Peripheral Artery Disease (PAD) encompasses arterial disorders excluding the coronary vasculature, but in most guidelines is limited to branches of the lower aorta. In this review, we will focus on obstructive arterial disease limited to the lower extremities. When compared with open surgical revascularization for PAD, peripheral vascular intervention (PVI) offers a much lower periprocedural risk, but it is limited by lower initial success with occlusive disease. Although significant progress has been made, further challenges still remain such as restenosis after infrainguinal and particularly infrapopliteal PVI.

Endovascular therapy is embraced by a wide variety of operators, including interventional cardiologists trained in vascular disease, interventional radiologists, and vascular surgeons trained in endovascular techniques. Key factors for the successful implementation of an endovascular program are the

**Abstract:** Advances in endovascular therapies during the past decade have broadened the options for treating peripheral vascular disease percutaneously. Endovascular treatment offers a lower risk alternative to open surgery in many patients with multiple comorbidities. Noninvasive physiological tests and arterial imaging precede an endovascular intervention and help localize the disease and plan the procedure. The timing and need for revascularization are broadly related to the 3 main clinical presentations of claudication, critical limb ischemia, and acute limb ischemia. Many patients with claudication can be treated by exercise and medical therapy. Endovascular procedures are considered when these fail to improve quality of life and function. In contrast, critical limb ischemia and acute limb ischemia threaten the limb and require more urgent revascularization. In general, endovascular treatments have greater long-term durability for aortoiliac disease than femoral popliteal disease. Infraopliteal revascularization is generally reserved for critical and acute limb ischemia. Balloon angioplasty and stenting are the mainstays of endovascular therapy. New well-tested innovations include drug-eluting stents and drug-coated balloons. Adjunctive devices for crossing chronic total occlusions or debulking plaque with atherectomy are less rigorously studied and have niche roles. Patients receiving endovascular procedures need a structured surveillance plan for follow-up care. This includes intensive treatment of cardiovascular risk factors to prevent myocardial infarction and stroke, which are the main causes of death. Limb surveillance aims to identify restenosis and new disease beyond the intervened segments, both of which may jeopardize patency and lead to recurrent symptoms, functional impairment, or a threatened limb. ( Circ Res. 2015;116:1599-1613. DOI: 10.1161/CIRCRESAHA.116.303503.)

**Key Words:** endovascular procedures • intermittent claudication • peripheral artery disease
Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ABI</td>
<td>ankle-brachial index</td>
</tr>
<tr>
<td>BMS</td>
<td>bare-metal stents</td>
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<tr>
<td>CDT</td>
<td>catheter-directed thrombolysis</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomography angiography</td>
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<tr>
<td>CTOS</td>
<td>chronic total occlusions</td>
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<tr>
<td>CLI</td>
<td>critical limb ischemia</td>
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<tr>
<td>ALI</td>
<td>acute limb ischemia</td>
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<tr>
<td>DCBs</td>
<td>drug-coated balloons</td>
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<tr>
<td>DES</td>
<td>drug-eluting stents</td>
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<tr>
<td>IC</td>
<td>intermittent claudication</td>
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<tr>
<td>ISR</td>
<td>in-stent restenosis</td>
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<tr>
<td>MRA</td>
<td>magnetic resonance angiography</td>
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<tr>
<td>PAD</td>
<td>peripheral artery disease</td>
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<tr>
<td>PVI</td>
<td>peripheral vascular intervention</td>
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<tr>
<td>SFA</td>
<td>superficial femoral artery</td>
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<tr>
<td>TLR</td>
<td>target lesion revascularization</td>
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ability to select patients who are likely to benefit over medical therapy and experience outcomes comparable with surgical intervention, skill with the range of technology available (especially the treatment of chronic total occlusions [CTOs]), and careful surveillance for restenosis or new de novo disease that may limit long-term durability.

Selection of Patients With PAD for PVI

The recommended screening test for suspected PAD is the ankle-brachial index (ABI) and establishes the diagnosis of PAD in patients with signs and symptoms suggestive of lower extremity ischemia. PAD is defined as an ABI<0.9 with values from 0.91 to 1.0 considered borderline abnormal.4 An ABI>1.0 is normal although ABI>1.4 is typical of PAD patients with calcified, noncompressible lower extremity arteriopathy. The presentation, evaluation, and medical management of PAD is covered by earlier reviews in this series and in published guidelines by the American Heart Association and American College of Cardiology.1-3 Claudication typically presents as leg cramping with exercise that is relieved by rest. However, many patients present with atypical symptoms such as leg fatigue, numbness, or the leg giving way when walking, and have abnormal findings on physiological or imaging tests.5 Even without symptoms, an ABI<0.9 requires close clinical surveillance because it indicates an elevated risk of other cardiovascular disease, warranting intensive secondary prevention measures and monitoring for the onset of symptoms, which may be gradual.1,6

The medical treatment of intermittent claudication (IC) is discussed elsewhere.7 This includes tobacco cessation, a regular exercise program, optimizing blood pressure and statin therapy. Supervised exercise programs are the gold standard, but the lack of financial reimbursement for this indication limits its availability. Home-based exercise programs may represent a feasible alternative for those unable or unwilling to exercise under supervision.8 Cilostazol is the only medication that improves walking distance and time to symptoms.9 However, its success is highly variable, may cause unacceptable symptoms (eg, diarrhea), is contraindicated in those with a low ejection fraction, and requires several weeks of treatment to realize any potential benefit. An improvement in walking distance has also been reported after treatment with atorvastatin and ramipril.10,11

