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REVIEW

Advances in Endovascular Treatment of Critical Limb Ischemia

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Critical limb ischemia (CLI) represents the most severe clinical manifestation of peripheral arterial disease. In the absence of timely revascularization, CLI carries high risk of mortality and amputation. Over the past decade, endovascular revascularization has rapidly become the preferred primary treatment strategy for CLI, especially for the treatment of below-the-knee disease. Advances in percutaneous devices and techniques have expanded the spectrum of patients with CLI who are deemed candidates for revascularization. This review will focus on advances in endovascular options for the treatment of CLI, in particular for below-the-knee disease. (*Circ J* 2011; **75:** 756–765)

Key Words: Angioplasty; Peripheral arterial disease; Stents

Critical limb ischemia (CLI) represents the most severe clinical manifestation of peripheral arterial disease (PAD) and is defined by the presence of chronic ischemic rest pain, ischemic ulcers, or gangrene attributable to objectively proven arterial occlusive disease.[1] CLI is a chronic disease process that ultimately leads to limb loss if left untreated and perhaps death from development of sepsis. In the absence of timely revascularization, CLI carries a 25% risk of mortality and another 25% risk of amputation over the next year.[2]

Prompt revascularization is the preferred primary treatment for patients with CLI. However, amputation without revascularization continues to be performed for many patients with CLI. Recent series have reported revascularization rates of only 40% in patients with CLI.[3] The low revascularization rates are partly because patients with CLI are referred late in their condition and also there is no agreed upon definition of a non-salvageable limb.[4,5]

Over the past decade, endovascular revascularization has rapidly become the preferred primary treatment strategy for CLI enabled by advances in percutaneous devices and techniques.[6,7] The low morbidity of percutaneous procedures compared with surgical revascularization has expanded the spectrum of patients with CLI who are deemed candidates for revascularization. In patients who are poor candidates for surgery, such as those with poor distal targets, a lack of adequate saphenous vein for bypass grafting, and those with severe medical comorbidities, endovascular therapy might offer the only opportunity for limb salvage. Recent series have reported limb salvage rates up to 90% can be achieved with endovascular therapy in CLI patients.[8] Endovascular intervention should not preclude the possibility of subsequent surgery, and in fact there is often a role for both modalities in so-called 'hybrid' procedures in patients who are not candidates for completely percutaneous endovascular revascularization as a result of complex anatomy or suboptimal lesion location.

Most of the currently available endovascular therapies are designed primarily for intervention in the aorto-iliac and superficial femoral artery segments. The next frontier and innovation in endovascular therapies for CLI is targeted towards below-the-knee (BTK) vessels. The anatomy and physiology of BTK vessels, such as smaller vessel diameter, heavy calcification, long total occlusions, and poor outflow represent unique challenges to endovascular therapy. Recent advances have enhanced our ability to use endovascular procedures to treat CLI involving BTK disease with comparable results to open surgery. This review will focus on advances in endovascular options for the treatment of CLI, in particular for BTK disease.

Diagnosis and Assessment

The diagnosis of CLI is largely clinical and straightforward based on history and vascular examination. The severity of symptoms from limb ischemia might be classified using either the Fontaine or Rutherford classification (**Table 1**). Although CLI is primarily a clinical diagnosis, it should be

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Table 1. Fontaine and Rutherford Classification

Fontaine		Rutherford		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue damage
		III	6	Major tissue damage

Table 2. Summary of Recommendations of the TransAtlantic Inter-Society Consenus II Working Group Guidelines*

Arterial stenosis	Usually endovascular (Type A)	Endovascular preferred (Type B)	Surgery preferred (Type C)	Usually surgery (Type D)
Infrarenal aorta and Iliac	Stenosis ≤3 cm	Stenosis ≤3 cm, Stenosis 3–10 cm, Unilateral CIA or EIA occlusions	Bilat CIA occlusions, Unilateral CIA and EIA occlusions	Aortic occlusion, Bilateral EIA occlusions, Disease extending into aorta and/or CFA
Femoral popliteal	SFA stenosis ≤10 cm or occlusion ≤5 cm	SFA stenosis or occlusion ≤15 cm; popliteal stenosis	SFA stenosis or occlusion >15 cm; recurrent disease	Complete SFA or popliteal occlusions
Infrapopliteal	None**	None**	Stenoses ≤4 cm or occlusions ≤2 cm	Diffuse disease or occlusions >2 cm
Outcomes	Excellent†	Excellent†	Angioplasty/stent only has modest results and is indicated when surgery contraindicated or patient reasons	Endovascular approach not advised unless symptoms are limb threatening and surgery is not possible

CIA, common iliac artery; EIA, external iliac artery; SFA, superficial femoral artery.
*The presence of calcification or multiple lesions generally moves a recommendation towards open surgery (eg, Type B to Type C).
**Infrapopliteal interventions have severe outcomes if unsuccessful; therefore there is no Type A or B recommendation.
†Excellent results obtainable via an endovascular approach.

confirmed objectively and early in the disease process through ankle-brachial index (ABI), toe systolic pressures, or transcutaneous partial pressure of oxygen ($TcPO_2$). Once the diagnosis is confirmed, the goals of treating CLI are to relieve ischemic pain, heal ischemic ulcers, prevent limb loss, improve patient function and quality-of-life, and prolong survival. In CLI patients, non-invasive parameters are useful in assessing the likelihood of wound healing. An ABI <0.5, ankle systolic pressure <50 mmHg, toe systolic pressure <30 mmHg and $TcPO_2$ <30–50 mmHg are consistent with CLI and impaired wound healing potential.

