Atherosclerotic Peripheral Vascular Disease Symposium II: Executive Summary

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Atherosclerotic Peripheral Vascular Disease Symposium II
Executive Summary

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The Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group was commissioned by the American Heart Association (AHA) to provide a forum to address important and emerging issues in this multidisciplinary area of clinical science. The working group was a primary outgrowth of the AHA Atherosclerotic Vascular Disease Conference held in Boston, Mass, in July 2002. It was created in recognition of the fact that atherosclerosis is a systemic disease with important sequelae in many regional circulations in addition to the heart, including the brain, kidneys, mesentery, and limbs. Its mission is to provide a forum for the multiple disciplines engaged in research, evaluation, and management of patients with noncoronary atherosclerosis. The goals of the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group are to develop a strategy to increase awareness of atherosclerotic vascular disease, identify important gap areas in knowledge that require further clinical investigation, and develop programs that will facilitate prevention and treatment of peripheral atherosclerotic diseases.

Developments in research and technology that are relevant to atherosclerotic vascular disease are emerging rapidly. As a result, greater opportunities to translate science to clinical practice are available. The American College of Cardiology/AHA practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic) provide many evidenced-based recommendations for diagnosing and treating patients with atherosclerotic vascular diseases.[1] Nevertheless, in some areas, the evidence has not matured sufficiently for definitive guidelines. Some of these areas have engendered considerable controversy among practitioners. Among these are the efficacy and outcome of screening programs for vascular disease and the appropriate and timely use of endovascular interventions. Accordingly, the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group convened the second AHA conference on Atherosclerotic Vascular Disease, which took place in Boston, Mass, in July 2006. The conference was also sponsored by the AHA Councils on Arteriosclerosis, Thrombosis, and Vascular Biology; Epidemiology and Prevention; Cardiovascular Radiology and Intervention; Cardiovascular Surgery and Anesthesia; Cardiovascular Nursing; Clinical Cardiology; Council for High Blood Pressure Research; Council on the Kidney in Cardiovascular Disease; and Stroke Council. It was cosponsored by the Society of Cardiovascular Angiography and Interventions, the Society of Interventional Radiology, and the Society for Vascular Medicine and Biology. The overall objectives of this conference were as follows: (1) to develop a consensus about the feasibility, importance, and efficacy of screening for atherosclerotic vascular diseases; (2) to provide a state-of-the-art review of contemporary imaging modalities, specifically computed tomographic angiography (CTA) and magnetic resonance angiography (MRA); (3) to address recent developments and controversies with regard to the appropriate and timely use of interventions in patients with various manifestations of atherosclerotic vascular disease; and (4) to recommend nomenclature for atherosclerotic vascular diseases that could be adapted by clinicians and scientists to facilitate communication.

The conference was divided into the following 8 themes that were addressed by individual writing groups: (1) Nomen-

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These proceedings were approved by the American Heart Association Science Advisory and Coordinating Committee on June 2, 2008. A copy of these proceedings is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. LS-1882). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit http://www.americanheart.org/presenter.jhtml?identifier=3023366.

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Table 1. Major Vascular Terms

Recommended	Previous Terms	Pathophysiology	Anatomy	Duration and Severity	Comments
Vascular diseases		Diseases of arteries, veins, and lymphatics; includes atherosclerosis and nonatherosclerotic diseases	All vessels without anatomic designation	Acute to chronic; asymptomatic to severe	Broadest term to describe all vascular diseases: coronary, cerebral, peripheral, renal, and mesenteric artery occlusive disease, aneurysms, venous and lymphatic diseases
Peripheral artery disease	Peripheral vascular disease, peripheral arterial disease, peripheral arterial occlusive disease, arteriosclerosis obliterans	Atherosclerosis, thrombosis, noncardiac emboli, inflammatory, etc	Stenosis or occlusion of upper- or lower-extremity arteries	Acute to chronic. May be asymptomatic. Symptoms and signs range from asymptomatic with functional limitations to intermittent claudication, rest pain, ulcers, and gangrene	Limited to artery disease; excludes renal, coronary cerebral, mesenteric, and aneurysms
Mesenteric artery disease	Visceral or mesenteric ischemia or angina, intestinal ischemia/angina	Atherosclerosis, thrombosis, emboli, extrinsic compression, vasculitis	Celiac trunk, superior mesenteric artery, inferior mesenteric artery	Acute to chronic. Most patients are asymptomatic. Symptoms include postprandial pain and weight loss	
Renal artery disease	Renal artery stenosis, renovascular disease	Atherosclerosis, thrombosis, emboli, arterial dysplasia	Main renal arteries and extrarenal branches	Acute to chronic, mild to severe	Associated with hypertension and/or renal insufficiency
Cerebral artery disease	Cerebral vascular disease (confused with cardiovascular disease); extracranial arterial occlusive disease	Atherosclerosis and nonatherosclerotic causes such as dissection, arterial dysplasia	Aortic arch to intracranial vessels	Acute and chronic. Symptoms and signs of stroke and transient ischemic attack depend on affected territory	May be asymptomatic
Extracranial cerebral artery disease	Cervical carotid disease, vertebral-basilar insufficiency	Atherosclerosis and nonatherosclerotic causes as above	Aortic arch, carotid, vertebral, and extracranial vessels	As above	Excludes intracranial artery diseases
Intracranial cerebral artery disease		Atherosclerosis and nonatherosclerotic causes	Intracerebral vessels	As above	Excludes extracranial artery diseases (although may coexist)

clature for Atherosclerotic Vascular Diseases; (2) Screening for Atherosclerotic Vascular Diseases: Should Nationwide Programs Be Instituted?; (3) Vascular Magnetic Resonance and Computed Tomographic Imaging; (4) Stroke Intervention: State of the Art; (5) Controversies in Carotid Artery Revascularization; (6) Controversies in Abdominal Aortic Aneurysm Repair; (7) Lower-Extremity Revascularization: State of the Art; and (8) Intervention for Renal Artery Disease.

