Peripheral Arterial Disease: Update of Overview and Treatment

Todd C. Schirmang, MD, Sun H. Ahn, MD, Timothy P. Murphy, MD, Gregory J. Dubel, MD, Gregory M. Soares, MD

Peripheral arterial disease (PAD) is widely used to describe a common disease process in which blood flow to the lower extremities is impaired as a result of atherosclerotic occlusive disease. PAD, an under-diagnosed and under-treated disorder with substantial morbidity and mortality, affects up to 10 million people in the United States. The pathophysiology of peripheral arterial disease and the risk factors for developing PAD are similar to those for atherosclerotic disease occurring at other sites. Risk factors include cigarette smoking, diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia. Peripheral arterial disease can be diagnosed by performing a directed history and physical examination and using a relatively simple, noninvasive screening test, the ankle-brachial index, which measures the severity of the disease and provides valuable prognostic information. Treatments for PAD include medical therapy and endovascular or surgical revascularization. Optimal medical therapy includes claudication pharmacotherapy, participation in a supervised exercise program, tobacco cessation, and modification of treatable risk factors. Patients with lifestyle-limiting claudication who do not respond to medical management or those with critical limb ischemia should be referred to a vascular specialist for potential revascularization.

Epidemiology

Approximately 10 million Americans are affected by PAD and as many as 3 million experience claudication, its primary lower extremity ischemic symptom.[1] The estimated prevalence of PAD in people older than 70 years is between 14% and 29%.[2,3] In addition, PAD is an important manifestation of systemic atherosclerosis, associated with increased rates of cardiovascular ischemic events and death.[1-3] The prevalence of both PAD and claudication increases with age and exposure to common risk factors, and this prevalence is increasing. In the Framingham Heart Study, the annual incidence of **intermittent claudication (IC)** in people younger than 44 years was 6 cases per 10,000 person-years in men and 3 cases per 10,000 person-years in women. In people older than 65 years, the annual incidence increased 10 fold, to 61 cases per 10,000 person-years in men and 54 cases per 10,000 person-years in women.[4]

Only 10% of patients with PAD have IC, the classic symptom that manifests as a cramping pain in the legs that is induced by exercise and is relieved with rest. Approximately 50% of patients with PAD have atypical lower-extremity symptoms and 40% are asymptomatic.[5] The heterogeneity of clinical presentations may explain why PAD is under-diagnosed and treated in only 25% of affected patients.[6] However, all patients with PAD, whether classic ischemic leg symptoms are present or not, have limited physical activity, impaired walking speed and endurance, and functional decline.[3] Left untreated, PAD can lead to limb amputation.

PAD is a strong predictor of systemic atherosclerosis and is considered a **coronary artery disease (CAD)** risk equivalent.[7,8] PAD is associated with a fivefold increased risk of heart attack and a two- to threefold greater risk of stroke and total mortality.[7] The 10-year risk of death in people diagnosed with PAD is 40% and has remained largely unchanged since 1950.[9] After multivariate adjustment for age, sex, and other risk factors for cardiovascular disease, patients with PAD had a 3-fold higher risk of all cause death and a 6-fold higher risk of cardiovascular-related death than patients without PAD.[10] The international REACH registry recently evaluated cardiovascular outcomes in more than 68,000 individuals and demonstrated that one in five patients with PAD will suffer a heart attack or stroke, be hospitalized, or die due to cardiovascular events within 1 year.[7] In patients with PAD, the combined rates of heart attack, stroke, and hospitalization are equal to or greater than the rates of those with established coronary artery disease.

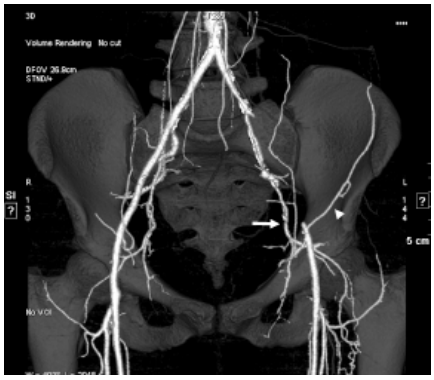

Figure 1a.

