Atherosclerotic Vascular Disease Conference
Writing Group V: Medical Decision Making and Therapy
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Atherosclerosis is a systemic disease with manifestations in multiple vascular beds. In each regional circulation, clinical events result from progression of the atherosclerotic lesion, superimposed thrombosis, and other dynamic processes, including ulceration, plaque rupture, intramural hemorrhage, fragmentation, and embolism. Evaluation and management of patients with atherosclerosis must be linked to these mechanisms, recognizing regional differences in natural history, morbidity, and effectiveness of therapeutic interventions. This section covers medical management of carotid artery disease, aortic disease, renal artery stenosis, and peripheral arterial disease.

Carotid Artery Disease
Stroke has multiple clinical manifestations that depend on the distribution and severity of neuronal damage. Among the most feared consequences of stroke are paralysis, aphasia, and dementia, all of which lead to loss of independence. Approximately 70% to 85% of all strokes are ischemic, and 15% to 30% are hemorrhagic.1,2 Ischemic strokes are the result of carotid artery stenosis, lacunar infarctions, cardiac embolism, or aortic atherosclerosis, or they may have no identifiable cause. Clinicians must understand the causes and mechanisms of stroke to institute effective measures for prevention.

The morphological features of carotid atherosclerotic plaque are similar in most respects to plaques found elsewhere and include a lipid-rich core and fibrous cap. Superimposition of thrombus often complicates carotid plaque and leads to cerebral emboli, causing stroke. In patients with asymptomatic carotid artery stenosis, the annual risk of stroke is 1.3% to 3.3%, with the highest rates in those with the greatest stenoses3–5; in symptomatic patients, annual stroke risk is 2% to 3% for those with transient monocular blindness and ≈4% for those with transient cerebrovascular ischemia manifested as hemiparesis, hemiparesthesia, or speech disturbance; in all symptomatic patients with carotid artery stenosis >70%, annual stroke risk increases to ≈15%.6

In the context of atherosclerosis, the presence of carotid artery disease identifies patients at increased risk for fatal and nonfatal myocardial infarction and stroke. For example, in the Cardiovascular Health Study, the 6-year risk of myocardial infarction or stroke was increased 3.6-fold to ≈40/1000 person-years in patients in the highest quintile of carotid intima-media thickness. Risk of stroke alone was increased 2.6-fold in patients in the highest quintile.7 Among stroke survivors, risk of death from another stroke is 18%, but ≈40% of survivors will die of other cardiovascular causes, notably myocardial infarction.8 To reduce the likelihood of stroke and death in patients with carotid artery disease, medical therapies should be implemented to modify atherosclerotic risk factors and inhibit thrombosis.

Risk Factor Modification
There is substantial evidence that antihypertensive, lipid-lowering, and antiplatelet therapies decrease stroke risk. In a meta-analysis of randomized, controlled trials, antihypertensive therapies, including diuretics and β-blockers, effectively lowered stroke risk by ≈40%.9,10 A reduction in diastolic blood pressure of 6 mm Hg produces a 42% reduction in incidence of stroke.9,11 ACE inhibitors also decrease the probability of stroke in high-risk populations, an effect that may be independent of the blood pressure–lowering potential of these agents. In the Heart Outcomes Prevention Evaluation (HOPE) study, the ACE inhibitor ramipril reduced stroke risk by 32% in patients at high risk because of coronary artery disease, cerebrovascular disease, peripheral arterial disease, or diabetes.12 In the Perindopril Protection Against Recurrent

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Stroke Study (PROGRESS), the ACE inhibitor plus a diuretic reduced risk of recurrent stroke by 43%.13

Secondary prevention trials in hypercholesterolemic patients with coronary artery disease have found that lipid-lowering treatment with statins reduced the risk of stroke.14 In the Scandinavian Simvastatin Survival Study (4S), simvastatin reduced risk of stroke by 23%;15 in the Cholesterol and Recurrent Events (CARE) trial, pravastatin reduced stroke risk by 32%;16 and in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, pravastatin reduced stroke risk by 19%.17 Similarly, in the West of Scotland Coronary Prevention (WOSCOP) study, a primary prevention trial of men with hypercholesterolemia, statin therapy reduced stroke risk by 19%.18 In the Heart Protection Study, which involved high-risk patients with atherosclerosis or diabetes and an average LDL cholesterol level of 131 mg/dL, simvastatin reduced stroke risk by 25%.19