Computer tomography (CT) and magnetic resonance (MR) angiography are emerging non-invasive modalities in the evaluation of PAD and help in the planning of complex procedures. The current generation of CT and MR imaging might not always provide specific information regarding BTK anatomy in great detail, but often will provide excellent images of the iliofemoral inflow arteries.

Limitations of Current Guideline Recommendations

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) provides classification for infrainguinal lesions, according to the arterial segments involved and 4 grades of complexity.[2] Treatment recommendation of less complex lesions (Type A and B) is endovascular therapy and more complex lesions (Type C and D) is surgery (Table 2). However, the TASC morphological criteria inadequately consider common anatomic conditions of multilevel disease in CLI as each lesion is classified separately, thus failing to describe the overall severity of the disease and no specific classification is provided for BTK arterial involvement. In CLI patients lesions are frequently long and involvement of the foot outflow arteries is common. Assignment of these type C and D lesion to surgery is based on outdated experience, not taking into account recent progress of endovascular techniques in CLI patients. The revised TASC-II guidelines state "There is increasing evidence to support a recommendation for angioplasty in patients with CLI and infrapopliteal artery occlusion".[2]

Trends in Lower Extremity Bypass Surgery, Endovascular Interventions and Major Amputations

Recent series have reported decline in the numbers of surgical procedures due to improved medical and endovascular interventions.[9] In the USA, between 1996 and 2006, the total number of all lower extremity vascular procedures almost doubled and endovascular interventions increased more than 3-fold (from 138 to 455 per 100,000; risk ratio (RR) 3.30; 95% confidence interval [CI] 2.9–3.7), while bypass surgery decreased by 42% from 219 to 126 per 100,000 (RR 0.58;

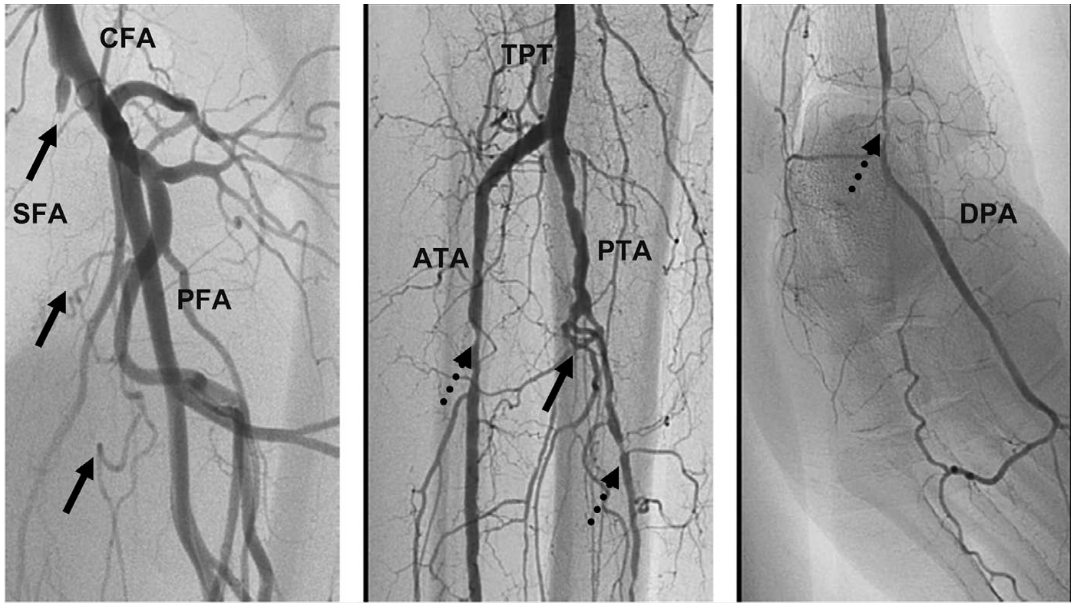

Figure 1. Critical limb ischemia is usually caused by multilevel disease but invariably involves below-the-knee arteries. ATA, anterior tibial artery; CFA, common femoral artery; DP, dorsalis pedis; PTA, posterior tibial artery; SFA, superficial femoral artery; TPT, tibial peroneal trunk. Solid arrows, occlusions; dotted arrows, stenosis.

95%CI: 0.5–0.7).[10] These changes far exceed simple substitution, as more than 3 additional endovascular interventions were performed for every 1 procedure declined in lower extremity bypass surgery. During this same time period, major lower extremity amputation rates have fallen by more than 25% from 263 to 188 per 100,000 (RR 0.71, 95%CI 0.6–0.8). However, further study is needed before any causal link can be established between lower extremity vascular procedures and improved rates of limb salvage.