Writing Group 1: Nomenclature for Vascular Diseases

Peripheral vascular diseases are important components of cardiovascular medicine. The high prevalence of these disorders in the clinical setting mandates effective communication among healthcare providers. The public health significance of these conditions requires clear and consistent terminology for community audiences. Therefore, the goal of Writing Group 1 was to suggest definitions, usage, and nomenclature of specific terms commonly used to describe vascular diseases by cardiovascular specialists and primary care communities. The major structural components of the vascular system consist of veins, lymphatic vessels, and arteries. Venous and lymphatic diseases were outside the scope of this conference. Diseases of arteries are classified further into atherosclerotic occlusive disorders, nonatherosclerotic occlusive disorders, and aneurysms.

Specific terminology for vascular diseases is provided in Table 1. The term "vascular diseases" should refer to all diseases of arteries, veins, and lymphatic vessels. Coronary artery disease was not included in Table 1 because it was outside the scope of this conference. "Atherosclerotic vascular disease" refers to diseases of arteries caused by atherosclerosis. The term "peripheral artery disease" (PAD) is recommended to describe disease that affects the lower- or upper-extremity arteries. PAD should replace "peripheral vascular disease," which was often used in the past to describe leg artery disease but is too nonspecific, because it

Table 2. Aneurysm Terminology

Recommended	Pathophysiology	Anatomy	Severity
Aneurysm	Affects all 3 layers of the affected artery; atherosclerosis, connective tissue, congenital, infection (mycotic), traumatic, dissection, inflammation	Affects all major peripheral arteries	Asymptomatic, symptomatic (depending on contiguous structures); ruptured, leaking (contained rupture)
Aorta			
Thoracic aortic aneurysm	As above	Ascending, transverse, arch, descending (DeBakey I or II or Stanford A or B)	As above
Thoracoabdominal aortic aneurysm	As above	Crawford class I–IV	As above
Abdominal aortic aneurysm	As above	Crawford class IV, suprarenal, pararenal, juxtarenal, infrarenal	As above
Aortic branch			
Visceral (celiac, superior mesenteric, inferior mesenteric, hepatic, splenic, renal) artery aneurysm	As above	All visceral branches of the aorta	As above
Peripheral			
Iliac, femoral, popliteal	As above		As above

can encompasses venous, lymphatic, and vasospastic diseases in addition to arterial disorders. Table 1 provides additional definitions for atherosclerotic vascular diseases as they apply to the noncoronary circulations. Definitions are provided for peripheral (lower- and upper-extremity), mesenteric (celiac, superior mesenteric, and inferior mesenteric arteries), renal, and cerebral artery (intracranial and extracranial) disease. These are further subdivided into the major manifestations of each disease. Universal use of the term "disease" is preferred rather than the selective use of the term "stenosis," for example, "renal artery disease" rather than "renal artery stenosis." This was done because an artery can have an occlusion or a stenosis with similar clinical manifestations, and the term "disease" was meant to cover both conditions. Some causes of these arterial diseases are listed in Table 1. Table 2 provides terminology for aneurysms of the aorta and its visceral and limb branches. Although the definitions vary, an artery can be considered aneurysmal when its diameter is increased by 50% compared with the normal dimension.

In addition, several terms are recommended for the clinical manifestations, assessment, and treatment of PAD. Patients with PAD who do not have symptoms are designated "asymptomatic." Effort-induced (usually walking) discomfort of the calf, thigh, and/or buttock, variably described as cramping, aching, tightness, pain, or fatigue, is termed "intermittent claudication." "Atypical claudication" is a term that refers to exertional leg pain that does not fulfill all the characteristics of classic claudication. "Critical limb ischemia" refers to pain in the feet or toes at rest, with or without ischemic ulcers or gangrene.

Terms are suggested for the hemodynamic and functional assessment of patients with PAD, including "ankle–brachial index," "peak walking time," and "claudication onset time." In addition, suggested nomenclature includes terms for interventions. "Endovascular revascularization" is the recommended term for catheter-based treatment of a peripheral artery stenosis, occlusion, or aneurysm. "Open revascularization" is the term recommended for open surgical treatment of an artery stenosis, occlusion, or aneurysm. The nomenclature process should be continually dynamic to reflect scientific and clinical advances in the diagnosis and management of vascular disorders.

Writing Group 2: Screening for Atherosclerotic Vascular Diseases: Should Nationwide Programs Be Instituted?

Controversy exists about the appropriateness and efficacy of screening programs to detect atherosclerotic vascular diseases. Writing Group 2 considered the noninvasive detection of 4 specific types of noncoronary atherosclerotic vascular disease: the ankle–brachial index for assessment of PAD; carotid duplex ultrasound for assessment of intimal–medial wall thickness, plaque, and stenosis; abdominal ultrasound for detection of an abdominal aortic aneurysm (AAA); and duplex ultrasound for the detection of renal artery disease.

First, screening criteria were reviewed with regard to the 4 measures. Specific criteria included the public health importance of the problem, a detectable latent phase, reasonable prevalence (at least in a targeted population), safety, precision, feasibility, ethical appropriateness, acceptability to potential screenees, cutoff levels validated by test characteristics, and cost-effectiveness.

In discussing each test, it was recognized that the "gold standard" would be a randomized clinical trial of each assessment in a targeted population with rigorous outcome criteria. However, such data are quite limited in this area. Thus, alternative forms of evaluation based on observational data are necessary, such as cost-effectiveness modeling, although rigorous studies of this nature are few.

