walls of each segment (total of 6 walls per side). A template can be used to identify these IMT values. If the IMT value is >1.3 mm, the actual thickness of each lesion is measured with ultrasound instrument calipers. IMT is an operational measurement definition of a single characteristic of atherosclerosis based on considerable information documenting that both the intima and media are involved in atherogenesis and the anatomical progression of lesions. Several pathological studies have demonstrated that increases in intimal thickness (fibromuscular hyperplasia) are associated with aging and that medial thickness (smooth muscle hypertrophy) is associated with hypertension, even in the absence of atherosclerotic plaque.

Cross-sectional associations between common carotid artery IMT and cardiovascular risk factors have been demonstrated in several studies.[14–16] Similarly, common carotid IMT has been associated with prevalent cardiovascular disease in cross-sectional studies.[15–18] Furthermore, ≥5 published studies found that carotid IMT measurement is a viable predictor of the presence of coronary atherosclerosis and its clinical sequelae.[19–23] Thus, carotid IMT defined by noninvasive B-mode ultrasound has been shown to be an independent risk factor for CHD events and stroke. The strongest data relating IMT measurement with incident cardiovascular events derive from the Atherosclerosis Risk in Communities (ARIC) Study.[21] In this study, the relation of carotid IMT to CHD incidence was studied over 4 to 7 years of follow-up in 4 US communities from samples of 7289 women and 5552 men aged 45 to 64 years who were free of clinical CHD at baseline. The hazard rate ratio comparing extreme mean IMT (≥1 mm) to not extreme IMT (<1 mm) was 5.07 for women (95% confidence interval [CI], 3.08 to 8.36) and 1.85 for men (95% CI, 1.28 to 2.69). The relation was graded (monotonic), and although the strength of the association was reduced by including major CHD risk factors, it remained elevated at a higher IMT.[21]

In the Cardiovascular Health Study,[23] associations between the thickness of the carotid-artery intima and media and the incidence of new MI or stroke in persons without clinical CVD were studied in 5858 subjects ≥65 years of age. The relative risk of MI or stroke increased linearly with IMT. The relative risk of MI or stroke (adjusted for age and sex) for the quintile with the highest thickness compared with the lowest was 3.87 (95% CI, 2.72 to 5.51). The association between cardiovascular events and IMT remained significant after adjustment for traditional risk factors, showing increasing risk for each quintile of combined IMT, from the second quintile (RR 1.54; 95% CI, 1.04 to 2.28), to the third (RR 1.84; 95% CI, 1.26 to 2.67), fourth (RR 2.01; 95% CI, 1.38 to 2.91), and fifth (RR 3.15; 95% CI, 2.19 to 4.52).

Several clinical intervention or prevention trials have illustrated the ability of carotid B-mode ultrasound imaging to monitor changes in IMT over time.[24–26] Many epidemiological and clinical studies have documented that the average

annual IMT progression rates are ≤0.03 mm. In such plaque monitoring studies, quantitative quality control of sonographers who perform the examinations and readers who make the measurements was found to be critical. Although serial measurements can be standardized in well-controlled research settings, protocols for sonographers to monitor IMT over time in a valid and reliable manner have not yet been implemented in clinical practice environments. This represents a barrier to routine use of IMT for serial assessment of plaque progression/regression in medical practice. Provided that technical issues of this type can be resolved by using standardized protocols for scanning and monitoring of IMT, this method would be useful in follow-up of patients treated for plaque progression or regression.

A further issue is whether B-mode ultrasound can provide information about individual plaques that are susceptible to rupture, with subsequent thrombosis and/or embolization. Several reports have indicated that B-mode densitometric evaluation gray scale intensity of plaques is feasible and valid when compared with the anatomic pathology of lesions. Although such information may not be specific for chemical components or metabolic byproducts within the arterial wall, gray scale intensity tissue characteristics are known within reasonable limits. Highly echogenic structures include fibrous connective tissue such as collagen and minerals, cholesterol monohydrate crystals, etc. Hypoechoic tissue includes necrotic regions of the plaque, recent hemorrhage into lesions, lipid filled cores, etc. Hypoechoic plaques, particularly those with thin fibromuscular caps, in combination with carotid IMT measurements, have the potential to identify unstable plaques prone to rupture. Further research is needed to establish this role for B-mode ultrasound.