Antiplatelet Therapy
Antiplatelet therapy is an established medical treatment for prevention of stroke in patients with atherosclerosis. A meta-analysis of 287 randomized trials of 135,000 high-risk patients found that antiplatelet therapy reduced risk of fatal and nonfatal stroke by 22%.20 In patients with prior stroke or transient ischemic attack, antiplatelet therapy reduced the risk of adverse cardiovascular events, including myocardial infarction, stroke, and vascular death, by 22%. Aspirin specifically reduced the risk of adverse cardiovascular outcomes by 23%. There was comparable efficacy in patients treated with doses of 500 to 1500 mg, 160 to 325 mg, and 75 to 150 mg.

The thienopyridine derivatives ticlopidine and clopidogrel also reduce risk of adverse cardiovascular events in patients with cerebrovascular disease.21-24 In the Ticlopidine Aspirin Stroke Study (TASS), which compared ticlopidine with aspirin,24 there was a 12% reduction in relative risk for nonfatal stroke or death in favor of ticlopidine. In the Clopidogrel Versus Aspirin for the Prevention of Recurrent Ischemic Events (CAPRIE) trial, there was a 7.3% reduction in risk of adverse cardiovascular events.21 In a systematic review of 4 trials including a total of 22,656 patients, 3 of which compared aspirin with ticlopidine and the other compared clopidogrel with aspirin, a 1% reduction in absolute risk was observed, as was a 9% odds reduction for adverse cardiovascular events and a 12% odds reduction for stroke in favor of the thienopyridines over aspirin.23

The European Stroke Prevention Study-2 compared low-dose aspirin (25 mg orally twice daily) with low-dose aspirin plus extended-release dipyridamole (200 mg twice daily) and found that combination therapy produced a 13% reduction in relative risk of stroke or death compared with aspirin alone.25,26 The Antithrombotic Trialists’ Collaboration analyzed 14 trials that compared aspirin plus standard dipyridamole with aspirin alone and found no difference between the 2 groups in reduction of risk of cardiovascular events.20 One trial of patients with ischemic stroke compared warfarin with aspirin and found no significant difference in risk of recurrent stroke or death between the 2 groups, but the rate of hemorrhage was higher in the warfarin group.27

Carotid Endarterectomy
Revascularization of the carotid artery is indicated in patients with significant carotid artery stenosis and relevant symptoms of cerebrovascular ischemia or nondisabling stroke, as discussed also in the next section on carotid revascularization. Three randomized clinical trials have found that carotid endarterectomy reduced the risk of ipsilateral stroke in patients with symptomatic carotid artery disease.28-30 All patients were treated with medical therapy that was considered optimal at the time the trials were conducted. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the 2-year risk of ipsilateral stroke was 9% for patients who underwent carotid endarterectomy and 26% for patients treated with medical therapy alone.28 In the European Carotid Surgery Trial (ECST), 3-year risk of ipsilateral stroke and perioperative death was 10.3% in patients who underwent carotid endarterectomy and 16.8% in patients who were treated medically.29 In the Veterans Affairs Cooperative Studies Program trial, which was terminated when the results of NASCET and ECST became available, stroke risk was 7.5% for patients who underwent carotid endarterectomy and 25.6% for patients treated with medical therapy alone.30

The use of carotid endarterectomy to treat patients with asymptomatic carotid stenosis remains controversial. One randomized trial compared carotid endarterectomy plus optimal medical therapy with optimal medical therapy alone in asymptomatic patients with carotid stenosis >60%.4 Five-year risk of ipsilateral stroke or perioperative stroke or death was 5.1% in patients who underwent surgery and 11% in those treated with medical therapy, accounting for a relative risk reduction of 53%. At the time this trial was conducted, optimal therapy did not include statins.

Summary
Patients with carotid atherosclerosis are at increased risk of stroke and other cardiovascular events, including myocardial infarction. Medical therapy should include risk factor modification such as optimal blood pressure control and lipid-lowering therapy with a statin, as well as antiplatelet therapy. Carotid endarterectomy plus medical therapy is more effective than medical therapy alone for patients with symptomatic severe carotid artery stenosis. The evidence favoring carotid endarterectomy for patients with asymptomatic carotid artery stenosis is less well established. The potential role of carotid stenting is discussed in the revascularization section of these proceedings.

