Atherosclerotic Vascular Disease Conference

Executive Summary

Atherosclerotic Vascular Disease Conference Proceeding for Healthcare Professionals From a Special Writing Group of the American Heart Association

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Atherosclerosis is one of the most important and common causes of death and disability in the United States and throughout the world. More than 25 million persons in the United States have at least one clinical manifestation of atherosclerosis, and in many more, atherosclerosis remains an occult but important harbinger of significant cardiovascular events. Throughout the last half of the past century, coronary artery atherosclerosis has been a major focus for basic and clinical investigation. As a result, considerable strides have been made in the development of programs to prevent and treat the clinical manifestations of coronary artery disease. The development of lipid-lowering, antithrombotic, thrombolytic, and catheter-based therapies in particular has had considerable impact in reducing death and disability from coronary atherosclerosis. Yet atherosclerosis is a systemic disease with important sequelae in many other regional circulations, including those supplying the brain, kidneys, mesentery, and limbs. Persons with cerebral atherosclerosis are at increased risk for ischemic stroke. Those with renal artery atherosclerosis are at risk for severe and refractory hypertension as well as renal failure. Patients with atherosclerosis affecting the limb, ie, peripheral arterial disease (PAD), can develop disabling symptoms of claudication or critical limb ischemia and its associated threat to limb viability. Moreover, once disease is apparent in one vascular territory, there is increased risk for adverse events in other territories. For example, patients with PAD have a 4-fold greater risk of myocardial infarction and a 2- to 3-fold greater risk of stroke than patients without PAD.

It is timely, therefore, to increase our scientific and clinical efforts to address atherosclerosis as a systemic disease and enhance our understanding of atherosclerosis as it applies to specific vascular territories. Accordingly, the American Heart Association organized a conference on atherosclerotic vascular disease (AVD) that convened in Boston in June 2002. The purposes of this meeting were to review our current understanding and knowledge of AVD, exclusive of that affecting the coronary arteries; to develop a strategy to increase awareness of AVD among clinicians; and to identify important gap areas in our knowledge that require additional clinical investigation and research support.

The conference was divided into the following 6 major themes for AVD: (1) epidemiology, (2) risk factors, (3) pathophysiology, (4) diagnostic imaging, (5) decision making and medical therapies, and (6) revascularization. For each theme, an invited panel of experts was asked to provide commentary on the current state of knowledge and provide suggestions for program development. This panel included cardiologists, vascular medicine physicians, epidemiologists, vascular surgeons, and interventional radiologists. This executive summary of the meeting provides the salient features of the discussions and recommendations.

Writing Group I: Epidemiology

The epidemiology of noncoronary atherosclerosis in the following 4 specific arterial beds is reviewed: cerebrovascular, aortic, renal, and peripheral (lower extremity). Unfortunately, the current level of knowledge differs widely by vascular territory.

Cerebrovascular Atherosclerosis

Stroke is the third leading cause of death and the principal cause of long-term disability in the United States today. There

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are 600 000 new or recurrent strokes occurring annually. The stroke mortality rate in the United States declined for many years, reaching a low of approximately 144 000 deaths in 1990 to 1992; since that time, mortality attributable to stroke has increased.

Approximately 85% of all strokes are ischemic, and of these, most are thromboembolic. The number of strokes attributable to carotid atherosclerosis approaches 20%. The prevalence of carotid artery stenosis has been estimated from high-resolution B-mode carotid ultrasonography. The carotid intima-media thickness correlates with the prevalence of vascular end points, including stroke and coronary heart disease (CHD). In the Framingham Heart Study, 47% percent of women and 37% of men had 0% to 10% carotid stenoses; 37% of men and 34% of women had carotid stenoses between 11% and 30%. Slightly more than 10% of the cohort studied had stenoses greater than 40%. There are ethnic differences in stroke and carotid atherosclerosis. Black populations have a 38% higher adjusted incidence of ischemic stroke than white populations, as well as higher stroke mortality. Black populations also have significantly greater common carotid intimal-medial thickness than non-Hispanic white populations.

Aortic Atherosclerosis

The principal clinical syndromes associated with aortic atherosclerosis are abdominal aortic aneurysms (AAAs), aortic dissection, peripheral atheroembolization, and the relatively newly recognized clinical syndromes penetrating aortic ulcer and intramural hematoma. Necropsy studies found AAAs in 4.7% of men and 1.7% of women age 56 to 74 years old. Thoracic aortic aneurysms seem to be considerably rarer. The true prevalence of AAA in asymptomatic patients is not well described. In one of the largest prospective screening studies, including more than 125 000 patients between 50 and 79 years of age, the prevalence was 4.3% and 1.0% for men and women, respectively (AAA $\geq$3.0 cm). Prevalence is low for both men and women younger than 50 years of age. The risk of rupture increases considerably as the size of AAAs increases. Once an AAA is greater than 6 cm in diameter, the risk of rupture is approximately 25% per year.

The prevalence of aortic atheromas among patients undergoing transesophageal echocardiography (TEE) for routine clinical indications is 8%; among those with known significant carotid disease, the prevalence is 38%. Among those with documented obstructive coronary disease, the prevalence approaches 90%. TEE studies have demonstrated an association between the presence of aortic atheromas and both stroke and other peripheral embolic events. One prospective study found that among those with protruding aortic atheromas on TEE, there is a 33% incidence of vascular embolic events over a 2-year follow-up period. Among patients presenting with symptoms suggestive of an acute aortic dissection, penetrating aortic ulcers are discovered in approximately 10%. Cardiovascular morbidity and mortality rates are increased in patients with aortic diseases. For example, the presence of aortic calcification is associated with a 2-fold increase in risk of cardiac death in men and women younger than 65 years.

