Advances in Interventional Cardiology

Endovascular Therapies for Peripheral Arterial Disease
An Evidence-Based Review

Christopher J. White, MD; William A. Gray, MD

Abstract—Peripheral arterial disease is one manifestation of systemic atherosclerosis. The prevalence of peripheral arterial disease increases with the age of the population. It is important to remember the significant association of coincident coronary artery disease, which is the major cause of mortality in these patients. Remarkable technological advances in the past decade, along with patient preference, have shifted revascularization strategies from traditional open surgical approaches toward lower-morbidity percutaneous endovascular treatments. The availability of stents, more than any other advance, has fueled the growth of catheter-based procedures by improving the safety, durability, and predictability of percutaneous revascularization. (Circulation. 2007;116:2203-2215.)

Key Words: claudication ▪ angioplasty ▪ stents ▪ angiogenesis ▪ peripheral vascular diseases

Peripheral arterial disease (PAD) is one manifestation of systemic atherosclerosis. The prevalence of PAD increases with the age of the population (Figure 1). It is important to remember the significant association of coincident coronary artery disease and cerebrovascular disease in these patients, because it represents the major cause of major morbidity and mortality in the PAD population. Remarkable technological advances in the past decade, along with patient preference, have shifted revascularization strategies from traditional open surgical approaches toward lower-morbidity percutaneous endovascular treatments. Catheter-based revascularization of the lower extremities was first performed by Charles Dotter and advanced by Andreas Gruentzig, who employed then newly developed inflatable balloon catheters that could dilate vascular stenoses. The availability of stents, more than any other advance, has fueled the growth of catheter-based procedures by improving the safety, durability, and predictability of percutaneous revascularization.

Endovascular therapy offers several distinct advantages over open surgical revascularization for selected lesions. It is performed with local anesthesia, which enables the treatment of patients who are at high risk for general anesthesia. The morbidity and mortality from catheter-based therapy is extremely low, especially compared with open surgical revascularization. After successful percutaneous revascularization, patients are ambulatory on the day of treatment, and unlike after vascular surgery, they can often return to normal activity within 24 to 48 hours of an uncomplicated procedure. Endovascular therapies generally do not preclude or alter subsequent surgery and may be repeated if necessary.

Multiple specialties, including interventional cardiology, have contributed to the advancement of the field of peripheral vascular intervention over the past several decades. The recognition of an unmet need for a trained cadre of clinicians to care for patients with PAD prompted the development of a core curriculum document (COCATS-11) and a multispecialty societal competency statement. The American Heart Association and American College of Cardiology have published guidelines and recommendations for the diagnosis and treatment of PAD. Improved patient and physician awareness of PAD and the availability of high-quality noninvasive diagnostic imaging have increased the number of patients seeking treatment for PAD.

Diagnostic Evaluation

Noninvasive Assessment
The initial assessment should include a physical examination, with the patient’s shoes and socks removed, to look for signs of acute or chronic peripheral ischemia and distal embolization and to determine the status of the peripheral pulses. The abdomen is examined for evidence of an aortic aneurysm, and blood pressure should be measured in both arms. Auscultation for bruits is performed at the neck and over the clavicles, abdomen, and femoral pulses.

Ankle-Brachial Index, Pulse-Volume Recordings, and Duplex Ultrasound
The single best initial screening test to perform in a patient suspected of PAD is the ankle-brachial index (ABI). The ABI is the ratio of the highest systolic arm blood pressure to the highest systolic ankle blood pressure, obtained with a handheld continuous-wave Doppler and blood pressure cuff. A ratio <0.9 is considered abnormal, and below 0.4 is often associated with limb-threatening ischemia. Falsely elevated

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ABI readings in noncompressible heavily calcified vessels commonly seen in diabetic patients or patients with renal failure can be assessed with a toe-brachial index performed with a small plethysmographic cuff on the great or second toe. Exercise testing is useful to determine the presence of PAD when the resting ABI is normal and to document the severity of symptom limitation and degree of improvement after treatment in patients with claudication.

Pulse-volume recordings with segmental pressures are also helpful in confirming the presence of obstructive disease and estimating its level and severity. Duplex ultrasound provides both vascular imaging and flow velocity information and has been shown to be an accurate diagnostic method with both sensitivity and specificity ≥90%.11

The American Heart Association/American College of Cardiology guideline document on peripheral vascular disease recommended that routine duplex ultrasound surveillance after lower-extremity endovascular procedures was not well established and was of questionable value.2 One strategy for follow-up would be to obtain a posttreatment ABI early after the procedure to establish a new baseline. Patients return for a follow-up clinical examination and ABI between 3 and 6 months after the procedure to assess continued patency and symptom relief. An imaging study to determine patency (duplex ultrasound or CT angiography [CTA]) of the treated lesion is performed if there is suspicion of restenosis, ie, return of symptoms or a significant (≥0.15) fall in the ABI. Annual follow-up with a goal toward continued risk factor management should include ABI determinations and interval histories.