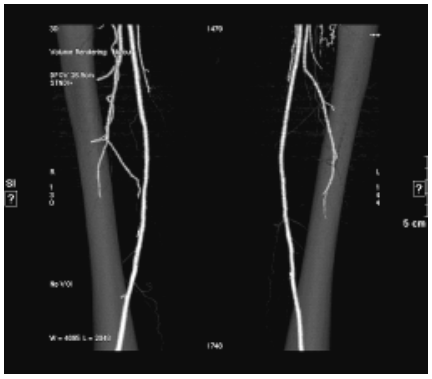

Figure 1b.

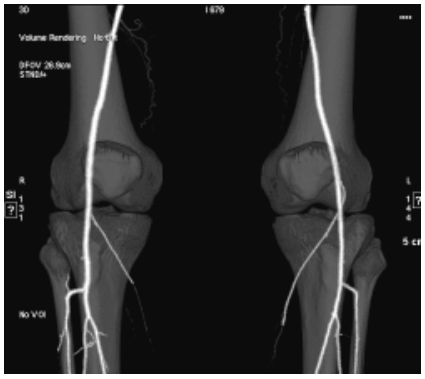

Figure 1c.

Figure 1. 60 year-old female with left thigh and calf claudication. (**a**) Volume-rendered 64–detector row CT angiogram frontal maximum intensity projection (MIP) image at the level of the pelvis shows a chronic long segment occlusion of the left external iliac artery with reconstitution of the left common femoral artery from internal iliac (arrow) and circumflex iliac artery (arrowhead) collaterals. Normal vessels are present on the right. (**b**) Bilateral superficial femoral arteries are normal. (**c**) Bilateral distal arteries in the calves were normal as well.

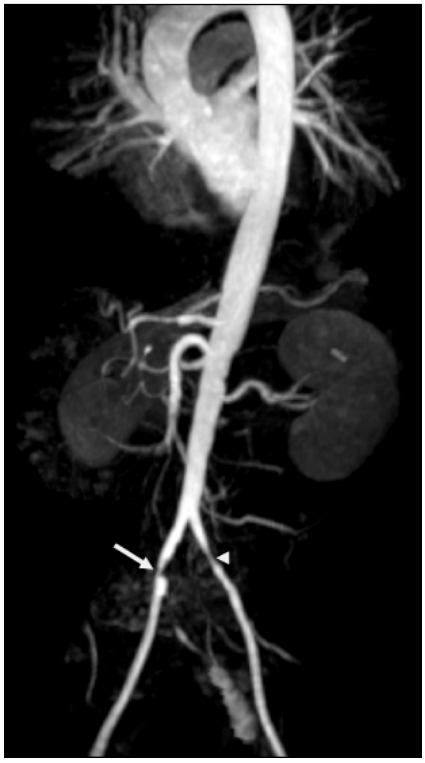

Figure 2. 66 year-old female with bilateral lower extremity claudication. Composite image of coronal oblique maximum intensity projections from a 3D gadolinium-enhanced MR angiogram examination demonstrates short segment stenoses of the right (arrow) and left (arrowhead) common iliac arteries. Internal iliac arteries are not well visualized on this image. Patent aorta, external iliac, renal, celiac, and mesenteric arteries.

Risk Factors

According to the third National Health and Nutrition Examination Survey, the prevalence of PAD increases with tobacco use, African American ethnicity, diminished renal function, diabetes mellitus, and hypercholesterolemia.[2] The risk of PAD progressing **to critical limb ischemia (CLI)** has also been shown to increase under the following conditions: ABI less than 0.7, age greater than 65 years, use of tobacco, and hypercholesterolemia.[3] Several biomarkers, including **C-reactive protein (CRP)**, lipoprotein(a), homocysteine, and D-dimer, have been shown to be associated with the development of systemic atherosclerosis.[11] High levels of some of these inflammatory biomarkers are also predictive of increased short-term mortality.[12]

Clinical Features

A careful history and examination will generally distinguish **intermittent claudication (IC)** from nonvascular causes that may mimic claudication (pseudoclaudication). The patient's lower legs and feet should be examined with shoes and socks off, with attention to pulses, hair loss, skin color, and trophic skin changes.

Clinicians should have a high index of suspicion for PAD, especially in patients who report lower-extremity pain and have diminished pulses, hair loss, or extremity coolness. Although patients with PAD are often asymptomatic, the classic presenting symptom of PAD is IC, a cramping leg pain that is induced by exercise and relieved with rest. Skin pallor occurring after passive elevation of the foot and/or dependent rubor (the onset of erythema after lowering the leg from an elevated position) are also signs suggestive of PAD. A diagnosis of PAD should be considered in patients who report muscular pain in the legs, especially if they belong to known high-risk groups, such as people older than 70 years, African American ethnicity, patients with diabetes or hyperlipidemia, smokers, and those with impaired renal function. The diagnosis can be confirmed in most persons by a noninvasive vascular ultrasound examination, which includes measurement of the ankle-brachial index.