Renal Artery Atherosclerosis

The incidence of end-stage renal disease in the year 2000 approximated 100 000 persons annually. The prevalence of this condition in 2000 was estimated at 372 000 persons. Prevalence data of renal artery stenosis come from studies of patients undergoing cardiac catheterization and thus cannot be considered reflective of general prevalence. An autopsy series of more than 2000 patients dying of stroke found that at least 1 renal artery was more than 75% stenosed in 10% of the patients studied.

Peripheral Arterial (Lower-Extremity) Disease

Although claudication, or a physical examination demonstrating absent or markedly diminished pulses, has been used by some to define PAD, an abnormal ankle-brachial index is generally used to indicate the presence of PAD. An ankle-brachial index of $\leq$0.90 is 90% sensitive and 95% specific for PAD. Severe PAD causing rest pain or ulceration generally occurs with ankle-brachial indices of less than 0.40. The age-adjusted prevalence of PAD is approximately 12% and may exceed 20% in persons older than the age of 70 years. Of those with PAD, only 10% to 30% have classic claudication. PAD progression over a period of approximately 5 years is predicted by both clinical factors and traditional risk factors. Among patients with PAD, evidence of CHD is common (85% by angiography), as is cerebrovascular disease (60% of patients presenting with PAD have a carotid stenosis of $>$30% by ultrasonography). In patients with established PAD, critical leg ischemia develops in 5% of patients over 5 years, with 1% to 4% proceeding to amputation. Among patients with PAD, the 5-year mortality in 1990 was approximately 30%; since then, mortality rates seem to have decreased as a result of risk factor modification and other medical treatments.

Many factors related to the development, outcome, and prevention of atherosclerosis in cerebrovascular, aortic, renal, and peripheral arterial territories are shared with coronary atherosclerosis. There remain important differences and knowledge gaps. Considerable opportunity exists through the sharing and dissemination of existing knowledge to dramatically improve both clinical and research efforts in the care and understanding of people with, or at risk of, noncoronary atherosclerosis. It is quite clear that once atherosclerosis is established in any territory, it is essential to prevent clinical events by aggressive secondary prevention efforts, because these individuals are at dramatically increased risk of cerebrovascular disease events.

Writing Group II: Risk Factors

Our current understanding of the risk factors for AVD is derived from data on 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 of the data from large populations about risk factors for noncoronary AVD are derived from studies focusing on CHD, such as Framingham, Atherosclerosis Risk in Communities (ARIC), Honolulu, and the Strong Heart studies. With

rare exception, these studies suggest that the risk factors for noncoronary AVD are generally similar to those for CHD. Thus, age, family history, dyslipidemia, cigarette smoking, hypertension, and diabetes constitute the major risk factors for cerebrovascular, aortic, renal, and lower-extremity AVD. Within these classic risk factors, studies indicate that for AVD, cigarette smoking and diabetes convey the greatest risks. A frequent form of dyslipidemia associated with AVD is the combination of elevated triglycerides and low HDL cholesterol. These changes in lipids occur in diabetes and contribute to the high incidence of AVD among diabetic patients. Variations in the prevalence of lower-extremity vascular disease have been related to gender and ethnicity. Diabetes is a greater risk factor for PAD among women than men and is associated with peroneal and tibial AVD. Cigarette smoking is associated with aortoiliac AVD and a hypoplastic aortoiliac syndrome in young women who are heavy smokers. PAD appears more prevalent among African-American and Hispanic populations. Smoking and male gender are risk factors for AAA. For cerebrovascular disease, African-American men and women have less vascular calcium and Japanese Americans have more intracranial than extracranial vascular disease.

The current approach to AVD risk estimation involves the assessment of factors such as age, gender, blood pressure, cigarette smoking, cholesterol, HDL cholesterol, and diabetes status. The findings of the Framingham Heart Study and similar trials have been used to develop risk equations for CHD, intermittent claudication, and stroke. A slightly different set of variables is predictive of outcomes for the various vascular beds. For example, the effects of cigarette smoking and diabetes mellitus are especially important for the development of PAD and intermittent claudication. The use of risk scores provides a reliable risk estimate, leading to targeted therapies and reduction in AVD events.

Generalizing beyond the source observational studies is an important issue for vascular disease risk estimation. 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 is essential. Differences in ethnicity and race, long-term exposures, and varying frequencies of risk factors across population groups are challenges to providing generalization of risk factor estimations. Experience with CHD prediction in Framingham has shown that the relative risks are usually similar across several different populations and that estimating equations may effectively rank persons in other populations, but the absolute risks may differ greatly. The difference in absolute risks translates into the need for more comparative studies and the development of strategies to estimate AVD risk equations across population groups.

Novel Risk Factors for AVD

CHD events can be predicted with multivariate equations that include traditional risk factors as variables. New factors, especially those that determine risk but have low correlations with existing factors, may be key to improving the current risk estimation approach. The compelling evidence for the role of inflammation in atherothrombotic vascular disease has fueled investigation of novel risk factors. Several novel markers for AVD are under investigation. These include lipoprotein(a), apolipoprotein (apo) A-1, apoB-100, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and homocysteine. In the evaluation of any such novel risk factor or marker, it is very important that its additive effect be directly confirmed in the presence of other established risk factors in a given population to determine its true value.

Studies among both men and women provide information about the additive value of certain novel risk factors. In a comparison of lipid and nonlipid risk factors for AVD prospectively 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. In men, a study comparing 11 biomarkers associated with the development of PAD revealed the ratio of total cholesterol to HDL cholesterol to be the strongest lipid predictor of risk. The addition of either CRP or fibrinogen to the lipid screening significantly improved predictive value, whereas the addition of apoB-100, lipoprotein(a), or homocysteine did not add significant value. 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. To date there are no large randomized clinical trials that demonstrate that reducing homocysteine is associated with improved outcomes. With regard to inflammatory markers, the Center for Disease Control and AHA scientific statement specifies that hs-CRP has the analysis and assay characteristics most conducive to use in clinical practice. The statement recognized hs-CRP as an independent marker of cardiovascular risk that might 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 results of large randomized clinical trials.