Noninvasive Angiography

Recent advances in noninvasive angiography (magnetic resonance angiography [MRA] and CTA) enable excellent noninvasive definition of the vascular anatomy.12 Noninvasive angiography with MRA and CTA has the potential advantage over invasive contrast angiography of allowing 3D reconstruction of the images, which permits evaluation of bifurcation lesions, eccentric plaques, and areas of vessel overlap. These imaging modalities also have the ability to image the vascular structures in toto, detecting aneurysms that are easily missed with conventional angiography because of chronic thrombus formation that obscures the true vessel lumen size.

CTA has advantages over MRA: Newer 64-detector machines have superior temporal and special resolution; images are rapidly acquired in a matter of seconds; the presence of pacemakers and defibrillators does not limit imaging; and metallic clips or stents that may cause significant image artifacts with MRA typically do not interrupt CTA (Figure 2). MRA, on the other hand, has advantages over CTA in that potentially nephrotoxic iodinated contrast and ionizing radiation are not required for imaging. MRA can image calcified vessels that may cause artifact with CTA, although with the selection of appropriate windows, this can be minimized in CTA. A randomized trial comparing CTA and MRA in patients being evaluated for PAD found no difference regarding the clinical utility or patient outcomes between the 2 imaging techniques but did demonstrate significantly lower cost associated with CTA imaging.13 Noninvasive imaging provides not only important diagnostic information to aid in
decision making and making recommendations to the patient but also invaluable data for the angiographer/interventionalist in planning access routes, equipment choices, and other elements of the invasive procedure.

Invasive Angiography

Catheter-based angiography is the standard method for diagnosing PAD against which all other imaging methods are compared for accuracy. These comparisons are problematic, because angiography is a 2D luminogram, without the advantages of the cross-sectional imaging with 3D reconstruction available to CTA or MRA. One clear advantage of invasive angiography is the ability to also investigate the hemodynamic or physiological consequences of the stenosis by measuring a pressure gradient across a stenosis, an especially important maneuver when iliac disease is clinically suspected but not obvious on angiography because of posterior plaque location.

Diagnostic digital subtraction angiography is reserved for patients in whom revascularization is planned or for those situations in which the results from noninvasive imaging are ambiguous. Digital subtraction angiography is preferred for its enhanced imaging capabilities compared with unsubtracted imaging techniques. Technically, digital subtraction angiography imaging of the abdominal aorta with bilateral lower-extremity runoff angiography requires an image intensifier large enough to include both legs in the same field (≥15 inches) and that has road-mapping capability and stepping-table acquisition.

Complications associated with catheter-based angiography are related to vascular access, catheter trauma, or systemic complications associated with contrast reactions or renal toxicity. Rates of major complications of peripheral vascular angiography range from 1.9% to 2.9%. Catheter-related trauma includes atheroembolism, vessel dissection, or perforation, which are rare (<1%) but often devastating events. Anaphylactoid contrast reactions occur in fewer than 3% of cases, and fewer than 1% require hospitalization. The risk of contrast-induced nephropathy is increased in patients with baseline chronic renal insufficiency, diabetes mellitus, or multiple myeloma and those who are receiving other nephrotoxic drugs, such as aminoglycosides. Patients who develop contrast nephropathy carry a poor prognosis. Optimal prevention requires vigorous hydration and the use of as little iso-osmolar contrast as possible; other modalities (N-acetylcysteine and/or intravenous bicarbonate pretreatment) can be considered, but their effectiveness remains unclear.

Clinical Syndromes

Intermittent Claudication

Impairment of the arterial circulation to the leg may cause exertion-related discomfort that affects specific muscle groups (ie, buttocks, thigh, or calf muscles) and is relieved with rest (Table 1). Patients with typical symptoms of intermittent claudication are the “tip of the iceberg” of symptomatic PAD patients, representing fewer than 20% of patients with objective evidence of PAD. It is critically important for the clinician to distinguish pseudoclaudication

<table>
<thead>
<tr>
<th>Fontaine Classification</th>
<th>Clinical Description</th>
<th>Grade</th>
<th>Category</th>
<th>Clinical Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
<td>0</td>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>IIa</td>
<td>Mild claudication</td>
<td>I</td>
<td>1</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>IIb</td>
<td>Moderate-to-severe claudication</td>
<td>I</td>
<td>2</td>
<td>Moderate claudication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>3</td>
<td>Severe claudication</td>
</tr>
<tr>
<td>III</td>
<td>Rest pain</td>
<td>II</td>
<td>4</td>
<td>Rest pain</td>
</tr>
<tr>
<td>IV</td>
<td>Ulceration or gangrene</td>
<td>III</td>
<td>5</td>
<td>Minor tissue loss ulceration or gangrene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

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There are atypical presentations of intermittent claudication that the clinician needs to consider, including lower-extremity “power failure” without pain, which may be indicative of aortoiliac disease, and buttck/hip claudication without ABI abnormalities, which may be related to bilateral internal iliac stenosis or occlusion.