Intermittent Claudication

IC is classically described as fatigue, discomfort, or pain that involves specific limb muscle groups during exertion due to exercise-induced ischemia. The symptom location often indicates the level of arterial involvement, with disease typically occurring at a level above the area of pain. For example buttock or thigh pain is often seen in patients with distal aortic or iliac artery occlusive disease. Health care professionals should be aware that the diagnosis of PAD can often be missed by relying only on clas-

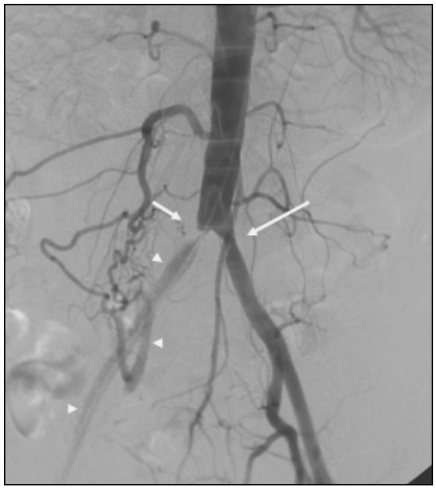

Figure 3a.

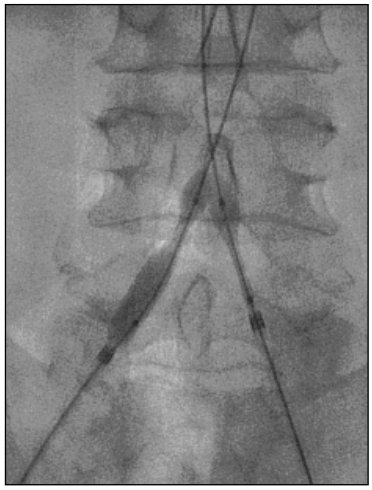

Figure 3b.

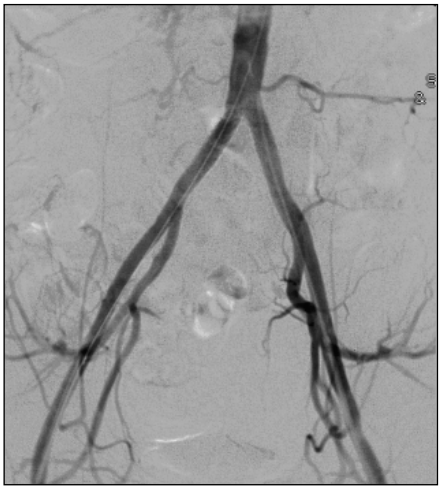

Figure 3c.

Figure 3. 52 year-old male with lifestyle altering right buttock and thigh claudication. His risk factors for PAD include smoking and hyperlipidemia. ABIs measured 0.71 on the right and 0.96 on the left. (**a**) AP image from a pelvic arteriogram shows a severe stenosis of the right common iliac artery origin (short arrow) with a moderate stenosis of the left common iliac artery origin (long arrow). There is delayed filling of the right iliac arteries (arrowheads) compared with the left. (**b**) Fluoroscopic image shows deployment of the bilateral common iliac artery stents. (**c**) Post stent placement arteriogram demonstrates technical success with no residual stenoses. Post procedure ABIs remain normal 4 years post treatment, 1.06 on the right and 1.08 on the left.

sical symptoms of claudication because the majority of patients with PAD are asymptomatic or have atypical symptoms.

Critical Limb Ischemia

When PAD progresses from IC to severe impairment of blood flow to the lower extremity due to arterial stenosis and occlusion, an individual is considered to have **critical limb ischemia (CLI).** CLI manifests clinically as persistent ischemic pain at rest that may lead to non-healing foot ulceration or gangrene. The pain may improve when the leg is in a dependent position and is exacerbated when it is elevated. While more commonly a chronic condition, limb ischemia may also occur acutely, typically as a result of embolism or thrombotic occlusion. A resting ABI value less than 0.4 strongly supports the diagnosis of CLI. CLI can be caused by a number of other disease entities, such as thromboembolism and vasculitis. Because CLI usually requires mechanical revascularization, referral to a vascular specialist is recommended.