Surgical vs. Endovascular Therapy for CLI

The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial compared percutaneous transluminal angioplasty (PTA) with surgery in 452 patients with CLI.[11] The primary endpoint, amputation-free survival, was similar for PTA and surgery at 1 year (71% vs. 68%, P=NS) and 3 years (52% vs. 57%, P=NS). Although there was no significant difference in mortality at 30 days, surgery was associated with a higher post-procedure morbidity. During the initial hospitalization, almost 3 times as many patients treated with surgery required admission to the intensive care or high dependency unit compared to those treated with PTA (27% vs. 7.5%), which resulted in higher cost of hospitalization in the surgical group. Angioplasty was associated with a higher immediate failure rate and 12-month re-intervention rates in the BASIL study. This did not affect the patients' candidacy for a second percutaneous procedure or subsequent surgery. BASIL demonstrated that endovascular therapy and surgery were comparable as first-choice therapy for CLI, but that PTA was less expensive and did not preclude subsequent treatment with surgery. Endovascular therapy was preferred if a patient was a candidate for either procedure, particularly if the patient's life expectancy was less than 2 years or without adequate vein for grafting because they are not expected to enjoy the long-term benefits of surgery.[11] Post-hoc analysis demonstrated that surgery was associated with a lower rate of amputation and death (hazard ratio 0.34, 95%CI 0.17–0.71) in patients alive at 2 years with the treated limb intact. In addition, the results of prosthetic bypass showed poor durability in BTK lesions.

Despite advances in endovascular interventions having expanded the options available for the invasive treatment of PAD, surgical bypass grafting remains the gold standard by which endovascular therapy is measured and is still favored for appropriate surgical candidates with adequate venous conduits for bypass.

BTK Disease

Approximately 30% of lesions of CLI cases are confined to the BTK arteries and most procedures include more proximal femoral and popliteal segments.[12] Disease in the tibial arteries tends to be diffuse and is usually associated with long segment stenoses and occlusions. The small calibre of the arteries, heavy calcification, slow flow of the distal beds, and poor run-off vessels represent significant challenges to endovascular interventions.

BTK intervention is appropriate for limb salvage, especially when there is focal tibial disease. Extensive tibial disease in a poor surgical candidate or a patient with no venous conduits for bypass is also reasonable. Whether endovascular therapy is appropriate as first-line treatment in all patients remain to be proven in randomized trials with long-term follow up. In a series of 993 patients with CLI who underwent endovascular revascularization, primary patency of successfully treated vessels at 5 years was 88% and limb salvage was achieved in 98% of patients.[12] A recent meta-analysis by Romiti et al, compared intermediate technical success, primary and secondary patency, limb salvage and survival for

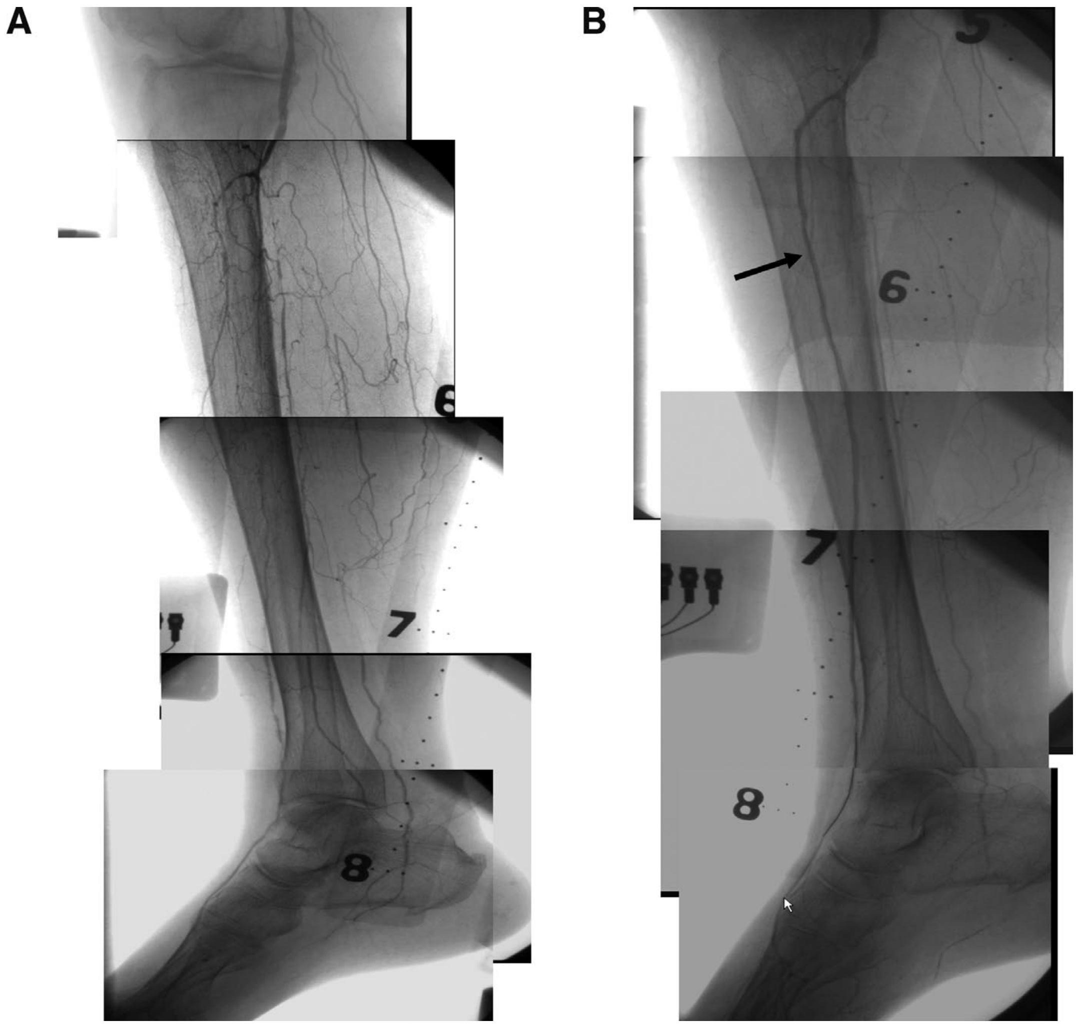

Figure 2. The primary goal of revascularization in critical limb ischemia is to achieve straight-line pulsatile flow to the distal extremity. (**A**) Total occlusions of all 3 tibial arteries; (**B**) patent anterior tibial artery (arrow) to dorsalis pedis artery after balloon angioplasty.