Patients with lifestyle-interfering claudication who have aortoiliac disease should undergo primary stenting as the initial therapy, because patients with proximal disease do not respond as well to exercise and medical therapy. Those with disease below the inguinal ligament should undergo a trial of medical therapy that consists of a walking program and cilostazol (if there is no history of heart failure). Cilostazol has objectively shown an increase in walking distance by as much as 50% compared with baseline. Under most circumstances, a dose of 100 mg twice per day should be administered on an empty stomach. The patient should be given a trial of 3 to 4 months of this therapy because it takes time for cilostazol to result in an increase in walking distance by as much as 50% compared with baseline. Under most circumstances, a dose of 100 mg twice per day should be administered on an empty stomach. The patient should be given a trial of 3 to 4 months of this therapy because it takes time for cilostazol to result in an increase in walking distance. If the patient does not respond adequately to medical therapy after this time period, a revascularization procedure is reasonable. In general, patients with claudication progress to limb loss at a rate of well under 5% per year, and therefore, revascularization is reserved for those patients with favorable anatomy who (1) fail conservative therapy and have lifestyle-limiting symptoms or (2) have vocational-limiting symptoms. The therapeutic goals for claudicants are symptom relief, increased walking distance, and improved functionality and quality of life. For this reason, durability of the procedure becomes important, because recurrent ischemic symptoms require repeated procedures.

Critical Limb Ischemia
Patients with critical limb ischemia (CLI; rest pain, nonhealing ulcers, or gangrene) typically have more extensive disease than do claudicants and require a more urgent revascularization approach to prevent tissue loss (Table 1). Many patients with CLI have multilevel disease, and the disease tends to be bilateral. Diabetic patients with CLI will more often have 3-vessel below-knee disease and may also have ulceration related to small-vessel disease that will not generally improve with revascularization.

In patients presenting with CLI, tobacco abuse is common, and diabetic patients are 10 times more likely to require amputation. They tend to be older, with almost 50% of patients undergoing amputations at >80 years of age. The clinical outcome for patients presenting with CLI is grim. Within 3 months of presentation, 12% will require an amputation and 9% will die, with a 1-year mortality rate of 22%. Anatomy suitable for endovascular therapy is often present in 1 or more below-knee vessels. Therapy must be designed to restore pulsatile, straight-line flow to the distal limb with as low a procedural morbidity as possible. Revascularization of an inflow obstruction or proximal stenosis alone is often insufficient to provide adequate flow to heal a foot ulcer. The guiding principle is that less blood flow is required to maintain tissue integrity than to heal a wound, so restenosis does not usually result in recurrent CLI unless there has been repeated injury to the limb. Therefore, the emphasis is less on long-term vessel patency and more on amputation-free survival.

The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial was a British multicenter randomized trial that compared an initial strategy of angioplasty with open surgery in 452 patients with CLI. The primary outcome was time to amputation or death (amputation-free survival). After 6 months, the 2 treatment strategies did not differ significantly in amputation-free survival (hazard ratio 0.73, 95% CI 0.49 to 1.07; Figure 3). There was no difference between the groups for quality-of-life outcomes, but for the first year of follow-up, costs associated with a surgery-first strategy were significantly lower than with a balloon angioplasty-first strategy.

<table>
<thead>
<tr>
<th>Character of discomfort</th>
<th>Intermittent Claudication</th>
<th>Pseudoclaudication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of discomfort</td>
<td>Buttock, hip, thigh, calf, foot</td>
<td>Same</td>
</tr>
<tr>
<td>Exercise induced</td>
<td>Yes</td>
<td>Yes or no</td>
</tr>
<tr>
<td>Distance to claudication</td>
<td>Consistent</td>
<td>Variable</td>
</tr>
<tr>
<td>Occurs with standing</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Relief</td>
<td>Stop walking</td>
<td>Often must sit or change body position</td>
</tr>
</tbody>
</table>

Adapted from Krajewski and Olin.

Figure 3. Amputation-free survival in patients with CLI randomized to initial bypass surgery (BSX) or balloon angioplasty (BAP) showing no difference in the BASIL trial. Reprinted from Adam et al with permission from Elsevier. Copyright 2005, Elsevier Inc.
higher than for angioplasty. For this reason, the authors concluded that a percutaneous-intervention–first strategy was the treatment of choice in patients who are candidates for either surgery or endovascular intervention.

There has been much interest in developing an agent that would stimulate angiogenesis in patients who have CLI but do not have the option for revascularization. Initial work has progressed in the areas of genes that code for various growth factors and the use of endothelial progenitor cells to stimulate angiogenesis. Preliminary reports have been variable, but none of the gene or cell therapy trials have provided a definitive answer as to either the safety or the efficacy of these approaches in patients with PAD.

