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CLI Therapy in 2016: Toward Meaningful Endpoints, Quality Benchmarks, CLI Training, and Centers of Excellence

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Disruptive innovations in medicine typically require multicenter, randomized controlled trials (RCTs) to validate their premises and be widely accepted as new standards of care. Unfortunately, in the field of CLI therapy, the almighty gold standard of science continues to fail in its quest for the holy grail. RCTs published to date have failed to show that CLI-dedicated therapies are efficient. However, a careful dissection of the studies will reveal that these were designed with primary efficacy and safety endpoints that do not correlate with the population at hand. It's time to start shifting gears and design studies that include "real world" patients (as currently utilized inclusion criteria would exclude most of the patients we deal with on a daily basis) and focus on functional outcomes such as time to wound healing and quality of life.

Of equal importance is the reigning lack of consensus regarding how to define "successful intervention" in CLI. Currently, there are no standards of practice or benchmarks to compare the outcomes of these rather complex procedures. A commonly utilized phrase to describe success in CLI therapy is the "establishment of in-line flow to the foot." However, the quality of this flow is never mentioned. Studies are needed to specifically look at matched pairs of angiographic results and outcomes in order to determine which of these should be considered "successful" on the basis of evidence, rather than on the basis of self-generated reports, which are clearly subject to bias.

Unfortunately, given the lack of evidence, there are no benchmarks. And given the lack of benchmarks, most of these procedures are performed solely based on the operator's experience (or lack thereof).

This problem is exacerbated by the current lack of training programs exclusively dedicated to the treatment of CLI, which in turn is a field that has experienced a rather large explosion of devices and technologies. This dichotomy reflects, on one hand, a group of new operators who graduate from their endovascular programs (interventional cardiologists, interventional radiologists, and vascular surgeons) without adequate training in the management of infrapopliteal disease and CLI. And, on the other hand, it provides operators with a plethora of new devices that lack comparative data, thus contributing to confusion.

CLI training programs will allow operators to be exposed to all aspects of CLI diagnosis and management, acquire experience in the use of the ever-growing variety of devices, and become familiar with the intricate planning and execution of CLI interventions. These programs will likely emerge from "CLI Centers of Excellence," a concept born from the analysis of DEBATE-BTK, which revealed that positive results are attainable in large-volume, dedicated multidisciplinary programs with prespecified and aggressive wound management protocols with low threshold for revascularization. With specialized training, more operators will begin to think along similar pathways, and the creation of standards of practice will come as a natural and beneficial consequence, leading to improved quality and clinical outcomes. ■

It's time to start shifting gears and design studies that include "real world" patients ... and focus on functional outcomes such as time to wound healing and quality of life.

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Current Noninterventional Therapies for Critical Limb Ischemia Patients

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Critical limb ischemia (CLI) represents the "point of no return" in the clinical spectrum of the patient with peripheral arterial disease (PAD). Surgery and more recently percutaneous endovascular treatments has become the mainstay of management of CLI. However, the role of medical management in treating the symptoms and complications of severe limb hypoperfusion is less well established. The use of noninterventional therapies has a role as primary treatment in patients who have failed to improve symptoms. These therapies can also help those who are unsuitable or unfit for revascularization, as adjuvant treatment after revascularization procedures, and to reduce the incidence of cardiovascular events. Additionally, medications can have a role as adjuncts or alternatives in patients who are unsuitable for revascularization or those who have suboptimal results. Newer techniques such as the use of growth factors, gene therapy and stem cells are being investigated, as well as novel pharmacological agents, management of novel risk factors and new applications of are likely to increase treatment options in the future. The goals of treatment include pain control, limb salvage, wound healing, maintenance of ambulatory status, improvement in quality of life, and reduction of major adverse cardiovascular events.[2,3]

Prevention

Preventive measures should constitute the cornerstone of managing patients with CLI, especially among patients without tissue loss. Primary prevention efforts should be directed at measures to avoid skin breakdown. These include skin moisture, adequate footwear or orthotics, adequate toenail care and education on preventing foot trauma or falls. Patients need to be educated on being proactive and inspecting their feet daily and taught to contact the team if there is evidence of any new skin breakdown or any change in pre-existing wounds. Secondary prevention is of paramount importance and should address smoking cessation, blood pressure and glycemic control, lipid lowering, and antiplatelet agents.

Wound Care

Meticulous wound care is critical for patients with CLI and tissue loss. Underlying infection should be treated and necrotic tissue debrided. Topical therapies with recombinant growth factors and hyperbaric oxygen are being investigated.[4]

Pharmacotherapy

There are no medical therapies specifically approved for the treatment of CLI in the United States. Primary pharmacotherapy with cilostazol, prostaglandins, pentoxifylline, and novel agents may play a role. Adjuvant pharmacotherapy is directed to achieve secondary prevention of myocardial infarction and stroke, as well as to improve outcomes after revascularization procedures. These include aggressive medical management of comorbidities such as diabetes, hypertension and hyperlipidemia.

Cilostazol (Primary and Adjuvant)

Cilostazol is approved in Japan for the management of CLI, including ulceration and pain. There are no prospective trials evaluating the benefit of cilostazol in CLI.

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While objective prospective data for the use of cilostazol in CLI are limited, case studies demonstrate successful wound healing in both upper and lower extremity arterial wounds associated with CLI.[5,6] Similar to its role in intermittent claudication (IC), the mechanisms by which cilostazol improves tissue perfusion and wound healing in CLI remain elusive. Cilostazol has been shown to improve skin perfusion pressure, suggesting a role in improving microvascular function.[7] In addition, patients with CLI successfully treated with endovascular intervention may benefit from adjunctive cilostazol, as shown by Soga et al,[8] who demonstrated improvement in amputation-free survival (AFS) and limb salvage in patients treated with cilostazol compared with placebo (47.7% vs 32.7% ; $P<.01$), as well as reduction in binary restenosis, reocclusion and target lesion revascularization (TLR) in patients with infrapopliteal disease treated with percutaneous transluminal angioplasty (PTA).[9]

Pentoxifylline (Primary)

Intravenous pentoxifylline has been compared to placebo in 2 studies of patients with CLI with conflicting results; one trial showed improvement in rest pain[10] while the other did not.[11] No further investigations have been performed, and there are no trials investigating the use of the available oral pentoxifylline preparations in patients with CLI.

Prostanoids (Primary)

PGE-1, prostacyclin, iloprost, lipoecaprost, and ciprostene have been studied in CLI. The use of intravenous PGE-1 or iloprost for 7 days to 28 days in patients with CLI currently has an ACC/AHA level IIB recommendation based on level A evidence for the efficacy and safety of the therapy, with the caveat that small numbers of patients are likely to benefit. However, oral iloprost was found to be ineffective and, as such, there is a class III recommendation against use of this agent in CLI.[1,3] In a recent Cochrane systematic review of 20 trials, a small but statistically significant benefit was seen for prostanoids. This review suggests prostaglandins are generally effective at improving rest pain and ulcer healing. However, the effect on amputations and mortality was not significant.[2,3,12]

ACE Inhibitors and Statins (Adjuvant)

In a prospective observational study of 553 consecutive patients with diabetes and CLI undergoing revascularization, therapy with ACE inhibitors and statins was recorded.[13] At 2 years, the life expectancy was improved among patients receiving combined therapy with ACE inhibitors and statins, however there was no improvement among patients treated with either agent alone. Another retrospective study of patients with CLI undergoing below-the-knee interventions determined that treatment with statins did not affect overall survival, cardiovascular death, AFS, limb salvage, or repeat revascularization at 4 years.[14] However, in another study, amputation rates at 12 months post PTA improved from 21.1% in patients receiving aspirin alone to 11.1% when lovastatin was used in conjunction with aspirin.[15]

Antiplatelet Therapy (Adjuvant)

All patients with PAD and CLI should be considered for antiplatelet therapy to reduce the incidence of cardiovascular events and for their beneficial effect on graft and stent patency. The relative risk of infrainguinal graft occlusion in patients treated with aspirin was 0.78 in one meta-analysis.[16] A recent Cochrane review demonstrated that antiplatelet agents improved graft patency rates to a greater extent in patients with prosthetic grafts compared with those with venous grafts.[17] The use of adjuvant dual antiplatelet therapy (DAPT) with clopidogrel and aspirin following below-knee bypass graft surgery did not show an improvement in the composite primary endpoint of index graft occlusion or revascularization, above-ankle amputation, or death compared with aspirin alone. However, the combination did improve outcomes in a subgroup analysis of patients with prosthetic grafts, without significantly increasing major bleeding rates.[18]

The consensus regarding the most effective postoperative antithrombotic regimen is contentious. Platelet inhibition is preferable following PTA when compared to vitamin K antagonists.[19] Currently, long-term low-dose aspirin or clopidogrel are recommended following PTA, as this has been shown to improve revascularization patency; however, there is no evidence that this regimen improves outcomes in CLI.[20] Higher doses of aspirin failed to significantly improve patency rates and were associated with higher rates of gastrointestinal side effects.[21] Following successful PTA, patients who received 3 months of dalteparin in addition to low-dose aspirin daily exhibited a reduction in restenosis at 1 year compared to those who only received low-dose aspirin. (45% vs. 72%; $P=.01$). However, the addition of dalteparin only had a beneficial effect when patients had undergone PTA for CLI; in less severe PAD, the addition of deltaparin conferred no benefit.[15] More recently, ticagrelor has been used in patients with CLI who had high on-clopidogrel platelet reactivity (HCPR) undergoing peripheral endovascular interventions. In this small series, it showed to be safe and efficacious.[22]

Anticoagulants (Adjuvant)

The evidence for use of adjuvant anticoagulation has been summarized in a recent Cochrane review, which concluded that patients undergoing infrainguinal venous grafts are more likely to benefit from vitamin K antagonists such as warfarin than platelet inhibitors; which did not hold true among patients with prosthetic grafts.[23] However, the evidence was not conclusive, and the authors recommended further RCTs with larger numbers of patients comparing antithrombotic therapies with either placebo or antiplatelet therapies.

Folate and Vitamin B12 (Adjuvant)

In a parallel observational study of 169 patients with CLI undergoing surgical revascularization, 66 had hyperhomocysteinemia at baseline. They were treated with Vitamin B12 and folate for a mean of 12 days, achieving normalization of their homocysteine levels after 3 weeks. After revascularization, there was no difference in outcomes between the cohort of patients who had hyperhomocysteinemia at baseline but were treated to normalization of homocysteine levels, compared to those who had normal homocysteine levels at baseline. The study also showed through a multivariate logistic regression analysis, that untreated hyperhomocysteinemia was a strong predictor of graft occlusion and limb loss, suggesting that aggressive preoperative treatment of hyperhomocysteinemia may improve clinical outcomes in patients undergoing surgical revascularization for CLI.[24]

Novel Agents

Treprostinil sodium (primary)

Treprostinil sodium, a prostacyclin analogue, was studied in an open-label pilot study in 10 patients with CLI and no plans for revascularization. Treprostinil was administered by continuous subcutaneous infusion. Three patients benefited from wound healing. In addition there was reported improvement in rest pain and decreased use of pain medications.[25] Further investigation of an oral treprostinil diethanolamine (UT-15C SR) is ongoing.[26]

Naftidrofuryl (primary)

A recent Cochrane review of intravenous administration of naftidrofuryl, a 5-hydroxytryptamine type 2 antagonist ($5\text{-}HT_2$) included 8 trials with a total of 269 patients.[27] The trials were generally of low quality, and the duration of treatment was short. A number of endpoints were studied and showed nonstatistically significant trends toward reduction in pain and necrosis scores. Therefore, there is currently insufficient evidence to support the use of this drug for treatment of CLI.

Sarpogrelate (adjuvant)

Sarpogrelate is a $5\text{-}HT_2$ antagonist approved for clinical use in Japan for patients with PAD. Its mechanism of action is not well known, but it has been shown to reduce platelet aggregation, improve endothelial function, and enhance peripheral circulation with favorable effects on cardiovascular diseases, skin ulcers, and intermittent claudication. This agent was studied in 67 CLI patients who underwent revascularization and compared with 67 matched controls, it showed improvement in AFS.[28]

Ozone (non-specific immunomodulation therapy) (primary)

Intramuscular injection of autologous blood exposed to a gas mixture of oxygen/ozone induced increased levels of transcutaneous partial pressure of oxygen in patients with CLI, who were deemed not to be candidates for revascularization. These preliminary results indicate that intramuscular injection of immunomodulation therapy may improve wound healing and limb salvage in CLI patients.[29]

Urokinase

Urokinase was tested in an open, prospective, noncontrolled, multicenter study in 77 type 2 diabetic patients with CLI and diabetic foot ulceration who were not candidates for surgical or endovascular revascularization based on interdisciplinary consensus. Urokinase was administered for 21 days as an intravenous infusion. After 12 months, 33% of the surviving patients showed completely healed ulcers without having major amputation. The total survival rate was 85%, AFS 69%.[30,31]

The future of CLI treatment is as exciting as it is challenging.

Therapeutic Neovascularization

Therapeutic neovascularization is an exciting upcoming modality in the treatment of patients with CLI. Various types of gene and cell-based therapies that promote neovascularization are being investigated in patients with CLI. Gene therapy for CLI has primarily focused on genes coding for angiogenic growth factors.

