**Feature:**

# Emerging Vascular Approaches For Healing Diabetic Ulcers

- By David E. Allie, MD

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Given the severe ramifications associated with the combination of critical limb ischemia (CLI) and diabetic foot ulcers, this author emphasizes the potential impact of revascularization procedures in reducing the number of lower extremity amputations. Accordingly, he offers a closer look at recent advances in this arena and their place within the armamentarium for CLI.

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It is vital to review the "non-surgical revascularization toolbox" for lower extremity treatments for critical limb ischemia (CLI). Consider an analysis of the most recent United States and European data on the number of amputations performed every year. Approximately 160,000 to 180,000 lower extremity amputations are performed every year in the U.S. and a 10 percent yearly increase in these numbers has been projected as well. In Europe, it has been estimated that 40,000 to 50,000 lower extremity amputations occur each year.[1-2] It is been estimated that 80 percent of all amputations are preceded by a diabetic foot ulcer (DFU) and that most DFUs are preventable.

Still, worldwide there is an amputation in a patient with diabetes every 30 seconds. This underscores the association of DFU and CLI.[3] Within one year of being diagnosed with CLI, 40 to 50 percent of the now 21 million U.S. patients with diabetes will experience a major amputation and 30 to 40 percent will die.[1-2,4] Moreover, 30 to 50 percent of diabetic amputees will face contralateral CLI and undergo a second limb amputation within three to five years of ipsilateral amputation.[1-2] It has been estimated that the total cost of treating CLI in the U.S. alone is $10 to $20 billion per year and that just a 25 percent reduction in amputations could save the U.S. healthcare system $2.9 to $3 billion yearly.[1-2]

## Emphasizing The Importance Of Vascular Evaluation

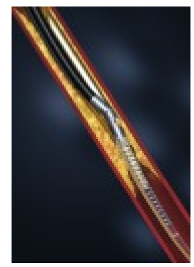
In an analysis of 417 U.S. CLI patients, 67 percent had a primary amputation as initial CLI treatment and less than one half (49 percent) had any diagnostic vascular evaluation with only 34 percent having an ABI and 16 percent having angiography.[1]

inherent risks. Magnetic resonance angiography has also been advocated but it has significant limitations including artifacts (stents, pacemakers, etc.).

Recently 16-64 channel non-invasive CT angiography (CTA) has become available and is now my non-invasive tool of choice in the diagnosis and, importantly, the treatment planning of CLI. It has the advantages of speed (< 30-second scan), safety (arm vein access), simplicity (outpatient < 10-15 minute procedure), fewer complications (hemorrhage, emboli, etc.), superior imaging and resolution, three-dimensionality and overall lower costs.[5] CT angiography has the potential to identify revascularization anatomy and targets often missed with traditional DSA. Indeed, CTA has revolutionized how we diagnose, plan and treat CLI. It belongs on the top shelf in our CLI tool box.

Given the recent improvements in non-invasive CTA vascular imaging and the safety of DSA, it is my opinion that no CLI patient should be scheduled for an amputation without at least CTA vascular imaging and preferably have limb salvage DSA beforehand. Indeed, our healthcare industry's next challenge should be to change our "pathway to amputation" to a "pathway of revascularization," especially with the dramatic improvement in infrapopliteal diagnostic and revascularization treatment options over the last three years. Let us take a closer look at these improvements in treatment.

## A Guide To Balloon-Based Interventions



*Here one can see the SilverHawk limb salvage catheter (FoxHollow Technologies) performing plaque excision.*

**Percutaneous transluminal angioplasty (PTA).** Researchers have reported several excellent tibial PTA (balloon angioplasty without stents, lasers or plaque excision) results in the management of CLI. Dorros, et al., reported tibial PTA as a primary treatment in 235 CLI patients with a 91 percent five-year limb salvage rate with low complications.[6] Faglia, et al., reported PTA as the first treatment in 993 diabetic patients with CLI.[7] During 26 +/- 15-month follow-ups, 1.7 percent underwent major amputation with 87 (8.8 percent) patients experiencing clinical restenosis. They reported a five-year primary clinical patency rate of 88 percent.[7] In a meta-analysis of four PTA reports treating a total of 702 CLI patients, the limb salvage rates were 79 to 91 percent with low complications and acceptable re-intervention rates (9 to 15 percent), and digital bypass surgery (DBS) rates (2 to 15 percent).