Peripheral Artery Disease

The ankle–brachial index has many attractive features for use in targeted screening programs. It is inexpensive, can be performed quickly, and has high validity and good reproduc-

ibility. In addition, it can be used to assess 2 separate problems. First, it can help detect early PAD and, with appropriate intervention, help prevent progression to critical leg ischemia and amputation. Second, it robustly predicts future ischemic cardiac and cerebral events and thus can be used to detect persons who would benefit from aggressive medical therapy. This risk prediction has recently been demonstrated to be independent of and to add incrementally to the Framingham risk score.[2] Finally, screening can be targeted to high-risk groups, which facilitates yield and cost-effectiveness. No randomized trial data on screening are available, nor to the best of our knowledge are there currently plans to obtain such data. Nevertheless, the above characteristics suggest that a cost-effectiveness analysis would be supportive of screening for PAD in targeted populations.

Carotid Artery Disease

Carotid ultrasound screening potentially provides information on 2 distinct but related issues: First, it can determine the presence of a stenosis significant enough to indicate the need for intervention to prevent a future stroke. Second, it can provide evidence of overall future atherosclerotic event risk. Measurements include the presence of plaque, the degree of any stenosis, and the intimal–medial thickness of the carotid arteries at selected sites. Ultrasound screening for carotid artery stenosis cannot be recommended at this time, because no randomized clinical trials are available to support routine screening, even in "at-risk" patients, but such studies, along with cost-effectiveness analyses, would be helpful. Also, measurement of carotid wall thickness appears to allow discrimination of risk even in young adults, but methods are technically challenging and need further evaluation and refinement before they can be considered for population-based screening programs.

Abdominal Aortic Aneurysm

Ultrasound screening for AAA can be performed safely, quickly, inexpensively, and accurately. A large, prospective study in men 65 to 74 years of age has demonstrated the utility and cost-effectiveness of ultrasound screening in reducing aneurysm-related deaths.[3] The frequency of routine re-imaging to assess aneurysm growth rates can be correlated reliably to the size of the aneurysm at the index screening. Current American College of Cardiology/AHA guidelines recommend ultrasound screening of AAAs for men ≥60 years of age who are siblings or offspring of patients with AAAs (Class 1) and men 65 to 75 years of age who have ever smoked (Class 2a).[1]

Renal Artery Disease

Although duplex ultrasound of the renal arteries can be performed safely and with a high degree of accuracy, routine screening for the presence of renal artery disease cannot be recommended at this time. There are several reasons for this: (1) No evidence indicates that identifying renal artery disease in patients without clinical manifestations will be of any benefit to the patient. Treatment is only advised for specific clinical manifestations (hypertension, renal failure, and pulmonary edema), not for "asymptomatic" renal artery stenosis. (2) Noninvasive screening of renal artery disease by duplex ultrasound is not readily available. Far fewer laboratories are capable of performing high-quality renal artery duplex ultrasound than ultrasound in other vascular territories; therefore, it would be difficult to initiate a widespread screening program. (3) No cost–benefit data are available on the use of duplex ultrasound to screen for renal artery disease. (4) Other imaging tests, such as MRA or CTA, clearly would not be cost-effective. The ongoing Cardiovascular Outcomes in Renal Atherosclerotic Lesions Trial (CORAL), a randomized treatment trial of patients with renal artery stenosis, should provide additional insight.[4]

Recommendations

Recommendations refer to the use of the 4 tests discussed above for screening in appropriately targeted populations. The low cost, high yield, and strong prognostic significance of the ankle–brachial index suggest it would be appropriate as a screening tool. No randomized trial data for this exist, nor is such an evaluation planned. A careful cost-effectiveness analysis is a high priority. Carotid duplex ultrasound is more expensive and more technically challenging than the ankle–brachial index. Randomized screening trial data for carotid duplex ultrasound are unavailable, and no studies of this nature are currently planned. A cost-effectiveness analysis would be useful. No recommendation for ultrasound screening for carotid artery disease can be made at this time. Ultrasound for AAA detection has strong clinical trial support in appropriate populations, and its use is likely to become more widespread. Finally, duplex ultrasound for renal artery disease has the weakest evidence base among the screening tests discussed herein and thus is problematic for use in screening; however, an ongoing treatment trial of patients with renal artery stenosis should provide additional insight.

Writing Group 3: Vascular Magnetic Resonance and Computed Tomographic Imaging

Over the past 10 years, there has been rapid adoption of new technology that has enabled imaging of the vascular system in a noninvasive manner with CTA and MRA for carotid, renal, and peripheral vascular diagnostic examinations. The goal of Writing Group 3 was to review the evidence-based approach to selection of these imaging modalities.

Multidetector-row computed tomographic (CT) scanners provide excellent images of the vascular tree from the head to the distal segments of the extremities. CTA allows acquisition of high-resolution volumetric data sets that can be viewed in multiple planes and with a variety of visualization techniques. Compared with catheter-based angiography and MRA, CTA is faster and more comfortable for patients, although it has been suggested that the interpretation time may be longer than for the other imaging modalities. Physicians should be able to review images in more than the standard transverse

plane, because multiplanar reformations, curved planar reformations perpendicular to the median arterial centerline, volume rendering, and maximum-intensity projections all have different advantages and disadvantages. Rapid advances in MRA technology in the past several years have led to improved resolution, anatomic coverage, and speed of image acquisition. The lack of radiation exposure and noninvasive nature of MRA offer advantages over CT in many settings. Traditional MRA techniques include both multislice (2-dimensional) and volumetric (3-dimensionsal) time-of-flight techniques. These have shown excellent utility in carotid and intracranial applications. However, most carotid, body, and peripheral MRA currently is performed with gadolinium-enhanced sequences to improve examination speed, anatomic coverage, and small-vessel resolution. Intravenous injection of gadolinium shortens the T1 relaxation time of blood, which leads to a transiently higher intravascular signal that can be captured with proper MRA sequence timing.