A number of phase 1 clinical trials and long-term follow-up studies have evaluated the safety and potential efficacy of a variety of growth factors, including hepatocyte growth factor (HGF),[32-35] vascular endothelial growth factor (VEGF),[36] and fibroblast growth factor (FGF),[37] or a combination of growth factors.[38] The majority of these studies have shown safety, but in some, there has been a trend toward potential benefit. A few small RCTs of HGF showed improvements in pain scores and toe brachial index (TBI) compared with placebo.[39,40] However, in a larger RCT (n=104), HGF was not associated with significant differences in ankle brachial index (ABI), TBI, pain relief, or wound healing compared with placebo.[41] In an RCT of nonviral 1 (NV1) FGF vs placebo, there was a significant reduction in risk of amputation.[40] However, once again, in a larger RCT of the same growth factor, no significant improvement in the time to major amputation was found.[43] Similarly, in a small RCT (n=54) ofVEGF, no significant difference in amputation rate was demonstrated in patients with CLI and diabetes, although some benefit was seen in a number of secondary outcomes, including pressure indices and clinical improvement.[44] Overall, clinical results have been mixed over a variety of endpoints, including changes in hemodynamics, transcutaneous oxygen tension, pain, ulcer healing, amputation, and survival. Results from several phase 1 and 2 trials were relatively promising. However, evidence of benefit in phase 3 trials is lacking.[45]

More recently, use of bone marrow-derived or peripheral blood-derived multipotent or pluripotent stem cells as well as endothelial progenitor cells (EPC) have been employed. Several phase 2 trials have been performed using different bone marrow-derived and EPC-derived cellular therapies. These therapies are delivered through either direct arterial or intramuscular injection.[47] Autologous cultured adipose-derived stroma/stem cells have been used in a phase 1 study for the treatment of CLI, adding yet another cell line to the armamentarium.[48]

Overall, as in the gene therapy studies, cell therapy appears to have a good safety and tolerability profile. Results have shown variable improvement on ABI measurements, transcutaneous oximetry of the tissues, wound healing, and pain symptoms. In most trials, AFS and overall mortality have not been affected, although the studies were not powered to show effect on these endpoints.[49-52]

Several meta-analyses, including a Cochrane review, of phase 1 and 2 trials of cell-based therapies suggest that these treatments are safe and potentially beneficial over a similar spectrum of outcomes to those studied in gene therapy trials for CLI.[53,54] Several phase 3 randomized trials are under way that will help address these unanswered questions.[55]

Hyperbaric Oxygen

There is no proven benefit of hyperbaric oxygen in CLI as primary therapy. A Cochrane review of the effect of hyperbaric oxygen on ulcer healing in patients with diabetes concluded that the therapy increased the rate of ulcer healing at 6 weeks but not at 1 year and there was no significant difference in the risk of major amputation.[56] Studies directed at analyzing the adjuvant role of hyperbaric oxygen combined with wound care and revascularization would likely show faster healing times.

Summary

The pathophysiology of CLI is complex and involves both macrovascular and microvascular pathology. Therefore it is not surprising that therapeutic modalities are multifold, spanning many health care specialties and requiring substantial institutional infrastructure to provide optimal patient care.[57] The future of CLI treatment is as exciting as it is challenging. There is increasing focus on optimal wound care and prevention, adherence to proven medical therapies, improving revascularization results with novel endovascular and surgical techniques and devices, and ongoing investigation into promising therapies like therapeutic angiogenesis. ■

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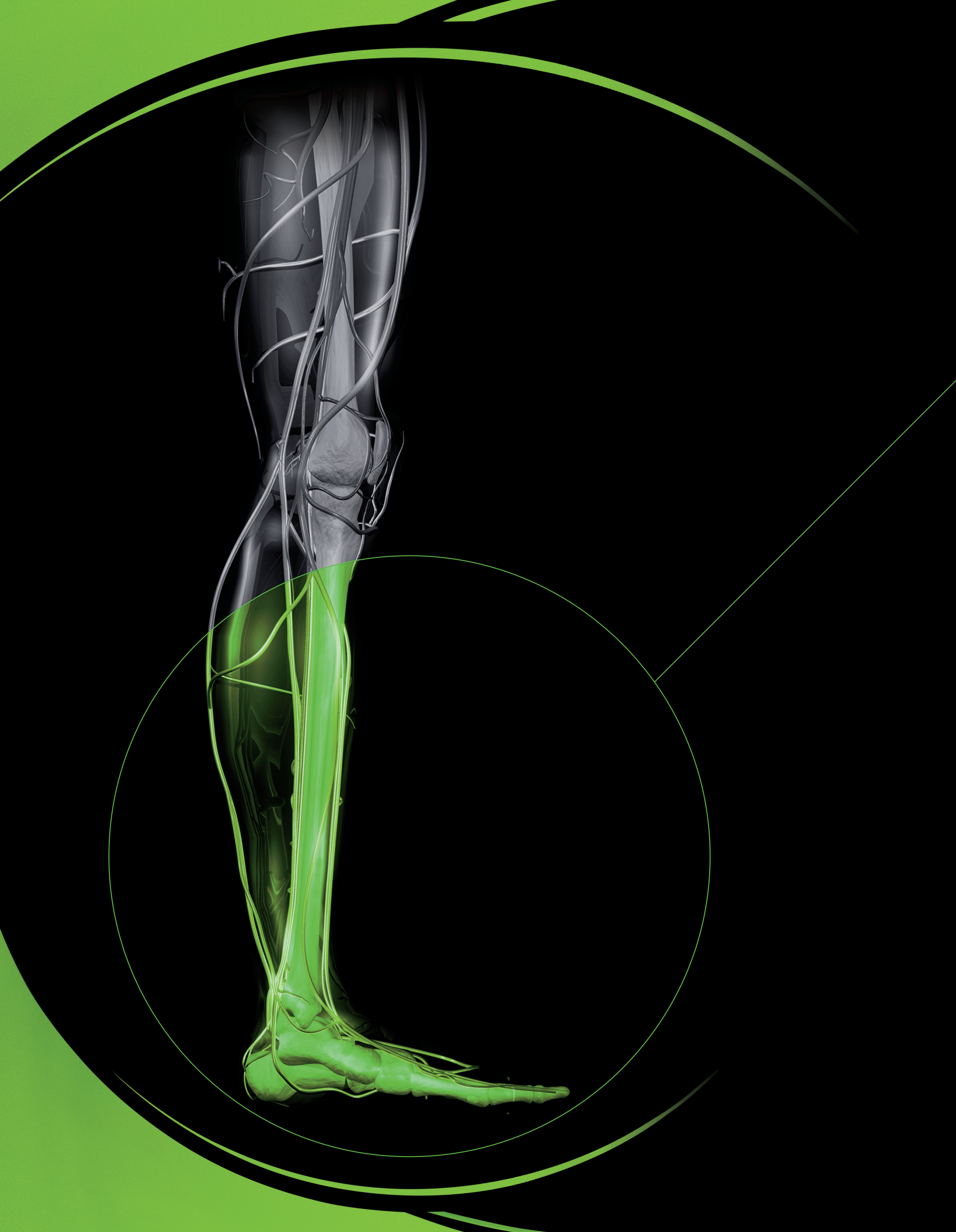

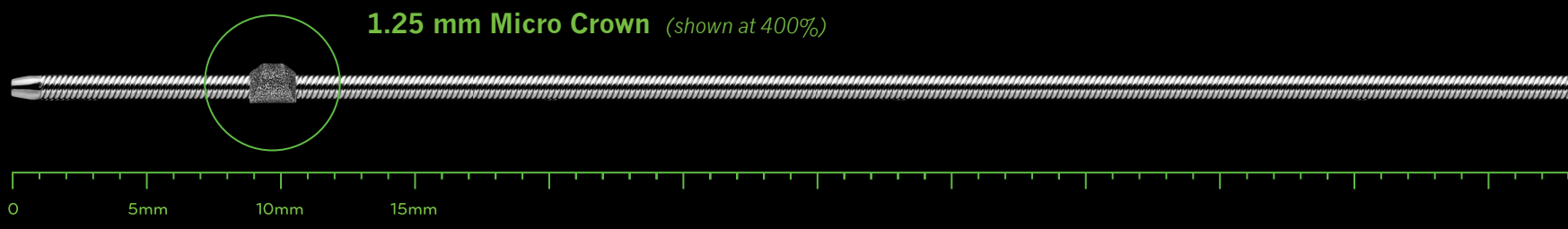

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Case Study*

72 y/o
female, Rutherford Category 4 with a medial plantar ulcer and osteomyelitis

2
previous fem-pop bypass surgeries

620 mm
lesion in the SFA and popliteal

Prior angioplasty treatment from an antegrade approach failed and below-the-knee amputation had been scheduled. Then physician performed an ultrasound-guided tibiopedal retrograde approach with a 4 Fr 1.25 mm Micro Crown.

Outcome

40 min
total treatment time

45 min
after treatment patient was able to ambulate

60 min
patient was discharged and walked out of the hospital

Results may not be typical

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Case study courtesy of Jihad Mustapha, MD, Metro Health Hospital-Metro Heart and Vascular in Wyoming, MI. Case study results may vary. Dr. Mustapha is a paid consultant for Cardiovascular Systems, Inc.

Does Practice Make Perfect? A High-Volume Center's Perspective on Successful Pedal-Loop Revascularization

Lanfroi Graziani, MD
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Lanfroi Graziani, MD

Although I have worked with arterial foot revascularization since 1995, it was in May of 2005 that the recanalization of chronic tibial artery occlusions in diabetic and dialysis patients with ischemic wounds was clearly established. The antegrade ipsilateral femoral approach technique adopted for these patients allowed huge technical advantages in almost all cases. As the effectiveness of our antegrade technique in tibial chronic total occlusions (CTOs) improved, reaching 85%, the limit of the approach was getting nearer. But limits in science are made to be overcome.

Case Presentation

On May 4, 2005, a 71-year-old female with diabetes presented with a 6 month history of a very painful nonhealing ulcer of her heel. Her transcutaneous oxygen pressure ($TcPO_2$) was as low as 26 mmHg, but previous consultancies done at other teaching hospitals excluded the existence of foot ischemia due to the presence of a good dorsalis pedis pulse. It was obvious via a detailed foot angiogram there was an occluded deep plantar artery resulting in an uncrossable posterior tibial artery and a plantar arch interruption.

At that time, the plantar arch seemed a sensitive "taboo" territory, untouchable for any endovascular activities. Vascular specialists knew how important the area was, but indications for treatment didn't yet exist. The reason for the taboo was based on the potential damage to the thin deep plantar and lateral plantar arteries generating the precious metatarsal and digital branches. In our experience with diabetic macroangiopathy and angioplasty recanalization of foot arteries, we learned that the uniform circumferential degenerative thickening of the disease usually protects the artery from rupture if dilated at high pressure with a low-compliance balloon. At the same time, this characteristic ensures a superb angiographic result if a prolonged dilation, using low-profile long balloons, is adopted. Therefore, it was decided to cross the Rubicon, accepting the possible consequences of a nonreturn technique.

Intervention

The recently available new generation of low-profile over-the-wire balloons tapered to .014″ was used, in combination with a hydrophilic .014″ wire. A small bend was created at the wire tip and the deep plantar artery occlusion was carefully crossed intraluminally with gentle drilling movements. Dilation was performed as usual and the final result was near superb, to the delighted surprise of the entire clinical team. After recanalization, the pain immediately ceased and $TcPO_2$ rose to 38 mmHg 10 days later. Thus the "loop technique" for recanalization and plantar arch reconstruction was born.

Discussion

The loop technique now represents a crucial resource in a relatively large number of cases of ischemic diabetic foot, with almost no surgical alternatives. I performed the first pedal-loop intervention case at Abano Terme Hospital in May 2005. My staff were equally as emotional to have participated as the patient, who received the first ever successful pedal-loop revascularization.

After more than 10 years using this technique in a center that is a leader in number and complexity of below-the-knee (BTK) procedures performed, some key points of the technique are now evident. As in our original description published in 2006, the pedal-plantar loop technique performance is possible in plain plantar arch recanalization (Type A) and retrograde tibial artery recanalization through a reconstructed plantar arch (Type B).

Tips for the Pedal-Plantar Loop Technique

The Type B pedal-plantar loop procedure is the most effective, assuring a concurrent perfusion to the freshly recanalized plantar arch from both tibial conduits. Anatomically, the plantar arch may be considered equivalent to a left anterior descending artery–posterior descending artery combination that generates several branches perfusing crucial territories like metatarsal-digital branches.

Subintimal recanalization in the plantar arch almost invariably causes branch exclusion with dramatic consequences in outcome and risk of limb loss. Intraluminal crossing should be the preferred technique.

Highly steerable polymeric hydrophilic stainless steel .014″ coronary wires, such as the PT Graphix Super Support (Boston Scientific), are ideal for crossing the tortuous and often calcified plantar arch. Tapered .009″ to .014″ hydrophilic coronary wires, such as the Fielder XT (Asahi), are indicated in cases of very thin, calcified vessels.

New approaches like digital access and direct tibial or pedal puncture are worthy of special comment. Selective digital artery puncture is normally technically possible in the presence of very limited occlusive disease and mostly for retrograde tibial artery recanalization. Direct tibial artery puncture may be used rarely to cross the plantar arch, serving as an alternative retrograde approach for tibial artery recanalization in almost all cases. These procedures expose the operator to direct radiation to the head and brain, and considering that diffuse foot artery obstructive disease is extremely common in ulcerated CLI cases, digital access may be very rarely used. An antegrade ipsilateral femoral approach ideally covers all pedal-plantar loop technique cases.