Future research is needed to determine the role of screening methods such as carotid intima-media thickness, serial markers of inflammation, and activation of the coagulation system in assessing stroke risk; to identify appropriate candidates for carotid imaging in the absence of symptoms; and to define thresholds for and cost-effectiveness of risk factor interventions in patients at risk of stroke.

Aortic Diseases
Diseases of the aorta related to atherosclerosis include occlusive disease, aneurysm, dissection, intramural hematoma, and penetrating aortic ulcer. Medical decision making for aortic diseases must take into account natural history, clinical...
Aortic Aneurysm

Aortic aneurysms associated with atherosclerosis typically occur in the descending thoracic and abdominal aorta. Although a direct causal relationship between atherosclerosis and aortic aneurysms is not well established, there are common pathophysiologic features. These include molecular and cellular changes that perturb the aortic matrix such as increased levels of matrix metalloproteinases, particularly matrix metalloproteinase-9; interleukin-6; tissue plasminogen activator; and prostaglandin E2, as well as decreased production of elastin, collagen, tissue inhibitor of matrix metalloproteinases, and plasminogen activator inhibitor-1.34–36 Nonatherosclerotic causes of aortic aneurysms include inherited connective tissue disorders such as Marfan syndrome and Ehlers-Danlos IV syndrome; vasculitides such as Takayasu arteritis and giant cell arteritis; infections such as syphilis, tuberculosis, staphylococcus, and salmonella; and trauma. Aortic aneurysms may also develop at sites of chronic aortic dissection.

The average rate of growth of an aortic aneurysm is 1 to 4 mm per year.36,37 Predictors of growth include the size of the aorta at initial assessment, active smoking, and hypertension, a family history of aortic aneurysm in male first-degree relatives, and the presence of atherosclerotic disease in other vascular beds.34,35 Nonatherosclerotic causes of aortic aneurysms include inherited connective tissue disorders such as Marfan syndrome and Ehlers-Danlos IV syndrome; vasculitides such as Takayasu arteritis and giant cell arteritis; infections such as syphilis, tuberculosis, staphylococcus, and salmonella; and trauma. Aortic aneurysms may also develop at sites of chronic aortic dissection.

Management of small aortic aneurysms has been the subject of several recent investigations. The Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study and the United Kingdom Small Aneurysm Trial randomly assigned patients with abdominal aortic aneurysms that were 4.0 to 5.5 cm in diameter to elective surgical repair or surveillance.43–45 In each study, surgical repair was to be undertaken for aneurysms in the surveillance group that reached 5.5 cm in diameter or grew by >1 cm per year. In ADAM, 5-year mortality was not significantly different between the 2 groups. Similarly, the United Kingdom Small Aneurysm Trial found that elective repair of abdominal aortic aneurysms did not improve the 5-year survival rate compared with a surveillance strategy.46 The early surgery group had a 5-year mortality rate of 25.1% compared with 21.5% in the surveillance group. After 8 years of follow-up, a marginal benefit was observed in those who underwent early surgery.44 In the early surgery group, the mortality rate was 7.1/100 patient-years; in the surveillance group, it was 8.3/100 patient-years. This benefit was not an endorsement of the early surgery strategy, however, because long-term improvement in survival was related chiefly to lifestyle changes, specifically smoking cessation.

Comparable information derived from controlled trials is not available for thoracic aortic aneurysms. Current indications for surgery for thoracic aortic aneurysms are related to the presence of symptoms and size of the aneurysm. Relevant symptoms include chest or back pain attributable to the aneurysm, compression of contiguous structures, severe aortic regurgitation, and embolization. Surgical repair is recommended for ascending aortic aneurysms >5.0 to 5.5 cm, except in Marfan syndrome; for Marfan syndrome, the recommended indication is >4.5 cm. Surgical repair is recommended for aortic arch aneurysms >5.5 to 6.0 cm, descending thoracic aortic aneurysms >5.0 to 6.0 cm, and thoracoabdominal aortic aneurysms >5.0 to 6.0 cm.