Diagnosis

Ankle-Brachial Index

Calculation of the ankle–brachial index is recommended as the initial screening test. This relatively simple, inexpensive, noninvasive test can quantify the severity of PAD and also predict the risk of future cardiovascular events.[2] A recently published meta-analysis suggests that the ABI is a more accurate predictor of an individual's risk of future myocardial infarction or stroke than the traditional predictve method, the Framingham risk score.[13] An abnormal result (0.9 or less) is sufficient to make the diagnosis of PAD in the appropriate clinical setting. When the disease is suspected on the basis of clinical observations but the resting ABI is normal, the ABI should repeated after exercise. Options include toe raises (standing flat-footed and raising the heels off the ground repeatedly) or walking on a treadmill. These patients may have normal resting blood flow, but in the setting of exercise and associated vasodilation, pressure gradients develop across the areas of stenosis, leading to symptoms and an abnormally low value for the ankle–brachial index.

ABI values between 1.0 and 1.4 are normal. Values between 0.9 and 1.0 are borderline, usually occurring in asymptomatic individuals. Patients with claudication typically have ABI values ranging from 0.50 to 0.90, while those with CLI have values of 0.40 or less. An ABI greater than 1.40 suggests poorly compressible, calcified arteries, typically seen in those with diabetes or chronic renal failure. When the resting ABI is combined with exercise treadmill testing, functional capacity can also be assessed. The distance walked can then serve as a baseline functional capacity measure that can assist with future comparisons after either conservative or invasive PAD treatments. If the diagnosis of PAD is uncertain or if revascularization is being planned, imaging with duplex ultrasound, **computed tomographic angiography (CTA),** or **magnetic resonance angiography (MRA)** may be useful.

...the diagnosis of PAD can often be missed by relying only on classical symptoms of claudication because the majority of patients with PAD are asymptomatic or have atypical symptoms.

Computed Tomographic Angiography and Magnetic Resonance Angiography

Both CTA and MRA can localize and quantify arterial stenosis in patients being considered for revascularization. Both CTA and MRA obtain images of vascular structures in cross-section that can be reformatted into three-dimensional angiographic images. (Figure 1) In general, CTA is considered to have better spatial resolution than MRA. (Figure 2) However, with the ongoing development of new MR scanning protocols and as experience with MRA increases, its accuracy may approach that of CTA or contrast angiography.[13] In a randomized trial comparing MRA with CTA for imaging of peripheral arterial disease, the two techniques were found to be roughly similar in terms of diagnostic accuracy, ease of use, and clinical outcome, but total diagnostic costs were lower for CTA.[14]

CTA exposes the patient to iodinated contrast material and radiation, whereas the more expensive MRA does not carry these risks. Because of the possibility of inducing contrast-induced nephrotoxicity, CTA is relatively contraindicated in patients with decreased renal function. In general, MRA cannot be performed in patients with implanted devices such as pacemakers, defibrillators, and metallic aneurysm clips. Gadolinium, the contrast agent used for MR angiography, recently has been linked to development of **nephrogenic systemic fibrosis (NSF)**, especially in patients with a GFR less than 30 mL/min or those receiving long-term dialysis.[15] At our institution, CTA is the preferred noninvasive imaging method; MRA is used when CTA is contraindicated.

Catheter Angiography

The gold standard for diagnosis and evaluation of PAD is catheter-based **digital-subtraction angiography (DSA)**, which can confirm or exclude PAD and can also be used for treatment if appropriate. Angiography can determine the location and severity of stenotic lesions and estimate the degree of calcification. If the stenosis is amenable to percutaneous revascularization, such procedures often can be performed in the same setting. Serious complications of this procedure, which are infrequent, include allergic reactions to the contrast material, bleeding, contrast induced nephropathy, and vessel dissection, thrombosis, or embolization. Alternative contrast agents, such as carbon dioxide, can be used in patients with limited renal function or those with allergies to iodinated contrast material.

Treatment

Risk Factor Modification

Peripheral arterial disease is a strong predictor of systemic atherosclerosis and is considered a CAD risk equivalent.[7,8] Therefore, optimization of cardiovascular risk factors is essential for prevention and management of PAD. Conservative treatment options include cessation of tobacco use, medication therapy, participation in a supervised exercise program, and control of high blood pressure and blood sugar and cholesterol levels.