patients treated with PTA with venous bypass grafts.[8] Limb salvage rates were similar up to 3 years (82.4% and 82.3%, respectively) whereas 3-year primary patency rate was significantly lower after endovascular therapy (48.6%) compared to surgery (72.3%). The 35–40% discrepancy between limb salvage and primary patency rate could be partially explained by differences among assessment methods. Furthermore, duplex ultrasound, ABI measurement, and angiography might not represent precise methods to detect extent of ischemia in CLI, whereas $TcPO_2$ measurement compares more favorably with a CLI condition.[13]

Goals of Endovascular Therapy for CLI

The aim of revascularization is to improve total arterial flow to the affected limb to relieve ischemic pain, improve healing of ulcer, avoid or reduce level of leg amputation, reduce duration and rate of hospitalizations, improve mobility, quality-of-life and survival. The principle is that less blood flow is required to maintain tissue integrity than to heal a wound, so restenosis does not always result in recurrent CLI unless there has been repeated injury to the limb. Therefore, the goal of endovascular therapy should emphasize more on limb salvage and less on long-term vessel patency.

CLI is usually caused by multilevel disease but invariably involves BTK arteries (**Figure 1**). Procedural success of endovascular revascularization for patients with CLI has been defined as dilation of all critical inflow lesions with a residual stenosis <30% and straight-line pulsatile outflow in at least one tibial vessel to the pedal arch (**Figure 2**).[14,15] This usually involves treatment of multiple arterial segments at the same setting. The current guidelines recommend that inflow disease (ie, the iliac and femoral vessels) should be addressed prior to treatment of outflow lesions (ie, popliteal and infrapopliteal arteries).[16]

Anatomy suitable for endovascular therapy is often present in 1 or more BTK vessels. The results of BTK intervention are closely related to degree of tissue damage.[8] With minor tissue damage, small improvement in perfusion might be enough for wound healing, even if patency is short term.

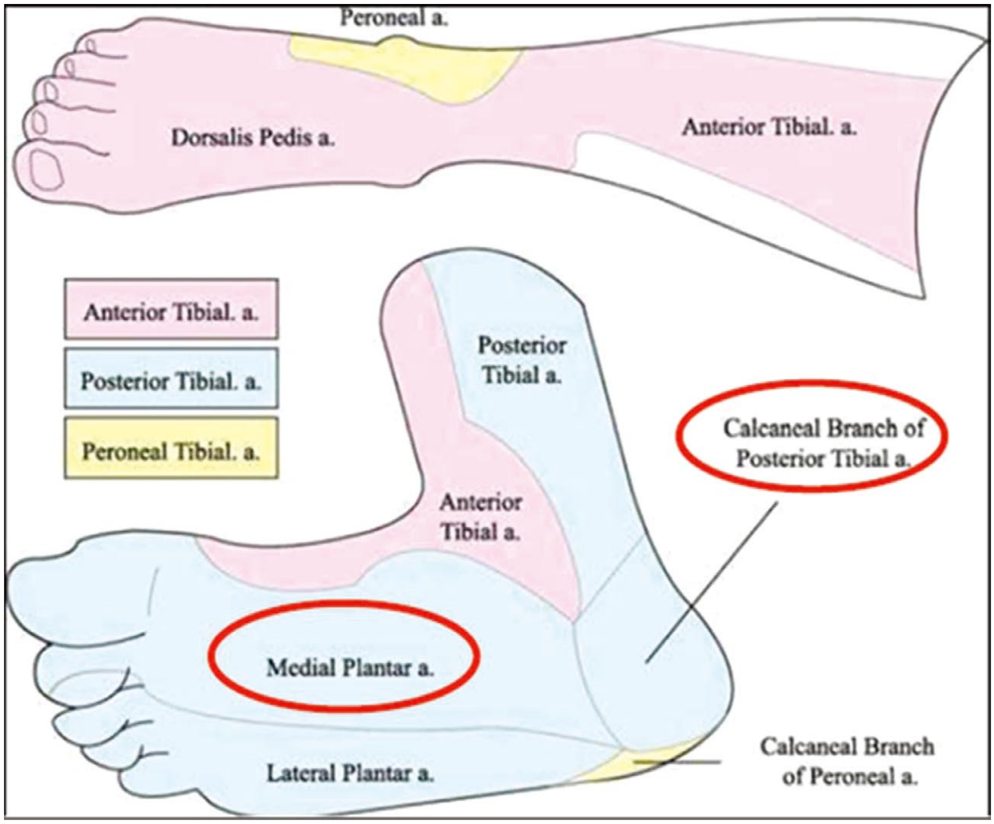

Figure 3. Angiosomes of the foot and ankle.

Unfortunately, many patients present late with extensive tissue damage. Revascularization of one tibial vessel is often not adequate for limb salvage. Multiple tibial vessel reconstruction might be required to improve overall foot perfusion.