There are several similarities between plantar arch and coronary artery interventions. A guiding catheter is needed in both, but unfortunately, the 4 Fr type 2 Berenstein selective catheter (Cordis) is able to accommodate only a couple of crossing wires in the peripheral territory. Its distal bent is perfect to direct the wire towards the most favorable direction. The 100 cm, 4 Fr type 2 Berenstein selective catheter is our guiding catheter of choice in starting plantar arch crossing. Once the wire has engaged the origin of the plantar arch, the Berenstein catheter should be exchanged for a 2 mm x 80 mm over-the-wire (OTW) Amphirion Deep balloon (Medtronic). The Amphirion Deep acts as a probing as well as a dilating catheter to facilitate the catheter-wire system progression. It also serves as an angiographic catheter and a perfusion catheter for local drug delivery.

An OTW 0.014″ tapered small-vessel balloon represents the support catheter of choice. Balloon artery dilation in stenosed or occluded coronary arteries is not ideal because of the high risk of dissection or abrupt closure due to negative remodeling caused by the typically irregular, eccentric atheromasia involving those vessels. Alternately, in leg and foot arteries, the dominant disease is mainly degenerative, causing a homogeneous circumferential involvement with diffuse vessel wall thickening and surprisingly low incidence of dissection or closure with prolonged long-balloon dilation at high pressure. Prolonged dilation of 3 to 4 minutes at high pressure using long balloons represents the best technique for plantar arch reconstruction and tibial artery recanalization.

Degenerative disease involving BTK arteries, particularly in diabetic subjects, may focally coexist with calcified atherosclerosis or dense fibrosis, particularly in patients on dialysis. This very challenging, unfavorable picture is responsible for uncrossable and nondilatable short lesions, quite common using standard techniques. In these cases, coronary balloons, particularly noncompliant, are indicated. Selective use of noncompliant coronary balloons is crucial in cases of focal uncrossable and resistant lesions.

Unfortunately, miniaturized 5 Fr guiding catheters suitable for the tibial territory are commercially unavailable. Even adopting the antegrade ipsilateral femoral approach, crossing hard lesions in the plantar arch may be sometimes impossible without guiding catheter support. The alternative is a homemade tibial 5 Fr long sheath, achievable by trimming the distal pigtail of an unbraided polyamide 5 Fr aortic catheter shaft. Its large lumen is able to accommodate any sort of coronary balloon, making it possible to cross and dilate almost all resistant calcified lesions.

The pedal-plantar loop procedure in a diffusely diseased territory may expose the patient to some possible complications, even if the procedure has been properly accomplished. If calcified main vessels do not usually spasm, small arteries may. In addition, prolonged crossing maneuvers in that territory may mobilize fibrin from the diseased endothelium with consequent reflow phenomena, similar to what may happen in the coronary territory. A quick local delivery of a solution containing 100.000 U of urokinase plus 200µ of nitroglycerin and 50% contrast through the support catheter, delivered in a quick pullback local injection, may solve the problem in almost all cases.

Conclusion

The success of a pedal-plantar loop procedure is tied to the number of procedures performed. All interventionalists require proper and meticulous theoretical and hands-on training to build their technical skills. The pedal-plantar loop technique is a complex procedure by definition, but at the same time it is probably the most important to learn. In every discipline, practice improves performance. In extreme vascular interventions, interventionalists must routinely use the ipsilateral antegrade femoral approach. This approach is the key to accessing the lower-limb territory. Clear understanding of leg and foot arterial anatomy will guide interventionalists safely and effectively during a procedure that has no alternative. Because disease is usually multilevel, from the groin to the foot, there are many affected segments to treat appropriately.

There is no doubt that operators must perform a number of procedures correctly to be qualified. This is usually possible after an appropriate time spent in a qualified high-volume center. The learning curve may vary from 3 months to 12 months, depending on individual experience. The growing complexity of the procedure leads us to believe that fellowship-trained CLI therapists should do CLI therapy. ■

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1. The Phoenix Atherectomy System demonstrated a <1% distal embolization rate in the EASE trial.

Wrapping Up 2015: Top 5 Provocative Questions in CLI

J.A. Mustapha, MD; Larry J. Diaz-Sandoval, MD

J.A. Mustapha, MD

1) Tibial Patency vs Wound Healing and Limb Salvage: What Should Be the Focus?

To date, there have been 2 randomized controlled trials published and/or presented on the use of drug-coated balloon (DCB) therapy for below-the-knee disease (BTK), and unfortunately both have met the same fate: failure.[1,2] There are several potential explanations to dissect these undesirable results, which currently are only speculative. These include appropriate sizing of the balloons, adequate angioplasty technique, and lack of standardized protocol for wound care and follow-up post revascularization.

Beyond these theories, it is worth reflecting on the fact that both trials were designed to evaluate primary patency as the primary efficacy endpoint. Critical limb ischemia requires critical thinking. Analysis of the data that have emerged over the last 5 years to 10 years clearly shows that primary patency does not correlate with clinical outcomes in critical limb ischemia (CLI) as it does in patients with claudication. The time has come for us to start shifting the paradigm so we may adequately weigh the relative merit of functional outcomes such as time to wound healing (and therefore time to resume ambulation and independent activities), limb salvage, and quality of life as primary efficacy endpoints.

2) CLI Outcomes: Should It Only Be Treated at CLI Centers of Excellence?

If we analyze in depth the intricacies of DEBATE-BTK (Drug-Eluting Balloon in peripherAl inTErvention for Below the Knee Angioplasty Evaluation), we find that during the discussion, Liistro et al clearly point to the fact that their results could have been influenced by the fact that they run a dedicated, large-volume CLI practice that has in place a prespecified follow-up protocol for management of wounds with a low threshold for repeat revascularization.[3] This is a very important point, because it opens the door to the next big question: Is CLI therapy and its outcomes strictly bound to operator and center experience? If so, will results ever be generalizable or shall this entity be exclusively managed at CLI centers of excellence? Multicenter, randomized controlled trials and a dedicated multicenter CLI registry are under way in an attempt to answer these questions. These studies will likely bring to light the much-needed "real world" evidence to create the foundation for the practice of state-of-the-art CLI therapy.

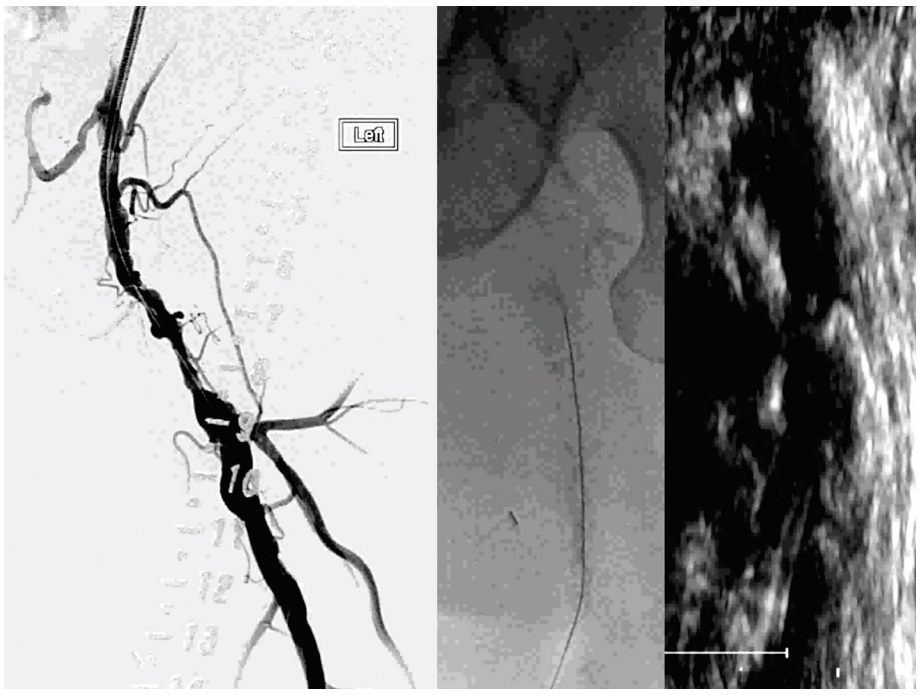

Figure 1. An inflow of diseased tibial arteries that do not fill with contrast during an ipsilateral common femoral angiogram. A very complex CTO (A), retrograde SFA Schmidt access in the occluded segment of the SFA CTO (B). The SFA/CFA CTO cap with variable density calcium deposit including acoustic shadowing (C).

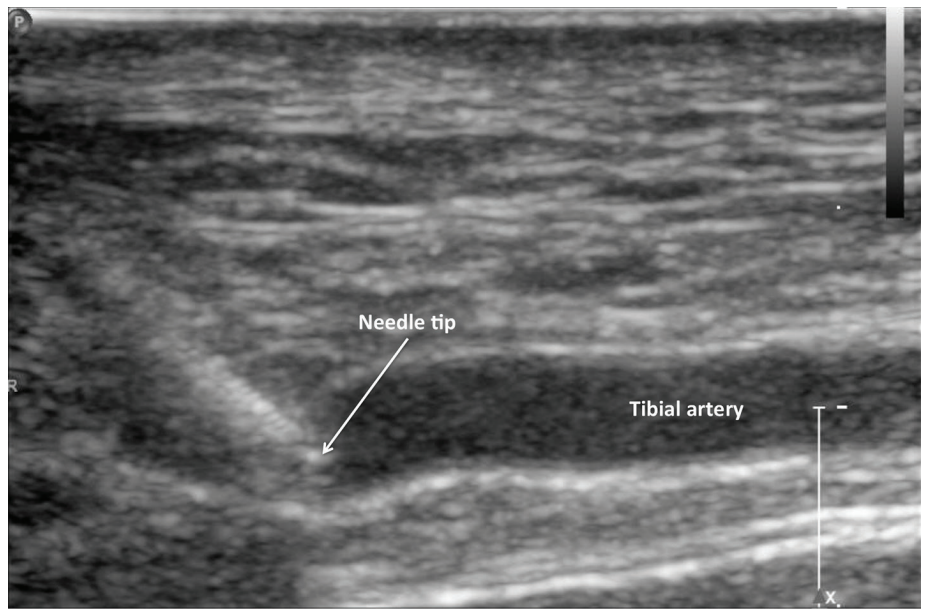

Figure 2. A retrograde tibial access in long access showing the semi-normal tibial artery with retrograde micropuncture needle in the center of the tibial artery.

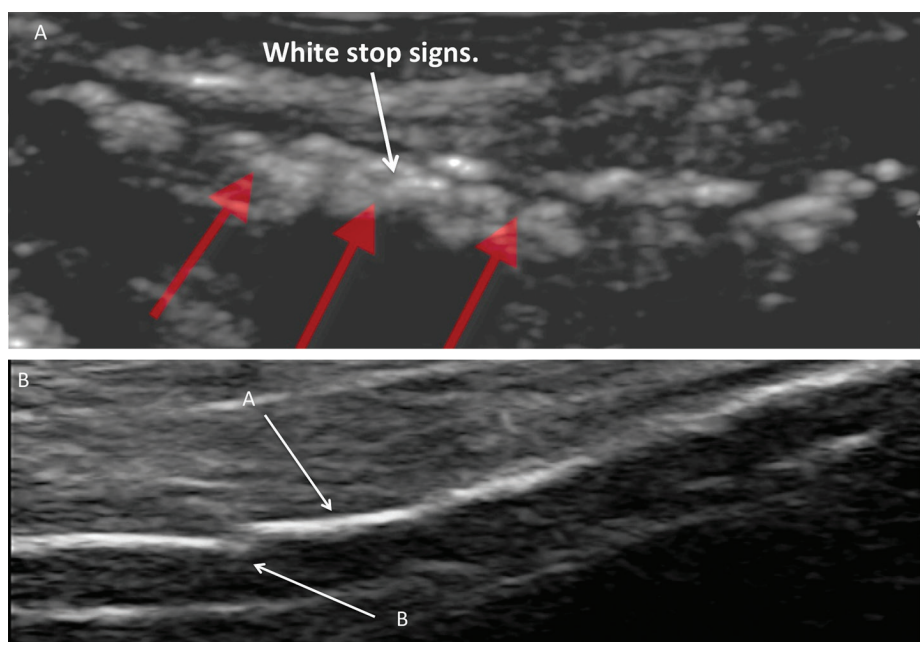

Figure 3. Combined medial and intimal calcification with multiple severe white stop signs. This is the artery that needs to be open in order to have a successful limb salvage procedure (A). The same vessel in its proximal segment, showing unique characteristics of severe medial calcification (arrow A) and arterial wall fracture (arrow B) (B). This type of medial calcification is actually easier to cross if the crossing tool is within the lumen.

3) What Would Be the Primary Endpoint for Your Real-World Patient?

In the "real world," most of our CLI patients (who have already been offered an amputation) do not meet eligibility criteria to be enrolled in current CLI trials; therefore, for purposes of this discussion we will design a hypothetical "study" for which the primary efficacy endpoint is wound healing and the safety endpoint represented by the rate of major amputations. Arterial patency is not included. At the end of this case-based exercise, we will make determinations of the potential adequacy of this design.

4) What Does It Take to Be a CLI Therapist in 2015? Are You One?