Preprocedural Noninvasive Assessment of PAD

Noninvasive anatomic imaging of PAD in symptomatic patients before endovascular therapy can assist preprocedural planning to maximize procedural success. Duplex ultrasound provides information on the location and the physiological severity of a stenosis. High-resolution computed tomography angiography (CTA) or magnetic resonance angiography (MRA) provides detailed assessment of vascular anatomy, disease burden and location, and lesion character depending on the modality used.12,13 Such imaging can supplement the results of physiological data from segmental leg pressures and pulse volume recordings.3 Imaging helps localize the lesions targeted for revascularization (which may require invasive hemodynamic confirmation), the selection of appropriate equipment or adjunctive devices, and the choice of arterial access site (ie, antegrade versus retrograde common femoral access, retrograde pedal access, etc). These considerations will determine the patient position on the procedure table, room preparation, and can help minimize procedure duration, contrast use, and radiation exposure. The selection of duplex ultrasound, CTA, or MRA depends on the institution. Duplex ultrasound requires trained technicians and experience in reading scans but avoids contrast and radiation exposure. CTA is faster and able to identify flow within stents, whereas MRA avoids x-ray exposure and is less influenced by vascular calcification. Both CTA and MRA use contrast enhancement with iodinated contrast for CTA, which is potentially nephrotoxic, and gadolinium for MRA, which may cause nephrogenic systemic fibrosis in patients with stage 5 chronic kidney disease.14 No guidelines or clinical outcomes data are available to guide the choice of modality for preprocedural imaging. This is chiefly dictated by local availability and expertise, as well as specific patient characteristics (ie, chronic kidney disease and the presence of MRI-incompatible devices).

Strategies for PVI

Revascularization is typically considered in patients with PAD who have developed any 1 of 3 distinct clinical presentations: (1) lifestyle-limiting claudication no longer responsive to conservative therapy (IC); (2) critical limb ischemia (CLI); or (3) acute limb ischemia (ALI). Although the first 2 clinical syndromes represent separate yet related stages of progressive PAD, ALI is frequently because of peripheral thromboembolism rather than occlusive PAD. The urgency and goals of treatment depend on the presenting syndrome, comorbidities, and anatomy (Tables 1 and 2).

Technological improvements in the equipment used for endovascular revascularization have increased options for complex lesions once exclusively treated by open surgery. For this reason, older guidelines using length of disease and its nature
(ie, stenotic versus occlusive) to guide the mode of revascularization may no longer be valid. Although the initial success of an endovascular procedure is lower with occlusions compared with stenoses, in the intermediate term, longer lesions are more consistently associated with restenosis. Lower risk endovascular techniques to revascularize focal anastomotic disease after bypass grafting or focal restenosis of peripheral artery stents are an attractive and feasible treatment strategy. Surgical revascularization is often preferred for disease in the common femoral or popliteal arteries; regions that may increase stent fracture because of greater compression, torsion, and stretch associated with flexion and extension of the hip and knee. However, even in these locations, single-center series suggest treatment comprised of percutaneous angioplasty with provisional stenting is associated with acceptable 12-month results particularly in high-risk surgical patients requiring limb salvage. Endovascular approaches without stenting in these regions include atherectomy and balloon angioplasty alone. The development of drug-coated balloons (DCBs) with adjunctive atherectomy may address some issues associated with stent placement in these challenging arterial segments although any flow-limiting dissections, recalcitrant recoil, or residual disease would still limit such an approach. Given the lack of standardized treatment strategies in this field, guideline statements on the appropriate use of endovascular intervention for both aortoiliac and femoropopliteal disease were recently published to provide evidence-based recommendations to help guide contemporary practice.

**Intermittent Claudication**

IC represents a progression of arterial obstruction caused by obstructive PAD causing ischemia with lower levels of activity. In contrast to both CLI and ALI where ischemia at rest threatens limb viability and requires urgent revascularization, the timing or need for revascularization in claudication is largely dictated by the degree of lifestyle limitation perceived by the patient. Although most patients with IC are at low risk for limb loss, diabetes increases this risk. The severity of IC symptoms is typically scored by either the Rutherford–Baker or Fontaine classification schemes (Table 3). An endovascular approach to treat lifestyle-limiting claudication in those with a reasonable likelihood of symptomatic improvement and acceptable procedural risk is appropriate. Most of the lesions responsible for IC are located in the femoropopliteal arteries (70%) with the remainder in the aortoiliac arteries. Isolated tibial disease is present in only 15% of this population. Accordingly, treatment paradigms derived from clinical outcome studies specified by anatomic level (ie, aortoiliac versus femoropopliteal) have emerged to guide therapeutic decision making. An initial endovascular approach is advocated for most types of iliac and femoropopliteal disease. For more complex aortoiliac disease (eg, long occlusions), such a strategy may be considered depending on the availability of local expertise.

**Aortoiliac Disease**

For focal aortoiliac disease, balloon angioplasty alone provides excellent long-term patency with provisional stent placement reserved for suboptimal result. No randomized studies comparing iliac stenting versus angioplasty only are currently available. The Dutch Iliac Stent Trial comparing stenting with balloon angioplasty and provisional stenting resulted in comparable clinical outcomes although this may have been caused by relatively low complexity TASC (Trans-Atlantic Society Consensus) A and B disease included in the trial. Given the increased recoil seen with ostial iliac disease and risk of dissection with the more complex disease now more frequently encountered (ie, total occlusions, ulcerated or calcified lesions, and aneurysmal segments) the use of primary stenting for aortoiliac disease has increased. A meta-analysis including 958 total patients with more complex aortoiliac disease found superior patency rates associated with primary stenting. Limitations of comparing different studies of stenting for occlusive aortoiliac disease include the varied spectrum of disease complexity, the differing segments of iliac artery treated, and the use of either balloon-expandable or self-expanding nitinol stents. There are currently no randomized data comparing outcomes of aortoiliac stenting with these 2 types of stents directly. Given the lack of external compressive forces and their relatively nontortuous course, iliac artery stenting with balloon-expandable stents offer enhanced radial strength and can be more precisely positioned to treat ostial disease. Self-expanding stents may avoid arterial rupture in long iliac lesions that significantly taper in diameter, are highly tortuous, or in close proximity of the hip joint. The Cordis Randomized Iliac Stent Project–United States (CRISP-US) trial showed equivalent outcomes after iliac stenting with either nitinol or stainless steel self-expanding platforms.