**Patient Selection and Outcomes**

**Aortoiliac Disease**

Revascularization options for patients with infrarenal aortic and iliac obstructive atherosclerotic disease are open surgery (ie, endarterectomy, bypass surgery, or extra-anatomic bypass [axillofemoral bypass]) or percutaneous endovascular repair. Aortoiliac and aortofemoral bypass procedures are associated with 74% to 95% 5-year patency rates, respectively, which are comparable but not superior to percutaneous therapies. Because many of these operations involve extensive abdominal incision, morbidity (eg, infection and bleeding) and mortality can become significant in the at-risk patient.

The availability of endovascular stents has significantly increased the number of aortoiliac lesions that may be treated percutaneously by providing a larger acute gain in luminal diameter, scaffolding the lumen to prevent embolization of debris, and enhancing long-term patency compared with balloon angioplasty alone (Figure 4). For common iliac bifurcation lesions, kissing-balloon–expandable stents have become the preferred option. In 1 series of 48 patients, all stents were placed successfully, and there were no major complications. All of the patients experienced symptomatic improvement, and the 2-year patency rate was 87%. Endovascular treatment for infrarenal aorta disease can be performed with lower morbidity than open surgery and with better durability than extra-anatomic bypass; there are, however, no randomized controlled trial data to compare.

Iliac intervention represents a very important skill set for any interventionalist in managing vascular access-site complications or in asymptomatic patients with aortoiliac stenotic or occlusive lesions; the indication for endovascular intervention includes the need for vascular access for angiography/intervention or to place an intra-aortic counterpulsation balloon. The TransAtlantic Inter-Society Consensus (TASC) document described characteristic lesion morphology for ideal (type A) and unfavorable (type D) iliac lesions (Figure 5) for endovascular therapy. Surgical and percutaneous treatments of TASC type B and C lesions have been compared in a nonrandomized observational study. There was no difference in limb salvage or patient survival at 5 years, but vessel patency was found to be reduced in limbs with poor runoff treated with stents compared with surgery. Other trials comparing surgery with percutaneous intervention for iliac occlusive disease include a randomized comparison of balloon angioplasty versus surgery for 157 iliac lesions, which found no difference in the 3-year cumulative rate for death, amputation, or revascularization failure. A second randomized controlled trial of surgery versus angioplasty in 102 patients with severe claudication and limb-threatening ischemia demonstrated no difference at 1 year for angioplasty or surgery. On the basis of these and other trial data, current recommendations favor endovascular procedures for TASC A and B lesions and for selected C lesions. Patients with TASC D lesions generally will be considered surgical candidates, but with newer technology (reentry devices and covered stent grafts), these patients increasingly are considered for endovascular therapy on a case-by-case basis.

In a comparison of interventional approaches to iliac disease, the immediate postprocedure results of a randomized trial of percutaneous transluminal angioplasty (PTA) that compared provisional stent placement (stent placement for unsatisfactory balloon angioplasty results) versus primary stent placement in iliac arteries demonstrated that pressure gradients across the lesions after primary stent placement (5.8±4.7 mm Hg) were significantly lower after angioplasty.
primary iliac (Palmaz-Schatz, Johnson & Johnson Interventional Systems, Co, Warren, NJ) stent placement versus balloon angioplasty also favored primary stent placement by demonstrating a 4-year patency rate of 94% for the stent group versus 69% for the balloon angioplasty group.42

There has been debate about whether stent architecture or composition, (ie, nitinol versus stainless steel) has any effect on restenosis rates. The recently completed Cordis Randomized Iliac Stent Project (CRISP) trial failed to show any difference in outcomes between iliac artery stents made of nitinol (SMART, Cordis, a Johnson & Johnson Company, Miami Lakes, Fla) and Elgiloy alloy of stainless steel (Wallstent, Boston Scientific, Natick, Mass) at 1 year.43

### Common and Deep Femoral Artery Disease

The diagnosis and management of common femoral artery (CFA) lesions is important for the vascular interventionalist, because the CFA provides the most commonly used vascular access for diagnostic angiography and interventional procedures. Obstructive disease of the CFA usually occurs in association with disease of other vascular territories, particularly the superficial femoral artery (SFA). Endarterectomy with or without patch angioplasty is the preferred surgical technique to treat the CFA.44–46 The immediate technical success rate exceeds 90%, but postoperative morbidity is significant, with wound infections, hematomas, and seromas affecting >15% of the patients. The 1-year primary patency rate exceeds 80%.