A real-world CLI patient has a nonhealing ulcer in the left heel. His angiogram reveals a severely diseased common femoral artery (CFA) and profunda artery (PFA), as well as a complex chronic total occlusion of the ostium of the superficial femoral artery (SFA) (Figure 1A). He has been deemed a no-option case after 2 failed endovascular procedures. This kind of patient requires that we be creative and use our scientific knowledge to create new techniques and approaches, always keeping an open mind and avoiding dogma. As such, we

Continued on page 12

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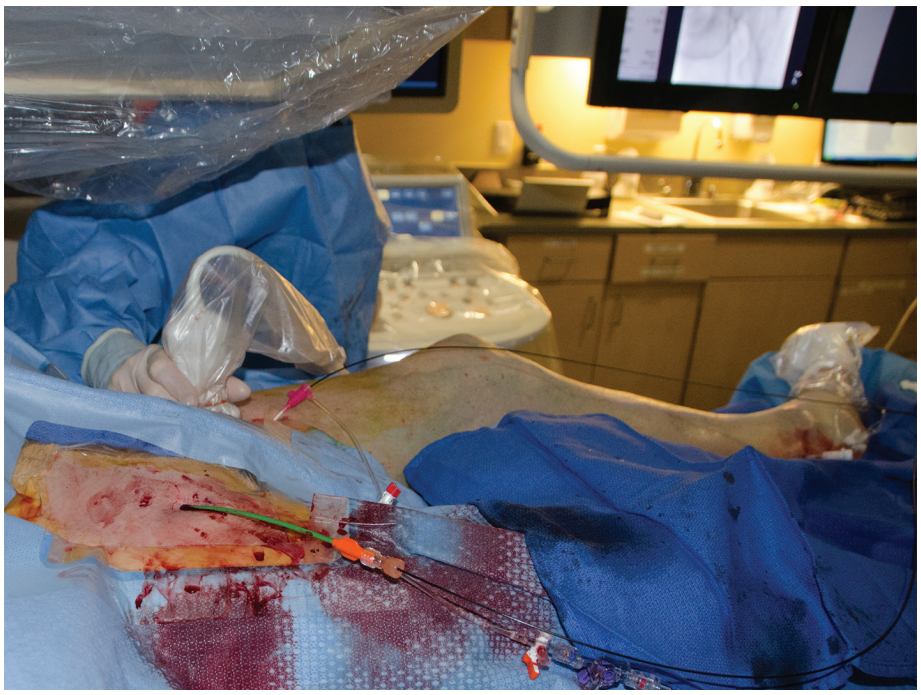

Figure 4. Multiple points of access are obtained in an attempt to salvage the limb.

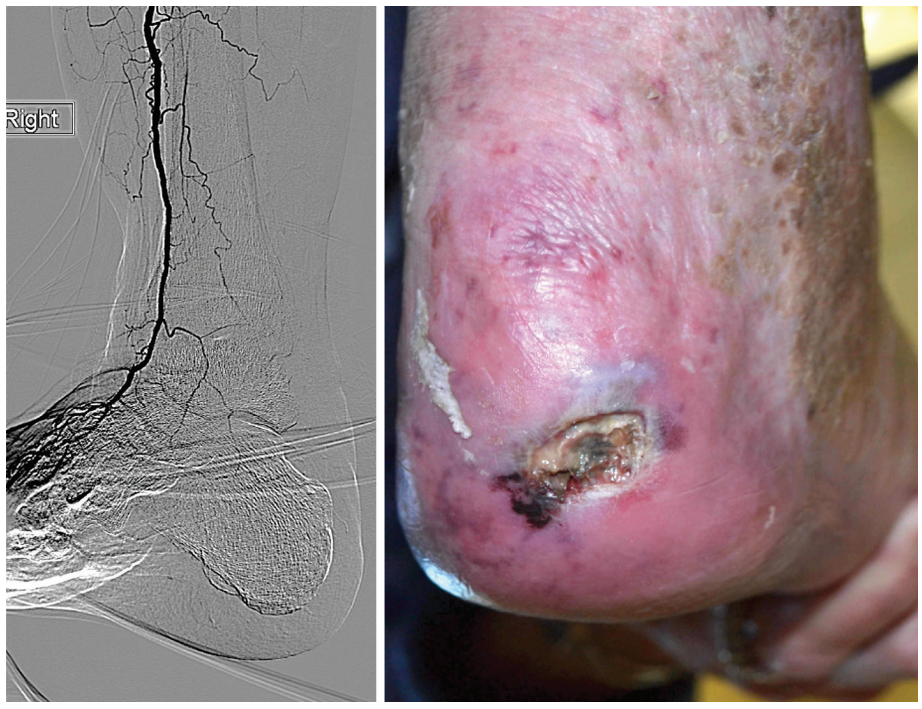

Figure 5. Late filling angiogram showing delayed flow into the ATA and no flow into the PTA, especially no flow into the heel where the ischemic ulcer is located (A). The affected foot with nonhealing ulcer in the medial heel (B).

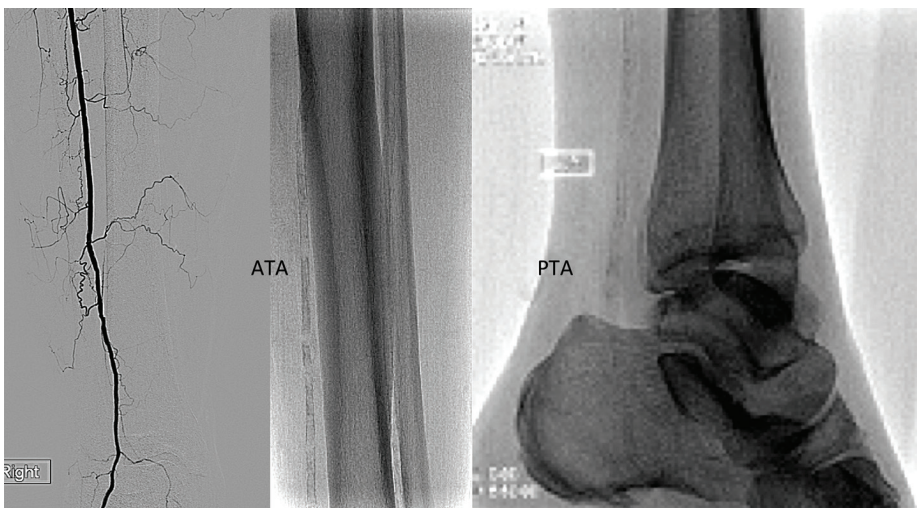

Figure 6. Angiogram with flow in the ATA (A). A closer look at the calcification (B). The ATA has severe medial calcification with intact flow. The PTA has severe medial and intimal calcification and no flow (C).

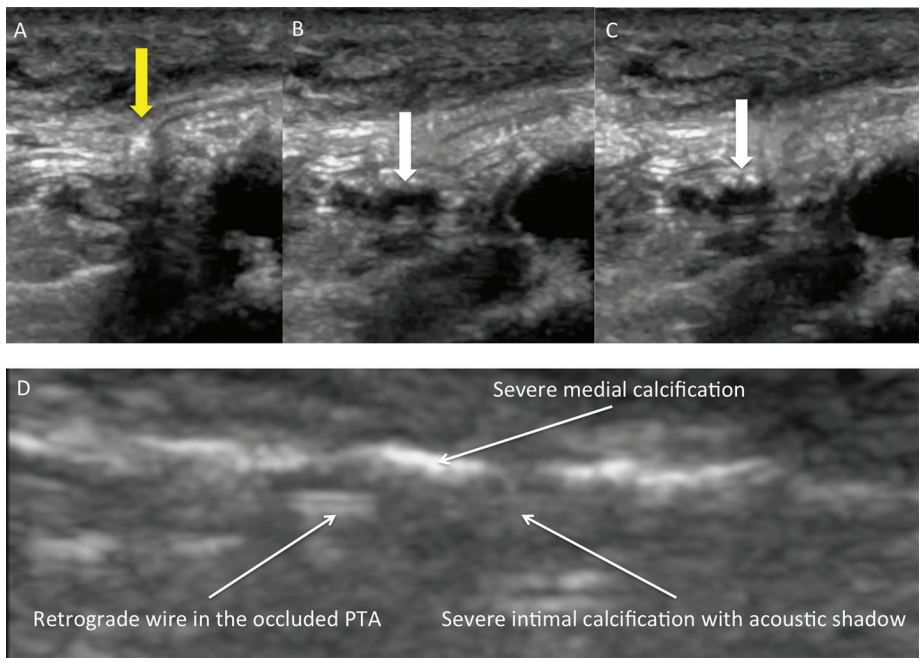

Figure 7. The stages of the needle entering an occluded tibial artery (A-C). Very challenging and the needle is best seen in panel A (yellow arrow). Long access of the PTA after the retrograde wire is maneuvered into the occluded PTA, and the severity of the combined intimal and medial calcium (D).

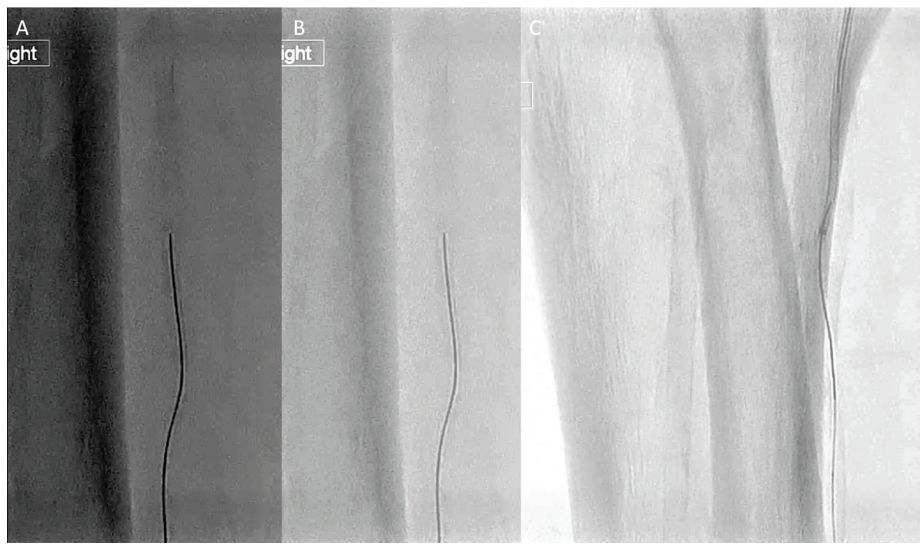

Figure 8. The retrograde wire at different stages (A-C). Retrograde wire entering the antegrade catheter with the retrograde wire snared (C).

Questions

Continued from page 10

performed extensive scanning with the use of extravascular ultrasound (EVUS), which allowed us to see the complexity of the chronic total occlusion (CTO) cap, with heterogeneous deposition of varying densities of calcium in the media as well as the severe intimal cluster, responsible for the acoustic shadowing artifact (which hinders visualization of the confines of the vessel and therefore increases the complexity of its crossing) (Figure 1B). The reconstitution is in the P3 segment of the popliteal and the tibioperoneal trunk (TPT) is occluded with no visible distal reconstitution. The anterior tibial tapers at the ankle and supplies a diminutive dorsalis pedis (Figure 2). Scanning of the distal posterior tibial artery (PTA) revealed multiple "white stop signs" (segments where calcium deposition creates complete luminal obliterations) and complex intimal and medial calcification (Figure 3A).

At this point, clinical decision making requires the integration of all previously mentioned pieces of complex data. The question requiring an answer is this: Should we embark on opening this complex SFA CTO if we will not be able to cross the tibial CTO and obtain good outflow into the pedal circulation feeding the affected angiosome? This is the typical conundrum we face on a daily basis when dealing with these complex patients, and unfortunately most of the issues here discussed were not taken into account when the current trials of novel CLI therapies were designed.

In an attempt to answer the question, we extended the EVUS interrogation of the posterior tibial artery (PTA) into its proximal segment (Figure 3B), which revealed a patent hibernating lumen with two distinctive features typically seen in CLI patients with end stage renal disease (ESRD) and diabetes mellitus (DM). The identification of this hibernating segment allowed us to think of a strategy that could break this rather long and complex CTO into three segments: the distal PTA to the hibernating lumen (seen in the high-resolution fluoroscopy without contrast along with

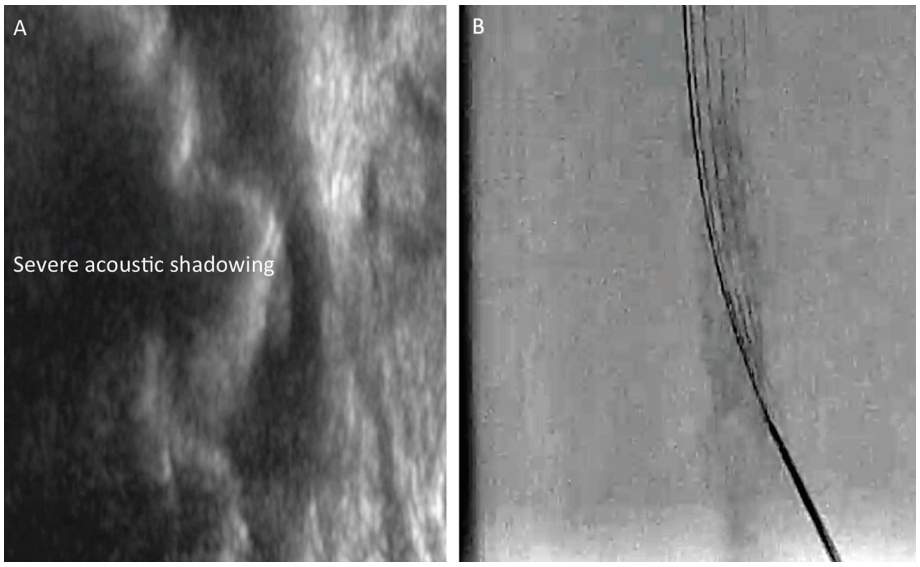

Figure 9. EVUS-guided access of the retrograde SFA (A). Fluoroscopy-guided retrograde advancing of the SFA wire after access (B).