CT and Magnetic Resonance Contrast Agents

Iodinated contrast agents used in CT increase the risk for contrast-induced nephropathy. Patients who are considered at highest risk are those with renal insufficiency, especially those with diabetes mellitus. Other risk factors for contrast-induced nephropathy include multiple myeloma, proteinuria, concomitant nephrotoxic drug use, hypertension, congestive heart failure, hyperuricemia, and dehydration. High-osmolar contrast is associated with twice the risk of contrast-induced nephropathy as low-osmolar contrast in patients with preexisting renal impairment. Conflicting observations exist about whether iodixanol, an isosmolar nonionic dimer, is less nephrotoxic than other low-osmolar contrast material. Overall, patients with preexisting renal insufficiency are at increased risk for contrast-induced nephropathy, no matter what type of contrast is used. Physicians and facilities using contrast material should have screening programs to identify patients at high risk for contrast-induced nephropathy so that procedures can be instituted for patient safety.

Gadolinium-based contrast agents used in MRA have long been touted as non-nephrotoxic. Recently, however, the safety of gadolinium in patients with severe renal insufficiency has come into question.[5] The use of gadolinium in patients with renal impairment has been linked to the development of nephrogenic systemic fibrosis. Nephrogenic systemic fibrosis is still considered to be rare, with only 90 cases reported at the time of a US Food and Drug Administration advisory warning; however, it can be severely debilitating and has been linked to patient death due to respiratory compromise from diaphragmatic and cardiac involvement. In addition, acute renal failure has been reported in patients receiving high doses of gadolinium chelates (>0.3 mmol/kg), which is a fairly typical dose for lower-extremity MRA examinations.[6] The patients most at risk are those with diabetic nephropathy and a low glomerular filtration rate. The greatest benefit of MRA compared with CTA in the recent past has been the use of non-nephrotoxic agents in imaging patients at high risk for iodinated contrast-induced nephropathy. That presumed benefit may no longer hold true. Physicians should be aware that there are potential nephrotoxic and systemic risks with the use of high-dose gadolinium chelates and should exercise caution in high-risk patients. Screening procedures are recommended before gadolinium use is considered in patients with any degree of renal insufficiency.

Clinical Applications

Cerebrovascular Disease

Duplex ultrasound is a well-validated screening tool for the presence of carotid artery stenosis; however, it can be operator and patient dependent, so results are often confirmed by additional testing before treatment. Additional testing with gadolinium-enhanced MRA and occasionally CTA is used. MRA or a combination of MRA and duplex ultrasound has a sensitivity and specificity of approximately 95% and 90%, respectively, compared with digital subtraction angiography.[7] CTA has a sensitivity approaching 100% for detecting >70% stenosis and a high negative predictive value.[8] CT and magnetic resonance imaging now go beyond brain structural analysis to allow a comprehensive physiological assessment of stroke and its causes. CT and magnetic resonance imaging can rapidly define both the "core" of the infarcted tissue and the "penumbra," which is the surrounding tissue at risk. The penumbra is a target for acute stroke intervention. Both the core and penumbra can be defined operationally with noninvasive CT and magnetic resonance studies that include perfusion imaging. Postprocessing algorithms create maps of the key blood-delivery perfusion parameters, including mean transit time, cerebral blood volume, and cerebral blood flow. With magnetic resonance imaging, diffusion-weighted imaging is able to detect ischemic changes within minutes of stroke onset much better than noncontrast CT. Perfusion imaging can determine whether there is tissue at risk beyond the early infarct core, that is, an ischemic penumbra that is rationally targeted for treatment.

Renal Artery Disease

Duplex ultrasound is a good technique for evaluation of renal artery stenosis; however; it is limited by operator experience, patient cooperation, and body habitus. Renal CTA and MRA are useful noninvasive imaging modalities when renal artery stenosis is suspected.

CTA has a sensitivity of 94% to 100% and a specificity of 92% to 99% for significant renal artery stenosis.[9] Contrast-enhanced MRA has a sensitivity of 88% to 100% and a specificity of 75% to 100%.[9] Studies comparing multidetector CTA and MRA have shown them to be equally sensitive and specific for the detection of renal artery stenosis; however, patient acceptance of CTA is higher than for MRA. CTA is better than MRA for assessment of renal arteries after stent placement.

Peripheral Artery Disease

CTA or MRA is used frequently to determine the vascular anatomy and to plan treatment of patients with PAD who have lifestyle-altering claudication or critical limb ischemia.

The choice of study should be based on regional availability and expertise. Multidetector CTA may visualize segments of arteries distal to occlusions that are not visible on routine digital subtraction angiography imaging. The sensitivity and specificity of multidetector CTA for PAD are 89% to 99% and 83% to 100%, respectively.[10,11]

Gadolinium-enhanced 3-dimensional MRA examinations can be performed with a bolus chase (moving table) sequence, which allows improved visualization of the peripheral arteries. The abdominal aorta and superficial femoral segments are imaged reliably with this technique, but problems can arise with imaging of the infrapopliteal arterial segments in some patients because of venous contamination. Other techniques are being developed to help eliminate this problem, including integrated parallel acquisitions and hybrid studies with dedicated stations at the calf and foot. Hybrid MRA of the calf and foot may be able to detect target vessels for revascularization that are not visible on standard digital subtraction angiography. Sensitivity encoding or parallel acquisition, either alone or in combination with dedicated peripheral phased-array coils, has increased the speed of image acquisition of MRA so that the timing of imaging at the calf or the resolution of the imaging can be improved.