Genetic Risk Factors

Evidence from several lines of research indicates that atherosclerosis is, at least partially, genetically determined. Carotid artery intimal-medial thickness, a surrogate marker of atherosclerosis in populations, is highly heritable. Between 64% and 92% of the variation in the common carotid artery wall thickness is explained by familial factors. Findings from the Framingham Heart Study indicate that up to 50% of the variation in abdominal calcification, another surrogate marker of atherosclerosis, is determined by familial factors. Because no major gene has been identified for atherosclerosis, research efforts now focus on finding genes that contribute to the intermediate traits (ie, other cardiovascular risk factors) that are more proximal on the pathway leading to atherosclerosis.

Although several mendelian disorders cause severe abnormalities in the risk factors for atherosclerosis and atherosclerosis per se, most atherosclerosis does 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 the development of

atherosclerosis. The environment, or context, to which these genes are exposed also exerts a substantial impact on the natural history of the atherosclerotic process. Candidate genes that influence atherosclerosis are likely to be genes contributing to inflammation, including hemostatic factors, dyslipidemia, hypertension, diabetes, homocysteine, and obesity. Of particular relevance are lipids and lipoproteins, because alterations in lipids, particularly elevated LDL, are a prerequisite for atherogenesis. 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. Blood-derived inflammatory factors also play a key role. Genes contributing to the inflammatory response that further the progression of the initial atherosclerotic lesion include interleukin 6, tissue necrosis factor α, and interferon. Collectively, variation in 1 or more of these genes may be etiologically relevant to the initiation or progression of atherosclerosis, although there is little known about the independent or interactive effects of these genes as risk factors for atherosclerosis in the population or differences in the frequencies of the at-risk alleles of these genes in different ethnic groups. Research is needed to understand the importance of these genes, alone or in combination, in defining AVD in clinical and population settings.

Identification of genetic loci that contribute to variation in atherosclerosis under specific environmental contexts would provide new insight into pathways and mechanisms, opening up new avenues for prevention or treatment of atherosclerosis in the future. Variations in lipid-related candidate genes (peroxisome proliferator-activated receptor α, phospholipid transfer protein, apoAI, and apoE) predict response to diet and pharmacological intervention. A consistent observation from these studies is that the lipid response to diet and pharmacological agents is highly variable. Candidate genes contributing to blood pressure (angiotensinogen and α-adducin) predict response to sodium-restricted diet and pharmacological therapy. Additional research is needed to understand the impact of candidate genes on atherosclerosis, but the available studies suggest candidate genes may play an important future role in screening for prevention and diagnostic testing to determine optimal treatments for individual patients.

Writing Group III: Pathophysiology

The process of atherosclerosis involves several highly interrelated processes, including lipid disturbances, platelet activation, thrombosis, endothelial dysfunction, inflammation, oxidative stress, vascular smooth cell activation, altered matrix metabolism, remodeling, and genetic factors. These processes are the same in PAD as in all vascular beds, but the rate of development and the progression of disease are variable.

Platelet activation and thrombosis have long been recognized to be important components of atherosclerosis. Thrombosis is most likely to occur at sites of plaque rupture or erosion. Although thrombosis is a critical process in acute coronary syndromes, it may have an even more important role in modulating the risk of acute ischemic events in AVD. The findings of the CAPRIE trial demonstrated that inhibition of the platelet ADP receptor with clopidogrel (compared with aspirin) is more effective in reducing cardiovascular events in patients with PAD than with coronary artery disease.

The endothelium participates importantly in the regulation of vascular tone, nutrient delivery and waste removal, inflammation, thrombosis, and coagulation. Endothelial regulation of these processes stems primarily from the production of autocrine and paracrine mediators, including, but not limited to, nitric oxide, prostaglandins, endothelium-derived hyperpolarizing factors, endothelin, and angiotensin II. Endothelial dysfunction occurs in the presence of risk factors even before atherosclerosis is evident. Subjects with atherosclerosis demonstrate an attenuated vasodilatation in peripheral vessels and often frank vasoconstriction in coronary vessels related to a decrease in the bioavailability of nitric oxide. A decrease in the bioavailability of nitric oxide and increase in the production of vasoconstrictors like angiotensin II creates an environment permissive for thrombosis and the development of atherosclerosis. In addition to adversely affecting blood flow and nutrient delivery, likely the most important aspect of endothelial dysfunction would be the increase in inflammation. Endothelial cells participate importantly in the recruitment, adhesion, and diapedesis of leukocytes into the vascular wall through the production of chemokines and cytokines and intracellular transcription factors like nuclear factor-κB and activator protein-1.

Inflammation develops concurrent with the accumulation of minimally oxidized LDL in the arterial wall. The endothelial cell expresses several adhesion molecules, including P- and E-selectins, intracellular adhesion molecule-1, and vascular cellular adhesion molecule-1, which binds to circulating leukocytes. Transmigration of the leukocytes into the arterial wall is mediated through chemoattractants, such as monocyte chemotactic protein-1. This leads to accumulation of inflammatory macrophages and T-cells within the arterial wall. The CD40 receptor and CD40 ligand are expressed on several inflammatory cells, including macrophages, B and T lymphocytes, endothelial cells, vascular smooth muscle cells, and fibroblasts. This system is felt to contribute to leukocyte adhesion, matrix degeneration, and cytokine-induced inflammation. Studies have shown that matrix metalloproteinases (MMPs) and other substances expressed by macrophages and other inflammatory cells lead to degradation of the fibrous cap, resulting in an unstable plaque susceptible to plaque rupture. CD40 may also play a role in plaque rupture through effects on MMP production and thrombogenicity. The factors responsible for the initiation of this inflammatory response are multifactorial. Hemorheological factors likely contribute, and the role of oxidized lipoproteins within the arterial wall is well established. Other lipoproteins, such HDL and VLDL, may play an important role as well. Evidence also supports a possible infectious cause attributable to such pathogens as *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex, and cytomegalovirus.