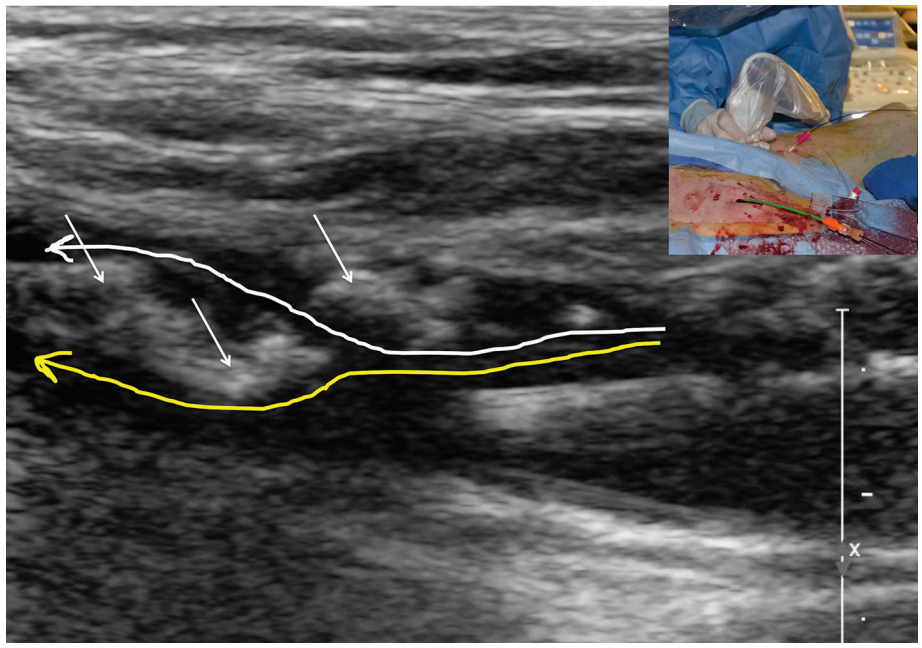

Figure 10. Retrograde EVUS-guided CTO crossing of severely convex and calcified SFA plaque. Arrows show the severe intimal calcium as part of the CTO.

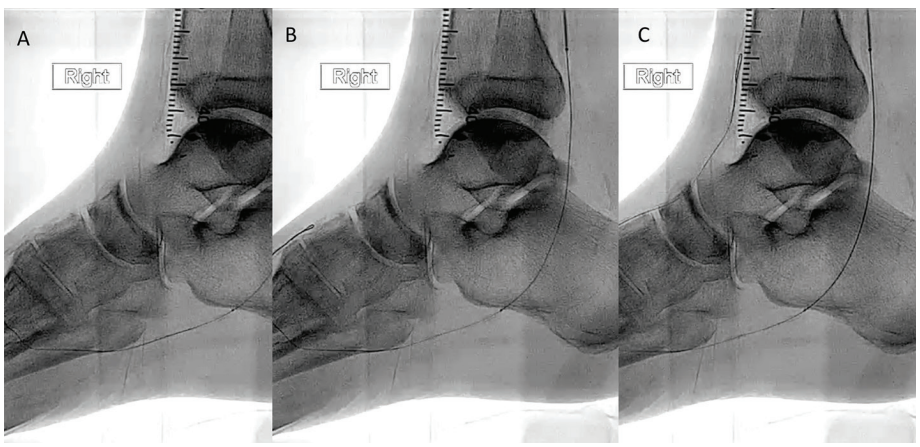

Figure 11. Wire just entering the anterior part of the pedal loop (A). Wire is now in the DP (B). Finally, the antegrade wire is advanced into the ATA (C).

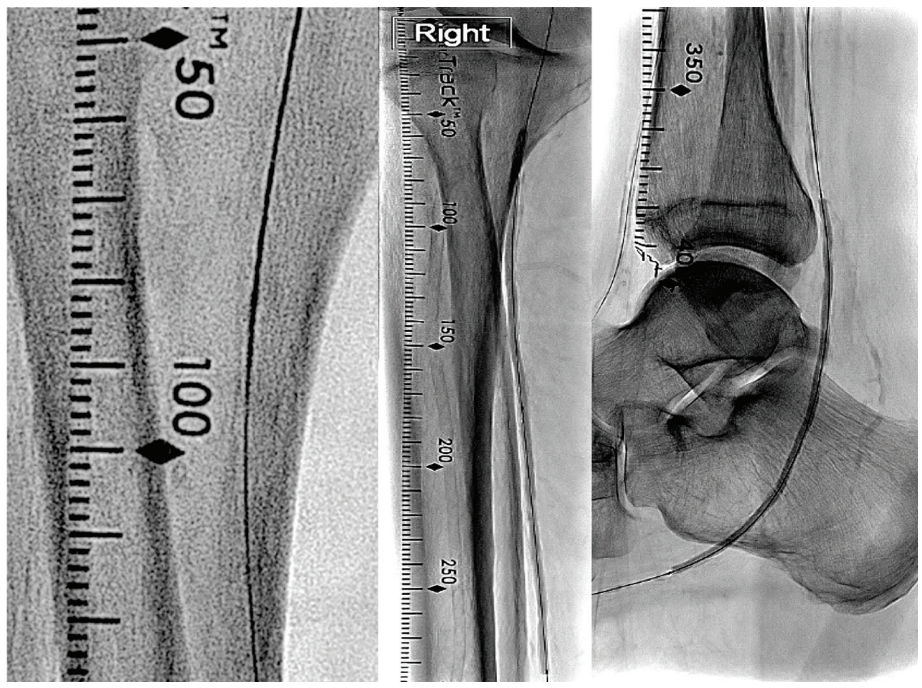

Figure 12. Orbital atherectomy starting at the level of P3 all the way to the take-off of the lateral plantar arteries (A). Balloon angioplasty in a chronically occluded tibial artery will need to be treated differently than SFA/popliteal (B). Here we will start with 2.5 mm balloon to treat the majority of the artery followed with tapered balloons, 2.5 mm x 3.0 mm, starting at the ankle strap at the plantar bifurcation followed with 3.0 mm x 3.5 mm from mid to proximal PTA followed with 4.0 mm to treat the TPT into the distal P3.

the calcium deposits and areas of vessel fracture: Figure 4); the proximal PTA (hibernating) to the P3 and then the SFA-popliteal CTO. We decided to potentially use 3 simultaneous approaches: retrograde contralateral CFA "up and over" to have support and attempt antegrade crossing of the proximal cap, retrograde tibial access to cross the tibial CTO, and the retrograde mid SFA Schmidt access, a modified technique utilized to access within the confines of the occluded vessel with ultrasound guidance. This would be in an attempt to break the femoropopliteal segment of >60 cm into 2 smaller pieces and therefore shorten the distance between the entry point and the proximal cap (Figure 5) to enhance the transmission of the crossing force to the tip of the wire/catheter/device (or combination of these) being utilized to penetrate and cross the cap. It is well known and understood that as the force vector lengthens, more of the energy applied at point "A" dissipates before reaching point "B." Therefore shortening the vector's length (i.e., accessing closer to the cap) will result in the linear transmission of a larger percentage of the force being applied to the crossing tools.

Given the lack of substantiated evidence, CLI therapists tend to make their decisions based on experience, which brings us to the next question: What if the operator does not have enough experience?

To be a CLI therapist in 2015, a clinician must be willing to do whatever it takes to salvage the limb (Figure 6). In our case study, we unsuccessfully attempted to cross the ostial CTO cap in antegrade fashion from the contralateral CFA retrograde access with "up and over" approach. Then, using EVUS guidance, we performed retrograde mid SFA Schmidt access into the occluded vessel (Figure 7) and successfully advanced the retrograde CTO crossing tools into the CFA (Figure 8) without compromising the ostium of the PFA, which would have been the likely result without using EVUS guidance. Once we were able to cross the proximal cap in retrograde fashion, the access was reversed. This allowed us to advance an antegrade catheter from the contralateral CFA all the way down to the P3 segment; however, we had no more pushability to cross into the occluded TPT. The next step consisted of obtaining ultrasound-guided retrograde Schmidt access in the occluded segment of the PTA (Figure 9). The retrograde wire was then successfully advanced with ultrasound guidance into the popliteal and then, using fluoroscopy, into the antegrade catheter (Figure 10). After access reversal, there was an antegrade wire at the level of the ankle strap. Multiple catheters were used in telescoping fashion to deliver enough support to cross the last PTA CTO segment and enter into the plantar arteries and around the pedal loop (Figure 11), which is vital, as it represents the outflow of the limb. Tibial angioplasty is then performed with a sequential, stepwise approach in order to obtain the most luminal gain without flow-limiting dissections. After orbital atherectomy of the entire PTA into the lateral plantar branch, we performed sequential angioplasty (Figure 12).

5) Is Flow to the Foot Enough? Role of Flow Dynamics in CLI

Once therapy has been delivered, the final step of tibial revascularization should be the assessment of flow dynamics in the tibial-pedal circulation. This includes the following:

1. Selective angiography from P3 to evaluate for the presence of equalization of flow between the treated tibial and the originally patent vessel (comparing "TIMI" flow; Figure 13 A and B).
2. The filling pressure (briskness of flow) of the target pedal vessels (in this case the calcaneal branches: Figure 13C).
3. Presence or absence of early tissue blush in the area of the wound.

When these components are present, there is a higher likelihood of ischemic tissue resolution. However, this represents the Achilles heel of current

Continued on page 17

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WARNINGS

• This device is intended for single-use only. Do not reuse. Do not resterilize. Do not use if the package is opened or damaged. • Use this device prior to the "Use By" date as specified on the device package label. Store in a dry, dark, cool place. • DO NOT use if it is suspected that the sterility of the device has been compromised. • Persons with known hypersensitivities to Nitinol and/or its components (e.g. nickel titanium) may suffer an allergic reaction to this implant. • Administer appropriate antiplatelet therapy pre- and post- procedure. • Careful attention should be paid when sizing and deploying the stent to prevent stent elongation. In the SUPERB clinical study, stent elongation was associated with a decrease in patency at 12 months.

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  • The safety and effectiveness of the Supera Peripheral Stent System has not been established in patients who:
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- This device is not designed for use with contrast media injection systems or power injection systems. • The flexible design of the Supera stent may result in variation in the deployed stent length.

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Potential adverse events include, but are not limited to:

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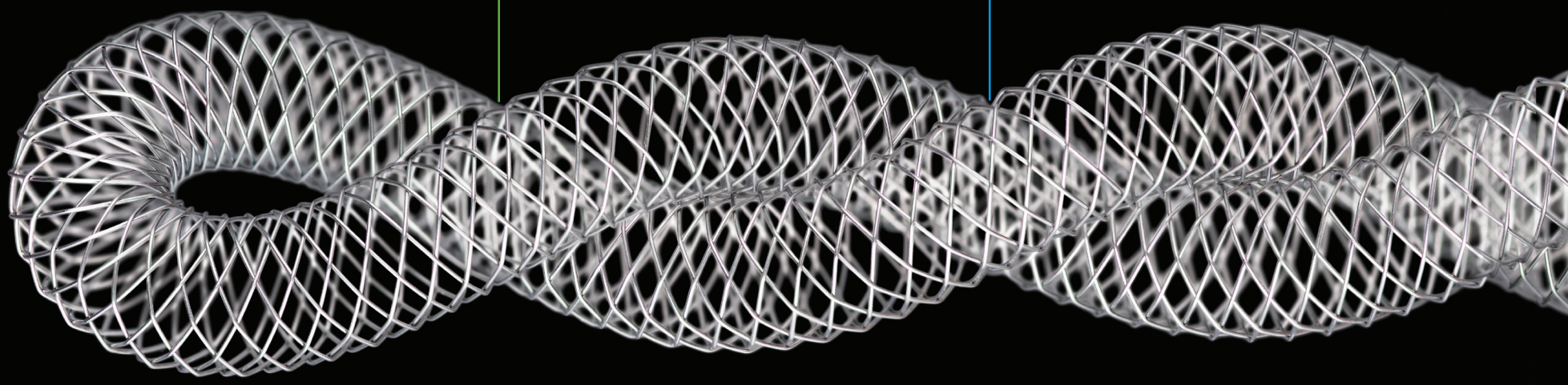

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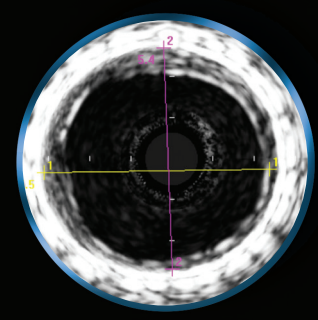

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Distal Tibial Bypass: A Snapshot of the Past and Glimpse Into the Future

George A. Pliagas, MD, FACS, FRCS(C)
From Premier Surgical Associates, Knoxville, Tennessee.