Restenosis remains the primary limitation of aortoiliac stenting although is less frequently seen than infrapopliteal interventions. Covered stents designed with polytetrafluoroethylene or Dacron lining were thought to prevent restenosis by providing a mechanical barrier to restenosis and neointimal hyperplasia from the adjacent vessel wall. However, experience derived from stenting with covered balloon-expandable or self-expanding stents of de novo aortoiliac disease has raised a variety of concerns. Small studies in the femoral and iliac arteries suggest similar rates of restenosis to noncovered stents at 12 months but possibly increased restenosis over a longer time frame. In 1 study, thrombotic occlusion of covered stents occurred in 10% of cases within 30 days of raising concerns over the long-term risks of stent thrombosis. Covered stents also occlude side branches important for distal collateralization, which are important in preventing ALI in the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Goals for Endovascular Therapy for Peripheral Arterial Disease by Clinical Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Goal</strong></td>
<td><strong>Angiographic Goal</strong></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>Symptom resolution without recurrence</td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>Limb salvage</td>
</tr>
<tr>
<td>Acute limb ischemia</td>
<td>Limb salvage</td>
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</table>
event of stent thrombosis. Covered stents do not eliminate the problem of restenosis, but likely shift its pattern from in-stent to edge-restenosis particularly if the stent is oversized. The Covered Versus Balloon-Expandable Stent Trial (COBEST) found a higher patency rate with covered compared with noncovered stents in complex aortoiliac disease; however, the restenosis rate in the noncovered stent group was unusually high. The Dutch Iliac Stent Trial: Covered Balloon-Expandable Versus Uncovered Balloon-Expandable Stents in the Common Iliac Artery (DISCOVER) trial, a prospective, double-blind, controlled, multicenter trial of 174 total patients with common iliac artery occlusions or stenoses >30 mm in length randomized to covered versus uncovered balloon-expandable stents is currently enrolling patients. Until the results of this or similar trials are available, the use of covered stents remains largely relegated to treating aneurysmal segments or iatrogenic arterial perforations.

In sum, given the superior patency associated with primary stenting and their inherent advantages in complex or ostial iliac disease, balloon-expandable stents are usually used to revascularize the majority of patients with IC and isolated occlusive aortoiliac disease. A provisional stent strategy for focal lesions of lesser complexity is a reasonable strategy particularly if little or no elastic recoil.

**Femoropopliteal Disease**

As the longest artery with the fewest side branches, fixed between the hip and knee joints, and the most common location of occlusive disease precipitating IC, the superficial femoral artery (SFA) is uniquely subjected to important and complex external mechanical stresses including flexion, compression, and torsion. Its distal segment traverses the adductor canal which further enhances compression during thigh contraction. Consequently, the primary patency and clinical outcomes for endovascular revascularization to treat IC in this location are significantly influenced by these repetitive mechanical stresses believed related to stent fracture, restenosis, and thrombosis.

**Self-Expanding Stents.** Now mostly made of nitinol, self-expanding stents possess thermal shape memory and are more resilient to mechanical stresses by expanding on deployment at body temperature and then re-expanding after external radial compression. Although these have revolutionized the treatment of infrainguinal PAD, long lesions (>200 mm) are still associated with relatively high rates of restenosis. The Vienna randomized trial showed that patients receiving self-expanding stents for femoral artery disease had lower rates of restenosis and better walking capacity than those treated by balloon angioplasty alone. However, the Femoral Artery Stenting Trial (FAST) in patients with shorter femoral lesions (<100 mm) showed no difference. The Randomized Study Comparing the Edwards Self-Expanding LifeStent Versus Angioplasty Alone in Lesions Involving the SFA and/or Proximal Popliteal Artery (RESILIENT) trial also suggested better outcomes with primary stenting using self-expanding stents compared with balloon angioplasty (12-month primary patency of 87.3% versus 45.2%) although the crossover rate to stenting in the angioplasty group was high (40%) and was included as an adverse end point. Post hoc analysis suggests that in short SFA lesions (<100 mm), outcomes after balloon angioplasty alone are similar to self-expanding stents. Schillinger et al randomized patients with obstructive femoropopliteal disease to self-expanding stents or balloon angioplasty with provisional stenting, and showed superior patency rates for stenting SFA lesions >100 mm at 6 and 12 months. Given the dismal patency rates associated with balloon angioplasty alone for SFA lesions >100 mm, the use of self-expanding stents for long SFA lesions is recommended whereas shorter lesions can be adequately treated with angioplasty and provisional stenting (Figure 1).

**Table 2. Common Endovascular Revascularization Strategies Stratified by Anatomic Level**

<table>
<thead>
<tr>
<th>Vessel Diameter</th>
<th>Conventional</th>
<th>Drug-Coated</th>
<th>Stenting (Bare-Metal)</th>
<th>Drug-Eluting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortoiliac</td>
<td>=7–10 mm</td>
<td>Focal disease</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Femoropopliteal</td>
<td>=5–7 mm</td>
<td>Focal disease</td>
<td>Recently approved</td>
<td>Diffuse disease</td>
</tr>
<tr>
<td>Infrapopliteal</td>
<td>=2–5 mm</td>
<td>Focal or diffuse disease</td>
<td>Provisional for poor balloon result</td>
<td>Coronary stents</td>
</tr>
</tbody>
</table>