The excess generation of oxygen-derived free radicals within the arterial wall represents an important pathological process in atherogenesis. The 2 best-characterized effects of reactive oxygen species are oxidation of LDL and scavenging

of endothelium-derived nitric oxide. Oxidized LDL induces a series of atherogenic processes, including transcription of proatherogenic genes and production of MMP and tissue factor, antagonizes endothelial cell production of nitric oxide, and favors vascular smooth muscle apoptosis.

The vascular smooth muscle cell plays a central role in atherosclerosis. Through growth factor and cytokine stimulation, vascular smooth muscle cells proliferate and secrete matrix proteins and enzymes. The atherosclerotic plaque is composed of equal amounts of cellular elements and matrix. The major constituents of the matrix are glycosaminoglycans, proteoglycans, collagen, elastin, fibronectin, laminin, vitronectin, and thrombospondin. Activated smooth muscle cells are largely responsible for the production of these matrix proteins.

As the plaque develops, vascular remodeling or a change in vessel size plays a critical role in determining the luminal patency. Glagov and colleagues originally described compensatory remodeling as an outward displacement of the arterial wall that compensates for the enlarging atheroma. Once the plaque enlarges to accommodate more than 40% of the vessel area, the vessel no longer enlarges and the lumen narrows as the plaque enlarges. All medium-sized arteries have been shown to remodel, including the carotid, iliac, femoral, and coronary arteries.

The vasa vasorum may contribute to the development of atherosclerosis as well. Although the development of the vasa vasorum in plaques is attributable to angiogenesis and has similarities to collateral formation, it is not the same. Collateral development is an integral although variable response to muscle ischemia produced by obstructive AVD. Collaterals provide a variable amount of flow but can be developed (under certain circumstances) well enough to minimize or eliminate ischemic symptoms.

AAA has a strong association with local aortic wall and systemic atherosclerosis, but a clear causal relationship is not established. Etiologic factors include a genetic susceptibility, because 15% to 20% of patients have a family history of the disorder. AAA is much more common in men than women (2 to 5 times) and more common in white than in black populations. Cigarette smoking is a major risk factor for AAA. The natural history is a gradual enlargement of the aneurysm until it exceeds 5.5 cm, when the risk of rupture rises exponentially. The primary pathophysiological process is chronic transmural inflammation with destruction of the media including loss of elastic fibers and smooth muscle cells. Elevation of inflammatory markers such as interleukin 6 and elevation of proteinases such as MMP9 and elastin are correlated with AAA and the expansion rate. Doxycycline inhibits MMP activity and can reduce AAA in experimental animals.

When a hemodynamically significant stenosis is present in PAD, distal pressure and flow are reduced. However, there is a poor correlation between the pressure drop across the limb and ischemic symptoms and function, particularly in lower-extremity PAD. This is largely attributable to the complex pathophysiology of claudication. Abnormalities in endothelial function and microthrombi, changes in blood viscosity, white blood cells, and platelet activation, and generation of oxygen free radicals all contribute to the reduced regional flow and ischemia. The clinical response to ischemia in obstructive atherosclerosis is highly dependent on the regional circulation. For instance, in lower-extremity PAD, claudication and limb ischemia are the principle clinical presentations, whereas in carotid artery disease, transient ischemic attack and stroke are the clinical presentations.

The development and progression of atherosclerosis is a systemic process that is complex and multifactorial. However, the important role that the regional circulation plays in the process and the variability in clinical presentation and natural history between circulatory beds cannot be overemphasized. Additional study of these factors is critical to our understanding of AVD and to the development of successful treatments.

Writing Group IV: Imaging

Requirements for proficiency for all of the imaging modalities include physician oversight, quality assurance programs, and standardization for acquisition of images, interpretation of the study, postprocessing procedures, workstations, and reporting.

Duplex Ultrasound

The term *duplex ultrasound* refers to B-mode real-time imaging and pulsed Doppler analysis of the velocity of flowing blood in arteries and veins. These allow for the quantification of the degree of stenosis; as an artery narrows, the velocity of blood flow increases. Duplex ultrasound is useful in screening for asymptomatic disease in individuals at high risk for abdominal aortic aneurysm and predicting future cardiovascular events (ie, intimal-medial wall thickness). Duplex is also useful for the diagnosis, treatment, and follow-up monitoring of patients with extracranial cerebrovascular disease, PAD, aneurysmal disease, renal artery disease, mesenteric artery disease, and the detection and treatment of pseudoaneurysms and arterial venous fistulas. Duplex is an excellent modality to follow patients after surgical or endovascular revascularization to identify restenosis. Duplex ultrasound may provide useful information on the likelihood of improvement in blood pressure and renal function after stent or surgical revascularization, as in the case of measuring resistive index in patients with renal artery atherosclerosis.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) has 2 fundamental advantages over other imaging modalities: contrast agents for MRA lack renal toxicity and images are obtained without ionizing radiation. Noncontrast MRA can be performed using time-of-flight methods, in which background tissue is suppressed while inflowing blood signal is bright on MRA images. The primary applications of time-of-flight MRA are for rapid screening for aortic dissection or aneurysm. Contrast-enhanced 3D MRA is a newer technique for acquiring noninvasive angiogram-like images. Contrast-enhanced 3D MRA uses an injected gadolinium-based contrast medium followed by rapid 3D MRI. Images are obtained during a breath hold and require approximately 20 seconds.

Presently the only indication for screening for asymptomatic aortic disease (for both MRA and computed tomographic angiography [CTA]) is in patients with a history of Marfan syndrome or inflammatory vascular diseases such as Takayasu's arteritis or giant cell arteritis to search for the presence of aneurysms. When techniques of identifying the vulnerable plaque become better, screening with MRA or CTA may become more widely accepted.