The CFA is located over the hip joint, and stent placement at this location risks the loss of a favored access site; there is also a theoretical concern with stent fracture. One solution is to use an open-architecture stent, such as a coil stent, which is resistant to fracture and will allow vascular access. Nitinol tube stents should probably be avoided if possible. Percutaneous treatment of the CFA with provisional stent placement compares favorably with the surgical results without the attendant morbidity associated with the open surgical procedure. We reported a procedural success rate of 95% of 20 patients, with improvement of the ABI from 0.54±0.21 to 0.82±0.18 after the procedure (P=0.0002).47 At almost 1-year of follow-up (11.4±6 months), there was improvement by at least 1 Rutherford class in 90% of the patients, and the ABI improvement was sustained (0.79±0.18). The event-free survival rate was 90%, and the rate of freedom from amputation and target-vessel revascularization was 95%.

The deep femoral artery (profunda femoris) is essential for maintaining limb viability when occlusive arterial disease affects the SFA. Historically, occlusive disease of the profunda femoris artery has been treated surgically. We reported the results of a consecutive series of patients with severe lower-extremity ischemia in whom PTA of the profunda femoris artery was performed alone or in combination with an additional (inflow) percutaneous revascularization procedure (Figure 6).48 Clinical success was obtained in 91% (29 of 32 limbs) by use of a combination of provisional stent placement with or without thrombolytic therapy for thrombotic occlusions. The only procedural complications were groin hematomas in 2 patients. Hemodynamic success (ABI ≥0.1) was achieved in 97% of the patients with a successful angiography.

### Table 3. Modified TASC Morphological Classification of Iliac Lesions

<table>
<thead>
<tr>
<th>A. Endovascular treatment of choice:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Single &lt;3-cm stenosis of CIA or EIA (unilateral/bilateral)</td>
<td></td>
</tr>
<tr>
<td>Two stenoses &lt;5 cm in CIA/EIA</td>
<td></td>
</tr>
<tr>
<td>Unilateral CIA occlusion</td>
<td></td>
</tr>
<tr>
<td>B. Endovascular more often used:</td>
<td></td>
</tr>
<tr>
<td>Unilateral EIA stenosis or occlusion</td>
<td></td>
</tr>
<tr>
<td>Bilateral CIA occlusion</td>
<td></td>
</tr>
<tr>
<td>C. Endovascular if possible:</td>
<td></td>
</tr>
<tr>
<td>Diffuse/multiple stenoses in any iliac segment (&gt;10 cm)</td>
<td></td>
</tr>
<tr>
<td>Unilateral occlusion of CIA and EIA</td>
<td></td>
</tr>
<tr>
<td>Bilateral EIA occlusions</td>
<td></td>
</tr>
<tr>
<td>Diffuse disease involving aorta and iliac arteries</td>
<td></td>
</tr>
<tr>
<td>Associated aneurysmal surgery requiring surgery</td>
<td></td>
</tr>
</tbody>
</table>

CIA indicates common iliac artery; EIA, external iliac artery.

than after PTA alone (8.9±6.8 mm Hg) but not after provisional stent placement (5.9±3.6 mm Hg).35 The primary clinical success rate, defined as an improvement of at least 1 clinical grade category, was not different for the primary stent group (81%) than for the PTA plus provisional stent group (80%). By using provisional stenting, the authors avoided stent placement in 63% of the lesions and still achieved an equivalent acute hemodynamic result compared with primary stent placement. At a mean follow-up of 5.6 years, there was no difference in repeat interventions between the 2 groups, with a target-vessel revascularization rate of 18% in the primary stent group and 20% in the provisional stent group.36 This approach is reasonable in relatively short, nonocclusive lesions but has not been tested in more complex subsets.

When data from trials with long-term outcomes are combined, 873 patients had an iliac stent acute procedural success rate >90%, with 3±1-year primary patency rates of 74% to 87% and secondary patency of 84% to 95%, which compares favorably with reported surgical patency rates.27,37–39 The 30-day mortality risk was 0.5%, much lower than the 4% weighted mortality risk for aortofemoral bypass.39 Variables that correlate with poor outcomes after iliac stent placement include occlusions rather than stenoses, longer lesions, female gender, and external iliac stent placement. Occlusions of the iliac arteries may be approached with a success rate of 90%, a serious complication rate of 1.4%, and a 3-year primary patency rate of 78%, with a secondary patency rate of 86%.40

The current American College of Cardiology/American Heart Association class I guideline recommendation is for primary stent placement in the iliac arteries (level of evidence B for common iliac arteries and C for external iliac arteries), and this is supported by a meta-analysis that reviewed >than 2000 patients.41 Procedural success was higher in the primary stent group, and there was a 43% reduction in long-term (4-year) failures for aortoiliac stent placement compared with balloon angioplasty alone. A European randomized trial of
graphic procedure, whereas the ABI improved from $0.5 \pm 0.2$ to $0.73 \pm 0.2$ ($P<0.01$). The in-hospital limb-salvage rate was 94%, and at 34±20 months, the rate of limb salvage and freedom from target-vessel revascularization was 88%. Symptomatic improvement was seen in 88% of the patients, who improved to Fontaine class 1 or 2A, and only 12% had Fontaine class 2B or 3 at follow-up (41% had Fontaine class 2B and 59% had Fontaine class 3 or 4 before the procedure). It appears that endovascular therapy for these critical lesions may be particularly valuable in patients at high risk for open surgery. Our data suggest that percutaneous therapy is safe and effective and may be considered as an alternative to surgical therapy in the occasional patient with anatomically suitable lesions who is critically dependent on patency of the profunda femoris artery because of SFA circulation compromise.