George A. Pliagas, MD, FACS, FRCS(C)

The decades of the 1970s through the turn of the century saw annual increases in the number of distal bypasses performed for nonhealing wounds and for advanced peripheral arterial disease.[1] Through sheer surgical ingenuity, surgeons of the time were able to utilize autologous conduits to perform vascular bypasses in the hopes of salvaging limbs.[2,3]

In an era when amputation was considered the most effective way to deal with limb ischemia, a 1974 statement from the Royal Society of Medicine indicated that limb salvage attempts were justified and less costly than amputation.[4] Forty years later, this concept continues to be true in terms of current-day economics.[5] With amputations costing the health system upwards of $10 billion, we cannot overlook the option of limb salvage procedures.[6-8]

I was nearing the end of my vascular training in 1989 and I was very familiar with the feel of the Mills valvulotome and its meticulous use in lysing the valves of the greater saphenous vein. I was taught to take great care and to use excellent vascular technique in order not to cause any intimal damage. Reviewing angiograms was a daily ritual and decisions were made about to which vessel to bypass.[9-11] The constant debate about utilization of in situ vein grafts vs reverse saphenous vein grafts was a sign of the times.[12,13] The objective became to try and bypass to the healthiest and most distal landing vessel available.[10,14] All vessels including the dorsalis pedis, distal posterior tibial, peroneal, common plantar, medial plantar, and lateral plantar were targets of vascular surgeons, with the aim to provide flow to the ischemic foot.[10,11,14]

The last decade of the twentieth century and the beginning of the twenty-first century brought significant endovascular changes to the realm of vascular surgery. As endovascular techniques became incorporated into everyday practice, the field of vascular surgery started having concerns.[15] It was in Chicago in 1996 during his presidential address to the 50th Annual Meeting of the Society for Vascular Surgery that Frank Veith, MD, stated, "current vascular surgeons will have to develop some level of catheter-guidewire-imaging skills to be fit enough to survive."[16]

By 2009, emerging national trends using Medicare databases showed that endovascular procedures increased between two- and three-fold, whereas open vascular surgery decreased by 20% to 42%.[17-19] This trend also showed a decrease in amputation rates across this population of patients.[17-19] Further studies are needed to see if there is a link between lower-extremity vascular procedures and improved rates of limb salvage in patients with peripheral arterial disease.[18]

The current concern is to ensure that the emerging trainees are well qualified to practice traditional lower-extremity vascular surgery. The addition of endovascular training has had an impact on fellowship training in a positive way. The total number of cases performed by fellows between 2000 and 2009 showed increases of 150% to 174%. This is largely due to an increase in diagnostic and therapeutic endovascular procedures but of interest is that fellows' open operative experience has been stable over the past decade.[20,21] Further assessment showed that femoral-popliteal bypasses increased in frequency by 27% and the number of infrapopliteal bypasses remained unchanged. Femoral endarterectomies showed a 234% increase from 3.2 cases per resident to 10.7 cases per resident.[21]

The increased frequency of femoral endarterectomies reflects the growing use of hybrid procedures as they are incorporated into the vascular surgeon's armamentarium in the battle for limb salvage. Hybrid concepts in vascular surgery have been utilized experimentally in the past to achieve 30-day immediate limb salvage results of 86%.[22] In a paper written by Lantis et al utilizing hybrid techniques combining superficial femoral arterial endovascular intervention and popliteal to distal bypass for patients with tissue loss, primary patency was 95% and secondary patency was 100%.[23] This correlates with an abstract presented at ISET in 2013, in which adjunctive therapy assisted primary patency and allowed selective decision making of hybrid techniques based on anatomic findings on initial angiography.[24]

The emergence of endovascular techniques changed the debate forum. It was no longer an issue of which style of bypass to use, but whether open bypass showed superior results to endovascular interventions. Each side has its proponents and there will always be questions.[25]

Endovascular skills allow for direct angiographic intervention on angiosomes responsible for the foot ischemia. Traditionally, vascular bypasses were performed to the patent disease-free distal vessel without concern for angiosomes. Recently, the focus on angiosome-directed revascularization has shown evidence that bypassing to the angiosome-affected distal vessel resulted in healing 91% of the time, whereas bypass to indirect distal vessels resulted in 62% of the wounds healing.[26] There are no randomized trials comparing direct revascularization to indirect collateral circulation bypasses and good surgical judgement should prevail in the selection of the arteries to be treated via angioplasty or with bypass.[27]

Lower-extremity bypass techniques did undergo some technique modification through the years. Direct angioscopy-assisted valve lysis ensured direct visualization and fewer early graft failures. It was combined with clipping or ligation of side branches through small incisions, thereby avoiding the traditionally long incision from groin to ankle. Harvesting of the saphenous vein through smaller incisions using subfascial techniques also allowed for reverse saphenous bypass without the traditional incision and allowed for better healing. This technique could be also utilized with the in situ technique.

Ultrasound assistance can also add an element of accuracy and evaluation of the caliber, size, and quality of the vein prior to bypass. It helps to plan the incision, especially in obese patients and identify large side collaterals.

Distal tibial vessels are occasionally unreconstructable precluding revascularization, resulting in major amputation. In 1976 an experimental model creating a distal arteriovenous fistula helped lead to functional revascularization of an otherwise ischemic limb.[28] The theory supporting this intervention is that a peripheral arteriovenous fistula is a potent stimulus to arterial collateralization in the extremity and that its utilization can be beneficial in some patients with inoperable disease. In 2011, Mutirangura et al published a small series of 26 patients with critical limb ischemia and unreconstructable distal vessels. Performing a pedal bypass with deep venous arterialization resulted in 73% of patients having complete healing of the ischemic ulcer and disappearance of rest pain within 6 months.[29] Efforts are currently under way to see if this technique can be performed in an endovascular manner.

After many decades of improvement in surgical technique and recent advances in endovascular skills, we are still left with questions regarding optimal treatment of critical limb ischemia. The BEST-CLI (Best Endovascular Versus Best Surgical Therapy) trial is a prospective, randomized, multicenter, superiority trial comparing best endovascular therapy with best open surgical therapy in patients with critical limb ishemia. It aims to answer questions that we have all asked as vascular specialists over the past six decades.[30]

The goal of every vascular specialist is to provide patients with the optimal care plan that allows for limb salvage if possible. Eighty-five percent of amputees surveyed would do everything to save their limb if faced with a similar scenario, regardless of the number of procedures.[31]

Vascular surgeons did rise to the occasion 19 years ago when Dr. Veith asked them to become endocompetent or become extinct.[32] Now our young

Now our young emerging vascular fellows will have to remember the gold standards of open vascular surgery as developed by their predecessors but also incorporate the newest endovascular skills, which will give them the best of both vascular worlds.

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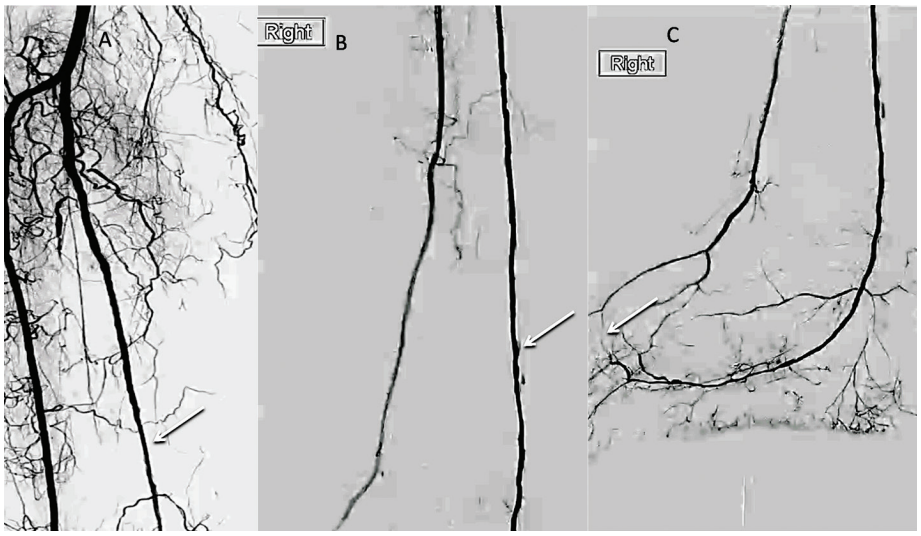

Figure 13. The P3/TPT into the PTA with flow (A). What is not ideal about the PTA here is the mid section, which appears to have acute luminal loss, a common threat in tibial revascularization (arrow). Distal tibial PTA shows a better luminal gain and a size comparable to the ATA (B). The PTA access site is stable (arrow). The pedal circulation is great due to the fact that is is filling simultaneously with the AT (C). Notice the nonconnected pedal loop (arrow) indicating competitive flow between the two. A good type of flow to have in an ischemic wound. Now all posterior flow will be directed to the wound and stolen by the anterior circulation.

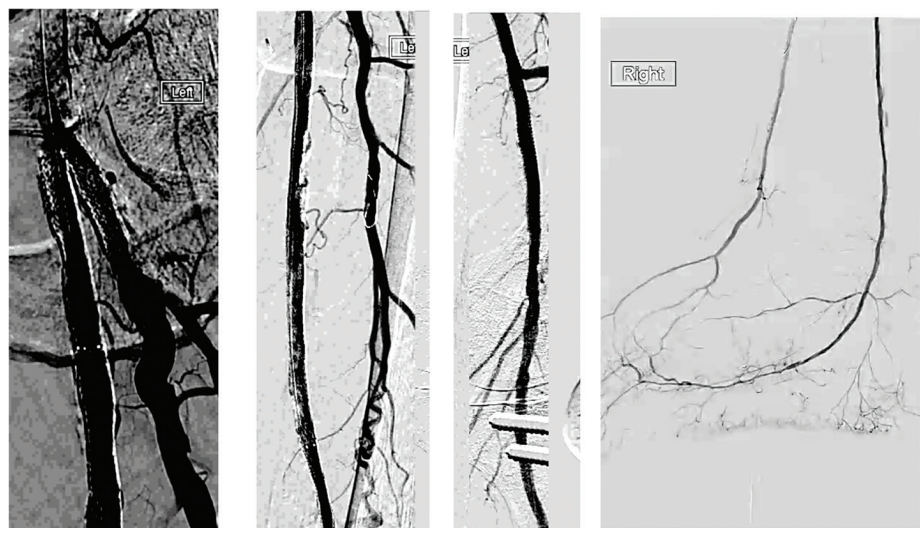

Figure 14. The final angiogram showing restoration of flow in all the arterial segments that were occluded, including the angiosome-directed flow to the calcaneal branches of the heel.

Questions

Continued from page 13

tibial interventions, which are considered successful when flow to the foot is achieved regardless of its quality. True interventional success should be defined as brisk flow into the target area with adequate tissue blush.

The final angiogram is shown in Figure 14. This patient's planned amputation was aborted. The limb was salvaged and has remained functional at 1-year follow-up.

SUMMARY

The primary efficacy endpoint of this hypothetical CLI case-based exercise design was wound healing, which was achieved here. The primary safety endpoint was also met, as there were no amputations. Arterial patency was not included, and we wonder whether this even matters. Improved quality of life and recovered independence were also documented. So in this exercise, we obtained "perfect" results. Interestingly, if this patient had been screened for any of the contemporary studies on novel devices for the treatment of CLI, he would have not qualified, as his baseline ABI was 0.74 and he had a heel ulcer.

Many more provocative questions are still unanswered, but it is clear that it is time for a paradigm change. Critical limb ischemia is not claudication, and therefore, it should be approached and treated differently. The creation of multidisciplinary teams and CLI centers of excellence, as well as the introduction of programs specifically designed to train individuals on how to become dedicated CLI therapists, are only pieces of the puzzle whose picture is only starting to be unveiled. Let's keep at it … we are getting closer. ■

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Distal Tibial

Continued from page 16

emerging vascular fellows will have to remember the gold standards of open vascular surgery as developed by their predecessors but also incorporate the newest endovascular skills, which will give them the best of both vascular worlds. This will ensure their patients are provided with the most optimal treatment plan for limb salvage. ■

Editor's note: Dr. Pliagas reports consultancy to CSI and Medtronic.

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Successful Crossing of CLI Lesion With Antegrade and Retrograde Approaches and Atherectomy

Louis I. Astra, MD
From Florida Hospital North Pinellas, Tarpon Springs, Florida.

Louis I. Astra, MD

As recently as 10 years ago, surgery was the primary treatment modality for severe peripheral arterial disease (PAD) and critical limb ischemia (CLI). Endovascular therapies were just being introduced as a feasible alternative. As experience and technologies evolved, the treatment of PAD has gradually shifted to a minimally invasive, endovascular approach. As the patient population aged, patients had more medical comorbidities, and a less invasive and less risky approach through endovascular interventions became more attractive. Also, despite advances in care for postoperative bypass patients, there were fewer ideal surgical candidates. These developments prompted a different way of treating patients who had more severe disease and were not ideal for aggressive surgical options. Interventionalists have gradually adopted a different approach, with endovascular therapies playing a more important role. In 2005, I started applying the skills I learned during residency with iliac stenting and began applying it to infrainguinal disease as well. Shortly thereafter, I began incorporating atherectomy into my practice. Finally, about 4 years ago, I incorporated pedal access into the treatment of tibial disease.

As time passes, skills need to progress in order to advance care. Technology has allowed us to treat more complex disease. Over the years, to keep up with the latest techniques and technologies, I have attended several courses and training opportunities, one of which was Dr. Mustapha's CLI course in Wyoming, Michigan, in 2014.

Of the peripheral interventions in my practice today, 60% are CLI, and this percentage is rising. Many CLI cases can be very challenging. Often, by the time the patient reaches the interventionalist, their disease has progressed to a critical stage and the patient is running out of options. A multidisciplinary team approach has been shown to be the most effective in the treatment of CLI, and I am dedicated to helping my hospital to grow in that regard and be able to treat more patients with CLI.