Contrast-enhanced MRA may be reformatted to provide information as to the cross-sectional size of an aortic aneurysm, the extent and origin of aortic dissection, as well as branch vessel involvement. Abdominal MRA can accurately identify disease in the abdominal aorta and its branches, particularly the renal arteries. MRA has become technically so good that it has virtually replaced diagnostic angiography in the evaluation of patients with PAD to determine what type of intervention may be best. The use of MRI for a variety of interventional procedures, including percutaneous angioplasty, transjugular intrahepatic portosystemic shunt procedures, stent placement, and embolization procedures, has been demonstrated in animal models. One group of investigators conducted a feasibility study to assess the potential application of vascular stent placement using MR guidance. Eleven of 12 stents were found to be correctly placed.

Computed Tomographic Angiography

CTA using a multidetector-row scanner acquires up to 16 simultaneous interweaving helices; 32-row and flat panel scanners are in development. CTA permits visualization of the anatomy from multiple angles and in multiple planes after a single acquisition, and there is excellent visualization of soft tissues and other adjacent anatomic structures. The multidetector-row CTA has an increased speed of acquisition with concomitant faster table feed and shorter exposure times. These features allow for greater longitudinal coverage for a given scan duration and greater spatial resolution (ie, imaging the thoracoabdominal, aortoiliac, and lower extremities). More rapid acquisition permits more uniform vascular enhancement, thin collimation scans of large anatomic territories during a single breath hold, improved visualization of small branch vessels and calcified plaque, and decreased pulse-related artifacts. The following 4 postprocessing techniques used in the workstation may be used: multiplanar reformation, maximum intensity projection, shaded surface display, and volumetric rendering. Postprocessed images alone should not be used for interpretation of CTAs.

There are no studies to date that support the widespread use of whole-body CT scans to detect asymptomatic disease. Multiple investigators have demonstrated a high degree of accuracy of CTA compared with the gold standard of conventional arteriography for extracranial carotid disease, PAD, aneurysmal disease (for diagnosis and before aortic stent graft or open surgical repair), dissection, penetrating aortic ulcer, renal artery, and other visceral arterial disease. CTA is the most widely used imaging modality for diagnosing aortic dissection and for follow-up after aortic stent graft procedures to identify endoleaks.

Digital Subtraction Angiography

Vascular imaging with ultrasound, CTA, and MRA has or soon will replace catheter-based techniques in the initial diagnostic evaluation of patients in most circumstances. Despite a paradigm shift away from conventional angiography as a purely diagnostic technique, its importance in intervention has increased dramatically.

The resolution of digital subtraction angiography (DSA) is less than that of screen film but can approach 3 to 4 line pairs per millimeter with current equipment. The standard imaging matrix is now 1024×1024, with image intensifiers that range up to 16 inches in diameter. Flat-panel image intensifiers will soon become available. Several major developments in DSA hardware and software contribute to greater diagnostic accuracy, faster procedures, and improved outcomes of interventions. Bolus chasing, rapid image acquisition, vessel diameter analysis, regional pixel shifting, image stacking, 3D reconstructions from rotational angiograms, and even angioscopic representations of DSA data are now routinely available.

Writing Group V: Medical Decision Making and Therapy

Atherosclerosis is a systemic disease, and its clinical sequelae may be manifest in multiple vascular beds. Evaluation and management of atherosclerosis must be linked to its pathophysiological mechanisms, cognizant of regional differences in natural history, morbidity, and effectiveness of therapeutic interventions.

Carotid Artery Disease

In the context of atherosclerosis, carotid artery disease identifies patients at increased risk for fatal and nonfatal myocardial infarction and stroke. Medical therapies that should be implemented to reduce the likelihood of stroke and death in patients with carotid artery disease include those that modify atherosclerotic risk factors and those that inhibit thrombosis. There is substantial evidence that antihypertensive, lipid-lowering, and antiplatelet therapies reduce the risk of stroke. In a meta-analysis of randomized, controlled trials, antihypertensive therapies, including diuretics and β-blockers, have been shown to effectively lower the risk of stroke by approximately 40%. ACE inhibitors also decrease the probability of stroke in high-risk populations, an effect that may be independent of their blood pressure–lowering potential. Secondary prevention trials in hypercholesterolemic patients with coronary artery disease have found that lipid-lowering therapy with statins reduced the risk of stroke. A meta-analysis of randomized trials of high-risk patients found that antiplatelet therapy reduced the risk of fatal and nonfatal stroke by 22%. In patients with prior stroke or transient ischemia attack, aspirin reduces the risk of adverse cardiovascular outcomes by 23%. A systematic review of 4 trials, 3 comparing aspirin with ticlopidine and 1 comparing clopidogrel with aspirin, found a 12% odds reduction for stroke in favor of the thienopyridines over aspirin.

Carotid artery revascularization is indicated in patients with significant carotid artery stenosis and relevant symptoms of cerebrovascular ischemia or nondisabling stroke, as discussed in the section on carotid revascularization. The use of

carotid endarterectomy to treat patients with asymptomatic carotid artery stenosis remains controversial. One randomized trial found a reduced risk of perioperative stroke or death in patients treated with carotid endarterectomy compared with those treated with medical therapy.

Aortic Diseases

Diseases of the aorta related to atherosclerosis include occlusive disease, aneurysm, dissection, intramural hematoma, and penetrating aortic ulcer. Aortic aneurysms associated with atherosclerosis typically occur in the descending thoracic and abdominal aorta. Although a causal relationship between atherosclerosis and aortic aneurysms is not established, there are common pathophysiological features. Risk factors for the development of abdominal aortic aneurysm include increasing age, tobacco smoking, hypertension, a family history of aortic aneurysm in male first-degree relatives, and the presence of other atherosclerotic diseases. The most feared consequence of aortic aneurysms is rupture, although because of coexisting systemic atherosclerosis, approximately 60% of patients die from other cardiovascular diseases, such as myocardial infarction. The probability of survival is inversely related to the size of the aneurysm. Large (>5.5 cm) AAAs should undergo surgical repair as long as the risk of rupture significantly exceeds the operative mortality. Endovascular stent graft repair of AAAs is a technique still in evolution but is being undertaken increasingly in appropriate candidates. Management of smaller aortic aneurysms (4 to 5.5 cm) has been the subject of several recent investigations that randomized patients to elective surgical repair or surveillance. The 5-year mortality rate was not significantly different between the 2 groups.

