

Atherosclerotic Vascular Disease Conference Writing Group II: Risk Factors

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The current understanding of risk factors for atherosclerotic vascular disease (AVD) embodies extrapolation of information derived from the traditional risk factors for atherosclerotic coronary disease, application of emerging novel risk factors, and study of new genetic mechanisms.

Traditional Risk Factors and Vascular Risk

Most data derived from large populations pertaining to risk factors for noncoronary AVD are found in studies primarily focusing on coronary heart disease (CHD), such as the Framingham Heart Study,¹ the Atherosclerosis Risk in Communities Study (ARIC),² the Honolulu Heart Study,³ and the Strong Heart Study.⁴ With rare exception, the evidence from these studies suggests that the risk factors for noncoronary AVD are generally similar and independent of the end organ (eg, brain, kidney, or skeletal muscle) subserved by a given arteriolar vascular bed. Thus, age, family history, elevated lipid levels, cigarette smoking, systolic and diastolic hypertension, and diabetes are the major risk factors for cerebrovascular, aortic, renal, and lower-extremity AVD. Within these classic risk factors for atherothrombotic vascular disease, several studies have suggested that cigarette smoking and diabetes are the strongest risk factors for AVD.^{5,6} There have also been observations that the most frequent form of dyslipidemia associated with AVD is the combination of elevated triglyceride levels and low HDL cholesterol.^{7,8} These latter changes in lipids are typically seen in patients with diabetes and are consistent with the high incidence of AVD among persons with diabetes. Across these studies there has been a paucity of data to precisely define ethnic/racial and gender differences that might contribute to variations in the prevalence and incidence of clinical events and mortality. Some variations in prevalence of lower-extremity vascular disease have been observed in relation to gender and ethnicity, however.⁹ Diabetes is a greater risk factor for peripheral artery disease among women than men and is associated with

peroneal and tibial AVD. Cigarette smoking is associated with aortoiliac AVD and a distinct hypoplastic aortoiliac syndrome in young women who are heavy smokers. The prevalence of peripheral artery disease also seems to be greater among African-American and Hispanic populations.¹⁰ In the case of cerebrovascular disease, African-American men and women have less vascular calcium and Japanese Americans have more intracranial than extracranial vascular disease. Finally, smoking and being male are risk factors for abdominal aortic aneurysm.

The use of risk factors to predict vascular disease events has several facets that deserve consideration. First, several types of risk can be estimated. Healthcare providers tend to focus on relative risk. Persons at higher relative risk of vascular disease often require more education and treatment than the other patients in a clinical practice, and to a physician, relative risk may translate into relatively more time spent with the patient or a stronger indication for intervention. On the other hand, absolute risk, the actual risk of an event over a specific period of time, may be more important and meaningful to the person being screened.

Another important type of risk is the population attributable risk (PAR), a key measure for organizations that monitor costs and resources. This risk is derived from the relative risk and frequency of the attribute in the population at large. PAR estimates can be developed only from population-based investigations, not case-control studies. High PAR percent estimates lead to development of prevention programs and strategies to reduce prevalence of the condition and the vascular disease risks associated with it.

Risk estimation with equations derived from population-based studies is dynamic. The current approach to vascular disease risk estimation involves assessment of factors such as age, gender, blood pressure, cigarette smoking, cholesterol, HDL cholesterol, and presence of diabetes. Drawing from the experience of the Framingham Heart Study and similar

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(*Circulation* 2004;109:2613-2616.)

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000128519.60762.84

studies, it is possible to estimate the risk for a future vascular event. Risk equations have been developed along these lines for CHD,^{11–13} intermittent claudication,¹⁴ and stroke.¹⁵ A slightly different set of variables is predictive with each outcome, and the relative risks associated with those factors may differ according to outcome. For instance, the effects of cigarette smoking and diabetes mellitus are especially important for development of peripheral arterial disease and intermittent claudication.

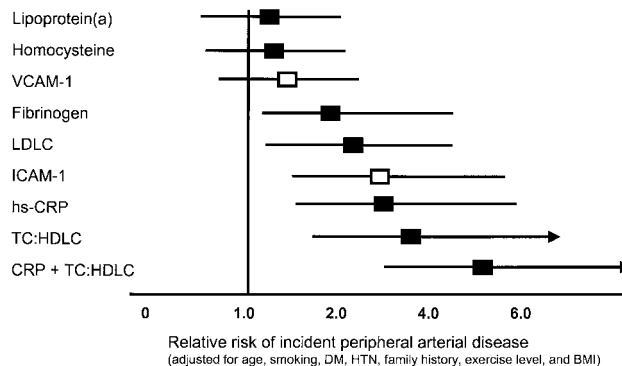
The use of estimating equations has advantages and disadvantages. A key asset is that risk for a vascular disease outcome can be estimated for most middle-aged patients and that the effects and interactions of several mild abnormalities in risk factors may have led to underestimation of risk in the usual clinical setting. Use of risk scores can provide a more reliable risk estimate, leading to more aggressive care and potential reduction in vascular disease events.