Recommendations

The writing group has identified the following important topics as areas for future research: (1) intravascular device safety at high-field-strength magnetic resonance imaging (3 Tesla and greater); (2) functional imaging for significant stenoses and clinical response to treatment; (3) lowering CT radiation exposure without sacrificing satisfactory image quality; (4) plaque characterization, especially in the carotid arteries; (5) prevention of contrast-induced nephropathy, including strategies to reduce the volume of contrast needed; (6) means of identifying patients at risk for developing nephrogenic systemic fibrosis; and (7) rapid techniques for visualizing blood vessels on magnetic resonance imaging that do not require the use of gadolinium-based contrast agents.

Writing Group 4: Stroke Intervention: State of the Art

Stroke remains a leading global cause of death and disability. Approaches to acute therapy for ischemic stroke include acute reperfusion, neuroprotection, and restorative and rehabilitative therapies. Writing Group 4 focused on novel and investigational therapies to reduce death and disability caused by an acute ischemic stroke.

Reperfusion Strategies

Intravenous recombinant tissue plasminogen activator administered within 3 hours of stroke onset is the most widely used acute therapy, with an estimated treatment rate of 2% to 4%.[12] The narrow time window, concerns about a 5% to 6% rate of intracranial hemorrhage, and lack of medical infrastructure limit its wider use. Mechanical clot removal and other endovascular approaches, although technically feasible and successful, may not work in some cases, and clinical efficacy remains somewhat limited. The use of new technologies such as telemedicine and air ambulances has the potential to extend and expand the use of acute therapies, such as intravenous recombinant tissue plasminogen activator, to a wider rural population that may be somewhat remote from large acute-care hospitals.

Neuroprotection and Restoration of Neural Function

Advances in understanding the complex and multiple mechanisms of cerebral ischemic cell death via necrosis or apoptosis have led to neuroprotection strategies as one approach to reduce ischemic brain injury and improve outcomes. Many of these strategies use agents that target 1 or more mediators of neuronal damage, including excitatory neurotransmitters and their receptors, free radicals, secondary mediators of neuronal damage, temperature, hyperoxygenation, inflammation, and other potential targets. Despite much success in animal models, neuroprotective strategies and agents have shown little to no efficacy in large human trials. Several newer approaches and treatments, such as the administration of magnesium in ambulances, intravenous albumin, and oral statin therapies, appear promising and are undergoing clinical testing. Restorative and regenerative strategies to reduce the degree of injury/disability include the use of growth factors (neuronal and glial) and agents that may enhance plasticity, including enhancement of synaptogenesis, angiogenesis, stem cell transplantation, amphetamines, transcranial magnetic stimulation, and constraint-induced movement therapy, among others. The treatment of systemic factors such as fever and hyperglycemia may improve overall recovery, although supportive data from human trials remain weak.

Stroke Centers

The establishment and use of stroke centers and stroke systems of care may expand and extend the utilization of approved therapies in a safe and effective manner. The development and certification of stroke centers may improve outcomes through a variety of processes: (1) standardized treatment protocols and infrastructure, (2) stroke teams and stroke units, (3) concentration of experience in stroke care, (4) tracking of disease performance measures, and (5) improvement of outcomes through quality-improvement processes. Despite the limitations of some acute-care approaches, much work is being done in many areas in an attempt to identify new therapies and optimize the use of existing treatments.

Writing Group 5: Controversies in Carotid Artery Revascularization

Carotid artery disease is a major cause of ischemic stroke, the risk of which is directly related to the severity of stenosis and the presence of symptoms. Stroke is the third leading cause of death in the United States, with approximately three quarters of a million strokes per year, and it is the leading cause of

functional impairment, with >20% of survivors requiring institutional care and up to one third having a permanent disability.[13] It is estimated that carotid artery disease is responsible for 15% to 20% of all strokes.[14] The standard therapy for carotid artery revascularization is carotid endarterectomy (CEA), which is being compared with percutaneous carotid artery stent (CAS) placement in several patient subsets. Writing Group 5 focused on 3 current controversies: (1) carotid artery revascularization in asymptomatic patients, (2) CAS in patients who are at increased risk for complications of CEA, and (3) the current role for CAS in patients with average or routine surgical risk.

Carotid Artery Revascularization in Asymptomatic Patients

The prevalence of asymptomatic extracranial carotid stenosis (≥50%) in persons >65 years of age is estimated to be between 5% and 10%, and fewer than 1% of patients are thought to have a severe narrowing (>80%).[15] In asymptomatic patients with ≥50% carotid artery stenoses, the annual risk of stroke is between 1% and 4.3%.[16] The asymptomatic patients at highest risk of stroke are those with more severe or progressive carotid artery stenoses. The natural history risk of having a stroke approaches 5.5% per year in persons with an asymptomatic carotid stenosis of >75%.[17]

CEA in asymptomatic patients with hemodynamically significant stenoses (60% to 99%), if performed with an acceptable (≤3%) perioperative risk of stroke and death, reduces ipsilateral stroke but does not increase 5-year survival.[18,19] CAS is a catheter-based procedure that does not require general anesthesia and avoids the postoperative surgical morbidity (eg, cranial nerve injury, cervical wound hematoma, wound infection) associated with CEA. The most current trial data in asymptomatic patients demonstrate that the rate of periprocedural complications of disabling stroke and death due to CAS approaches 3%.[20] Writing Group 5 reviewed the controversy about which carotid artery revascularization procedure to recommend in asymptomatic patients. Evidence from clinical trials of asymptomatic patients with severe (≥80%) carotid artery stenosis indicates that CAS is not inferior to CEA, and therefore, that CAS is an option that may be considered in patients with either anatomic or medical comorbidities that make CEA undesirable.[21,22] Medical therapy alone may also be an acceptable option for some patients. When carotid artery revascularization is considered for asymptomatic patients at average surgical risk, CEA remains the procedure of choice. Data from ongoing randomized clinical trials will provide additional information on the role of CAS versus CEA in asymptomatic patients.