Medical treatments for aortic aneurysms related to atherosclerosis include therapies proven to reduce the risk of myocardial infarction and death, such as smoking cessation, cholesterol reduction, and blood pressure control. No specific therapy has been definitively shown to reduce the rate of aortic aneurysm expansion. Antihypertensive therapy intuitively should reduce aneurysm growth by reducing wall tension, but there is no existing evidence to support this notion. β-Blocker therapy has been shown to reduce the rate of aortic root dilatation in patients with Marfan syndrome, but efficacy in patients with AAAs is not established.

The diagnosis of aortic dissection requires a high clinical index of suspicion and immediate availability of an imaging study to confirm or refute the diagnosis. Urgent diagnosis can be achieved with TEE, MRA, and CT angiography. The decision regarding which imaging test to use depends on institutional availability and the patient's clinical status.

Initial management of aortic dissection includes institution of agents to reduce blood pressure and aortic shear stress, ie, dP/dT. This reduction can be accomplished with β-adrenergic blockers, often in combination with other rapidly acting agents, such as nitroprusside. The outcome of therapy of patients with type B (distal) aortic dissection is generally better with medical than surgical therapy. The converse is true for patients with type A (proximal) aortic dissection. An aortic intramural hematoma resembles aortic dissection in many respects, except there is no intimal tear or contiguity of the intramural hematoma with the aortic lumen. The risk of rupture is approximately 35%. Prognosis is worse in patients with intramural hematoma complicating a penetrating aortic ulcer. Complex atherosclerotic lesions in the aorta are an important cause of stroke and peripheral embolism. Unfortunately, studies supporting efficacy of either antiplatelet therapy or warfarin in reducing emboli originating in the aorta do not exist.

Renal Artery Stenosis

Medical decisions made to diagnose and treat renal artery stenosis depend on a high index of clinical suspicion, confirmation of the diagnosis with appropriate imaging techniques, establishing a relationship between renal artery stenosis and either hypertension or renal insufficiency, and a likelihood of clinical benefit resulting from a medical therapy or revascularization procedure.

Treatment decisions for management of renal artery stenosis must take into account the likelihood of blood pressure reduction, renal preservation, or both. Medical therapy for renal artery stenosis typically uses drugs that inhibit the renin-angiotensin system, including ACE inhibitors and angiotensin receptor blockers. Additional agents may be necessary to reach target blood pressure goal. It is important to note that drugs that interfere with the renin-angiotensin system are likely to worsen renal function to the kidney affected by renal artery stenosis. For this reason, medical therapy might be used in a patient with unilateral renal artery stenosis and a small, poorly functioning or nonfunctioning kidney that is still producing renin.

Current evidence has found that renal artery revascularization procedures are rarely curative, although blood pressure levels may decrease. The failure of renal artery revascularization to substantially modify blood pressure in some patients depends on several factors, including the presence of underlying essential hypertension, intrarenal vascular disease, or renal parenchymal disease. After revascularization, renal function remains stable or improves in most patients.

Peripheral Arterial Disease

Medical decision making and management of patients with PAD must take into consideration 2 cardinal precepts. The first is that PAD is a marker of systemic atherosclerosis, and, as a result, patients are at increased risk for myocardial infarction, stroke, and death. Second, patients with PAD frequently have impaired functional status manifested by decreased walking speed or distance, intermittent claudication, or critical limb ischemia.

Therapies that should be implemented to reduce adverse cardiovascular outcomes include lifestyle changes, risk factor modification, and antiplatelet drugs. Smoking cessation reduces the risk of myocardial infarction and death as well as the risk of progression to critical limb ischemia and limb loss. Beneficial effects of lipid-lowering therapy, particularly with statins, have been derived from at least 4 large clinical trials in patients with coronary and noncoronary atherosclerosis. Current National Cholesterol Education Program guidelines recommend treatment of patients with PAD to reduce the LDL cholesterol level to <100 mg/dL.

Patients with PAD and hypertension should be treated with antihypertensive therapy to reduce the risk of stroke, coronary artery disease, congestive heart failure, and chronic renal insufficiency. ACE inhibitors favorably improve cardiovascular outcome in patients with coronary and noncoronary atherosclerosis, including PAD, an effect that is independent of their blood pressure–lowering properties. Diabetes mellitus is also recognized as one of the most important risk factors for the development and progression of PAD. It is well established that aggressive glucose control reduces the risk of microvascular events, such as retinopathy and nephropathy, in patients with type 1 or type 2 diabetes mellitus. Unfortunately, the evidence that aggressive glucose control reduces the risk of macrovascular outcomes is less compelling.

Antiplatelet therapy reduces the risk of cardiovascular events in patients with atherosclerosis. The Antithrombotic Trialists' Collaboration found that antiplatelet therapy was associated with a 23% odds reduction for adverse cardiovascular events in patients with PAD. In the CAPRIE trial, clopidogrel was associated with a more favorable outcome than aspirin in the subgroup of patients with PAD.

Therapies that improve functional capacity in patients with intermittent claudication include supervised exercise rehabilitation, pharmacotherapy, and revascularization. Meta-analyses of randomized and nonrandomized trials found that supervised exercise rehabilitation improved pain-free walking time by 180% and maximal walking time by 120% to 150%. Cilostazol, a phosphodiesterase III inhibitor, improves quality of life and treadmill time, the latter by approximately 40%, in patients with intermittent claudication. The use of pentoxifylline is more controversial, with several clinical trials finding improvement in maximal walking distance of approximately 20%. Revascularization is indicated to improve symptoms and quality of life in patients with disabling claudication and to prevent limb loss in patients with critical limb ischemia.