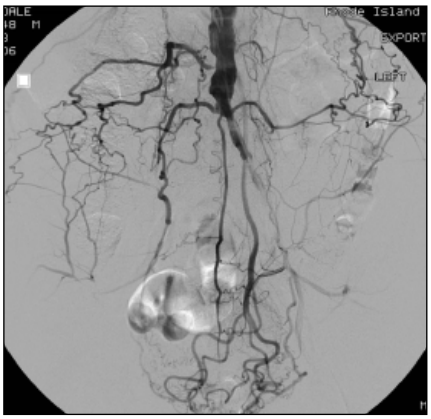

Figure 4a.

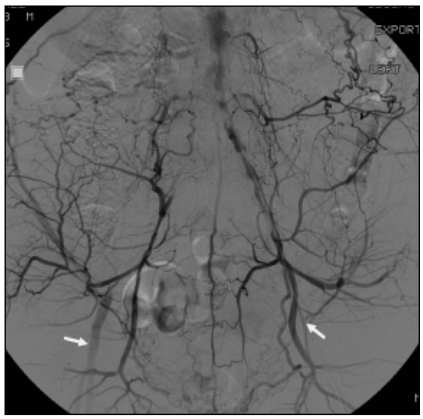

Figure 4b.

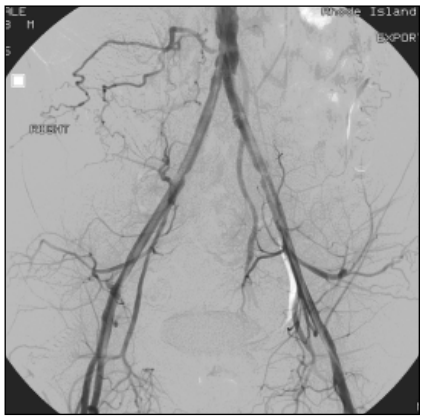

Figure 4c.

Figure 4. 57 year-old male with lifestyle altering buttock and thigh claudication. His risk factors for PAD include smoking and hypertension. ABIs measured 0.56 on the right and 0.68 on the left. (**a**) AP image from a pelvic arteriogram, early phase, shows chronic complete occlusions of both common and external iliac arteries with several collateral vessels present. (**b**) Delayed image from the pelvic arteriogram shows faint opacification of both common femoral arteries (arrows) through several collateral vessels. (**c**) AP pelvic arteriogram following endovascular revascularization with bilateral iliac artery stents shows widely patent iliac arteries without evidence of residual stenoses. Patient remains symptom free three years later and has since returned to work.

Smoking cessation slows the progression of PAD and reduces the risk of death due to vascular causes.[16] A combination approach to smoking cessation, including behavioral therapy, nicotine replacement, and medication, can be more effective than a single modality. Although tobacco cessation has not been shown to significantly improve overall and pain-free walking distance, stopping smoking does reduce the risk of cardiovascular events and progression to CLI.[17] Cholesterol reduction with use of statin medications improves cardiovascular outcomes in patients with PAD[18] and may also improve walking distance and physical activity levels in patients with IC.[19] Proper glycemic control is important to prevent the development of vascular complications. In patients with diabetes, a hemoglobin A_{1c} level of less than 7.0% should be targeted. It is hypothesized that for every 1% increase in hemoglobin A_{1c} level there is approximately a 25% increase in PAD risk .[20] Hypertension, like diabetes, is linked to the development of atherosclerosis and is a major risk factor for PAD. In patients with PAD, the recommended blood pressure goal is less than 140/90 mm Hg. In the diabetic patient, more aggressive blood pressure control is necessary, ideally below 130/80 mm Hg.

Antiplatelet Therapy

Antiplatelet therapy reduces the risk of adverse cardiovascular outcomes and death in patients with cardiovascular disease by approximately 25%.[21] Current recommendations are to use low-dose aspirin (81 mg) daily in patients with PAD to reduce the rate of myocardial infarction, stroke, or vascular death.[22] For patients unable to take aspirin, clopidogrel (Plavix) can be administered at a dose of 75 mg daily. Warfarin has not been shown to have any protective effect in PAD.