**Table 3. Rutherford-Baker and Fontaine Classifications of Chronic Peripheral Arterial Disease Severity**

<table>
<thead>
<tr>
<th>Symptom Complex</th>
<th>Rutherford-Baker Classification</th>
<th>Fontaine Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Stage 0</td>
<td>Stage I</td>
</tr>
<tr>
<td>Mild claudication</td>
<td>Stage 1 (symptoms with &gt;200-m walking)</td>
<td>Stage IIa (symptoms with &gt;200-m walking)</td>
</tr>
<tr>
<td>Moderate claudication</td>
<td>Stage 2</td>
<td>Stage IIb (symptoms with &lt;200-m walking)</td>
</tr>
<tr>
<td>Severe claudication</td>
<td>Stage 3</td>
<td>Stage III</td>
</tr>
<tr>
<td>Rest pain</td>
<td>Stage 4</td>
<td>Stage IV</td>
</tr>
<tr>
<td>Ischemic ulceration (limited to digits)</td>
<td>Stage 5</td>
<td>Stage IV</td>
</tr>
<tr>
<td>Severe ischemic ulceration or frank Gangrene</td>
<td>Stage 6</td>
<td>Stage IV</td>
</tr>
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</table>
Other concerns include stent fracture after SFA self-expanding stenting, which may lead to in-stent restenosis (ISR) and occlusion.\textsuperscript{43} The incidence of stent fracture seems to vary depending on the type of stent used, its design, the length of stented segment, and the number of stents implanted. One analysis suggests that no more than 2 stents should be implanted to treat SFA disease, and recommends avoiding multiple stents and limiting the total length of stenting as much as possible.\textsuperscript{44} New innovation in stent design may help decrease stent fracture without compromising clinical outcomes. Recently, the Complete Self-Expanding trial that used a new nitinol self-expanding stent to treat femoropopliteal disease demonstrated a low rate of target lesion revascularization (TLR) and no stent fractures at 12 months.\textsuperscript{45} The Supera Interwoven Nitinol Stent Outcomes in Above-Knee Interventions (SAKE) study also showed high rates of patency at 6 and 12 months with no stent fractures for femoropopliteal disease treated with the novel interwoven-wire Supera stent.\textsuperscript{46} Furthermore, the outcomes after popliteal stenting with the Supera stent from the Leizping Supera popliteal artery registry showed 6- and 12-month primary patency rates of 94.6% and 87.7%, respectively, with a significant increase in mean ABI (0.58 versus 0.97; \textit{P}<0.001) and no radiographic evidence of stent fracture at 15 months.\textsuperscript{47} Although the prospect of a feasible endovascular alternative to surgical intervention to treat occlusive popliteal disease is suggested by this observational study, more randomized clinical data on this topic are needed.

\textbf{Drug-Eluting Stents.} Restenosis remains one of the major limitations associated with long segments of SFA stenting, and stimulated the development of drug-eluting stents. The first trials (Sirolimus Coated Cordis SMART Nitinol Self-Expandable Stent for the Treatment of SFA Disease [SIROCCO I and II trials]) compared sirolimus-coated versus bare-metal self-expanding stents.\textsuperscript{48,49} Initial results were promising, but later results showed no clinical advantage with this particular stent platform, which was associated with a high rate of stent fracture (31\% of all patients).

Two studies have tested new platforms of self-expanding drug-eluting stents (DES) eluting other antiproliferative agents. The Superficial Femoral Artery Treatment with Drug-Eluting Stents (STRIDES) trial was a multicenter, nonrandomized, single-arm study assessing an everolimus-eluting self-expanding stent.\textsuperscript{50} Although stent fracture rates were low, the restenosis rates at 6 and 12 months were 6\% and 32\%, respectively (with a mean treated lesion length of 90 mm). The lack of a control group makes the interpretation of these results difficult. Recently, the Zilver PTX trial compared 24-month outcomes between a self-expanding stent eluting paclitaxel to balloon angioplasty alone.\textsuperscript{51} Although the study had a high crossover rate to stenting in the balloon angioplasty arm, patients receiving bail-out stenting in this arm were randomized to DES or bare-metal stents (BMS). Compared with the angioplasty only, the primary DES group showed higher primary patency with the DES (74.8\% versus 26.5\%) at 2 years. The provisional DES group also showed superior primary patency compared with the provisional BMS group (83.4\% versus 64.1\%). Subgroup analysis showed that treatment with DES was associated with superior outcomes for complex disease, including total occlusions and longer lesions (>70 mm), as well as high-risk patient cohorts such as those with diabetes mellitus or CLI (Rutherford class 4–6). A French study of the budgetary impact of using the more costly Zilver PTX stent showed net cumulative savings of €6 807 202 over 5 years by reducing the need for future reinterventions.\textsuperscript{52} A cost-effectiveness study in the United States is not yet available although this would suggest that tangible benefits in regards to both improved outcomes along with an overall reduction in healthcare expenditures could be realized for these particularly challenging lesions and patient populations. Although DES use for coronary revascularization requires a longer duration of dual antiplatelet therapy, the optimal length of treatment after peripheral DES implantation requires further investigation.

\textbf{Covered Self-Expanding Stents.} The use of covered self-expanding stents for obstructive femoropopliteal disease has been investigated to minimize the incidence of in-stent restenosis. The Viabahn endoprosthesis (W.L. Gore and Associates, Inc) was approved by the Food and Drug Administration in 2005 and remains the only covered stent

\begin{figure}[h]
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approved for treatment of SFA disease. An early trial of
patients with symptomatic SFA disease randomized to either
Viabahn stents or balloon angioplasty showed that ultrasound-
assessed primary patency (65% versus 40%) and clinical
improvement were better in the stent group.53 More recently,
the Viabahn Endoprosthesis Versus Bare Nitinol Stent in
the Treatment of Long Lesion Superficial Femoral Artery
Occlusive Disease (VIBRANT) trial randomized patients with
symptomatic complex lesions to Viabahn or conventional-
expanding stents and showed that ultrasound-assisted primary
patency was low and not statistically different between the
groups (53% versus 58% at 12 months and 24.2% versus
25.9% at 36 months), despite higher stent fracture in the
uncovered stent group (50% versus 2%).54 Data from the
Viabahn Endoprosthesis With Heparin Bioactive Surface
in the Treatment of Superficial Femoral Artery Obstructive
Disease (VIPER) registry evaluated the use of heparin-
bonded Viabahn stents and showed better primary patency
at 12 months (73%).55 The Viabahn Endoprosthesis with
PROPATEN Bioactive Surface Versus Bare Nitinol Stent in
the Treatment of Long Lesions in Superficial Femoral Artery
Occlusive Disease (VIASTAR) trial randomized patients to
either heparin-bonded Viabahn or bare-metal stents. A
per-protocol analysis showed a higher 12-month primary
patency rate (78.1% versus 53.5%; _P_=0.009) without an
increased incidence of stent thrombosis or ALI.56 However,
an intention-to-treat basis showed no difference in 12-month
primary patency (71% versus 55%; _P_=0.11) or freedom from
TLR (84.6% versus 77%). Longer term outcomes particularly
detailing the incidence of (late) stent thrombosis and restenosis
are still required.