Writing Group VI: Revascularization

Consideration of revascularization is divided into the following 4 separate areas: the aorta, the carotids, the renal arteries, and lower-extremity arteries. Atherosclerosis affects all of these areas, but manifestations, approaches to revascularization, and outcomes vary as a function of the area. The past decade produced dramatic changes in the approaches to treatment in these 4 areas, leading to remarkable advances and accompanied by significant questions. There has been a major paradigm shift as percutaneous treatment has become widely used. The Writing Group attempted to define the current approach to revascularization, the areas of concern, and the specific questions that merit additional investigation.

Aortic Revascularization

AAAs occur in up to 5% of men older than 65 years of age; most are small and require only infrequent follow-up. Data suggest that the risk of rupture is very low for AAAs 4.0 cm in diameter or less but rises exponentially for AAAs greater than 5 cm. AAAs between 4 and 5 cm in maximal diameter should be followed every 6 to 12 months to determine whether they are increasing in size. Intervention is indicated only if there is objective evidence (eg, from periodic CT scans) that an aneurysm is rapidly increasing in size or has a diameter greater than 5.5 cm, because these circumstances are associated with an increasing risk of rupture. Until the past 5 years, open surgery, which carried significant morbidity and mortality, was the only option, but AAA endografts have now come to be widely used. They seem to have an acceptably low incidence of morbidity and mortality, risk of rupture, and need for reintervention and survival rates that are thought to be equivalent to those with open repair. Interestingly, endografts do not have a cost advantage because of the high device cost and need for reintervention or conversion to open repair, despite a decreased length of hospital stay. Currently 3 devices are approved by the Food and Drug Administration, and others are in various stages of clinical trials. Major questions remain, however, including those regarding the need for repair of AAAs of less than 5 cm in diameter, the optimal endograft design, and the long-term outcomes with endografts.

Thoracic aneurysms are less common than AAA; however, the incidence of thoracic aneurysms is increasing. Five-year survival after diagnosis is 9% to 13%. Surgery carries an even higher incidence of morbidity and mortality than with AAA repair, making both medical therapy and percutaneous revascularization more attractive alternatives. Improved therapy is important, and numerous devices have been developed. Several small series have been published regarding the use of thoracic endografts. To date, no devices have been approved by the Food and Drug Administration for this indication. Thoracic aortic dissections (type A dissections, involving the ascending aorta) currently require emergent or urgent surgical repair, whereas those involving the descending aorta (type B dissections) have a more indolent course but still are associated with very high morbidity and mortality with both surgical and medical therapy. Nonsurgical repair using endografts, therefore, has great appeal. Experience to date using the same devices as used for thoracic aneurysm repair is limited but encouraging.

Renal Revascularization

It has been widely estimated that approximately 5% of hypertension is caused by renal artery stenosis, although the true incidence is unknown. There has been a large amount of experience worldwide with both balloon angioplasty and stent placement for the treatment of renal artery stenosis. It has become widely accepted that stent placement is preferable to angioplasty alone, because of improved immediate results and lower restenosis rates. Intervention is generally undertaken in patients with uncontrolled or poorly controlled hypertension and in patients with deteriorating renal function. Many reports have demonstrated that percutaneous repair of renal artery stenosis leads to long-term benefits, with better control of hypertension. Reports also suggest that in a large percentage of patients, the rate of deterioration of renal function is slowed and in some cases function is restored. In experienced hands, the complications of angioplasty or stenting are acceptably low. Because of safety, cost, and long-term efficacy, surgical repair is now rarely indicated.

With the availability of newer antihypertensive medications, such as angiotensin receptor blockers, the frequency of uncontrolled or poorly controlled hypertension should decrease. It is not clear whether treatment of the stenosis in patients with renovascular hypertension has long-term cardiovascular benefits, because a high percentage do not normalize blood pressure. However, patients are often not entirely compliant in taking medications, and even modest reduction in blood pressure as well as lowering the requirement for medications may help to limit the consequences of hypertension. Regarding patients with renal dysfunction, both the incidence of renal artery stenosis and the efficacy of percutaneous revascularization in preventing both progression of disease and cardiovascular sequelae require investigation. However, clinical studies do suggest that percutaneous revascularization prevents additional deterioration in renal function or even improves renal function in selected patients.

Despite the technical advances in percutaneous renal revascularization, optimal technique is still evolving. Embolic protection devices may prove useful, because microembolization to the renal circulation or to visceral and lower-extremity arteries is a real concern. Optimizing the stent design and characteristics and ancillary medications are additional areas that need further development.

Carotid Revascularization

Prior studies from a decade ago have clearly shown an advantage for surgical endarterectomy compared with medical therapy for symptomatic lesions with >70% stenosis and for asymptomatic lesions >60%. Since these studies, there have been major advances in medical therapy, in percutaneous revascularization, and in the understanding of the carotid atherosclerotic process. Angioplasty and stenting have been widely publicized and advocated for treatment. One study, however, showed worse outcomes with balloon angioplasty than with endarterectomy, and angioplasty alone has been essentially replaced by the concomitant use of stents. There are several sizeable series that suggest that carotid stenting in the hands of experienced practitioners has a complication and immediate success rate that rivals endarterectomy and a long-term restenosis rate that is marginally higher (3% to 4% versus 1%). The technology for carotid stenting is still in a state of evolution; questions remain regarding the specific stent type and design, the use of protection devices to decrease embolization risk, and the use of ancillary medications. The specific patient population to be treated remains unclear, as does the best means of providing education, training, credentialing, and oversight of those who perform carotid stenting. Although percutaneous treatment of carotid artery stenosis is inherently appealing, because it is minimally invasive, the results of several large ongoing multicenter trials comparing stenting with surgical endarterectomy are ongoing and should help define the role of percutaneous approaches.