FURTHER INFORMATION

- Instructions for patients about PAD and details about the Legs for Life National Screening program for PAD are available through the Society of Interventional Radiology (www.sirweb.org).
- The national nonprofit Peripheral Arterial Disease Coalition provides unbiased, up-to-date information on PAD. The PAD Coalition combines health information from about 62 major national vascular professional societies, health organizations and government agencies. (www.padcoalition.org)
- To learn more about the CLEVER study, visit the following NIH website: http://clinicaltrials.gov/ct2/show/NCT00132743
- For more information about PAD and ongoing clinical trials at the Vascular Disease Research Center (VDRC) at Rhode Island Hospital, visit the following website: http://www.lifespan.org/rih/services/vdrc

Drug Therapy Specific for PAD

The US Food and Drug Administration has approved two prescription medications for intermittent claudication: pentoxifylline (Trental), an oral methylxanthine derivative, and cilostazol (Pletal), a phosphodiesterase III inhibitor. A recent randomized controlled trial comparing the two drugs found cilostazol to be significantly more effective in improving walking distance than pentoxifylline, which was equivalent to placebo.[23] Cilostazol can improve pain-free and peak walking distances in patients with intermittent claudication and is taken orally at a dose of 100 mg BID. Cilostazol is associated with a greater frequency of minor side effects, including headache and diarrhea, and is contraindicated in patients with congestive heart failure.

Exercise Therapy for PAD

Exercise programs are relatively inexpensive, low risk treatment option compared to more invasive therapies. In patients with claudication, multiple randomized controlled trials have shown that supervised exercise programs are more effective at increasing walking distance than unsupervised ones.[24] Supervised exercise programs improve overall and pain-free walking distance and walking time by 50% to 200% from baseline, a level of improvement comparable to that achieved with bypass surgery and potentially better than that achieved with balloon angioplasty.[24-27] Supervised regimens include walking, leg exercises, or treadmill training for 30-60 minutes two to three times

per week. On the basis of findings of randomized controlled trials, the duration of the exercise program should be for 3 to 6 months to improve IC symptoms. Despite proof of the therapeutic benefit of supervised exercise in the PAD population, one of the factors limiting implementation of these programs is the lack of reimbursement by health care payors, so it is important to discuss this with the patient before making a referral.

Revascularization

Mechanical revascularization procedures, which include both endovascular procedures and open surgery (bypass), are used as adjuncts to medical treatment and exercise therapy to restore arterial flow in patients with PAD. Referral for such procedures should be considered in patients with lower extremity pain at rest, those with non-healing ulcers and gangrene, or for individuals with lifestyle-limiting claudication that persists despite risk factor modification, antiplatelet treatment, and participation in a supervised exercise program.

Rapid advances in percutaneous revascularization techniques and equipment have significantly changed the patterns of vascular reconstruction, particularly when lifestyle modifications and drug therapies fail. For purposes of revascularization, PAD is considered in terms of inflow (aortoiliac) and outflow (infrainguinal) occlusive disease. Although surgical bypass has been the traditional therapy for both types, percutaneous endovascular treatment with angioplasty and stents has increasingly become the preferred treatment method to optimize patient outcome while minimizing patient morbidity. (Figure 3) The choice of revascularization procedure depends on several factors, including the location, type, and characteristics of the lesion and co-morbid conditions that affect surgical risks and is best determined after consultation with a vascular specialist.

Endovascular treatment for IC may be more beneficial than exercise in improving symptoms and walking capacity in the short-term, but it is unclear whether this effect is sustained in the long- term.[25] The ongoing **CLEVER study (Claudication: Exercise Versus Endoluminal Revascularization)**, funded by the NIH, is a prospective, multicenter, randomized controlled clinical trial designed to compare the efficacy, safety, and health economic impact of four treatment strategies for patients with PAD and IC: (1) optimal medical care only (claudication pharmacotherapy), (2) optimal medical care plus endovascular stent placement, (3) optimal medical care plus supervised exercise program, and (4) optimal medical care plus endovascular stenting plus supervised exercise. The results should help clarify the role of these various treatment options in PAD and may help physicians identify patients who would benefit from revascularization procedures early in the course of the disease.

Conclusion

PAD is a preventable and treatable disorder with substantial morbidity and mortality, affecting an increasing number of individuals in the United States. The social and economic burden of PAD is expected to increase as the population ages. The mainstay of therapy includes lifestyle adjustment, tobacco cessation, and a supervised exercise program; however, long-term compliance is a challenge and early recognition of PAD is essential to allow implementation of these measures. Optimal treatment of hyperlipidemia, diabetes, and hypertension in conjunction with antiplatelet therapy improves cardiovascular outcomes in these patients. Cilostazol can alleviate the symptoms of IC and improves walking distance. Mechanical revascularization should be reserved for those patients with CLI or lifestyle-limiting claudication. Educational and screening programs directed toward health care professionals and patients with cardiovascular risk factors can help in early diagnosis and proper management of patients with PAD and will ultimately reduce cardiovascular morbidity and mortality.