CAS for Patients at Increased Surgical Risk for CEA

Anatomic features that increase CEA risk include prior ipsilateral CEA; contralateral carotid occlusion; scarring after prior neck operations and/or radiation therapy; contralateral laryngeal nerve palsy; chronic tracheostomy stoma; spinal immobility; prior cervical spine surgery; short, obese necks; and intrathoracic or intracranial (above C2) lesion locations. Medical comorbidities, such as unstable angina, congestive heart failure, the concurrent need for heart surgery, and severe renal dysfunction, also increase CEA risk. The Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy (SAPPHIRE) trial was a multicenter, prospective, randomized, controlled trial that enrolled patients at increased risk of CEA complications.[22] The 30-day ipsilateral major stroke or death rate was virtually identical for CAS (2.6%) and CEA (2.5%), and the 1-year primary composite end point demonstrated statistically significant noninferiority for CAS (12.2%) compared with CEA (20.1%).

In patients with increased surgical risk for CEA due to either unfavorable anatomic characteristics or medical comorbidities, CAS offers an alternative treatment. Because it is a less invasive procedure, CAS should be considered an option for patients who are at increased risk for surgical complications of CEA.

Role of CAS in Patients With Average Surgical Risk

Along with optimal medical management, CEA is the established treatment for symptomatic and asymptomatic patients with high-grade extracranial carotid stenosis. Clinical trials continue to investigate the efficacy of CEA compared with CAS for the prevention of stroke in patients with average surgical risk. On the basis of the current clinical trial evidence, controversy remains with regard to risks versus benefits of CAS and CEA in patients with average surgical risk, but consensus exists that more data are required, particularly from randomized trials, to determine the optimal role of CAS in the population with average surgical risk.[23–25]

Recommendations

The following important issues related to carotid artery revascularization strategies to prevent stroke should be addressed: (1) Assessment of the stroke-reduction benefit of "modern medical therapy" (atherosclerotic risk factor modification, lifestyle modification, etc) compared with any revascularization strategy for stroke prevention is critical to the selection of any treatment strategy. (2) Knowledge gaps remain with regard to optimal stroke-prevention strategies in the elderly, in women, and in asymptomatic patients. As the risk of any revascularization strategy increases (elderly) or the margin of benefit narrows (women; asymptomatic individuals), the periprocedural complication rate and the patient's life expectancy must be factored into the treatment recommendation. (3) Although intuitive and broadly accepted, it remains to be proven that emboli protection devices reduce the risk of CAS periprocedural complications. Better strategies or more effective methods may exist for reducing the periprocedural stroke rate with CAS, including flow reversal with proximal occlusion devices as an emboli protection strategy. (4) The comparison of CEA and CAS is difficult and complicated on many levels. Nonrandomized studies are encumbered by the variability in patient subsets, differences in end-point definitions, changing standards of

medical therapy, and differences in reporting standards. Randomized trials of CAS and CEA, although confounded by the rapid evolution of devices, changes in technical strategies, and widely variable operator qualifications, are needed to determine the role of CAS, especially in the population with average surgical risk.

While acknowledging that more evidence needs to be gathered, clinicians must make decisions and recommendations on the basis of the current available evidence and must weigh the potential risks and benefits faced by their individual patients. CEA remains the revascularization treatment of choice for stroke prevention in patients with average surgical risk, with CAS offered only within a US Food and Drug Administration–approved clinical trial. Current evidence supports CAS as a reasonable option in patients who are at increased risk for surgical complications of CEA.

Writing Group 6: Controversies in Abdominal Aortic Aneurysm Repair

AAAs are the result of a progressive degenerative process characterized by elastin depletion and inflammatory changes of the aortic wall. The process leads to gradual enlargement and a localized weakening of the aorta, with eventual rupture. The normal aortic diameter varies with age, sex, and body size. An infrarenal abdominal aorta with a diameter >3 cm is considered to be aneurysmal. The risk of rupture increases directly with aneurysm size, and the death rate associated with rupture approaches 90%. Open surgical repair has been performed for more than 50 years and is considered to be the standard of care for patients with AAA but is associated with a risk of death and a high rate of complications. Patients with AAA, especially those with larger aneurysms at high risk of rupture, are usually elderly, and most have multiple comorbidities, which increases the risk of surgical treatment.

Over the past decade, endovascular aneurysm repair (EVAR) has been introduced as a less invasive treatment alternative for patients with AAA. Endovascular devices are approved by the US Food and Drug Administration and are available for suitable patients with infrarenal AAA. These devices can be inserted safely with low mortality rates; however, unanswered questions remain about the long-term durability, reintervention rate, and cost of these procedures. The task of Writing Group 6 was to review the evidence that compares open surgical and endovascular aneurysm repair of AAA and to address areas of controversy that need further investigation.

The decision to recommend open surgical repair is based on the size of the aneurysm and the estimated risk of rupture, balanced against the patient's medical risk, comorbidities, and risk of operative death. Patients with AAA now have a less invasive therapeutic option to avoid aneurysm rupture: endovascular repair. Still, endovascular repair requires that the patient's aneurysm meets well-defined anatomic selection criteria. The operative mortality rate is lower with EVAR than with open surgical repair for average-risk patients who meet anatomic selection criteria.[26,27] The AAA-related mortality benefit with EVAR is maintained for at least 4 years. In addition, EVAR is associated with significant reduction in postoperative morbidity and more rapid recovery.