SFA and Popliteal Artery Disease

Comparative trial data for therapy in femoral-popliteal disease are available for medical therapy, PTA, stenting, brachytherapy, and laser therapy. Notably absent in spite of a prominent position in the marketplace are similar data for atherectomy, cutting balloons, and cryoplasty.

Medical therapy, intervention, and surgery have been compared in several trials in symptomatic patients with femoral-popliteal disease. A meta-analysis that compared PTA with exercise therapy in patients with intermittent claudication reported similar quality-of-life outcomes at 3 and 6 months but also found that functional capacity (ABI) improved more with endovascular therapy than with exercise. Cost-effectiveness and quality-of-life outcomes favor the performance of percutaneous therapy whenever feasible as a more effective treatment than exercise alone. A matched-cohort study of 526 patients with intermittent claudication found significant advantages for a revascularization strategy (surgery or PTA) compared with medical therapy. Revascularization was more effective than medical therapy for improvement in physical function, bodily pain, and walking distance. Patients with the greatest improvement in their ABI results had the best clinical improvement, which indicates that the degree of revascularization was related to a successful outcome. If the 5-year patency rate is estimated to be $\geq 30\%$, the authors concluded that percutaneous therapies would be superior to surgery.

Clinical success in patients with SFA lesions depends on a durable, long-lasting procedure. Multiple clinical trials in small numbers of patients had previously failed to show any advantage for stents compared with PTA (Table 4). A meta-analysis did, however, demonstrate better patency at 3 years for stents than for PTA in the most severely affected patients, those with occlusions and CLI. A recent randomized controlled trial demonstrated a better outcome for primary SFA stent placement than a strategy of provisional stent placement. Not only was restenosis significantly lower in the stent group at 6 and 12 months, but there was also better functional improvement (ABI) and walking distance in the primary stent group (Figure 7). An interesting observation was that stent fractures, which have been associated with restenosis in SFA lesions, were only reported in 2% of the primary SFA stent placements and 5% for the Wallstent (Boston Scientific), and 2% for the SMART stent (Cordis). There are differences regarding stent fracture among SFA stents that are presumably related to their composition and architecture. A recently published series found fracture rates of 28% for the SMART stent (Cordis), 19% for the Wallstent (Boston Scientific), and 2% for the SMART stent (Abbott Vascular). The issue of stent fracture is a complex one, with attendant restenosis being greater in the fracture territory and the length of lesion/presence of multiple overlapping stents also being an apparent contributing factor.

Brachytherapy

Adjunctive endovascular brachytherapy with an iridium 192 source at a prescribed dose of 12 to 14 Gy combined with PTA in de novo SFA long-segment stenoses was compared with PTA alone and demonstrated a delaying effect on the occurrence of restenosis. Early in the trial, there appeared to be a restenosis benefit for the endovascular brachytherapy and PTA group; however, at 5-year follow-up, the recurrence rate was equal at 72.5% in both groups, demonstrating a “catch-up” phenomenon (Figure 8). A similar dose regimen

![Figure 6. Left, Baseline angiography of tandem critical lesions (arrow) of the deep femoral (profunda femoris) artery. Right, Endovascular profundaplasty after balloon angioplasty.](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Table 4. Modified TASC Morphological Classification of Femoral-Popliteal Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Endovascular treatment of choice:</strong></td>
</tr>
<tr>
<td>Single &lt;3-cm stenosis (unilateral/bilateral)</td>
</tr>
<tr>
<td><strong>B. Endovascular more often used:</strong></td>
</tr>
<tr>
<td>Single 3- to 5-cm stenosis</td>
</tr>
<tr>
<td>Heavily calcified stenoses ≥3 cm</td>
</tr>
<tr>
<td>Multiple lesions each ≥3 cm (stenoses or occlusions)</td>
</tr>
<tr>
<td>Single or multiple lesions, in the absence of continuous tibial runoff, to improve inflow for infrageniculate bypass</td>
</tr>
<tr>
<td><strong>C. Endovascular if possible:</strong></td>
</tr>
<tr>
<td>Single stenosis or occlusion 5 to 10 cm</td>
</tr>
<tr>
<td>Multiple stenoses or occlusion, each 3 to 5 cm</td>
</tr>
<tr>
<td><strong>D. Surgery preferred, endovascular considered on case-by-case basis:</strong></td>
</tr>
<tr>
<td>Complete occlusion of CFA or SFA or popliteal and proximal crural arteries</td>
</tr>
</tbody>
</table>