Generalizing beyond the source observational studies is an important issue for estimation of vascular disease risk. The experience in Framingham, a suburb west of Boston in the northeastern United States, may not be directly applicable to the patient sitting in front of a physician. Testing the predictive capability of a health-risk appraisal instrument outside the locale where the data were collected has become a new field of research. Differences in ethnicity and race, long-term exposures, and frequencies of risk factors across population groups are challenges to providing generalization of risk factor estimations. Recent experience with CHD prediction in Framingham has shown that the relative risks are usually very similar across several different populations and that estimation equations typically effectively rank persons in other populations, but absolute risks may differ greatly. The difference in absolute risk translates into the need for more comparative studies and development of strategies to calibrate estimation of AVD risk equations across population groups.

Novel Risk Factors for AVD

CHD events can be predicted effectively with multivariate equations in which traditional risk factors are variables. The data suggest that newer factors, especially those that determine risk but have low correlations with existing factors, may be key to improving the current risk estimation approach. Furthermore, compelling evidence for the role of inflammation in atherothrombotic vascular disease has fueled investigation of novel risk factors.¹⁶ Several emerging risk factors for AVD are under investigation. Specific criteria have been established to qualify such risk factors, including consistency of prospective data, strength or independence of association, improvement of predictive value, standardization of the measure, low variability, high reproducibility, biologic plausibility, and low cost. Recently interest has focused on novel markers such as lipoprotein(a), apolipoprotein (apo) A-1, apoB-100, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and homocysteine, among others, to evaluate their additive value to traditional risk factors. In evaluation of any novel risk factor or marker, it is very important that the additive effect be directly confirmed in the presence of other

Novel Risk Factors as Predictors of Peripheral Arterial Disease



Novel risk factors as predictors of peripheral arterial disease. VCAM-1 indicates vascular cell adhesion molecule 1; LDLC, LDL cholesterol; ICAM-1, intercellular adhesion molecule 1; TC:HDL, total cholesterol-HDL cholesterol ratio; DM, diabetes mellitus; HTN, hypertension; and BMI, body mass index. Data from: Ridker et al¹⁸ and Pradhan et al (Pradhan AD, Rifai N, Ridker PM. Soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, and the development of symptomatic peripheral arterial disease in men. *Circulation*. 2002;106:820–825).

established risk factors in a given population to determine its true value.

Studies in both men and women provide information about the additive value of certain novel risk factors.^{17–21} In a prospective comparison of lipid and nonlipid risk factors for AVD among apparently healthy middle-aged women, the addition of hs-CRP to screening based on standard lipid levels improved prediction of increased risk for stroke and myocardial infarction.¹⁷ In men, a study that compared 11 biomarkers associated with development of peripheral arterial disease revealed the ratio of total cholesterol to HDL cholesterol to be the strongest lipid predictor of risk.¹⁸ The addition of either CRP or fibrinogen to lipid screening significantly improved predictive value, whereas the addition of apoB-100, lipoprotein(a), or homocysteine did not add significant value (Figure). Although homocysteine and lipoprotein(a) do not seem to add significant clinical predictive value in the general population for screening, they may be useful in the setting of premature or accelerated AVD.^{19,20} It is important to note that although therapy with vitamin supplements for elevated homocysteine can be accomplished with relative ease, there are no conclusions as yet from large randomized clinical trials to demonstrate that reduction of homocysteine is associated with improved outcomes. With regard to inflammatory markers, a scientific statement from the Centers for Disease Control and Prevention (CDC) and the AHA²² specifies that hs-CRP has the analytic and assay characteristics most conducive to use in clinical practice. The CDC-AHA statement recognized hs-CRP as an independent marker of cardiovascular risk to be used at the discretion of the physician to assist in global risk prediction. The clinical benefits of medical therapies based on elevated hs-CRP are unknown, and decisions about treatment strategies await the results of large randomized clinical trials.