The Angiosome Concept

In clinical practice, successful revascularization does not always result in limb salvage. Recently, the angiosome concept has been proposed to improve limb salvage in patients with CLI undergoing revascularization.[17] The foot is divided into 6 anatomic regions (angiosomes) fed by distinct source arteries arising from the posterior tibial (3), anterior tibial (1), and peroneal (2) arteries (**Figure 3**). The angiosome concept has been shown to be clinically useful in both bypass surgery and endovascular therapy for CLI. In a study of 203 critically ischemic limbs by Iida et al, patients undergoing endovascular therapy were divided into direct and indirect groups depending on whether feeding artery flow to the site of ulceration was successfully acquired or not acquired based on the angiosome concept.[18] Limb salvage rate was significantly (P=0.03) higher in the direct group (86%) than in the indirect group (69%) for up to 4 years after the procedure. The number of vessels with run-off flow did not influence the limb salvage rate in either the direct group (P=0.84) or the indirect group (P=0.90).

There are several limitations to the angiosome concept. First, angiosomes vary among patients where infrapopliteal arterial distribution might not completely identify the original angiosome. Second, revascularization of the target lesions according to the angiosome concept might not be possible due to technical barriers and lesion severity. Third, collateral flow might keep the ischemic angiosome vascularized to some extent, with the original vasculature changed to an alternative ischemic angiosome through collateralization.[19]

Advances in Endovascular Techniques and Devices

Arterial Access

The contralateral common femoral artery (CFA) approach with a long sheath up-and-over the aortic bifurcation is the most frequently utilized access to the lower extremity. Antegrade puncture of the ipsilateral CFA should be considered in cases of significant tortuosity of the iliac vessels, unfavorable aortoiliac bifurcation, and previous aorto-iliac reconstruction with bilateral common iliac artery stenting. Although antegrade puncture provides the advantage of a shorter distance to BTK vessels and better longitudinal support, obtaining antegrade access can be more difficult. Both approach the lesions in an antegrade fashion.

Antegrade recanalization attempts can fail in up to 20% of complex procedures. In this case, retrograde access via the distal tibial arteries can be achieved under direct angiographic or ultrasound guidance. This technique is valuable for patients with CLI with long total occlusions and can reduce failure rate. In a study of 51 patients who failed antegrade revascularization of complex total occlusions of the popliteal and/or BTK disease, 88.2% were treated via a percutaneous trans-

pedal access site and 11.8% via a trans-collateral intra-arterial technique.[20] The overall success rate was 86.3% and only 1 (1.9%) major complication (a pedal access site occlusion) and 4 (7.8%) minor sequelae (arterial perforation in 3 and a pedal hematoma without consequence) were documented. Although the retrograde approach can be applied successfully in patients with limited traditional revascularization options, it is a technically demanding endeavor. Securing access to the distal tibial artery can be challenging and traversing the totally occluded vessel and re-entry into the true lumen can also be very challenging.

Crossing Vessel Obstructions

Guidewire access across the obstruction to the distal segments is essential for device delivery and can be challenging with long segments of occlusion or heavy calcification. Hydrophilic-coated guidewires are effective. Stiffer guidewires similar to those used for coronary chronic total occlusions (CTO) might also be beneficial in resistant lesions. Dedicated peripheral CTO wires in 0.014 and 0.018 platforms are available up to 30 g in tip weight. Catheter support for the guidewire is helpful and necessary to traverse long segments of occlusion. More recently, alternatives to guidewires using ultrasound guidance, vibration, and blunt dissection have shown some promise but are more effective in larger diameter vessels.

Sub-Intimal Angioplasty

The technique of subintimal angioplasty was first described by Bolia et al for treatment of long occlusions that do not respond to conventional guidewire and angioplasty.[21] During this procedure, a guidewire is intentionally directed into the subintima to create a dissection plane, which is then extended distally beyond the occlusion where upon the wire is redirected back into the true lumen. Using this technique, complex lesions including long occlusions (>15 cm), highly calcified occlusions and diffuse tandem lesions can be effectively crossed with the guidewire and then treated using conventional methods. Subintimal angioplasty has been established as effective for patients with femoral occlusive disease and CLI but has not been as well described for patients with BTK disease.[22–24] This approach is useful in patients with extended occlusions or arterial calcification, which decrease the success rate of the more standard transluminal balloon angioplasty. The risk of embolization is potentially decreased because subintimal angioplasty does not disrupt atheroma within the native vessel lumen. A major limitation of this technique is that distal true re-entry of the guidewire back into the true can be difficult in small BTK vessels. Furthermore, some long totally occluded vessels have segments of hibernating lumens, which will be lost with subintimal angioplasty.

Dedicated BTK Balloon Angioplasty

Reasonably high technical success can be expected in balloon angioplasty patients, with primary success rates reported from 77% to 100%.[25] Recanalization of total occlusions is usually associated with lower technical success rates. The introduction of flexible low-profiles balloons in longer lengths (up to 210 mm) has facilitated BTK angioplasty procedures, improving procedure time and potentially reducing dissections in long segments of diffuse disease (Figure 4). Recently, Schimdt et al studied BTK angioplasty using dedicated 80–120 mm long low-profile balloons in 77 infrapopliteal arteries of 58 CLI patients with average lesion length of 18.4 cm.[26] Repeat angiography at 3 months showed no significant restenosis in 31.2% of treated arteries, restenosis in 31.2% arteries, and a re-occlusion in 37.6%. At 15 months, there were no major amputations, resulting in a limb-salvage rate of 100%.

Figure 4. Long low-profile below-the-knee balloons are flexible and available in lengths up to 210 mm.