References

1. Hirsch AT, Criqui MH, et al. *JAMA* 2001; 286:1317-24.
2. Selvin E, Erlinger TP. *Circulation* 2004; 110:738-43.
3. Hirsch, AT, Haskal, ZJ, et al. *Circulation* 2006; 113:e463.
4. Kannel WB, McGee DL. *J Am Geriatr Soc* 1985; 33:13-8.
5. Hiatt WR. *NEJM* 2001; 344:1608-21.
6. Becker GJ, McClenny TE, et al. *J Vasc Interv Radiol* 2002;13:7-11.
7. Steg PG, Bhatt DL, et al. *JAMA* 2007; 297:1197-206.
8. Grundy SM, Cleeman JI, et al. *Circulation* 2004; 110:227-39.
9. Murabito JM, Evans JC, et al. *Am J Epidemiol* 2005; 162:430-7.
10. Criqui MH, Langer RD, et al. *NEJM* 1992; 326:381-6.
11. Ridker PM, Stampfer MJ, Rifai N. *JAMA* 2001; 285:2481-5.
12. Vidula H, Tian L, et al. *Ann Intern Med* 2008; 148:85-93.
13. Ankle Brachial Index Collaboration. *JAMA* 2008; 300:197-208.
14. Ouwendijk R, de Vries M, et al. *Radiol* 2005; 236:1094-103.
15. Sadowski EA, Bennett LK, et al. *Radiol* 2007; 243:148-57.
16. Quick CR, Cotton LT. *Brit J Surg* 1982; 69(suppl):S24-S26.
17. Girolami B, Bernardi E, et al. *Arch Intern Med* 1999; 159:337-45.
18. Heart Protection Study Collaborative Group. *Lancet* 2002; 360:7-22.
19. Mohler ER, Hiatt WR, Creager MA. *Circulation* 2003; 108:1481-6.
20. Aboyans V, Criqui MH, et al. *Circulation* 2006; 113:2323-629.
21. Antithrombotic Trialists Collaboration. *BMJ* 2002; 324:71-86.
22. CAPRIE Steering Committee. *Lancet* 1996; 348:1329-39.
23. Dawson DL, Cutler BS, et al. *Am J Med* 2000; 109:523-30.
24. Leng GC, Fowler B, Ernst E. *Cochrane Database Syst Rev* 2000; 2:CD000990.
25. Watson L, Ellis, Leng GC. *Cochrane Database Syst Rev* 2008; 4:CD000990.
26. Fowkes FG, Gillespie IN. *Cochrane Database Syst Rev* 2000; 2:CD000017.
27. Creasy TS, McMillan PJ, et al. *Eur J Vasc Surg* 1990; 4:135-40.

Todd C. Schirmang, MD, is a fellow in Vascular and Interventional Radiology at Rhode Island Hospital and a Teaching Instructor of Diagnostic Imaging.

Sun H. Ahn, MD, is the Director of the Vascular and Interventional Radiology Fellowship Program at Rhode Island Hospital and an Assistant Professor (Clinical) of Diagnostic Imaging.

Timothy P. Murphy, MD, is the Founder and Medical Director of the Vascular Disease Research Center at Rhode Island Hospital and a Professor of Diagnostic Imaging.

Gregory J. Dubel, MD, is an Assistant Professor of Diagnostic Imaging.

Gregory M. Soares, MD, is the Director of Vascular and Interventional Radiology at Rhode Island Hospital and an Assistant Professor of Diagnostic.

All are at the Warren Alpert Medical School of Brown University.

Disclosure of Financial Interests

Todd C. Schirmang, MD, Sun H. Ahn, MD, Gregory J. Dubel, MD, Gregory M. Soares, MD have no financial interests to disclose.

Timothy P. Murphy, MD. Research Support: Cordis/Johnson&Johnson, Abbott Vascular, Boston Scientific, Bristol Myers Squibb Sanofi Aventis, and Otsuka Pharmaceuticals

Correspondence

Sun H. Ahn, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St
Providence, RI 02903
Phone: (401) 444-5194
e-mail: sahn@lifespan.org