Conclusions

Carotid artery B-mode ultrasound imaging is a safe, noninvasive, and relatively inexpensive means of assessing subclinical atherosclerosis. The technique is a valid and reliable means of measuring IMT, an operational measure of atherosclerosis. The severity of carotid IMT is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as MI. Writing Group III concluded that in asymptomatic persons >45 years old, 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 Assessment of Coronary Artery Disease Risk

Calcification within the coronary arterial wall is a recognized marker of atherosclerosis.[27] EBCT and helical CT are highly sensitive methods of detecting coronary calcium[28] and are being intensively evaluated as a noninvasive means of defining coronary atherosclerotic disease and identifying the asymptomatic but high-risk coronary artery disease (CAD) patient. EBCT uses an electron sweep of stationary tungsten target rings to generate x-ray images that can detect small amounts of calcium with considerable accuracy,[28] whereas helical CT uses a continuously rotating x-ray source. Both allow quantification of calcium area and density, and both are relatively high cost. Histologic studies support the association of tissue densities ≥130 Hounsfield units with calcified plaque.[29] EBCT calcium scores correlate with pathological examination of the atherosclerotic plaque.[30] Importantly, however, vulnerable plaque can be present in the absence of calcium.

EBCT calcium correlates with coronary angiographic findings. Studies have compared EBCT findings with coronary angiographic obstruction[31–33] and have confirmed high sensitivity of EBCT calcium scores for detecting obstructive CAD, at least in some patient populations. EBCT calcium scores appear to add to the prediction of angiographic CAD findings over and above associations with conventional risk factors.[33] Although EBCT is extremely sensitive for defining coronary calcium, the extent and site of calcium deposition do not equate with site-specific stenosis.[34] Sex differences appear to play a role in the development of coronary calcium. In 1 study, the prevalence of coronary calcium in women was half that of men until age 60, when the difference diminished. Several studies have documented that reliability of coronary calcium scores is high. Limited recent data suggest that EBCT calcium scores may be of value in follow-up of patients for progression or regression of atherosclerosis, including patients on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.[35]

Relatively few prospective data link coronary calcium scores with risk of subsequent CHD events. A multicenter EBCT calcium study by Detrano et al[36] reviewed event data in 491 patients who underwent both an EBCT calcium study and coronary angiography. Most patients were symptomatic and were referred for angiography because of suspected CAD.[36] A calcium score ≥100 was useful for separating patients with cardiac events from those without events. A logistic regression model, which included calcium score, age, sex, and coronary angiographic findings as independent variables, was used in EBCT calcium scores, which were a better predictor of heart disease events than the number of arteries with lumenal diameter stenosis ≥50%.

Risk-prediction data in asymptomatic persons (the primary focus of Prevention Conference V) are sparse. Arad et al[37] reported a strong correlation between coronary calcium and prediction of cardiac events in asymptomatic persons who underwent coronary calcium screening by EBCT in response to advertisements and physician referrals. In the most recent follow-up from this group,[38] 1136 asymptomatic persons were monitored for 3.6 years (mean). There were 40 cardiovascular events, including 2 deaths, 14 MIs, 14 coronary bypass operations, and 10 coronary angioplasties. For a coronary artery calcium score of 600, sensitivity was 80% and specificity 85% for predicting cardiac events. Other risk factors measured or reported at the time of EBCT, such as the presence of hypercholesterolemia, high-density lipoprotein (HDL) cholesterol, hypertension, diabetes mellitus, and family history, did not predict CAD events.[38] Reports from other groups suggest that the coronary calcium score adds to CAD risk prediction but may not be as strongly additive to traditional risk factors as suggested by the data of Arad et al.