Kudo and Ahn, et al., also recently reported a 10-year PTA experience in 111 CLI patients with 0.9 percent periprocedural mortality and initial technical and clinical success of 96.4 percent and 92.8 percent respectively.[8] The five-year primary patency, assisted patency and secondary patency were 31.4 percent, 75.5 percent and 79.6 percent respectively. The five-year limb salvage rate was 89.1 percent. The study authors concluded that PTA was safe and effective, and potentially the primary treatment for CLI. The same authors just published their 12-year experience in regard to tibial PTA versus bypass surgery in 192 CLI patients. These findings further reinforced their belief that tibial PTA is safe and effective in treating CLI.[9] It is clear that clinicians can obtain excellent limb salvage rates with PTA.

*The SilverHawk D5 "MiniHawk" (FoxHollow) has a 1.57 m crossing profile, allowing treatment in smaller infrapopliteal and pedal vessels down to 1.5 mm in diameter, as one can see here.*

Critical to the evolution of tibial interventions has been the development of a smaller 0.014-inch wire exchange and delivery systems. The new generation PTA systems have a smaller profile, thinner walls, longer shafts, higher strength, low pressure, hydrophilic coatings and tapering tips, and come in diameters from as small as 1.5 mm and a length of 12 cm. It was only two short years ago that I would do "almost anything" to avoid tibial PTA and its inevitable vessel dissections. However, I have now lowered my threshold for tibial PTA utilizing the new generation dedicated tibial balloons, especially when it comes to those difficult to treat CLI patients with long diffuse disease. We also now advocate longer (three- to five-minute) low-pressure inflations and are increasingly happy with PTA results.

**Specialty balloons.** The Peripheral Cutting Balloon® (Boston Scientific), originally designed for calcified coronary arteries, is now an option in tibial vessels, especially more discrete calcified lesions. The profile and tractability are somewhat inferior to the smaller PTA balloons but Ansel, et al., reported a one-year limb salvage rate of 89.5 percent in 72 CLI patients with popliteal and infrapopliteal disease.[10] There were no perforations and only 20 percent required adjuvant stenting for residual disease or dissection. We have found particular use for the cutting balloon in heavily calcified discrete lesions in larger proximal infrapopliteal vessels.

The novel AngioSculpt Scoring Balloon (AngioScope, Inc.) recently received FDA approval for tibial disease and is a variation of the Cutting Balloon with a spiral three-wire nitinol cage surrounding a semi-compliant balloon. Scheinert, et al., reported a European multimember registry of 56 lesions in 43 CLI patients. Initial results included 98.2 percent successful deployment, 89.3 percent sole therapy and 10.7 percent dissection rate. Specialty balloons for tibial vessels have significantly expanded our CLI toolbox.

## A Closer Look At Interventions For Plaque 'Debulking'

*Here one can see the MiniHawk in the process of successful revascularization.*

**Excimer laser atherectomy.** The pioneering work of Giancarlo Biamino, MD, has led to an understanding of the unique properties of pulsed excimer laser atherectomy. The 308 mm cool excimer laser catheter delivers intense controllable ultraviolet energy in extremely short pulsed durations, photoablating both atherosclerotic plaque and thrombus (clot) with reduced thermal injury and reduced potential for distal embolic complications. The diameter sizes range from 0.9 mm to 2.5 mm, making this technology especially applicable to infrapopliteal vessels and even pedal vessels on the foot. The recent Turbo (Spectranetics) laser design has added 20 to 30 percent more optical fibers and energy, enhancing the laser's efficiency and ease of use. The laser energy works by turning the plaque and clot into microgaseous elements that are absorbed immediately into the blood.

The recently reported landmark LACI trial enrolled 155 CLI patients with 423 lesions in 15 U.S. and German sites.[12] All patients were considered poor or non-surgical candidates with high comorbidities. The six-month LACI results included a 93 percent limb salvage rate with an overall low periprocedural complications and a six-month re-intervention rate of 16 percent with only 2 percent requiring bypass surgery.[12] The LACI trial clearly demonstrated that endovascular interventions in CLI could achieve high limb salvage rates (93 percent) in fragile and complex CLI patients with low complications who had no other surgical option except amputation. Similar results have been recently reported in the Belgium LACI and our own CIS group's LACI-equivalent studies.[13-14]