Medical treatment for aortic aneurysms related to atherosclerosis includes therapies proved to reduce 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 growth. Antihypertensive therapy intuitively should reduce aneurysm growth by reducing wall tension, but no evidence exists to support this notion. β-Blocker therapy has been shown to reduce the rate of aortic root dilatation in patients with Marfan syndrome.46 One noncontrolled study reported that use of β-adrenergic blockers reduced the growth rate of large abdominal aortic aneurysms, but a randomized controlled study found no significant benefit and a reduction in quality of life with propranolol therapy.47,48 Patients with aneurysms of a size deemed not to merit immediate surgical intervention should undergo surveillance with ultrasound, CT, or MRI every 6 to 12 months; aortic aneurysm repair should be undertaken if size criteria are met or rate of growth is >1 cm per year.

Aortic Dissection

Predisposing factors for aortic dissection include age, hypertension, inherited disorders of connective tissue, bicuspid
aortic valve, aortic coarctation, and pregnancy. Atherosclerosis is not considered a predisposing factor for aortic dissection except in an iatrogenic event that is a result of catheterization or surgery. 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. The International Registry of Acute Aortic Dissection (IRAD) has reported an overall hospital mortality rate of 27% for patients with aortic dissection, underscoring the need for prompt diagnosis and treatment.49,50 Clinical suspicion of aortic dissection should be prompted by symptoms of abrupt onset of severe anterior chest or interscapular pain in the absence of any other obvious cause, particularly when accompanied by pulse deficits, neurological abnormalities, aortic regurgitation, and shock. Urgent diagnosis can be achieved with transesophageal echocardiography, MR angiography (MRA), and CT angiography (CTA). Sensitivity for transesophageal echocardiography is 88%; for MRA, 100%; and for CTA, 93%.51 The selection of imaging test to use depends on institutional availability and expertise, as well as the patient’s clinical status. Many patients require 2 imaging tests for accurate diagnosis and therapeutic planning.

Initial management of aortic dissection includes agents to reduce blood pressure and aortic shear stress, ie, dP/dt. This reduction can be accomplished with β-adrenergic blockers, often used in combination with other rapidly acting agents such as nitroprusside. Drugs are typically administered parenterally in the acute stages. In patients with type B (distal) aortic dissection, outcome is generally better with medical therapy than with surgical therapy. In IRAD, the overall hospital mortality rate for patients with type B aortic dissection treated with surgery was 31% compared with 11% for those who received medical therapy only.49,50 The converse is true for patients with type A (proximal) aortic dissection.49,50 In IRAD, the mortality rate for patients with type A dissection treated with surgery was 26% compared with 58% for those who received medical therapy only.49,50 Thus, surgery is indicated for acute type A aortic dissections and acute type B aortic dissections associated with rupture, rapid expansion, or vital organ or limb ischemia. Some advocate surgical treatment for patients with Marfan syndrome who have type B dissection.

Aortic intramural hematoma resembles aortic dissection in many respects, except that there is no identifiable intimal tear or visible connection between the intramural hematoma and the aortic lumen. Intramural hematomas may result from rupture of vasa vasorum or hemorrhage into an atherosclerotic plaque.52 Patients tend to be older and present in ways that are indistinguishable from those with classic aortic dissection.53 The imaging tests used to diagnose aortic intramural hematoma are the same as those used for suspected aortic dissection. Risk of rupture is ≈35%.54 The prognosis is worse for patients with intramural hematoma that is a complication of penetrating aortic ulcer and in those with large aortic diameters at the time of presentation.55 Indications for surgery are generally the same as those for aortic dissection, although some controversy exists.

A penetrating aortic ulcer is an ulceration of an atherosclerotic plaque that extends beyond the internal elastic lamina and into the aortic media.56 Penetrating aortic ulcers tend to occur in older persons with a heavy burden of atherosclerosis and occur predominantly in the mid to distal descending thoracic aorta. The natural history includes containment within the aortic media (intramural hematoma), formation of false aneurysms, or rupture. Risk of rupture is ≈40%.57 Diagnostic testing includes MRA, CTA, and conventional angiography. Treatment considerations include initial medical therapy for uncomplicated descending thoracic penetrating aortic ulcer and surgical repair or endovascular grafting for patients with false aneurysm or true rupture.55

Complex atherosclerotic lesions in the aorta are an important cause of stroke and peripheral embolism. Unfortunately, no data support the efficacy of either antiplatelet therapy or warfarin in reducing emboli originating in the aorta.