Case Report

A 61-year-old male with prior medical history significant for insulin-dependent diabetes mellitus, coronary artery disease, PAD, hypothyroidism, hyperlipidemia, and hypertension. His social history was significant for former smoking of 50+ pack-years.

The patient presented with severe paresthesias (rest pain variant) in his right leg, with symptoms increasing. He had a prior history of worsening claudication for many years. He had no palpable pulses in either foot. Monophasic Doppler signal was obtained of his right posterior tibial (PT) artery. There were no cyanosis or ulcers. An intervention had been attempted 1 month prior from the antegrade approach, as well as by accessing the PT, but revascularization was not achieved due to the inability to pass a wire through the lesion.

The patient presented days later with increasing rest pain. Various catheter and wire options and approaches were considered for treatment. Antegrade access via the right groin was ultimately chosen. Access was gained to the PT with the intention of crossing the lesion from the retrograde approach first. A Regalia XS 1.0 wire (Asahi) was used, which quickly met the distal cap with significant resistance. A .018″ CXI angled catheter (Cook Medical) provided support and was able to penetrate through the distal cap in a retrograde direction and then through the proximal cap, while staying intraluminal.

From there, access was reversed to an antegrade approach. The wire was exchanged for a Viperwire (Cardiovascular Systems, Inc.) and orbital atherectomy was performed in the PT with a Diamondback 1.25 mm micro crown (Cardiovascular Systems, Inc.). Several passes were done on low and medium speeds, with nitroglycerin given between runs. Balloon angioplasty was performed with a 3 mm balloon at 4 atmospheres of pressure.

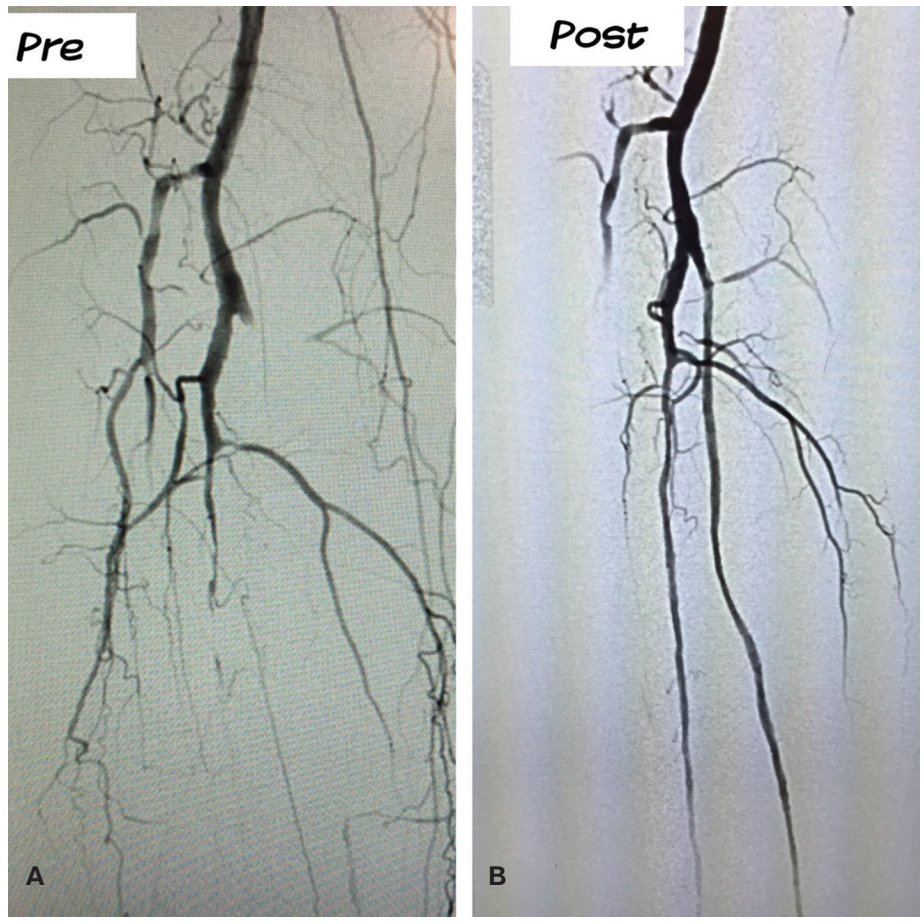

Figure 1. Below-knee popliteal artery, anterior tibial occluded proximally, peroneal occluded proximally, short posterior tibial stump (A). Peroneal and post tibial were patent post procedure (B).

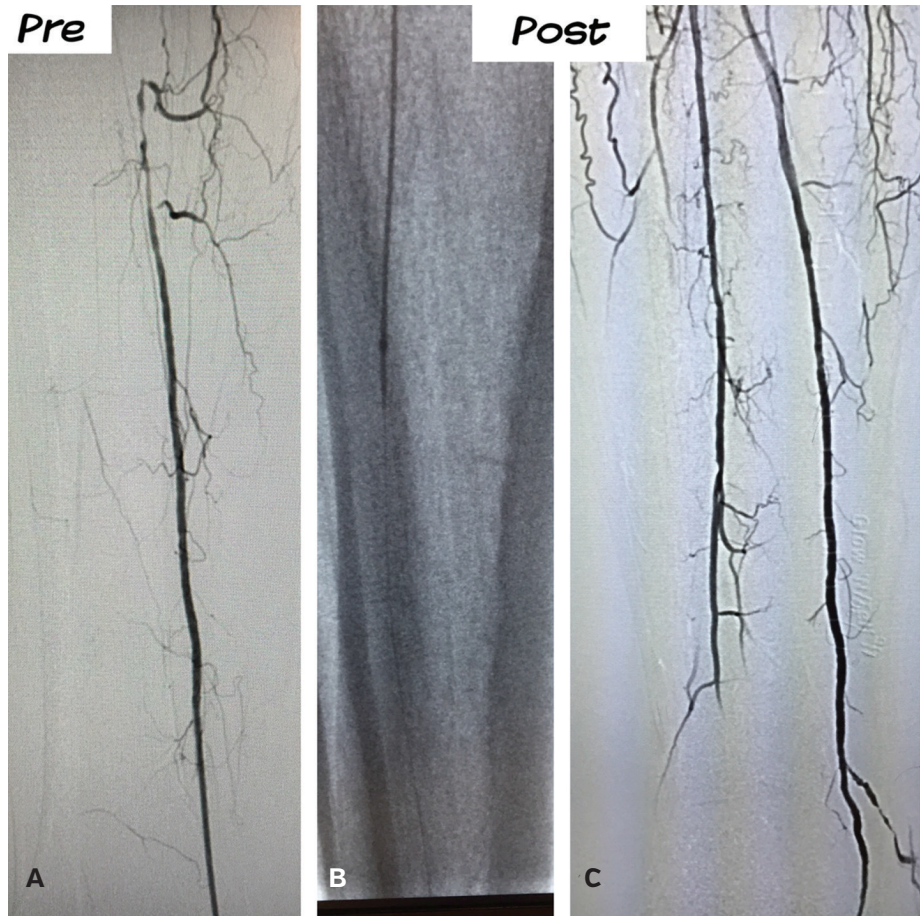

Figure 2. Retrograde injection through distal posterior tibial sheath showing point of reconstitution and adequate distal run-off (A, B). Distal peroneal and post tibial arteries were patent post procedure (C).

Intervention was then undertaken on the occluded peroneal artery. A Whisper guidewire (Abbott Vascular) was used to cross the occlusion, supported with the CXI catheter, and then it was exchanged for the Viperwire and treated with the same 1.25 mm micro crown and 3.0 mm balloon. The procedure resulted in successful revascularization of 2 tibial vessels and the patient now has 2-vessel run-off to the foot. ■

Editor's note: Dr. Astra reports no disclosures related to the content herein.

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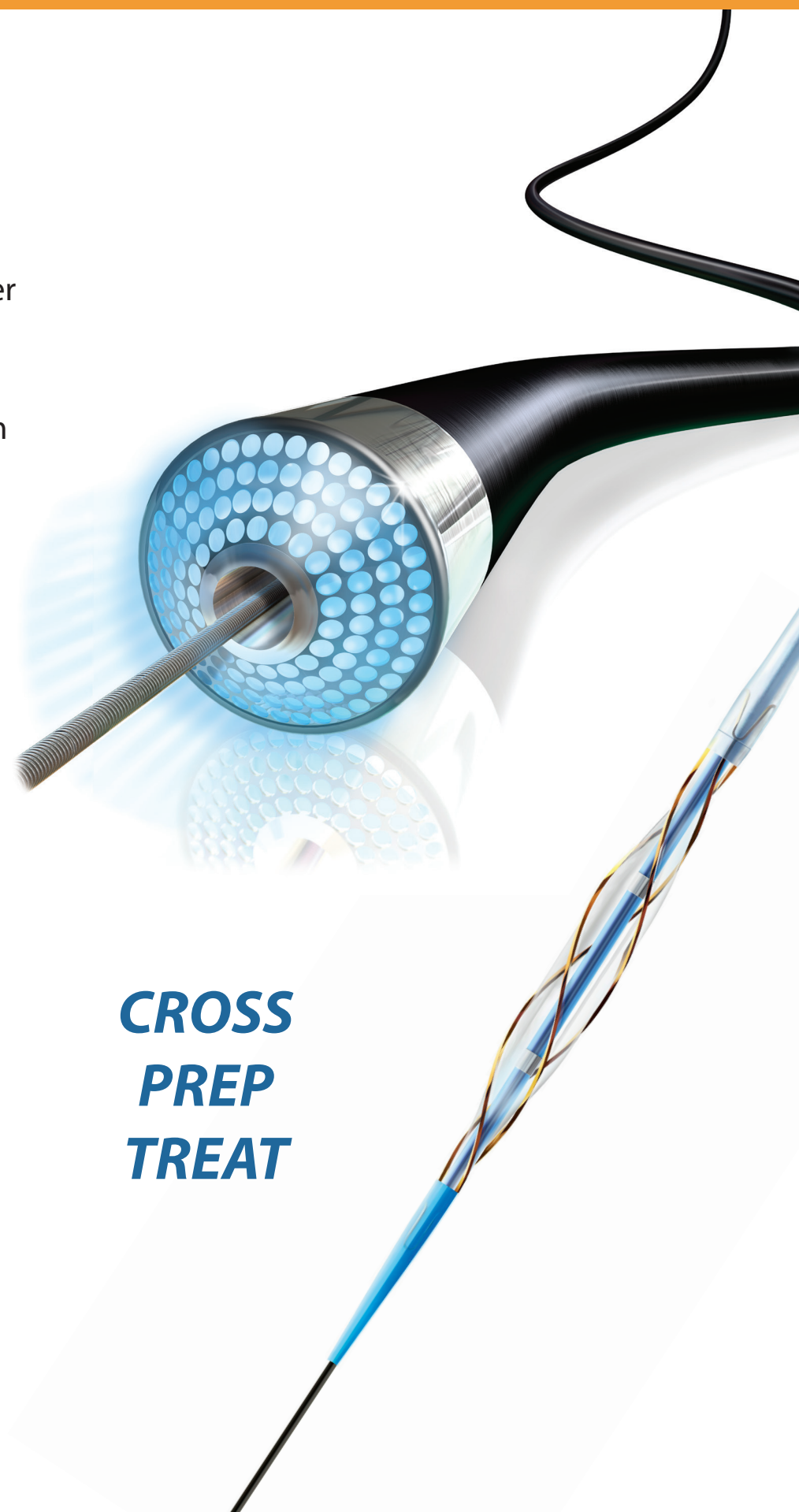

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Role of the Foot and Ankle Surgeon in Critical Limb Ischemia

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Matthew Regulski, DPM

The role of the foot and ankle surgeon is to recognize, treat, and facilitate the management and dispensation of proper and quality care for those suffering from peripheral vascular disease with concomitant chronic wounds. Of all chronic wounds, 70% to 90% are found on the lower extremities. The most common are venous, pressure, and diabetic ulcers. Venous ulcers show an annual incidence afflicting 2.5 million Americans annually, at a cost of approximately $24 billion. Pressure ulcers affect 2 million people annually at a cost of $1.3 billion and diabetic ulcers affect 1.5 million people annually at a cost of between $6 billion and $10 billion.[1,2]

If we look at the etiology of the diabetic foot ulcer, which encompasses the spectrum of neuropathy, deformity, and ischemia with an inciting traumatic event, we find that chronic inflammation is the link between endothelial dysfunction and insulin resistance that engenders a dysregulated metabolism and eventuates clinical vascular disease. Chronic inflammation perpetuates the chronic wound phenotype, as well as the progression of the atherosclerotic lesion, which will progress to a thrombotic or embolic cascade and lead to a critical limb.

The foot and ankle surgeon must understand the seriousness and the urgency behind the diagnosis of peripheral vascular disease (PVD) and refer the patient to a vascular specialist promptly for evaluation. A diabetic neuropathic ischemic ulcer has a greater mortality than breast cancer, prostate cancer, or lymphoma, and in fact, diabetes kills more people annually than breast cancer and AIDS combined.[2]

Every 30 minutes a limb is lost to a landmine, but every 30 seconds a limb is amputated due to diabetes. The mortality rates following amputation are up to 40% at 1 year and 80% at 5 years. With a projected number of 550 million diabetics in the world by the year 2030, which constitutes about 10% of the world's population, the ability to recognize and treat limb ischemia and the resultant chronic wound will be in grave demand.[3]

I see thousands of wound patients per year, and it still baffles me that many of them have never had a vascular test, or at least not a timely one, when they developed the ulcer. Clinicians must remember that palpation of pulses does not include or exclude the diagnosis of vascular disease. There must be some type of quantifying vascular test performed so that a timely treatment can be dispensed to prevent complications.