**White and Gray**  
Endovascular Therapies for PAD
in patients receiving stents failed to reduce recurrence rates but did lead to an increased rate of thrombotic occlusion.\textsuperscript{60} When patients with restenosis after PTA were compared, those receiving brachytherapy did have a restenosis benefit at 1 year compared with de novo lesions, which did not benefit.\textsuperscript{61} A novel approach has been to deliver external-beam irradiation to de novo SFA lesions after PTA. At 1-year follow-up, there was a significant benefit for the group treated with 14 Gy in a single treatment session compared with the control and lower-dose groups.\textsuperscript{62} The late catch-up phenomenon demonstrated for endovascular brachytherapy suggests that a longer follow-up will be necessary to determine the benefit for external-beam radiation to prevent restenosis. There are no intravascular brachytherapy delivery devices available in the United States to treat 5- to 6-mm-diameter SFA vessels.

\textbf{Debulking Strategies}

There has been the expectation that by “debulking” atherosclerotic plaque, the primary patency of the SFA could be improved. The PELA (Peripheral Excimer Laser Angioplasty) trial randomized 251 patients with claudication and a total SFA occlusion to either PTA or laser-assisted PTA. There was no difference in clinical events or patency rates at 1 year of follow-up. There is currently no convincing evidence that laser-assisted angioplasty adds any patency benefit to conventional therapy.\textsuperscript{63,64}

Several generations of directional atherectomy catheters continue to either fail to demonstrate incremental benefit over the less-expensive PTA alone or have simply avoided comparative trials with conventional therapy.\textsuperscript{65} Self-reported registry data with the SilverHawk device (FoxHollow Technologies, Redwood City, Calif), which is considerably costlier than either a balloon catheter or stent, are not controlled and therefore difficult to interpret. There have been safety concerns raised with regard to the incidence of distal embolization and perforation.\textsuperscript{66–68}

\textbf{Cryoplasty}

The ability to impact the biology of restenosis with thermal manipulation of the tissue has seen failed attempts with heat, and now there is a device that delivers cold via a balloon to the tissues, in an attempt to induce apoptosis and reduce restenosis. There have been registry series published that
have shown a restenosis rate by duplex ultrasound of \(\approx 30\%\) at 9 months. This device, however, has not been tested in any comparative trials despite its commercial availability for several years. Because its claims to efficacy remain unsupported by comparative data, its significant associated costs remain difficult to justify.

**Cutting-Balloon Angioplasty**

The cutting balloon is a niche device that has been approved for use in undilatable arteries. There is no evidence to support any indications for this device beyond that use, including no evidence of benefit for the cutting balloon in treating in-stent restenosis. The device has been recalled by Boston Scientific due to potential shaft separation of the catheter.

**Drug-Eluting Balloons and Stents**

Initial attempts at transferring the benefits of drug elution seen in the coronaries for both balloons and stents to the femoral-popliteal arteries have not yet been successful. A 2-phase randomized controlled trial of sirolimus-eluting nitinol stents compared with bare-metal nitinol stents in de novo femoral arteries with an average lesion length of 8.5 cm was performed in patients in European centers. After 18 months of follow-up, there appeared to be no advantage for the restenosis rate of the drug-eluting stent (20.7%) over the bare-metal nitinol stent (17.9%). In the initial phase of the trial, failure of the drug-coated stent was attributed to stent fractures, seen in 18% of cases, but in the second phase of the trial, stent fractures were only seen in 8% of cases and were not associated with restenosis.

A US randomized trial (Cook Group) using a paclitaxel-coated nitinol stent without polymer coating versus a bare-metal nitinol stent is under way. The results of that trial are pending, it appears that developing a delivery platform and determining dosimetry for the SFA will require more testing. The randomized THUNDER trial (local Taxan with short time exposure for redUctioN of restenosis in Distal artEries) comparing a drug-eluting balloon with a noncoated balloon in de novo SFA lesions has completed enrollment.

**Covered Stents**

Covered stents have been used effectively to treat vascular perforations and to exclude aneurysms. Several small trials have shown a restenosis rate by duplex ultrasound of \(\approx 30\%\) at 9 months. This device, however, has not been tested in any comparative trials despite its commercial availability for several years. Because its claims to efficacy remain unsupported by comparative data, its significant associated costs remain difficult to justify.