*Here one can see the MiniHawk in the process of successful revascularization.*

**Plaque excision.** The SilverHawk plaque excision catheter (FoxHollow Technologies) is a device that allows plaque removal. The SilverHawk is a catheter with a carbide cutting blade system (8,000 rpm) that excises atherosclerotic plaque that is collected in the nosecone for removal and potential tissue analysis. The recently introduced SilverHawk DS or "MiniHawk" has a lower profile (1.57 mm), and allows treatment in smaller infrapopliteal and pedal vessels down to 1.5 mm in diameter. Currently, there are several intriguing multicenter tissue analysis trials underway in an effort to analyze the extracted plaque. Researchers involved with these studies are attempting to unlock important cellular and genotypic information that has the potential for far reaching global cardiovascular clinical implications.

Kandzari, et al., recently reported a multicenter experience utilizing plaque excision in CLI patients with the first generation SilverHawk device.[15] They reported excellent limb salvage rates of over 90 percent with a procedural success rate of 99 percent and a 1 percent adverse event rate. The emergence of the low profile MiniHawk will likely further extend the application of plaque excision down into pedal vessels of the foot. Both excimer laser and plaque excisional atherectomy have revolutionized our capabilities in treating CLI and infrapopliteal disease.

## What About Cryotherapy-Based Interventions?

*This photo shows specimens of plaque excision.*

The PolarCath (Boston Scientific) is a novel PTA system that simultaneously dilates and rapidly cools the immediate tissue within contact from 37ºC to –10ºC to a known depth of only 510 µm. This system enables surgeons to avoid deep vessel wall injury with less dissection. The "freezing" occurs via the controlled inflation of a dual balloon system with nitrous oxide. In concept, this triggers a controlled form of dilation and smooth muscle cell death (apoptosis). This results in less elastic recoil, negative (constrictive) remodeling and less inflammatory response. Therefore, there is less cell proliferation (less neointimal hyperplasia). Cryoplasty has the potential for fewer dissections and less need for stenting in this more controlled plaque microfracture environment (8 atm pressure, 20-second balloon inflation time and –10ºC temperature).

The PolarCath is now available in infrapopliteal diameter sizes down to 2.5 mm diameter with newer balloon lengths to 8 cm. Researchers recently reported the 12-month results of the 16-site multicenter, below-the-knee CHILL study in 111 patients with infrapopliteal vessels that were > 2.5 mm but < 5 mm.[16] The acute procedural success was 97 percent with an 85 percent freedom from amputation rate. At a mean follow-up of 112 days, the freedom from major revascularization was 94 percent with a 14 percent target limb revascularization rate.

*This photo depicts a classic distal embolic event and the end-stage result of massive distal microemboli.*

We have just completed a one-year follow-up on 50 CLI patients utilizing the PolarCath in infrapopliteal lesions. Final analysis is underway with a one-year limb salvage rate of 94 percent. There were very few dissections and we found that cryoplasty was particularly beneficial in CLI patients with suboptimal results after infrapopliteal debulking.

## What You Should Know About Infrapopliteal Stenting Devices

**Bare metal stents.** The absence of a reliable infrapopliteal stent over the years has been a contributing factor to many interventionalists not aggressively treating infrapopliteal disease. Even if only as a "bailout" as in coronary interventions, infrapopliteal stents are a necessary component of the CLI toolbox and now should be evaluated as a potential primary therapy.

Fierling, et al., reported encouraging acute and one-year results utilizing bare metal stents (BMS) in infrapopliteal lesions.[17] Siablis, et al., compared bare metal stents versus drug-eluting stents (Cypher, Cordis Corporation) as a "bail-out" in CLI patients after PTA.[18] The six-month limb salvage rates were equal but the drug-eluting stents group had less rest pain (7.7 percent) in comparison to the bare metal stents group (18.5 percent). Researchers reported the six-month primary patency as 68.1 percent in the bare metal stents group and 92 percent in the drug-eluting stents group.[18]

*This photo depicts a classic distal embolic event and the end-stage result of massive distal microemboli.*

Small diameter (4 mm) self-expanding nitinol stents are now available with the introduction of the Xpert stent (Abbott Vascular Devices). The main attraction for this stent would be in patients with longer flow-limiting dissections, which may be propagated by balloon expandable stenting, and in lesions extending proximally into the popliteal artery.