Several important issues must be considered on the use
of covered stents to treat obstructive PAD. First, although
ISR after covered stents does not seem to be associated with
the length of stented segment as has been noted with un-
covered stents (perhaps by providing a barrier to neointimal
ingrowth), edge-restenosis can still occur, particularly if
the stent is oversized. Second, covered stents are associated
with a higher risk of stent thrombosis. Third, covering im-
portant collateral vessels may incur ALI if stent thrombosis
were to occur. Recent design modifications of the Viabahn
stent, including contoured edges and heparin bonding, may
help address these issues. Most notably, when compared
with DES, relatively lower primary patency rates are seen
with covered stents. Given these concerns, covered stenting
still requires longer term outcomes data and rigorous com-
parison with DES.

**Drug-Coated Balloons.** A recent innovation, DCBs have
potential benefits applicable to endovascular therapy. By
avoiding stent implantation and its attendant risks, including
thrombosis, fracture, and the need for prolonged antiplatelet
therapy, DCB may offer an innovative alternative to treat
common femoral, SFA, popliteal, and tibial disease. Preclinical
validation studies have suggested that homogenously
distributed drug delivery can be achieved with DCB.57 The
potential limitations include the lack of a mechanical scaffold
to address elastic recoil or dissection and the uncertainty
of delivering effective, homogenous concentrations of
antiproliferative agents to calcified or tortuous arterial
segments.

In the Local Taxane with Short Exposure for Reduction
of Restenosis in Distal Arteries (THUNDER) trial, 6- and
12-month rates of restenosis and TLR were lower after balloon
angioplasty with paclitaxel-coated versus uncoated balloons
for de novo SFA disease.58 The Paclitaxel-Coated Balloons
in Femoral Indication to Defeat Restenosis (PACIFIER) tri-
al also demonstrated improved end points for DCB versus
conventional angioplasty at 12 months.59 The Drug-Eluting
Balloon Evaluation for Lower Limb Multilevel Treatment
(DEBELLUM) trial randomizing patients with claudication or
CLI and de novo femoropopliteal and infrapopliteal disease to
DCB or conventional angioplasty showed less late lumen loss,
TLR, and adverse events with significantly more improve-
ment in ABI and Fontaine class at 12 months.60 More recently,
the Lutonix Paclitaxel-Coated Balloon for the Prevention of
Femoropopliteal Restenosis (LEVANT I) trial demonstrated
significantly decreased mean late lumen loss for de novo SFA
disease treated with the lower paclitaxel dose Lutonix DCB
versus conventional balloons in patients treated with either
angioplasty only or after stenting.61 The Drug-Eluting Balloon
in Peripheral Intervention for The Superficial Femoral Artery
(DEBATE-SFA) trial randomizing patients to upfront DCB or
conventional angioplasty followed by stenting showed simi-
larly encouraging outcomes at 12 months.61

Widely available elsewhere, DCBs have only recently been
approved by the Food and Drug Administration for use in the
United States. Although offering extremely attractive advan-
tages, continued study of this technology is required. Longer
term outcomes of international DCB registries have shown
that the occurrence of restenosis after DCB angioplasty for
de novo disease increases by 50% between 12 and 24 months.62
A similar catch-up phenomenon has also been described after
DCB angioplasty to treat ISR after SFA stenting.63 Cautious
optimism is needed to temper the enthusiasm associated with
this technology. Potentially revolutionary, DCB could greatly
extend the spectrum of disease treatable by increasing endo-
vascular options for disease over joints, bifurcations, or long
segments of disease in small vessels. They could potentially
require less dual antiplatelet therapy duration than DES with-
out eliminating future surgical options. However, several areas
of uncertainty regarding DCB angioplasty exist including its
efficacy compared with DES, as well as its utilization to treat
calcified lesions and tortuous arterial segments. Several clin-
ical studies of this novel technology are ongoing.

**Infrapopliteal Disease.** Most studies of infrapopliteal revascularization include more
CLI than IC patients.64,65 and IC alone is an uncommon indi-
cation.66 More recent trial data on infrapopliteal revascular-
ization with DES are generally geared toward ascertaining
important CLI outcomes (ie, limb salvage rates and ampu-
tation-free survival) rather than the relief of IC symptoms.
The YUKON Drug-Eluting Stent Below the Knee (YUKON-
BTX) study did report significantly greater improvement in
mean Rutherford class in the IC cohort treated with sirolimus-
eluting DES versus BMS for obstructive infrapopliteal disease
(−2 versus −1 change in mean Rutherford class; _P_=0.03)
and less target vessel revascularization (7.9% versus 18.2%; \(P=0.04\)) at 33 months.\textsuperscript{67} With a scarcity of clinical outcomes data, the complexity of the infrapopliteal vasculature, and the technical demands of below-the-knee interventions, infrapopliteal revascularization is usually reserved for CLI only (see below) and is not currently recommended for the routine treatment of IC.