Summary
Atherosclerosis is more often associated with abdominal and descending thoracic aortic aneurysms than with ascending aortic aneurysms. There is a relationship between the size of aortic aneurysms and risk of rupture. Recent data suggest that surveillance is appropriate for patients with an abdominal aortic aneurysm 4.0 to 5.5 cm in diameter, but many will require repair within 5 years because of expansion. Surgical or endovascular repair is indicated in most patients with abdominal aortic aneurysms ≥5.5 cm in diameter unless high-risk comorbid conditions exist. Surgical repair outcomes are vastly better when surgery is performed before symptom onset. There is a positive relationship between surgical case volume and outcome in patients undergoing abdominal aortic aneurysm repair.58 In addition, endovascular repair of abdominal aortic aneurysms has demonstrated good short- and mid-term results with regard to aneurysm-related deaths; however, the need for secondary interventions may be as high as 12% per year over 3 years.59,60 Acute aortic syndromes include dissection, intramural hematoma, and penetrating aortic ulcer. Prompt diagnosis and treatment will reduce morbidity and mortality from these conditions.

Future research is needed to better define the diameter-risk relationship of aortic aneurysms on the basis of gender, race, and body size; to identify target populations for abdominal aortic aneurysm screening programs; to find novel medical therapies to reduce rate of expansion and rupture of aortic aneurysms; to better define the size threshold for repair of thoracoabdominal aortic aneurysms; and to determine the best method for detection, characterization, and treatment of complex aortic atheroma.

Renal Artery Stenosis
Renal artery stenosis has 2 principal clinical manifestations: hypertension and ischemic nephropathy. Although renovascular hypertension occurs as a consequence of activation of the renin-angiotensin-aldosterone pathway, hypertension associated with atherosclerotic renal artery stenosis is not usually renin dependent. Ischemic nephropathy results from a loss in glomerular filtration, leading to excretory dysfunction. Medical decisions to diagnose and treat renal artery stenosis depend on a high index of clinical suspicion, confirmation of diagnosis with appropriate imaging techniques, establishment
of a relationship between renal artery stenosis and either hypertension or renal insufficiency, and a likelihood of clinical benefit resulting from medical therapy or revascularization.

Clinical features that suggest renal artery stenosis are abrupt onset of hypertension in persons ≥50 years of age, an accelerated or a marked rise in blood pressure level over the patient’s usual measurement, malignant hypertension, or hypertension refractory to ≥3 antihypertensive drugs. Supportive findings include the presence of an abdominal or flank bruit on physical examination, unexplained congestive heart failure, the presence of atherosclerotic disease affecting other circulations, and unexplained hypokalemia. Manifestations of ischemic nephropathy include elevated creatinine level, a rise in creatinine after institution of an ACE inhibitor or angiotensin receptor blocker, and small kidney size detected during imaging.

Diagnostic studies to assess renal artery stenosis may be broadly categorized as physiological assessment or imaging examinations that define renovascular anatomy. Physiological tests include peripheral plasma renin activity, captopril-simulated plasma renin activity, renal vein renin activity, and captopril renal scintigraphy. Unfortunately, the predictive value for measures of plasma renin activity to identify atherosclerotic renal artery stenosis is low because these measures may be influenced by medications or other medical conditions and because hypertension is generally not renin dependent. Although the sensitivity and specificity of captopril renal scintigraphy are both >90%, it is heavily influenced by renal parenchymal disorders and obstructive uropathy and is therefore not a practical screening test. When there is a high index of clinical suspicion, an imaging study should be used to confirm the diagnosis of renal artery stenosis. These techniques, including renal duplex ultrasonography, MRA, and CTA, are reviewed in detail in the previous section. Invasive contrast angiography is indicated to confirm diagnosis and to provide additional anatomic information such as the presence of aortic occlusive or aneurysmal disease, accessory renal arteries, and the extent of intrarenal vascular disease if a revascularization procedure is planned.