**Drug-eluting stents.** The initially excellent drug eluting stent results in coronary interventions now mandate strong consideration for their use in infrapopliteal disease. The early results with drug-eluting stents in treating CLI look promising. In a randomized study, Scheinert, et al., compared drug-eluting stents to PTA and reported 12-month patency of 84 percent in the drug-eluting stents group versus 53 percent in the PTA treatment group.[19] In another randomized study, Scheinert, et al., compared drug-eluting stents and bare metal stents in 60 CLI patients with a 6.5 month mean follow-up. Most variables analyzed significantly favored the drug-eluting stents.[20] Angiographic follow-up at a mean of 6.5 months revealed in-stent obstruction rates with bare metal stents at 17.4 percent in comparison to 0 percent with the drug-eluting stents treatment group. Researchers also found that 39 percent of the bare metal stents group had in-stent restenosis (ISR) whereas none of the drug-eluting stents group had in-stent restenosis. Clinically, the bare metal stents group exhibited a 10 percent amputation rate and 23 percent target lesion revascularization (TLR), while the drug eluting stents group had no in-stent restenosis and no amputations.[20]

*This photo shows specimens captured during critical limb ischemia intervention in a single runoff 2.5 mm peroneal artery.*

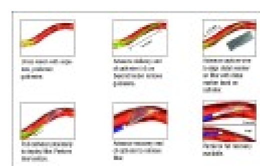
Similar clinical results have been confirmed by Siablis, et al., in the "bailout" trial in which they observed significantly reduced in-stent restenosis and amputation rates by utilizing drug-eluting stents.[18] Clearly, bare metal stents, self-expanding stents and drug-eluting stents are also deserving of a top shelf position in the toolbox of treatments for CLI.

## How Distal Anti-Embolic Interventions Can Aid Patients

The emergence of distal protection devices (DPD) has raised concerns about the incidence of distal embolization (DE) during all of our vascular interventions.[21-22] Distal macro- and microembolization can be particularly catastrophic in the CLI patient with poor and oftentimes only a single, vessel runoff. The Spider FX (ev3, Inc.) is a user-friendly DPD system designed primarily for coronary and carotid artery stenting but it is now seeing expanded use with CLI. Vascular interventionalists can position the fine mesh net filter system before intervention in distal vessels between 3 and 7 mm, and allow capture and removal of macro- and microembolic debris as small as 100 microns created during the intervention.

This DPD strategy has allowed vascular surgeons to perform more aggressive plaque debulking and interventional strategies with less risk of distal embolic injury to the already compromised downstream microcirculation. Distal protection devices have become mandatory during carotid stenting and are common in complex coronary interventions. I now utilize a DPD in the majority of my CLI interventions. In my opinion, it allows even more aggressive revascularization and facilitates improved outcomes. I predict widespread adoption of this DPD strategy in treating CLI.

## What The Literature Reveals About Distal Bypass Surgery



*The illustration above shows the Spider FX (ev3, Inc.) distal protection device positioned to capture emboli debris.*

**Distal bypass surgery (DBS).** As a cardiothoracic and vascular surgeon who has acquired endovascular skills over the last two decades, I must emphasize that distal bypass surgery (DBS) is still considered the gold standard by many and is absolutely a necessary tool in the CLI toolbox.

In a landmark article, Pomposelli, et al., reported a decade experience with pedal bypass in 1,032 CLI patients (92 percent with diabetes) with excellent five- and 10-year limb salvage rates of 78.1 percent and 59.8 percent respectively.[23] Researchers have also reported excellent surgical limb salvage results using arm veins, composite veins (anastomosing multiple veins together) and donor veins. Neville, et al., have reported greater than 80 percent five-year limb salvage rates utilizing a local vein cuff at the distal pedal anastomosis between the tibial artery and a long segment of prosthetic graft.[24]

## In Conclusion

Our non-surgical endovascular CLI toolbox is no longer bare. Over a dozen novel, non-surgical interventional technologies have exploded onto the scene in just the last three years. Indeed, evidence-based data now substantiates aggressive creative endovascular and surgical strategies to facilitate limb salvage.

It is now incumbent upon our healthcare system to provide the education and awareness that these tools exist and work toward a longer-term goal of decreasing the number of primary amputations still performed today without even the consideration of revascularization. We have the CLI revascularization tools today. We must prioritize multidisciplinary education if we are to change the all too common referral pattern of “primary amputation” to one of “primary limb salvage.”

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*For further reading, see “Vascular Intervention In Difficult Wounds” in the July 2002 issue of Podiatry Today.*