### Critical Limb Ischemia

Representing the most severe clinical manifestation of chronic PAD, CLI is defined by the presence of chronic ischemic rest pain, ulceration, or gangrene caused by critically diminished perfusion attributable to occlusive arterial disease and usually associated with an ABI<0.4 and toe pressure <30 mm Hg (ie, Rutherford–Baker stages 4–6 and Fontaine stages III and IV; Table 3). CLI has a 25% mortality rate at 12 months, and nearly half of all untreated CLI patients will progress to major amputation within this timeframe.\textsuperscript{68,69} Major amputation of a limb (ie, above the ankle) is associated with loss of independence, diminished quality of life, and poor overall survival.\textsuperscript{70} If the extent of the limb amputation is investigated particularly for the potential to diminish the need for future reintervention. The early experience has been promising. In the initial study using the IN.PACT paclitaxel-coated Amphilion
balloon (Medtronic) to treat 109 limbs with long infrapopliteal lesions (>80 mm) in 104 mostly CLI patients, 12-month rates of clinical improvement (91.2%), complete wound healing (74.2%), TLR (17.3%), and limb salvage (95.6%) were encouraging.88 Notably, angiographic restenosis occurred much less frequently at 3 months compared with a historical balloon angioplasty control group (27.4% versus 69%). Versus conventional angioplasty alone, DCB are associated with lower rates of restenosis and target vessel revascularization and potentially higher rates of wound healing.89 For CLI in diabetic patients, the Drug-Eluting Balloon in Peripheral Intervention for Below The Knee Angioplasty Evaluation (DEBATE-BTK) trial showed significantly less restenosis, TLR, and target vessel occlusion after treatment with DCB versus conventional angioplasty.89 Although these early experiences seem promising, concerns have recently arisen. The IN.PACT DEEP prospective, multicenter randomized trial of 358 CLI patients designed to compare infrapopliteal angioplasty with the Amphirion DCB (Medtronic) versus standard angioplasty was terminated prematurely because of a trend toward more major amputation in the DCB arm (8.8% versus 3.6%; P = 0.08).90 These results have led to withdrawal of this platform from the market. Some have surmised that the coating of paclitaxel on this balloon after wrapping, compared with coating with an antiproliferative drug prior to balloon wrapping as occurs with other DCBs, may have led to inadequate drug delivery to the vessel wall and these negative results.91 Although attractive in concept, the use of DCB for this indication requires further careful evaluation. Several trials outside of the United States are ongoing to hopefully elucidate whether this promising new technology can be used in a safe and efficacious manner to treat infrapopliteal CLI.92 The recent approval of the Lutonix DCB by the Food and Drug Administration will allow for United States registry studies that will complement those ongoing elsewhere to help better understand outcomes related to its use. In addition, a rigorous comparison of infrapopliteal DCB and stenting (see Infrapopliteal Stenting for CLI section of this article) would be an important area of future investigation.

**Infrapopliteal Stenting for CLI.** Because of the typically small diameter vessels, coronary BMS and DES have been used for infrapopliteal stenting. Several unique issues must be considered. Because of the diffuse nature of tibial disease, extensive infrapopliteal stenting in conjunction with poor outflow may elevate the risk of stent thrombosis. The use of DES, in particular, may amplify this risk further because of issues related to delayed re-endothelialization. Suboptimal stent expansion and apposition or flow-limiting dissection because of severely calcified small-vessel disease may also be encountered.

Small, single-center nonrandomized studies have shown that rates of major amputation, surgery, and TLR are lower for patients with CLI treated with DES versus BMS.93,94 The YUKON-BTX trial randomizing CLI and IC patients to sirolimus-eluting DES or BMS demonstrated significantly higher event-free survival (65.8% versus 44.6%; P = 0.02) and lower amputation rates (2.6% versus 12.2%; P = 0.03) with a trend toward lower target vessel revascularization (9.2% versus 20%; P = 0.06) at 33 months for those treated with DES.57 For the trial’s CLI cohort in particular, no significant difference in death or target vessel revascularization was shown although the rate of major or minor amputation was lower with DES (5.3% versus 22.6%; P = 0.04). Rates of limb salvage were equally high in both arms (97.4% versus 87.1%; P = 0.10). In the Drug-Eluting Stents in the Critically Ischemic Lower Leg (DESTINY) trial, significantly higher primary patency (85% versus 54%; P = 0.0001) and freedom from repeat revascularization (91% versus 66%; P = 0.001) at 12 months was shown for patients with CLI treated with everolimus-eluting DES versus BMS.95 The incidence of major amputation and death were, however, not different. Infrapopliteal stenting has also been compared with angioplasty for patients with CLI. The Comparing Angioplasty and Drug-Eluting Stents in the Treatment of Subjects with Ischemic Infrapopliteal Arterial Disease (ACHILLES) trial randomized 200 patients with CLI to either sirolimus-eluting DES or angioplasty and showed that angiographic restenosis (22% versus 42%; P = 0.019) and vessel patency (75% versus 57%; P = 0.025) were significantly superior for the DES group96 However, no difference in freedom from TLR or amputation was shown. Studies by others have demonstrated similar results.97,98

Thus, DES seems to offer less repeat revascularization compared with BMS and possibly less amputation, but the value of its routine use compared with balloon angioplasty is less certain. Ongoing and future trials will hopefully clarify the clinical efficacy and cost-effectiveness of DES for this indication. Primary balloon angioplasty with provisional stenting, using either BMS or DES based on operator discretion, for a suboptimal angiographic result or flow-limiting dissection remains a reasonable strategy for infrapopliteal revascularization for CLI at this time.

**Acute Limb Ischemia**

ALI is the sudden decrease in limb perfusion (defined as within 14 days) that threatens limb viability. It is associated with a grave prognosis, with amputation rates ranging between 5% and 30% and mortality rates as high as 18%.99,100 In the vast majority of cases, ALI is caused by peripheral embolization of intracardiac thrombus, typically due to atrial fibrillation. Other mechanisms include embolization of aneurysm-associated thrombus, iatrogenic causes from arterial catheterization, mechanical issues related to peripheral bypass grafts, paradoxical embolism, or in situ thrombosis of diffuse atherosclerosis. In contrast to thrombotic ALI, embolic ALI typically presents with the acute onset of severe symptoms likely owing to the lack of well-developed distal collateralization. Emboli typically lodge at branch points in the circulation (ie, aortoiliac and femoral bifurcations and the tibial trifurcation) where the arterial caliber diminishes. Thrombotic ALI may occur anywhere along the arterial tree although a common site is the SFA. Mortality rates with surgical revascularization can be as high as 25%.101 Systemically administered thrombolytic agents are generally ineffective, whereas catheter-directed thrombolysis (CDT) has greater efficacy and represents a potential alternative to surgery.