Treatment

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 involves the use of drugs such as ACE inhibitors and angiotensin receptor blockers to inhibit the renin-angiotensin system, and these agents are highly effective for achieving blood pressure control. Additional agents may be necessary to reach the target blood pressure goal. It is important to note that drugs that interfere with the renin-angiotensin system may decrease perfusion and filtration of the kidney affected by renal artery stenosis. Although these changes in renal perfusion and filtration function are unlikely to adversely affect global renal function in a patient with unilateral renal artery stenosis or with a small, poorly functioning kidney that is still producing renin, patients with bilateral renal artery stenosis may develop renal insufficiency because filtration function of both kidneys may deteriorate after initiation of an ACE inhibitor or angiotensin receptor blocker.

Unfortunately, most studies suggest that renal artery revascularization for treatment of atherosclerotic renal artery stenosis rarely cures hypertension; cure rates of percutaneous transluminal angioplasty, stenting, and surgery range from 6% to 21%. In ≈30% of cases, there is no improvement in blood pressure. The failure of renal artery revascularization to significantly modify blood pressure in some patients depends on several factors. Underlying essential hypertension may contribute to the development of atherosclerosis, and renal artery stenosis may be another manifestation of generalized atherosclerosis. Renal artery revascularization would not be expected to improve essential hypertension. Also, patients with intrarenal vascular disease or renal parenchymal disease may have persistent activation of renin-angiotensin system activity despite renal artery revascularization. Predictors of improvement in blood pressure after revascularization of atherosclerotic renal artery stenosis include a baseline mean blood pressure >110 mm Hg, a lateralizing renal nuclear medicine study, and bilateral renal artery stenosis.

Studies to assess the effect of renal artery revascularization on renal function have generally been conducted in patients who underwent the procedure for management of hypertension. After surgical and percutaneous revascularization, creatinine remains stable or improves in >70% of patients and deteriorates in the remainder. Factors that contribute to the lack of benefit include the presence of irreversible renal parenchymal disease, distal embolization, contrast-induced nephropathy, and acute tubular necrosis. A measure of underlying renal parenchymal disease or small-vessel, intrarenal vascular disease is the renal resistance index. This index is useful for identifying patients who are likely to improve after revascularization. In patients with a renal resistance index of <80, there is a high probability of >10 mm Hg reduction in blood pressure and stabilization of creatinine clearance. In contrast, if the renal resistance index is >80, no improvement in blood pressure and worsening renal function are likely after renal revascularization because of preexisting renal parenchymal disease.

Medical decisions should consider the relative benefits and risks of continued medical therapy versus renal revascularization. The latter is favored in patients who have bilateral renal artery stenosis and a serum creatinine level >1.5 mg/dL, unilateral renal artery stenosis and fractional glomerular filtration rate ≤40%, ACE inhibitor–induced renal failure, hypertensive crisis, and nonischemic pulmonary edema. Medical therapy is favored over renal revascularization in patients with unilateral renal artery stenosis and serum creatinine level ≥2.5 mg/dL, renal length <7 cm, proteinuria >1 g/d, severe diffuse intrarenal vascular disease, and target kidney renal resistance >80, all of which provide evidence of underlying advanced nephropathy.

Summary

Renal artery stenosis is prevalent and associated with hypertension and renal insufficiency. Candidates for screening include patients with accelerated hypertension or new-onset
hypertension after 50 years of age, azotemia after administration of an ACE inhibitor, and unexplained recurrent congestive heart failure. The effect of medical therapy and/or revascularization on the natural history of renal artery stenosis, blood pressure, and renal function is poorly defined. Thus, there is a need to establish indications and optimal timing for revascularization, to identify biochemical markers to detect renal injury during interventions, and to identify the best technique to monitor patients after revascularization.

Peripheral Arterial Disease

Medical decision making and management of patients with peripheral arterial disease must take into consideration 2 cardinal precepts. The first is that peripheral arterial disease is a marker of systemic atherosclerosis, and affected patients frequently have coexisting coronary artery disease and cerebrovascular disease. As a result, they are at increased risk for myocardial infarction, stroke, and death. Second, patients with peripheral arterial disease frequently have impaired functional status as manifested by decreased walking speed or distance, intermittent claudication, or critical limb ischemia manifested as rest pain or skin ulcerations threatening limb viability. Therefore, management of these patients must use therapeutic strategies that decrease risk of adverse cardiovascular events, reduce mortality, improve functional status and quality of life, and preserve limb viability.