Alternative Angioplasty Technologies

(1) Cryoplasty Endovascular cryoplasty (Boston Scientific, Natick, MA, USA) has been introduced as an alternative to traditional angioplasty. A single-patient-use inflation unit is used to forcibly inject liquid nitrous oxide into a triple-layer angioplasty balloon. The nitrous oxide undergoes a phase change to a gas and draws in energy. As the balloon inflates, the surface temperature is driven down to –10°C. In theory, the addition of cold therapy might affect the outcome of simple angioplasty by altering the vessel's response to dilation and by inducement of smooth muscle cell (SMC) apoptosis. Results from in vitro studies have shown that arterial SMC were found to be susceptible to freeze-induced apoptosis at a temperature range of –5° to –15°C.[27] Theoretically, a reduction in organized SMC apoptosis could alter the intimal hyperplastic response at the area being treated.

Laird et al published the initial safety data on cryoplasty therapy in 102 patients. Eighty-four percent of the lesions treated were in the superficial femoral artery. In all limbs treated, a 94.1% initial technical success rate was reported. Fewer than 10% of treated lesions required stenting.[28] Follow-up of this initial group was extended and revealed durable results, with freedom from target lesion revascularization of 75% at 1,253 days.[29] The BTK Chill trial studied primary cryoplasty of BTK occlusive disease in CLI patients and yielded similar results.[28]

(2) Cutting Balloon Angioplasty Resistant and bifurca-

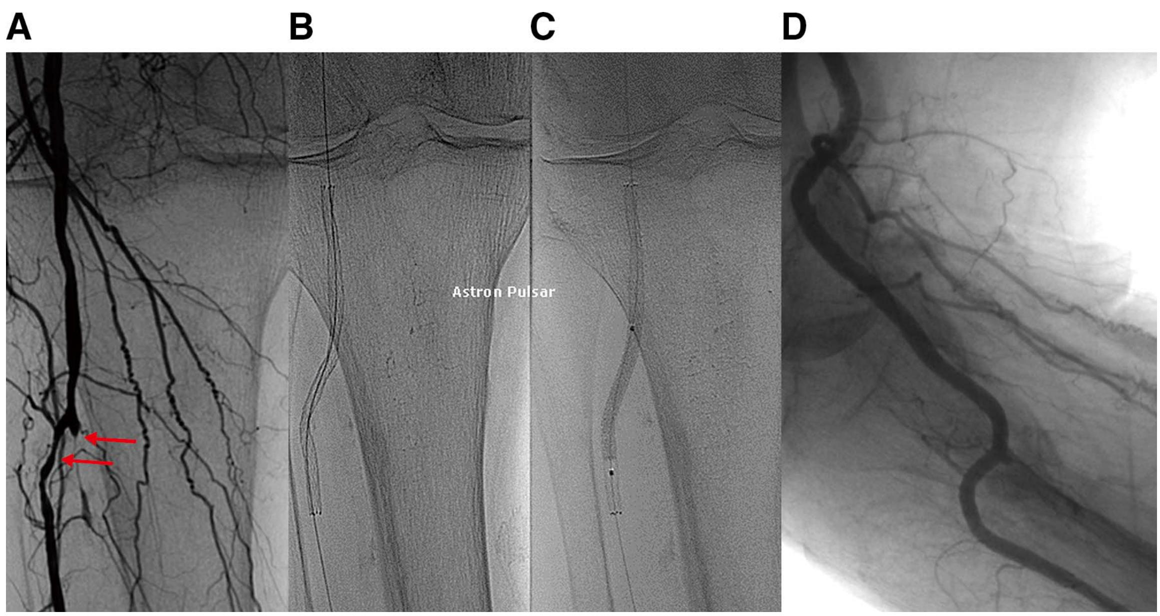

Figure 5. Self-expanding below-the-knee stents. (**A**) Stenosis of the anterior tibial artery (arrows); (**B**) implantation of a 4 mm× 80 mm self-expanding stent following flow limiting dissection post balloon angioplasty; (**C**) post dilatation of the stent; (**D**) final result with lateral projection of bent knee showing conformity of the stent.

tion coronary stenoses might respond to cutting balloon angioplasty. The cutting balloon features 3 or 4 atherotomes (microsurgical blades), which are 3–5 times sharper than conventional surgical blades. The atherotomes, which are fixed longitudinally on the outer surface of a non-complaint balloon, expand radially and deliver longitudinal incisions in the plaque and vessel, relieving its hoop stress. Data on cutting-balloon angioplasty for CLI however, remains for the most part limited to small case series. One such series examined its role in 11 patients with infra-inguinal disease and described a primary patency rate of 81% at 3 months follow-up.[30]

(3) Drug-Eluting Balloons (DEB) The concept of DEB is based on the local delivery of drugs and avoiding systemic exposure to the drug. Advantages of this technology are the possibility of a homogeneous drug transfer as compared to stent-mediated drug release, in which the drug is only delivered at the contact site of the stent struts with the vessel wall. Furthermore, DEB allow for a drug concentration that is highest at the time of the vessel wall injury that occurs during balloon angioplasty and therefore can prevent the initiation of the chain of events that will eventually lead to neointimal proliferation. The absence of metal struts makes the technique suitable for treating long lesions, especially in small-diameter vessels and areas in which flexion and compression of stents might occur. The absence of a stent allows the artery's original anatomy to remain intact and the absence of the polymer that is included in most drug-eluting stents (DES) could decrease chronic inflammation, which is considered a cause for late thrombosis, thus obviating the need for long-term dual-antiplatelet therapy.[31] Most of the currently available DEB uses paclitaxel, which has been approved by the US Food and Drug Administration and is widely used in oncological therapy. Paclitaxel is a potent inhibitor of SMC proliferation, SMC migration, and extracellular matrix formation in vitro, with all 3 phases of the restenosis process effectively inhibited.[32] The usual dose of paclitaxel used is 3 μg/mm^2 of the balloon surface. The total dose of paclitaxel administered to the patient is well below doses used in cancer treatment.