In an early study randomizing patients with ALI of <7 days duration to either CDT or operative intervention, the 12-month amputation rate was 18% in both arms but all-cause mortality...
was significantly higher for the surgical arm (84% versus 58%; \( P=0.01 \)).\textsuperscript{101} CDT was equally effective for both embolic and thrombotic ALI. The Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial randomized patients with ALI to CDT or surgery and showed that for patients with symptoms for <14 days, endovascular therapy resulted in significantly greater 6-month limb salvage (89% versus 70%; \( P=0.02 \)) with a trend toward lower all-cause mortality.\textsuperscript{102} The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial randomized patients with ALI with symptom duration of <14 days and native arterial or bypass graft occlusion to CDT or surgery.\textsuperscript{103} Rates of amputation-free survival at 12 months were equivalent (65% versus 69.9%; \( P=0.23 \)) although major hemorrhagic complications were more frequent in the thrombolysis group (12.5% versus 5.5%; \( P=0.005 \)). On the basis of these trials, endovascular approaches are a viable treatment option for many patients with ALI. Specific clinical details may compel the selection of one treatment strategy over another. For example, the risk of 30-day stroke (1.3% versus 0%) and major hemorrhage (8.8% versus 3.3%) is higher for CDT although patient comorbidities may make the risks of general anesthesia and open surgery prohibitive.\textsuperscript{104}

Prompt restoration of perfusion to the ischemic zone is required to achieve limb salvage. Contemporary treatment of ALI requires a rapid clinical assessment, early systemic heparinization, and timely management based on the Rutherford classification for ALI (Table 4 and Figure 2). For patients with a viable or marginally threatened limb (Rutherford class I and IIa), an upfront endovascular strategy can be considered based on the availability of local expertise. An immediately threatened limb (Rutherford class IIb) is a surgical emergency, often requiring fasciotomy to minimize ischemia from compartment syndrome caused by reperfusion injury. For a marginally threatened limb, the critical clinical determinants that would suggest that an endovascular option could still be exercised include only mild sensory loss without motor impairment (best tested by toe dorsiflexion against resistance), still audible arterial Doppler signals, and the presence of capillary return. Motor impairment indicates the need for urgent surgical intervention. Irreversible damage with frank infarction as indicated by a profound loss of all sensory function, paralysis, the lack of capillary refill, and inaudible arterial and venous Doppler signals (Rutherford class III) is an indication for surgical amputation (Table 4).

Several areas of uncertainty still exist in regards to optimal endovascular therapy for ALI. This includes a comparative analysis of various endovascular approaches (ie, CDT, ultrasound-assisted CDT, adjunctive mechanical or aspiration thrombectomy), as well as the types of thrombolytic agents and adjunctive anticoagulants that are most efficacious for the treatment of embolic versus thrombotic ALI. The role of hybrid interventions also remains largely undefined.

**Adjunctive Devices for PVI**

The success of PVI is oftentimes limited by the complexity of disease, including heavy calcification and long CTOs, where traditional techniques have lower procedural success rates.\textsuperscript{105} To address these obstacles, a variety of specialty adjunctive devices have been developed to facilitate primary wire crossing and plaque debulking. Although promising, no randomized clinical data are available to support the routine use of these specialty devices.

**Devices Facilitating Wire Crossing**

CTOs are present in 40% of patients with PAD and are typically associated with lower rates of successful wire crossing.\textsuperscript{106,107} A wide array of devices specially designed to assist wire crossing across long lengths of severe disease is available.

**Devices Facilitating Crossing Occlusions**

Several devices have been developed although the clinical experience with them is usually limited to small studies since no randomized trial data are available. In general, these devices use a variety of different specialized technologies to assist in penetrating and negotiating through CTOs. The Frontrunner XP system (Cordis) is a 6F catheter tipped with a small hinged jaw that is able to perform controlled blunt microdissection through plaque. The Crosser CTO system (Bard Peripheral), which relies on vibrational energy to penetrate and dissect through plaque, has been described in a few small, single-center observational series.\textsuperscript{108,109} The TruePath CTO (Boston Scientific) system is designed with a 0.0018” diamond tip rotating at 13,000 rpm for mechanical recanalization. The Turbo Elite catheter (Spectranetics), which delivers short pulses of ultraviolet energy to ablate atherosclerotic tissue and thrombus, has been investigated in the Laser-assisted Angioplasty for Critical Ischemia international registry of 145 patients and showed a technical success rate (defined as residual stenosis <50%) of 86%.\textsuperscript{110} A collection of specialty catheters (Wildcat, Ocelot, Kittycat, and Kittycat2; Avinger) has also been developed recently that once engaged within the plaque are rotated in a clock- or counterclockwise manner to traverse through CTOs; no clinical outcomes data are yet available.\textsuperscript{111,112} The SafeCross CTO system (Spectranetics) combines optical coherence reflectometry imaging with radiofrequency ablation to penetrate CTOs.
Devices Facilitating Distal Lumen Re-entry

Several devices are designed to direct wires into the true lumen after dissecting through the artery wall around plaque. The Pioneer Reentry catheter (Volcano) has a curved needle housed in its tip and an integrated phased-array ultrasound transducer that helps redirect a guidewire into the distal lumen. The Outback LTD Reentry catheter (Cordis) is designed with a blunt atraumatic tip to house a needle to similarly direct a wire into the distal lumen. Finally, the Viance catheter (Covidien) is designed with a blunt atraumatic tip to minimize perforation, and distal re-entry is achieved using an Enter balloon (Covidien) with an asymmetrical wire exit port that directs a wire into the true lumen. The OffRoad balloon (Boston Scientific) has a similar type of design facilitating distal true lumen re-entry.

The routine use of devices to either cross occlusions or achieve distal re-entry cannot be recommended because of the current lack of randomized data comparing these devices with conventional techniques in conjunction with alternate access (eg, retrograde via a pedal artery). Subintimal crossing using a stiff, looped guidewire in conjunction with a supportive balloon catheter has been associated with a high rate of success, and in a recent study, shorter procedure time and equal 36-month patency compared with standard techniques.113,114 There are no published data comparing the efficacy of these diverse platforms.

Atherectomy Devices

Atherectomy devices are designed to debulk plaque and likely improve compliance within a treated segment for angioplasty and stenting. However, there are no randomized comparative data to support their incremental value beyond standard techniques.

Directional Atherectomy

The SilverHawk plaque excision system (ev3) uses directional atherectomy to excise and remove plaque from one side of the arterial wall. The Determination of Effectiveness of the SilverHawk Peripheral Plaque Excision System for the Treatment of Infraroungual Vessels/Lower Extremities (DEFINITIVE-LE) multicenter registry study reported a 12-month primary patency rate of 78% for patients with IC and 95% for patients with CLI.115 However, the lack of a randomized design with a comparison stenting arm makes the interpretation of these results difficult.