Genetic Risk Factors

There is compelling evidence from several lines of research that indicates that atherosclerosis is at least partially genetically determined. Carotid artery intima-medial thickness, a commonly used surrogate marker of atherosclerosis in populations, is highly heritable. From 64% to 92% of variation in common carotid artery wall thickness is explained by familial factors.^{23,24} Recent evidence from the Framingham Heart Study suggests that up to 50% of the variation in abdominal calcification, another surrogate marker of atherosclerosis, is determined by familial factors.²⁵ To date, a major gene for atherosclerosis in general, or peripheral arterial disease in particular, has not been detected. Much of the research effort has focused on finding genes that contribute to intermediate traits (ie, other cardiovascular risk factors) that are more proximal on the pathway to atherosclerosis.

Although several mendelian disorders cause severe abnormalities in the risk factors for atherosclerosis and atherosclerosis as such, most atherosclerosis cases do not show classic mendelian inheritance. Atherosclerosis is likely to be caused by genetic variation in multiple cardiovascular candidate genes that each exert a small effect on development of peripheral arterial disease. The environment, or context, in which these genes are exposed also has a substantial impact on the natural history of the atherosclerotic process. Candidate genes that influence peripheral arterial disease are likely to contribute to inflammation, including hemostatic factors, dyslipidemia, hypertension, diabetes, homocysteine, and obesity. Indeed, many of these cardiovascular risk factors have a genetic basis. Lipids and lipoproteins are particularly relevant because alterations in lipids, particularly elevated LDL, are a prerequisite for atherogenesis. Several of the more well-known and established genes that play a role in determining lipid abnormalities include apoE, the scavenger receptor, hepatic lipase, lipoprotein lipase, cholesterol ester transfer protein, and the apoA1/CIII/AIV cluster. Moreover, blood-derived inflammatory factors also play a key role. Genes that are established as determining monocyte adhesion, migration, and differentiation include E- and P-selectin, vascular cell adhesion molecule, monocyte chemoattractant protein, macrophage colony-stimulating factor, and peroxisome proliferator-activated receptor γ . Several genes contribute to the inflammatory response that furthers progression of the initial atherosclerotic lesion, including interleukin 6, tissue necrosis factor α , and interferon. Collectively, variation in 1 or more of these genes may be etiologically relevant to initiation or progression of atherosclerosis. Little is known, however, about the independent or interactive effects of these genes as risk factors for atherosclerosis in the population, nor about the differences in frequencies of the at-risk alleles of these genes in different ethnic groups. More research is needed to understand the importance of these genes, alone or in combination, in defining atherosclerosis in clinical and population settings.

There is considerable interest in understanding how genes that contribute to peripheral arterial disease respond to varying environmental contexts. Identification of genetic loci that contribute to variation in atherosclerosis under specific environmental contexts would provide new insight into path-

ways and mechanisms, opening up new avenues for prevention and treatment of peripheral arterial disease in the future. Numerous studies show that variation in lipid-related candidate genes (peroxisome proliferator-activated receptor α , phospholipid transfer protein, apoAI, and apoE) predicts response to diet and pharmacological intervention,^{26–30} suggesting the existence of genetic determinants of the lipid response to environmental modification. One important and consistent observation from these studies is that the lipid response to diet and pharmacological agents is highly variable. Similarly, candidate genes that contribute to blood pressure (angiotensinogen and α -adducin) predict response to sodium-restricted diet and pharmacological therapy.^{31,32} Much research remains to be done to understand the full impact of candidate genes on peripheral arterial disease, but the results obtained thus far suggest that candidate genes may play an important future role in screening for prevention and diagnostic testing to determine optimum treatments for individual patients.

Recommendations

- Develop a global risk score for AVD similar to that for CHD developed in Adult Treatment Panel III (ATP III)
- Develop a global risk score for subclinical AVD and identify predictors of progression to clinical disease
- Gather more information about the relation of family history and ethnicity to AVD
- Determine the frequency of genetic variations in AVD-related genes across ethnic groups; assess the interaction of genes with other genes and the environment in relation to AVD; evaluate the combination of alleles within genes (haplotypes) with AVD
- Promote risk factor identification and intervention in families of patients with AVD
- Heighten public awareness of lower-extremity arterial disease (LEAD) and its relation to AVD risk factors
- Establish optimal therapeutic targets for AVD risk reduction for special populations, such as persons with diabetes and the elderly
- Expand the knowledge base for risk factors in renovascular disease
- Include noninvasive assessments of AVD in clinical trials of risk factor treatments for patients with CAD
- Develop and promote programs that successfully implement optimum treatment of AVD risk factors and include incentives to insurance companies to implement reduction of multiple cardiovascular risk factors
- Investigate the importance of emerging risk factors in AVD
- Identify trends in established and emerging AVD risk factors, including biological and social risk factors

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KEY WORDS: AHA Conference Proceedings ■ atherosclerosis ■ inflammation ■ peripheral vascular disease ■ risk factors