The theoretical benefit of the expanded polytetrafluoroethylene (ePTFE)-covered nitinol stent graft (Viabahn, WL Gore & Associates) is that in-growth of tissue between the stent struts, which plagues SFA stents, is prevented; however, edge restenosis may not be avoided, and concerns about stent thrombosis must be addressed. In a study of 60 limbs treated with a covered stent, 2 patients had major procedural complications that required surgical correction, which is unusual for PTA. Thrombotic occlusion of the covered stent was seen in 10% of cases within 30 days, and the 1-year SFA patency rate was 67%, with the presumption that late occlusion may represent edge restenosis and thrombosis. The authors concluded that the Viabahn covered stent was not a device for all types of occlusions. The disadvantages were that the radial force was too low, and the risk of thrombosis was increased in the first few months after placement. The randomized VIBRANT study (VlaBahn veRsus bAre Nitinol stenT) is under way comparing the Viabahn covered stent with bare-metal nitinol stents to assess the performance of these 2 platforms.

**Tibial and Peroneal Artery Disease**

Below-knee angioplasty has traditionally been reserved for patients with CLI because of the fear of limb loss should a complication occur. Current practice standards have broadened somewhat in that patients with severe claudication who have extensive, multilevel disease may have this intervention performed to improve “outflow” in their infrapopliteal ves-

**Figure 8.** Kaplan–Meier plot of cumulative recurrence rate after femoropopliteal balloon angioplasty compared with angioplasty with brachytherapy showing no difference. Numbers at bottom of figure indicate number of patients at risk. EBT indicates endovascular brachytherapy. Reprinted with permission from Wolfram et al. Copyright 2006, the Radiological Society of North America.
sels, although no systematic study data exist to support this indication for intervention. Isolated tibioperoneal disease does not generally cause lifestyle-limiting claudication, unless it occurs in the proximal tibioperoneal trunk and affects the common inflow to all 3 vessels.

The adaptation of coronary equipment has improved the results of tibioperoneal interventions (Figure 9). Current procedural success rates for below-knee intervention in limb-salvage patients range from 60% for occlusions to >90% for more ideal lesions.78,79 Limb-salvage rates at 2 to 5 years are 80% to 90% with modern endovascular techniques.

Optimal treatment of tibioperoneal disease requires appropriate patient and lesion selection for treatment. Focal stenoses have the best outcomes, because those with fewer than 5 separate lesions are associated with a higher success rate. Occlusions <6 cm in length have better outcomes than longer lesions. Strategically, straight-line, pulsatile flow to the foot is the goal of therapy in patients with CLI. Success is measured more by relief of rest pain, healing of ulcers, and avoidance of amputation and less by long-term vessel patency. When trying to heal ischemic ulcers, the basic principle is that it takes more oxygenated blood flow to heal a wound than it does to maintain tissue integrity.

Drug-Eluting Stents
Preliminary results of the use of balloon-expandable, coronary, drug-eluting stents in tibial vessels have been reported.80 The largest series, a nonrandomized comparison of tibioperoneal bailout stenting in 58 patients (29 bare-metal stents and 29 sirolimus-eluting stents [Cypher, Cordis]) demonstrated a marked reduction in restenosis at 6 months from 55% in bare-metal stents to 4% (P<0.001) in the drug-eluting stents.81 Although these results are encouraging and very “coronary-like,” more rigorous comparisons and longer follow-up are required, especially concerning late thrombosis risk as seen in the coronary application of drug-eluting stents.

Angiogenesis
Not infrequently, the severity of infrapopliteal disease abolishes most if not all of the named vasculature, and percutaneous mechanical revascularization is not possible. Therapeutic angiogenesis with growth factors such as vascular endothelial growth factor and fibroblast growth factor used as agents has been proposed as a means of maintaining limb viability.

Although reports of efficacy are episodic, 2 randomized controlled studies have had conflicting results. In the first trial, 190 patients with intermittent claudication underwent a 3-way randomization to placebo or 1 of 2 intra-arterial infusions of recombinant fibroblast growth factor-2, which led to an almost 1-minute improvement in walking time in the active-treatment groups over the placebo group and no differences between the 2 fibroblast-growth factor-2 dose groups.22 In a second randomized trial in claudicants, intramuscular injection of adenoviral vascular endothelial growth factor 121 (AdVEGF121), also in 2 doses, did not confer a walking time advantage over placebo.23 The cause of this variability in study results is likely related to multiple factors, including routes of administration, dosing, degrees of ischemia in the populations tested, and differences in the agents used. Although the promise of effective angiogenesis is tantalizing, especially in the “unrevascularizable” limb, much work remains to be done.

Summary
The endovascular treatment of lower-extremity PAD continues to evolve, with the expectation of improvement in acute
success rates and safety and the anticipation of improving long-term durability with newer technologies ranging from local drug delivery to bioabsorbable stents. Percutaneous procedures will continue to replace open surgery. The current evidence base to support decision making is quite shallow compared with the field of coronary intervention, and reporting standards for PAD intervention are generally lacking, but there is an increasing resolve on the part of physician-investigators, government regulators and payers, and industry to undertake the difficult but necessary task of collecting more definitive data.

Disclosures
Dr White serves on the advisory board for Baxter Cellular Therapies. Dr Gray serves on the advisory board for Abbott Vascular-Scientific.

References