Recommendations

On the basis of this evidence, we believe that EVAR is the preferred method of treatment for average-risk patients with AAA and suitable anatomy; however, EVAR requires long-term surveillance with imaging studies to determine endograft position, aneurysm size, and the presence or absence of endoleak. High-risk patients with large AAAs (>5.5 cm) who have anatomy suitable for endovascular repair can be treated successfully with EVAR. Patients with unsuitable anatomy for EVAR who are at high risk for surgery should undergo careful risk–benefit assessment to weigh the risk of rupture versus risk of open repair versus life expectancy. These patients should be monitored closely. If the risk of rupture increases to more than the risk of surgery (ie, the aneurysm enlarges, becomes painful or tender, or shows signs of rupture), open repair is recommended.

Writing Group 7: Lower-Extremity Revascularization: State of the Art

Percutaneous intervention for PAD has evolved from balloon angioplasty for simple focal lesions to multimodality techniques for treatment of severe arterial insufficiency. Writing Group 7 addressed the role of standard endovascular techniques (eg, balloons, stents) in the management of patients with acute or chronic critical limb ischemia. It also reviewed the role of drug-eluting stents, atherectomy devices, reentry catheters, and brachytherapy, as well as their potential complications and appropriate remedies. The problem of restenosis, particularly of the superficial femoral artery, was also addressed. Treatment algorithms for aortoiliac and infrainguinal disease are provided. Although few randomized, controlled trials are available to guide decisions for revascularization of peripheral arteries, treatment recommendations are made with the best level of evidence.

Acute Limb Ischemia

Acute limb ischemia is classified according to the Rutherford clinical categories (I, II, and III).[28] Patients with nonreversible limb ischemia should undergo amputation. All others should undergo arteriography with stratification by location of disease and ease of guidewire traversability to discern the best endovascular or surgical option. Initial catheter-directed thrombolytic therapy is recommended for patients who have ischemia of ≤14 days' duration or graft occlusions, and initial surgical revascularization is recommended for those with ischemia of >14 days' duration or native arterial occlusions.[1] Several issues should be considered for future investigation of acute limb ischemia. These include (1) the relationship between the duration, severity, and extent of ischemia and the time available for successful treatment; (2) objective markers for determining the severity of ischemia, to

better triage patients to appropriate and timely therapy; (3) prevention of reperfusion injury in limbs; and (4) quality-of-life assessment relative to catheter-based and surgical treatment.

Critical Limb Ischemia

Critical limb ischemia is usually caused by multilevel disease, which makes generalization of treatment difficult. The publication of the BASIL trial (Bypass versus Angioplasty in Severe Ischemia of the Leg), in which 1-year outcomes in patients with critical limb ischemia were similar with catheter-based and surgical revascularization, has stimulated interest in the endovascular treatment of these patients.[29] The complication rates for both endovascular and surgical treatments showcase the high-risk nature of this patient subset, making a strong argument in favor of minimally invasive therapy. Patients with extensive necrosis or infectious gangrene and those who are nonambulatory may best be served with primary amputation. Ambulatory patients with long occlusions or heavily calcified arteries who have adequate venous conduits are best served by surgical bypass. Conventional end points for surgical revascularization of patients with critical limb ischemia include primary patency rates of approximately 60%, a secondary patency rate of 78%, a survival rate of 84%, and a limb salvage rate of 88% at 1 year.[30]

Superficial Femoral Artery Disease

The treatment for superficial femoral artery disease remains controversial. Multiple strategies have been used to improve the long-term durability of superficial femoral artery disease treatment. Balloon angioplasty remains the standard, with placement of bare nitinol stents as either a primary or secondary treatment strategy. Atherectomy (rotational, directional, or ablative) has had variable results. Removal of plaque with these devices appears attractive; however, incomplete plaque removal, inability to control the depth of atherectomy, and distal embolization have limited the use of atherectomy. New catheters and wires have improved on the initial technical success rates for endovascular revascularization but have failed to minimize the risk of restenosis/reocclusion. Drug-eluting stents may offer an improved short-term benefit; however, long-term data are scant and unimpressive to date. There is no consensus for the treatment of superficial femoral artery in-stent restenosis.

Management of Access-Site Complications

Complications with percutaneous procedures occur most frequently at the access site. The initial management of suspected bleeding from the groin must include direct pressure by hand at the access site and aggressive fluid resuscitation. Most acute bleeding problems can be handled with endovascular techniques such as balloon tamponade or covered stents. Surgical intervention should be considered for tense or infected hematomas. Pseudoaneurysms can be treated with ultrasound-guided compression or direct thrombin injection. Acute ischemia of a limb can occur from distal embolization or thrombosis of the access site or treatment site. Medical therapy with aggressive anticoagulation or systemic thrombolysis will not be adequate in most cases. Percutaneous intervention with balloon angioplasty, stents, thrombectomy devices, and catheter-directed thrombolytic agents often can resolve ischemia rapidly. Surgical options should be available and used if endovascular techniques fail to resolve the ischemia.

Recommendations

Clinical investigations of catheter-based therapy for PAD should consider clinical end points in addition to arterial patency and limb salvage, such as short-term morbidity, long-term morbidity, procedural mortality, symptomatic improvement, limb salvage, quality of life, functional status, and the overall cost of primary and secondary procedures. Armed with this information, physicians can make objective decisions, and patients can be properly advised before a procedure.

Writing Group 8: Intervention for Renal Artery Disease

The primary goal of Writing Group 8 was to address current controversies related to interventions for renal artery disease and to recommend important areas for clinical research and advocacy. The 4 areas covered by this writing group include (1) management of asymptomatic renal artery disease, (2) treatment of ischemic nephropathy, (3) prevention and treatment of atheroembolism with renal artery interventions, and (4) treatment of renal in-stent restenosis.