In the Arad study, physicians were aware of the calcium score and may have preferentially recommended intervention on that basis; therefore, these data are subject to referral bias. After the Prevention Conference V ended, a further report suggested that the EBCT calcium score was about equal to the Framingham risk score for predicting future coronary events.[39]

Conclusions

The presence of coronary calcium correlates strongly with coronary atherosclerosis. Because the severity of coronary atherosclerosis is well known (from pathological or angiographic studies) 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 independent of the traditional coronary risk factors needs further study. This latter uncertainty must be weighed against the costs of measurement and the risk that the test results may create enough concern for patients and their physicians to lead to inappropriate and invasive coronary evaluation. Because of these uncertainties and concerns, Writing Group III was reluctant to advocate the use of EBCT for routine risk assessment despite its promise. The greatest potential for coronary calcium scores appears to be in the detection of advanced coronary atherosclerosis in patients who are apparently at intermediate risk. Conversely, low or absent coronary calcium scores may prove valuable in determining a low risk for CAD events. Some clinicians and researchers currently recommend the use of the coronary calcium score in risk assessment in these ways. However, the majority opinion of Writing Group III was that until there is more definitive information about the additive value of calcium scores in asymptomatic persons, coronary calcium measurement should not be recommended for routine risk assessment in asymptomatic populations. Selected use of the coronary calcium scores in a patient with intermediate coronary disease risk may be appropriate. The Prevention Conference V participants look forward to further research on coronary calcium screening and its relation to future clinical events. Such studies should be performed in as unbiased a manner as possible so that use of the calcium score does not confound occurrence of subsequent clinical events. Further studies of the role of calcium scores in patient follow-up for assessing clinically relevant progression or regression of CAD are also needed.

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. However, some current imaging modalities such as angiography, although useful for evaluating lumenal narrowing and the consequences of reduced flow, are poor for evaluation of the vessel wall and characterization of plaque. MRI has been shown to characterize tissue noninvasively in many different study systems.[40–42] Therefore, research has begun to focus on the use of in vivo MRI to evaluate the vessel wall in several animal models and humans. A combination of MR techniques was used to image in vitro carotid, aortic, and coronary artery specimens obtained at autopsy; all the different components of plaque were identified.[43–45] Subsequent work imaging carotid arteries in vivo in patients referred for endarterectomy showed a high correlation with pathology.[46]

A recent study of patients with plaques in the thoracic aorta showed that in comparison with transesophageal echocardiography, plaque composition and size are accurately characterized and measured with MRI.[47] Carotid and aortic atherosclerotic assessment with MRI may lead to its use as a screening tool for predicting future cardiovascular events and evaluating therapeutic interventions. These techniques have already been adapted for the study of plaques in different animal models.[48,49] A goal for MRI is imaging plaque in vivo in coronary arteries, which is difficult because of their size and cardiorespiratory motion. Studies in an in vivo pig model[50,51] and normal human subjects suggest that the MRI technique may eventually be applicable to the study of human coronary arteries in vivo.

Conclusions

MRI is a promising research tool, but its use appears to be limited to only a small number of research laboratories at this time. With further development, MRI may provide a means of understanding the progression and prevention of atherosclerosis and coronary disease. Writing Group III concluded that MRI is not yet appropriate for use in identifying patients at high risk for CAD. The Prevention Conference V participants have recommended that more studies of MRI in CHD risk prediction should be encouraged. Additional technical development in this area is expected and should be of considerable value in the application of this emerging technology.

Endothelial Function Studies and Risk for CAD

Endothelial cells play a central role in inhibiting the development of atherosclerosis and its thrombotic consequences. Endothelial cell production of nitric oxide inhibits monocyte, leukocyte, and platelet adhesion to the vessel wall; decreases permeability to low-density lipoprotein; and inhibits smooth muscle cell proliferation. High-resolution ultrasound techniques can noninvasively study endothelial function by measuring endothelium-dependent vasodilator responses to various stimuli and can be used in clinical as well as population-based settings.