In the THUNDER trial, 154 patients with femoropopliteal disease were randomly assigned to treatment with paclitaxel-coated catheters, uncoated catheters with paclitaxel dissolved in the contrast medium, or uncoated catheters (the last tool mentioned being the control group).[33] The use of paclitaxel-coated balloon catheters significantly lowered the incidence of restenosis at 6 months and the rate of target lesion revascularization at 6, 12, and 24 months. Adding paclitaxel to the angiographic contrast medium did not have a significant effect.

Two currently enrolling randomized trials (the IN.PACT DEEP and the EURO Canal studies) will evaluate the clinical utility and angiographic outcomes of angioplasty using DEB in the BTK arteries in comparison with plain balloon angioplasty.

Atherectomy

Fibrocalcific atherosclerotic disease of the infrapopliteal vessels can pose a significant challenge. Plaque excision and various athero-ablative techniques have shown some promise in achieving high procedural success rates.

(1) Excimer Laser Atherectomy The Excimer Laser system (Spectranetics, Colorado Springs, CO, USA) utilises pulses of ultraviolet energy to remove a tissue layer of 10 μm by a photochemical process. Laser atherectomy provides the potential for thrombus ablation as well as playing a role in platelet inhibition; this provides the prospect of laser atherectomy tailored towards treatment of long occlusive disease and challenging lesions. To date however, neither the patency rates nor the clinical outcomes after 1 year of follow-up have shown any difference when compared to angioplasty alone, albeit with high technical success rates.[34] The excimer laser

atherectomy device was associated with less distal embolization however, and a trend towards a lower stent implantation rate. In a study of 145 patients with CLI, not deemed to be surgical bypass candidates, the limb salvage rate of 93% at 6 months with excimer laser atherectomy was highly promising in providing additional therapeutic modalities to patients with CLI.[35]

(2) Excisional Atherectomy The SilverHawk Plaque Excision System (ev3 Endovascular Inc, Plymouth, MN, USA) is an antegrade cutting device. Upon advancement of the catheter through a lesion, a high-speed cutting blade is switched on which rotates at 8,000 times a minute, shaving away atherosclerotic plaque. Several passes are required and the nosecone of the catheter is used for storage of the excised ribbons of plaque. This device was studied by Zeller et al in the treatment of 45 de novo, 43 restenotic, and 43 in-stent restenotic femoropopliteal lesions.[36] Vessel patency was recorded at 73%, 42%, and 49% respectively in the 3 groups after 18 months follow-up, with an 86% technical success rate after atherectomy alone and 100% after adjunctive therapies. The authors arrived at the conclusion that use of this device was in favour of de novo lesions, with poor outcomes in restenotic lesions.

(3) Rotational Atherectomy Rotational atherectomy devices include the Pathway Medical Jetstream G3 device (Pathway Medical Technologies Inc, Kirkland, WA, USA) and the Orbital Atherectomy System (Cardiovascular Systems, Inc, St. Paul, MN, USA). Both technologies use abrasion of plaque material in order to scrape away both hard and soft plaque. The former catheter includes distal ports located at the tip, which are designed to provide independent infusion and aspiration functions for the active removal of fluid, excised tissue, and thrombus from the peripheral vascular treatment site. The Orbital System uses an eccentric, diamond-coated abrasive crown which moves in an orbital path within the vessel, potentially creating a lumen larger than the diameter of that crown, with the residual tiny particles generated from the sanding of the lesion passing through the capillary bed.

Stenting

Restenosis after PTA remains a problem that significantly affects mid- and long-term outcomes. However, stents are not widely used in the BTK vessels compared to ileofemoral disease.[37] The main reason is that the small caliber and slow flow in these vessels increase the risk of stent thrombosis and intimal hyperplasia. The traditional indications for stenting are for "bail-out" after failed or unsuccessful balloon angioplasty, such as flow limiting dissection or elastic recoil. A meta-analysis of 640 patients showed that BTK stent implantation after failed or unsuccessful balloon angioplasty was associated with favorable clinical results in patients with CLI.[38] With advances in stent technology, there is increasing evidence to support primary stenting in CLI with BTK disease. Balloon expandable bare-metal stents and DES and self-expanding nitinol stents have been used.