Asymptomatic Renal Artery Disease: Indications for Treatment

Atherosclerotic renal artery disease may contribute to refractory hypertension, renal insufficiency, and increased cardiovascular mortality. It is important to note, however, that hypertension, renal insufficiency, and multisystem atherosclerosis are common independent entities; therefore, when evaluating patients with renal artery disease, physicians must distinguish between “association” and “causation.” It is impractical to categorize patients with renal artery disease as “symptomatic” or “asymptomatic,” because symptoms relevant to hypertension and renal insufficiency may not be present until end-organ damage or uremia occurs. Therefore, we propose a uniform grading system in clinical trial design and reporting. Grade I renal artery disease defines the presence of renal artery stenosis without clinical manifestations (normotensive and normal renal function). Grade II renal artery disease denotes renal artery stenosis in patients with medically controlled hypertension, normal or stable renal function, and no evidence of volume overload. Grade III renal artery disease denotes renal artery stenosis in patients with uncontrolled clinical symptoms, which include medically refractory hypertension, progressive renal dysfunction, or evidence of volume overload. Patients in grade II and III

categories have significant renal artery lesions (>60% diameter stenosis by quantitative analysis).

Available data do not establish an imperative for revascularization of renal artery stenosis. Therefore, all renal artery disease patients should undergo cardiovascular risk factor modification and monitoring for potential symptoms (eg, congestive heart failure or renal dysfunction). Given the absence of level I evidence supporting renal revascularization as therapy for hypertensive patients with renal artery disease, such patients should be considered for enrollment in CORAL.[31] This National Institutes of Health–sponsored trial will randomize >1000 hypertensive patients with >60% diameter renal artery stenosis to optimal medical therapy plus renal artery stent implantation or no renal artery stent. The incidence of composite cardiovascular and renal end points (death, stroke, myocardial infarction, doubling of serum creatinine, and hospitalization for congestive heart failure and renal revascularization therapy) will be determined over a 5-year period of follow-up.

Ischemic Nephropathy: Selecting Patients for Treatment

In some patients, high-grade renal artery stenosis may threaten renal function; however, it is difficult to establish the potential risks and benefits of revascularization in any individual patient. The predictable benefit of renal revascularization, however, may be most evident where the entire renal mass is affected—that is, both kidneys or a solitary kidney. The level of hypertension and the severity of the initial stenosis predict the risk of progression from a stenosis to occlusion. This risk approximates 50% over 5 years for stenotic lesions >60% at the time of initial detection.[32] Large-vessel atherosclerosis is frequently superimposed on microvascular disease related to chronic hypertension, aging, and diabetes, and this may explain why renal function fails to improve after successful stenting. Most patients with renal insufficiency who undergo stenting experience no appreciable change in their baseline creatinine (ie, stabilization), but they may benefit from the consequent improvement in blood pressure control and a reduced risk of developing volume overload.

Atheroembolization in Renal Interventions: Prevention and Management

Renal atheroembolization impairs renal function and may lead to end-stage renal disease and death. Preexisting renal insufficiency and longstanding hypertension are independent predictors of progression to end-stage renal disease when atheroembolization has occurred. Management of atheroembolization is palliative, and there are no established therapies to mitigate its consequences. As such, the proper technique for cannulation of the renal artery and placement of a stent (eg, "the no-touch technique") should be considered. Atheroembolization directly into the renal bed occurs at all stages of renal interventions and may be most pronounced during balloon predilation, before stent placement, and during stent deployment. The use of occlusion balloons or filters may reduce the incidence of distal atheroemboli and may minimize the potentially deleterious effects on renal function, but their efficacy has not been clearly established by randomized clinical trials.

Treatment of Renal In-Stent Restenosis

In-stent restenosis, defined either by duplex ultrasound or angiographic criteria, occurs in approximately 17% to 22% of patients within 12 months.[33,34] Vessel diameter <6 mm, female sex, smoking, longer stent lengths, and incomplete stent apposition are all associated with in-stent restenosis. Multiple therapies to address renal in-stent restenosis are available, including balloon angioplasty, repeat stenting, cutting balloons, lasers, and atherectomy. Balloon angioplasty remains an effective treatment, with patency rates at 6 to 11 months between 75% and 79%.[35,36] To date, no data are available on the use of statins, antiplatelet agents, oral antiproliferative agents, or warfarin to reduce the incidence of renal in-stent restenosis.

Recommendations

Renal artery stenting is widely available and frequently used to treat patients with renal artery stenosis and hypertension; however, it is still not known whether percutaneous revascularization adds incremental value to optimal medical therapy to prevent the adverse consequences of renal artery disease. Accordingly, Writing Group 8 recommends that physicians enroll hypertensive patients with atherosclerotic renal artery stenosis into the CORAL trial so that outcomes data necessary to answer some of the issues raised in this document can be acquired.

In patients with declining renal function due to ischemic nephropathy, when obstructive renal artery disease affects the entire renal mass, renal artery stenting can be expected to either improve or stabilize function in the majority of patients and to result in a reduction in risk of volume overload. However, this potential benefit must be weighed against the potential risk of worsening renal function due to procedure-related atheroembolization and/or contrast-induced nephropathy, other adverse events, and in-stent restenosis. Therefore, additional research in this area is recommended.

Proper catheter techniques, including paying close attention to atherosclerotic burden of the perirenal aorta, may reduce the risk of atheroembolism. Use of distal protection devices may reduce the incidence of atheroembolism; however, their efficacy should be tested in randomized clinical trials.

In-stent restenosis may be reduced by use of the shortest possible stent, dilated to its maximum but safe diameter (preferably to at least 6 mm) to effect good vessel-wall approximation. Once renal in-stent restenosis develops, balloon angioplasty appears to be as effective as any other intervention. The role of newer technology, devices, and medications is promising, but no data are available to support their routine use for the treatment of renal in-stent restenosis, and further investigation is recommended.

Disclosures

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*Modest.

†Significant.

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