The most frequently used endothelial-directed vasodilator stimulus is an increase in blood flow. Increases in fluid shear stress stimulate endothelial cell release of nitric oxide, causing prompt dilation of the artery. To produce this stimulus, most investigators use ischemia-induced hyperemia in the distal forearm, resulting in a 2- to 5-fold increase in brachial blood flow. High-resolution 2D ultrasound measures the diameter of the artery before and after the flow stimulus.[52,53] Responses to other vasomotor stimuli, such as the cold pressor test or mental stress, have also been examined. Clinical studies, generally each with a small number of subjects, found that brachial flow-mediated vasodilator responses may reflect an important element of the vascular

health state. For example, patients with risk factors for CHD[54,55] as well as those with established CHD[56] have impaired vasodilator responses. Lipid-lowering therapy,[57] antioxidants, and estrogen replacement have each been shown to improve these responses, and in some studies, changes are evident in as little as 4 to 6 weeks.

Investigators are still seeking to improve the methods for ultrasonographic analysis of brachial artery vasomotion. Progress has been made on methodological issues such as duration of ischemia required for an appropriate flow stimulus and characterization of the time course of the vasodilator response. However, lower-frequency ultrasound images have hampered accurate quantification of brachial artery diameter, and inter-reader variability has led to difficulties in replicating data and quantifying the real magnitude of response. To achieve optimal results, careful attention must be paid to details such as minimizing the patient's stress or discomfort, recent fat intake, cigarette smoking, and other transient exposures that may alter sympathetic tone. More precise analysis techniques are now available in the form of automated continuous estimation of brachial artery responses. The technique is skill- and labor-intensive and not yet easily used in routine clinical practice.

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.

High-Sensitivity C-Reactive Protein as a Marker of Risk for CAD

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 tPA and plasminogen activator inhibitor-1 (PAI-1) antigens, and inflammatory parameters such as fibrinogen and C-reactive protein (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 total plasma homocysteine]; (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 above that already achievable by use of established cardiovascular risk factors.[58] Regarding the latter point, the demonstration that a given marker has predictive value in univariate analysis is not sufficiently compelling because the observed association may be the result of confounding by traditional risk factors [eg, this is a problem for fibrinolytic markers such as tPA and PAI-1; data on the additive value of Lp(a) and homocysteine are also inconsistent].

Laboratory evidence and findings from pathology studies suggest that the inflammatory process plays an important part in the atherosclerotic process.[59] 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 that of traditional CVD risk factors. Several prospective studies[60–65] of hs-CRP have shown a consistent relation between baseline concentration of CRP and future CVD events. Perhaps the most intriguing data are those from the Physicians' Health Study,[60,63] which found that healthy male physicians in the highest CRP quartile at baseline had a 2-fold higher risk of stroke, a 3-fold higher risk of MI, and a 4-fold higher risk of severe PAD. Furthermore, these increased risks were independent of all other measured CVD risk factors and were not modified by smoking status. Similar findings have also been reported for initially healthy women in the Women's Health Study[64] as well as in a population-based prospective cohort from the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg Cohort.[65] Thus, hs-CRP shows promise as a new test for improving CVD risk assessment. Standardized commercial tests for hs-CRP should soon be available so that risk assessment with hs-CRP can be considered outside of research settings. In this regard, CRP could be considered a marker of existing arterial disease, as opposed to a primary risk factor leading to future disease.

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.[66] Commercially available hs-CRP may become available in the near future. Writing Group III concluded that further studies of this approach to risk prediction are warranted and should be undertaken before this measurement can be recommended as an addition to the routine assessment of coronary risk.

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KEY WORDS: AHA Conference Proceedings ■ atherosclerosis ■ tests ■ prevention ■ risk factors ■ prognosis ■ risk assessment