Rotational Atherectomy

Several rotational atherectomy devices are available including the Rotablater (Boston Scientific), which consists of a rotating diamond-encrusted burr, the Jetstream G2 device (Pathway Medical), which uses differential cutting and aspiration, and the Diamondback 360° Orbital Atherectomy System (Cardiovascular Systems), which consists of an eccentric, diamond-coated, abrasive crown that ablates a variable radius modulated by crown rotational speed.116

A recent meta-analysis showed no clear benefit associated with atherectomy alone compared with balloon angioplasty.117 Therefore, the indications for peripheral atherectomy remain largely undefined for infraroungual interventions. Anecdotally, the use of atherectomy has typically been reserved for heavily calcified lesions, which may limit stent or balloon expansion, or areas where stent fracture is a concern (ie, common femoral and popliteal arteries). Although registry data have suggested that distal embolization is a rather frequent occurrence, its incidence was low in the contemporary nonrandomized DEFINITIVE-LE study.118 Although no high-quality data are available to guide the use of distal protection for atherectomy, it is often used particularly in the presence of poor or single-vessel distal run-off.

Surveillance After PVI

There are no consensus guidelines on the optimal timing and type of surveillance after PVI and its impact on patency remains uncertain.83 The optimal frequency of clinical follow-up after a PVI should probably be based on specific factors such as the presenting clinical syndrome (ie, IC versus CLI or ALI), the complexity of the intervention, and the anatomic disease that was treated.

Pharmacotherapy

After PVI, the treatment of blood pressure, statin therapy to control lipid levels, smoking cessation and regular exercise are important secondary prevention measures to help minimize future cardiovascular risk. Lifelong monotherapy with low-dose aspirin is usually used after all endovascular procedures. Aspirin is justifiable to reduce cardiovascular events in general and may help prevent thrombosis at the site of a peripheral intervention.119 In trials of femoral BMS, clopidogrel was used in conjunction with aspirin for 1 to 3 months.37,120 Because no randomized outcomes data to guide therapy are available, treatment should be individualized based on factors such as bleeding risk. In addition, clinical studies mostly in Japanese patients suggest that cilostazol may have a sizeable effect in reducing ISR.121–123 The routine administration of cilostazol after PVI has not been incorporated into any consensus guideline statements as of yet but may be a reasonable in selected patients with recalcitrant ISR.

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Table 4. Rutherford Classification of Acute Limb Ischemia128

<table>
<thead>
<tr>
<th>Rutherford Class</th>
<th>Prognosis</th>
<th>Clinical Examination</th>
<th>Doppler Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I: viable, not threatened</td>
<td>Not immediately threatened</td>
<td>Normal</td>
<td>Audible</td>
</tr>
<tr>
<td>Class IIa: marginally threatened</td>
<td>Salvageable with prompt therapy</td>
<td>Minimal loss</td>
<td>Often inaudible</td>
</tr>
<tr>
<td>Class IIb: immediately threatened</td>
<td>Salvageable if treated immediately</td>
<td>Mild sensory loss and rest pain</td>
<td>Usually inaudible</td>
</tr>
<tr>
<td>Class III: irreversible</td>
<td>Irreversible tissue and nerve damage</td>
<td>Profound loss</td>
<td>Inaudible</td>
</tr>
</tbody>
</table>

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Clinical Surveillance

Routine ABI shortly after intervention is recommended to establish a baseline to guide future surveillance. Surveillance using duplex ultrasound after surgical revascularization has been adopted although no studies directly comparing routine surveillance with no surveillance have been conducted. Controversy also exists on the best and most cost-effective method of surveillance. The timing of evaluation after peripheral revascularization has been studied retrospectively, but no prospective randomized data focusing on this are yet available to guide management. Our experience has suggested that restenosis most frequently occurs between 3 and 6 months after an intervention so clinical follow-up for recurrent signs or symptoms of restenosis are typically scheduled for 1 to 3 months after the intervention, then every 6 months for 1 year then at longer intervals. The exact timing and frequency of surveillance is not uniform and should be tailored to important issues such as the presenting clinical syndrome, the complexity of intervention performed and the anatomy treated.

Surveillance includes inquiring about recurrent symptoms, compliance with medical therapy and a supervised walking program, as well as general cardiovascular risk factor optimization. The physical examination focuses on the quality of all pulses and lower extremity perfusion, tissue integrity, and a survey for the stigmata of distal embolization. The ABI is a quick office-based assessment of infragingual patency, and more sophisticated tests including segmental leg pressures, pulse volume recordings, and duplex ultrasound may also help detect early restenosis.

The cost-effectiveness of routine vascular laboratory testing or duplex ultrasound is uncertain. Early detection may lead to a less complex reintervention if it identifies a stenosis rather than an occlusion. The value of close surveillance after femoral interventions is likely greater in patients with long lesions. The definition of a significant change in noninvasive testing that warrants reintervention is also debated. Recurrence of symptoms associated with decreases in ABI≥0.15 (the intradividual variability of ABI measurement) and duplex ultrasound showing an incremental increase in the peak systolic velocity ratio of >3-fold between adjacent arterial segments are criteria consistent with a significant restenosis.

Future Directions

Several promising new therapies such as DES and DCB are being validated. The early data guiding management with these novel devices have largely been based on intermediate-term (ie, 12 months) results and longer term outcomes are still required. With growing sentiment to control healthcare expenditures, studies on the cost-effectiveness of these novel and more costly treatments are also necessary, particularly for the specialty adjunctive CTO and atherectomy devices, which still deserve randomized study versus more conventional, less costly techniques. There is a need for more uniform trial design with regard to end points, which have varied widely. Anatomic end points such as duplex ultrasound-assessed binary restenosis have traditionally been reported for many trials with an unclear association with more important functional end points such as walking performance.


Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and interwoven nitinol stent registry.


Endovascular Intervention for Peripheral Artery Disease
Arun K. Thukkani and Scott Kinlay

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