Therapies should be implemented to reduce adverse cardiovascular outcomes, including lifestyle changes, risk factor modification, and use of antiplatelet drugs. Cigarette smoking is 1 of the most important risk factors for development and progression of peripheral arterial disease. Smoking cessation reduces risk of myocardial infarction and death in patients with peripheral arterial disease. In addition, smoking cessation reduces risk of progression to critical limb ischemia and limb loss. Beneficial effects of lipid-lowering therapy, particularly with statins, have been derived from 4 large clinical trials. Three trials focused on patients with coronary artery disease and found that statin therapy reduced the risk of nonfatal myocardial infarction or death resulting from coronary artery disease by 24% to 34%. The Heart Protection Study found that lipid-lowering therapy with a statin reduces risk of adverse cardiovascular events and death in patients with coronary artery disease to reduce the LDL cholesterol level to <100 mg/dL.

Hypertension is a risk factor for peripheral arterial disease and increases risk of stroke, coronary artery disease, congestive heart failure, and chronic renal insufficiency. Antihypertensive therapy reduces the risk of these adverse cardiovascular outcomes. Therefore, patients with peripheral arterial disease and hypertension should be treated to the target levels recommended by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. It is important to emphasize that β-adrenergic blockers are not contraindicated in patients with peripheral arterial disease. Indeed, these drugs not only lower blood pressure but also reduce the risk of myocardial infarction and death in patients with coexisting coronary artery disease and prior myocardial infarction. ACE inhibitors also favorably improve cardiovascular outcome in patients with atherosclerosis. The HOPE study found that the ACE inhibitor ramipril decreased risk of myocardial infarction, stroke, and cardiovascular death by 22% in patients with coronary and noncoronary atherosclerosis, including >4000 persons with peripheral arterial disease.

Diabetes mellitus is also recognized as 1 of the most important risk factors for development and progression of peripheral arterial disease. It is well established that aggressive glucose control reduces risk of microvascular events such as retinopathy and nephropathy in patients with type 1 or 2 diabetes mellitus. Unfortunately, the evidence that aggressive glucose control reduces risk of macrovascular outcomes is less compelling. A retrospective analysis of the Diabetes Control and Complications trial found that compared with standard insulin therapy, intensive insulin therapy resulted in a 42% reduction in risk for cardiac and peripheral events, an observation that was not statistically significant, perhaps because of inadequate power. In the UK Prospective Diabetes Study of patients with type 2 diabetes mellitus, optimal treatment with insulin or sulfonylureas caused only a borderline-significant reduction in incidence of myocardial infarction. There was a nonsignificant 35% reduction in risk of amputation or death from peripheral arterial disease with aggressive glucose control. The efficacy of treating other atherosclerotic risk factors associated with peripheral arterial disease is not established. Hyperhomocysteinemia, for example, is an independent risk factor for peripheral arterial disease. Clinical trials are ongoing to determine whether B-complex vitamins such as folic acid that reduce homocysteine levels are effective in reducing adverse cardiovascular events in patients with hyperhomocysteinemia and atherosclerosis, including those with peripheral arterial disease. Antiplatelet therapy reduces risk of cardiovascular events in patients with atherosclerosis. The Antithrombotic Trialists' Collaboration involved 42 trials and 9716 patients with peripheral arterial disease. Among those treated with antiplatelet therapy, there was a 23% odds reduction for adverse cardiovascular events, including myocardial infarction, stroke, or vascular death. The CAPRIE trial, which compared the efficacy of 325 mg of aspirin per day with 75 mg of clopidogrel per day, included 6452 patients with peripheral arterial disease. In this subgroup, clopidogrel reduced risk of myocardial infarction, stroke, and vascular death by 24%. The efficacy of combination therapy with aspirin and clopidogrel is currently under investigation in a large clinical trial.