Peripheral Artery Revascularization

PAD remains underdiagnosed and undertreated. Associated symptoms are often mild, and progression to signs and symptoms presaging limb loss is unusual. PAD is inherently important, however, because of the associated morbidity, ie, limitation of activity and limb loss, and because it is a marker for other cardiovascular disease. It also acts as a risk factor, because it limits activity and exercise regimens. Because the natural history of symptomatic PAD, as addressed in prior sections, is generally benign, the major questions regarding PAD concern not only how to perform revascularization but when.

Isolated PAD of the abdominal aorta is unusual and, if focal, can be treated effectively with angioplasty and stenting. Surgery should be considered for lesions longer than 3 cm. Similarly, long segments of the femoral-popliteal arteries may also be better treated by surgery. Focal lesions and long-segment occlusion confined to the iliac arteries can be effectively treated with percutaneous techniques such as catheter-directed thrombolysis (even for chronic iliac occlusions), angioplasty, and stenting. Angioplasty alone in the femoral-popliteal arteries has been shown to be effective as well. Interestingly, although stent placement has supplanted angioplasty in most arterial beds, in the infrainguinal arteries, results with stents have, in general, been disappointing. Most trials have been small and limited, yet the incidence of occlusion seems to be higher, and not lower, with stent placement in the femoral arteries than with balloon angioplasty.

In the distal abdominal aorta and in the iliac arteries, data suggest that long-term outcomes with percutaneous intervention are as good as with surgical revascularization. In the femoral-popliteal arteries, there are fewer data. In the infrapopliteal arteries, experience is still more limited. Available studies suggest, however, that patency rates are high with angioplasty of focal lesions. Longer lesions still require surgical bypass.

Several small studies have addressed the utility of newer ancillary approaches to accompany percutaneous revascularization. These include brachytherapy, the use of covered stents, the use of new stent designs, and the use of drug-eluting stents. Additional technical and pharmacological advances (eg, thrombectomy devices and platelet receptor antagonists) require further evaluation.

Recommendation

The field of AVD has been advancing at an increased pace as the importance of the disease and its early recognition is better appreciated by the medical community. The AVD working group identified several areas that deserve increased attention if the problem of AVD is to be more effectively identified and treated. The specific recommendation can be found in the individual reports published online.

A major limitation of the field is the lack of a consensus concerning the terms that should be used to define the disease. A commonality of definitions is critically needed. We propose that *atherosclerotic vascular disease* be used to refer to the disease because it involves the entire vascular system and that specific terms be used for individual vascular beds, such as *peripheral arterial disease* or *atherosclerotic renal artery stenosis*.

In addition, there is a critical need for definitions for each specific disease entity. What should be the definition for an *abdominal aortic aneurysm*? Should it be adjusted for body mass? Should gender-specific definitions be included? These definitions are critical in determining the incidence of the various conditions as well as their natural history. These latter subjects are also understudied, and the incidence and prevalence in various ethnic and racial groups is poorly defined. Many of the currently published data are from academic referral centers, and the incidence of disease in the community is poorly defined. Even less data are available concerning the presence of subclinical disease and its natural history.

Although risk factors for coronary artery disease are well defined, less is known about risk factors in AVD. In particular, it is likely that just as cardiovascular risk is increased in the presence of multiple risk factors and global risk is helpful in defining that risk, a global risk score for AVD would be of equal value. In particular, additional work needs to be done in defining the genetic factors that predispose to AVD.

The process of atherosclerosis is well defined, but the regional differences in disease expression and the role of pathophysiological influences have been poorly studied to date. A better understanding of the role of lipid abnormalities, thrombosis, inflammation, genetic factors, matrix metabolism, and vascular remodeling in AVD is critical. The various peripheral circulations have important pathophysiological differences that influence the development of disease. How does each of these regions respond to ischemia? Why do some vascular beds and some patients develop collaterals? What are the interactions between vascular beds? For instance, why is coronary atherosclerosis accelerated in the presence of renovascular disease? Does aortic disease lead to acceleration of PAD? The importance of diabetes in AVD cannot be overestimated, but the disease is often more diffuse and distal. What are the underlying mechanisms responsible for this pattern of disease and the rapid progression of disease seen in these patients? Improved methods to image and study vascular disease are needed as well.

Advances in vascular imaging have allowed safer and more detailed anatomic and functional assessment. However, more rapid and less expensive techniques are still needed to optimally screen individuals at increased risk for AVD.

Endovascular and surgical therapy for AVD have both made remarkable progress; however, the optimal therapy in many clinical settings is still unclear. Unlike coronary revascularization, there is a relative paucity of randomized clinical trials in this field. Although the most randomized trials have been conducted in the area of carotid disease, definitive trials in the area of renal artery stenting and stenting of PAD are lacking. Even with carotid stenting, there is not yet definitive evidence for equivalency with carotid endarterectomy. In addition, there is inadequate information concerning the long-term outcome of endovascular stent grafts for AAA and little information concerning percutaneous treatment of thoracic aneurysms and dissection. Recent advances in percutaneous approaches, including distal protection devices, drug-eluting stents, and platelet glycoprotein IIb/IIIa antagonists, will undoubtedly improve the outcome in all vascular beds. One of the factors that has slowed progress in this area has been the disagreement and competition between cardiologists, vascular surgeons, and interventional radiologists as to credentialing and certification.

The working groups made several recommendations. First, they recommended to the AHA to establish an interdisciplinary working group that would draw membership from the 13 councils to begin to address the issues outlined in this report. Second, they recommended that a consensus conference on nomenclature, definitions, and measurements be convened. Third, the working groups recommended that the AHA and other national organizations increase the public and professional awareness of AVD. Fourth, and most importantly, the conferees felt that increased funding from the AHA, NIH, and other organizations was mandatory to understand the pathophysiology, prevention, epidemiology, imaging, medical therapy, and revascularization of AVD. Partnerships between organizations and industry could also be highly fruitful in advancing the field. In addition, improvements in reimbursements for all aspects of the identification and management of patients with AVD are also needed to ensure optimal treatment of these patients.

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