(1) Nitinol Self-Expanding Stents The beneficial effect of nitinol stents in the femoropopliteal arteries in terms of significantly improving of patency rates compared with stainless steel stents or balloon angioplasty with optional stenting is well described.[38–40] Nitinol stents for BTK vessels are designed for small vessels and not a large vessel stent in small vessel. They have thin struts which optimizes lumen and flow. These self-expanding nitinol stent are available in diameter of 3 to 8 mm and lengths of 20 to 120 mm and compatible with a 4F sheath. The flexibility of these devices is beneficial in tortuous BTK anatomy. For the moment, the literature provides scant but encouraging information about the utility and effectiveness of bare nitinol stent placement in BTK lesions.[38] A retrospective study of 53 patients with CLI undergoing BTK stenting with dedicated BTK self-expanding nitinol stents showed 76% primary patency rates and 89% amputation-free survival at 24 months.[41]

(2) Balloon Expandable DES Numerous reports have evaluated the role of balloon-expandable DES in BTK arteries.[42–44] In a single-center, prospective registry, it was found that in patients with CLI who underwent BTK revascularization with angioplasty and "bail-out" use of a DES or bare-metal stent, lesions treated with DES were associated with significantly better primary patency, reduced binary restenosis, and fewer repeat interventions at 3-year follow-up.[43] However, no significant differences were seen with regard to overall 3-year patient mortality and limb salvage. A recent study evaluated the efficacy and safety of using DES as a primary strategy to prevent amputations in 118 limbs of 106 patients with BTK CLI.[44] There were 228 DES implanted (83% Cypher [Cordis, Johnson & Johnson, Warren, NJ, USA], 17% Taxus [Boston Scientific, Maple Grove, MN, USA]). The number of stents per limb was 1.9±0.9, and 35% of limbs received overlapping DES. The 3-year cumulative incidence of amputation was 6%, survival was 71% and amputation-free-survival was 68%. Target limb revascularization occurred in 15% of patients.

Despite the encouraging results with the use of DES BTK, a major concern remains the length of the stents and their cost. Most of the BTK lesions are long, and therefore, the application of several short to 38 mm DES is unlikely to be cost-effective. Moreover, balloon-expandable stents are not flexible and can collapse or fracture in the infrapopliteal segment.[45,46]

Hybrid Revascularization

A significant number of patients are not candidates for completely percutaneous endovascular revascularization due to complex anatomy or suboptimal lesion location. These patients might benefit from hybrid therapy, a combination of open surgery and endovascular repair that achieves complete revascularization with a less extensive operative procedure and decreased risk of peri-operative complications. Hybrid therapy enables patients who are considered high-risk for traditional open surgery to be repaired using less invasive methods. Hybrid reconstructions are increasingly used for multilevel revascularization procedures in high-risk patients to achieve complete revascularization with a less extensive operative procedure, shorter duration of operation, and decreased risk of peri-operative complications.[47–49]

The endovascular and open portion of the procedure might be performed simultaneously or sequentially. Before the advent of modern endovascular operating suites, which have the capabilities of a traditional operating room and high-quality fluoroscopy, procedures were often performed sequentially, as imaging in the radiology suite was superior to the imaging in the operating room using a portable C-arm. Now, many hospitals contain operating rooms equipped with state-of-the-art digital fluoroscopy systems that include large image intensifiers, as well as software for road-mapping and quantitative analysis.

Surveillance Post Intervention

Close follow-up of revascularized patients is necessary after

the initial procedures and repeat revascularization procedures might be necessary in case of secondary failure. This active surveillance program using clinical evaluation, $TcPO_2$, and Doppler ultrasound assessment, sustained and aggressive medical therapy to control cardiovascular risk factors, is effective in reducing not only CLI recurrences, but also adverse cardiovascular and cerebrovascular events.

Objective Performance Goals for Critical Limb Ischemia Trials

Design and execution of clinical trials in the CLI population are challenging, in part because of the lack of consensus on cohort definitions and relevant endpoints. Recently, the Society for Vascular Surgery undertook an initiative to define therapeutic benchmarks and objective performance goals for CLI safety and efficacy measures that could be utilized in the assessment of new devices in CLI.[50] Data from 3 large randomized controlled trials of surgical bypass for CLI were analyzed using venous bypass grafting as the standard for comparison. Major adverse limb event (MALE) was defined as amputation (trans-tibial or above) or any major vascular reintervention in the index limb after revascularization. Freedom from peri-operative (30-day) death or any MALE was suggested as the primary efficacy endpoint for a single-arm trial design in CLI, with an observed rate of 76.9% for the surgical bypass controls at 1 year. Specific high-risk subgroups were also defined from the surgical dataset, based on clinical (age older than 80 years and tissue loss), arterial anatomy (infrapopliteal disease), and conduit quality (inadequate saphenous vein) characteristics. These objective performance goals define a new set of benchmarks for assessing the performance of revascularization therapies in CLI, and should facilitate clinical trial design and device development in this arena.

Conclusions

CLI occurs when arterial perfusion is reduced below a threshold level that results in rest pain and/or tissue breakdown in the lower extremities. Without prompt revascularization, CLI might result in loss of a limb and/or life. The primary goal of revascularization is the re-establishment of pulsatile, straight-line flow to the distal extremity. Achieving direct flow based on the angiosome concept has been proposed as important for limb salvage in CLI. Over the past decade, endovascular revascularization has quickly become the preferred primary treatment strategy in CLI patients with an increasing array of percutaneous devices and techniques for the treatment of CLI. With appropriate patient preparation, careful vascular access management, and effective methods to traverse the segments of obstruction, the interventional tools presently available can achieve excellent outcomes with wound healing and limb salvage rates that compare favorably with surgical procedures. Balloon angioplasty, particularly applied with low-profile long balloons, is the mainstay of therapy. DEB are promising but their clinical value awaits further studies. Stents are mainly indicated for failed balloon angioplasty, while adjunctive therapies such as atherectomy devices lack data demonstrating improved efficacy compared with conventional balloon angioplasty. A combination of open and endovascular therapy is an option for some patients with complex multilevel disease. In addition to prompt revascularization, atherosclerotic risk factor modification, lifestyle changes and pharmacological therapies must be aggressively implemented in this population to minimize morbidity and mortality.

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