The efficacy of oral anticoagulants in reducing adverse cardiovascular outcome in patients with atherosclerosis has been examined in a meta-analysis that comprised primarily trials of patients with coronary artery disease. Compared with placebo, oral anticoagulants reduced risk of adverse cardiovascular events but was associated with a significantly increased risk of major bleeding. One trial in patients with peripheral arterial disease compared the efficacy of a warfarin derivative with aspirin on infrainguinal graft patency in patients with peripheral arterial disease. There was no significant difference between the 2 groups in the composite
secondary end point of vascular death, myocardial infarction, stroke, or amputation.

Therapies that improve functional capacity in patients with intermittent claudication are broadly categorized as 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% in patients with claudication. The greatest efficacy was achieved when rehabilitation involved exercise sessions of 30 minutes at least 3 times per week.

Cilostazol is a phosphodiesterase III inhibitor that improves treadmill time and quality of life in patients with intermittent claudication. Although it has vasodilator and platelet-inhibitory properties, its precise mechanism of action is not known. In a meta-analysis of 6 prospective trials, cilostazol improved pain-free walking distance by 36% and maximal walking distance by 38%.

Pentoxifylline, a methylxanthine derivative, is also available for treatment of patients with intermittent claudication. This hemorheologic agent decreases blood viscosity and increases erythrocyte deformability. Several clinical trials have found that pentoxifylline improves pain-free and maximal walking distances by 30% and 20%, respectively. One trial compared pentoxifylline, cilostazol, and placebo and found that cilostazol improved pain-free and maximal walking distances compared with placebo, but pentoxifylline did not.

To ameliorate symptoms and prevent limb loss, revascularization procedures are indicated for patients with disabling claudication or critical limb ischemia. The indications and results of catheter-based and surgical revascularization are discussed in the next section.

Summary
Peripheral arterial disease is a common manifestation of atherosclerosis that is easily detected by use of the ankle-brachial index. Peripheral arterial disease impairs functional capacity, even in the absence of classic symptoms of intermittent claudication and critical limb ischemia. The risk of myocardial infarction, stroke, and death is substantially increased in patients with compared with those without peripheral arterial disease. Risk factor modification and antiplatelet therapy reduce risk of ischemic events in patients with peripheral arterial disease. Exercise rehabilitation includes walking capacity in patients with intermittent claudication caused by peripheral arterial disease. Cilostazol is also useful for improving walking distance in patients with intermittent claudication. 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.

There is a need to determine the efficacy of intensive glucose control and lipid-lowering therapy to reduce progression of peripheral arterial disease; to find more effective pharmacotherapies for patients with intermittent claudication and critical limb ischemia; and to further define when medication, endovascular therapy, or bypass surgery is most appropriate in patients with symptomatic peripheral arterial disease.

These conference recommendations do not necessarily represent official AHA policy. However, the ACC/AHA Task Force on Practice Guidelines initiated development of a clinical practice guideline for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). Several participants in this conference serve on the writing committee for that guideline, which should be published late in 2004.

Recommendations

AHA Program Initiatives
- Develop educational programs to enhance risk factor modification programs aimed at noncoronary atherosclerosis.
- Promote broad-based rehabilitation and secondary prevention programs that include exercise, smoking cessation, dietary modification, lipid lowering, and diabetes management for patients with atherosclerosis.
- Create database registries that incorporate the varied manifestations of systemic atherosclerosis, including carotid, aortic, renal artery, and limb atherosclerosis.
- Publish ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic).
- Promulgate focused research funding addressing noncoronary atherosclerosis.

Research Initiatives
- Assess the cost-effectiveness of interventions for acute stroke management.
- Define the size thresholds for repair of thoracic aortic aneurysms.
- Assess the impact of medical therapy (eg, blood pressure control) on rates of expansion of aortic aneurysms.
- Define the population likely to benefit from endovascular treatment of renal artery stenosis in terms of blood pressure, renal function, and mortality.
- Assess the long-term outcomes of medical therapy with and without catheter-based interventions for patients with intermittent claudication.

Advocacy Priorities
- Encourage federal allocation of funds to support clinical trials of treatment for atherosclerotic vascular disease.
- Explore coalescence of resources for urgent care of patients with acute ischemic syndromes (myocardial infarction, stroke, limb ischemia).
- Foster intersocietal initiatives to enhance identification and management of atherosclerotic vascular disease.

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