All chronic wounds are hypoxic. In this low oxygen environment, there is no collagen synthesis, angiogenesis, resistance to infection, or epitheliazation.

Clinicians must remember that palpation of pulses does not include or exclude the diagnosis of vascular disease.

Limb salvage is not for one discipline alone. It will require a multidisciplinary team including, but not limited to, foot and ankle surgeons, vascular specialists, infectious disease specialists, endocrinologists, nephrologists, internists, orthopedic surgeons, general surgeons, plastic surgeons, nutritionists or dieticians, pedorthists, and nurses.

In the chronic wound, we will have biofilm formation, which consumes the oxygen in the wound bed, contributing to this hypoxic environment. This in turn will perpetually stimulate the immune system to come to this wound to clear the bacteria. White blood cells require molecular oxygen for their oxidative burst, which releases hydrolytic enzymes to destroy the biofilm. Unfortunately, they have a very difficult time destroying the biofilm, because it is resistant to this action. It is protected by an extracellular polymeric substance, which is a gelatinous sugar produced by these chronic wound bacteria. Therefore, with this deadly interplay of immune system cells and bacteria consuming all the available oxygen necessary for wound healing, and the more proximal obstruction of flow caused by the chronic inflammation as well, this vicious cycle of tissue destruction can lead to a critical limb, infection, and very possibly amputation.

Limb salvage is not for one discipline alone. It will require a multidisciplinary team including, but not limited to, foot and ankle surgeons, vascular specialists, infectious disease specialists, endocrinologists, nephrologists, internists, orthopedic surgeons, general surgeons, plastic surgeons, nutritionists or dieticians, pedorthists, and nurses. It is a total team effort, because diabetes and vascular disease attack every system in the body.

When clinicians see a patient for the first time presenting with pain in the feet and the legs, with or without a wound but perhaps risk factors, and a musculoskeletal cause is ruled out, it is critical that they open their eyes to the possibility of underlying vascular disease. If a patient has a wound, the clinician must perform a thorough vascular exam and set the patient up with a more robust vascular test to decipher the arterial tree. This would include arterial Doppler studies with toe pressures, as we know that ankle pressure can be misleading and falsely elevated in the diabetic due to vascular calcifications. The digital arteries usually do not get calcified and so are more honest about the vascular flow to the digits. Skin perfusion pressures are extremely reliable and easy to obtain, and give us a tremendous measurement of the oxygen perfusion pressure in the microcirculation of a specific area in the extremity. This is very useful in predicting the healing potential of the wound and the limb.

Once the foot and ankle surgeon has referred the patient to the vascular specialist and the limb is being perfused, there are several advanced modalities that are needed to heal a chronic wound. Even though these topics are beyond the scope of this article, we are now into the realm of using mesenchymal stem cell grafts and injectables to repair, regenerate, and reconstruct dysfunctional tissue that is persisting in the chronic wound.

The role of the foot and ankle surgeon in the detection of PVD is crucial to the survival of the limb and the patient. I cannot stress enough that when foot and ankle surgeons see a patient with a nonhealing wound and pain, they must perform a vascular study. Patients with leg or foot pain that is not musculoskeletal in nature and who have risk factors for vascular disease need a vascular study. Clinicians need to have a high suspicion of vascular disease in the diabetic population, because most diabetic patients will die of myocardial infarction and stroke. Vascular disease and diabetes are becoming rampant in western society. All specialties must come together to diagnose and treat these pathologies, otherwise the outcomes will be disastrous.

We must not look at the hole in the patient, but we must look at the whole patient. ■

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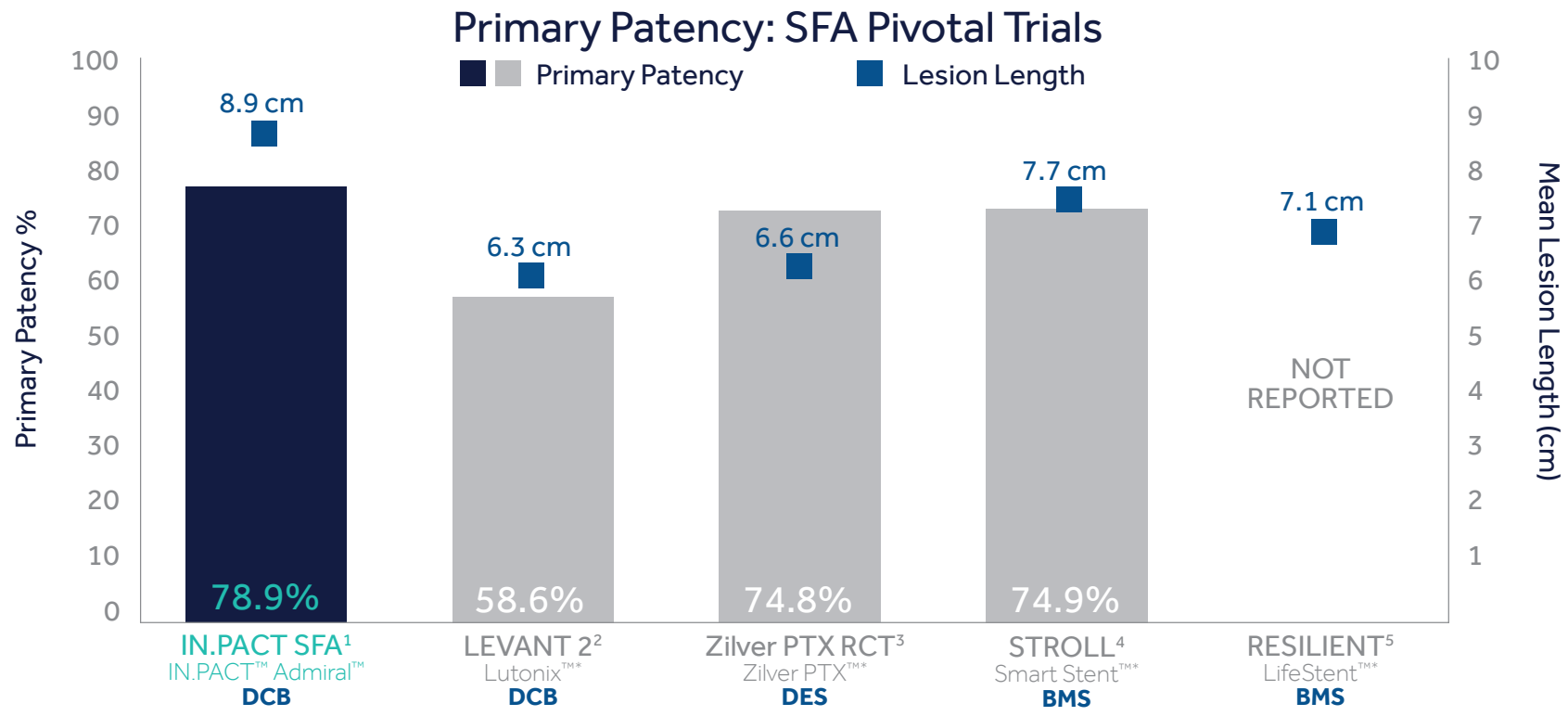

[1] IN.PACT SFA Trial: Laird, TCT 2015: 2-year data primary patency is defined as freedom from clinically-driven TLR and freedom from restenosis as determined by DUS PSVR < 2.4. Primary Efficacy reported on Kaplan-Meier survival analysis. [2] LEVANT 2 Trial, SVS 2015: Primary patency is defined as the absence of target lesion restenosis defined by PSVR of >2.5 and target lesion revascularization. Primary Efficacy reported on Kaplan-Meier Survival analysis, not pre-specified. [3] Zilver PTX: Dake et al., JACC 2013: Primary patency is defined per-lesion by duplex ultrasonography (patent = PSVR < 2.0) or angiography if available (patent = diameter stenosis < 50%). [4] STROLL Trial: Grey, ISET 2013: Primary patency is defined per-lesion by duplex ultrasonography (patent = PSVR ≥ 2.5) and target lesion revascularization.
[5] Resilient Trial: Katzen, VEITH 2009. Primary Patency is defined per-lesion by duplex ultrasonography, PSVR ≥ 2.5. Primary Efficacy reported on Kaplan-Meier survival analysis.

Note: Primary patency rates are not directly comparable: chart is for illustration only. IN.PACT SFA/ LEVANT 2 represent DCB arms of trial: Zilver PTX represents DES arm of trial.
*Based on 2-year primary patency outcomes from FDA pivotal trials.

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Contraindications
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- The safety and effectiveness of the IN.PACT Admiral DCB used in conjunction with other drug-eluting stents or drug-coated balloons in the same procedure or following treatment failure has not been evaluated.
- The extent of the patient's exposure to the drug coating is directly related to the number of balloons used. Refer to the Instructions for Use (IFU) for details regarding the use of multiple balloons and paclitaxel content.
- The use of this product carries the risks associated with percutaneous transluminal angioplasty, including thrombosis, vascular complications, and/or bleeding events

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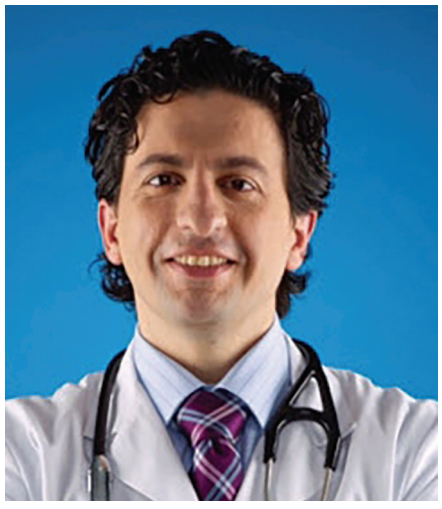
Becoming a CLI Operator: Stuck Between a Rock and a Hard Place

Fadi Saab, MD
From Metro Health Hospital, Wyoming, Michigan.



Fadi Saab, MD

Treating patients with critical limb ischemia (CLI) requires a dedication to treat the complex, multilevel, multivessel disease present in these patients with significant comorbidities. Endovascular revascularization has been adopted across multiple disciplines including vascular surgery, interventional radiology, and cardiology.

When I joined my current practice, I found myself immediately humbled by the vast number of CLI patients presenting with multiple comorbidities and complex multivessel, multilevel disease. I immediately discovered that while my training created the building blocks to treat peripheral vascular disease (PVD), it fell short in preparing me for CLI patients. As an interventional cardiologist, I was not prepared to treat these patients. However, I am now 4 years out of fellowship and my practice has a large volume of PVD patients, 80% of whom are CLI patients.

What does it take to become a CLI operator? During my journey, I have learned that the traditional body of knowledge surrounding CLI is limited. I have learned that tackling complex CLI requires the operator to depart from traditional modalities of revascularization. So, the physician wishing to become a CLI operator must self-educate, stay current, and be hyperfocused on all aspects of CLI care.

As the call for building CLI centers increases around the country, the need for CLI specialists is growing. In a recent publication through the American College of Cardiology, the necessary steps to create a CLI center were outlined.[1]

Prerequisites

Identify a mentor. Identifying a mentor to discuss clinical and academic challenges can prove to be very helpful.

A deep understanding of the infrainguinal and infra-ankle anatomy. Self education should begin here. A strong understanding of angiosomes and angiosome-directed therapy is crucial.

Learn noninvasive evaluation of the CLI patient. Before clinicians perform their first CLI procedure, they must become expert in the CLI patient evaluation. The first encounter with a CLI patient, and physical assessment of the foot, is very important. Understand the value of and timing for noninvasive imaging, such as ankle-brachial index (ABI), pulse volume recordings (PVR), handheld Doppler exam, arterial duplex, computed tomography, and magnetic resonance imaging. These are tools that can help you identify early signs of CLI. The sense of urgency to act upon a CLI patient can make the difference in outcomes for the patient between limb preservation and major amputation. However, interventionalists must be cautious when relying on noninvasive imaging studies to make a final diagnosis. I have seen a significant number of patients that are mislabeled as nonischemic simply because diagnostic tests fell short of diagnosing CLI. A common example is a normal ABI in diabetic patients whose wound may be labeled as a diabetic ulcer when, in reality, it is an ischemic ulcer. Figure 1 shows an example of a CLI patient whose wound was mislabeled as a nonischemic ulcer. Selective angiography revealed evidence of plantar disease causing the ischemic ulcer.

Become familiar with extravascular ultrasound (EVUS). There are many areas the operator can focus on to increase the skill set necessary to tackle complex CLI cases. Learning the use of EVUS to assist in access and crossing can insure a higher degree of success and safety in antegrade and tibial access and CTO crossing.

Attend advanced and hands-on training courses. Attend every training course available to you at educational conferences and vendor-sponsored events. Seek out hands-on cadaveric training courses and ultrasound workshops. Attending advanced training courses allows you to learn from the successes and failures of CLI experts.

Develop and educate your team. Provide opportunities to attend training courses and conferences focused on endovascular and CLI therapies, such as the Amputation Prevention Symposium (www.amptheclimeeting.com). Staff awareness is crucial. Investment in your front-line staff, from the person answering the phone in your office to nurse practitioners and/or physician assistants, pays off. Little training is necessary to be able to identify a patient needing urgent therapy.

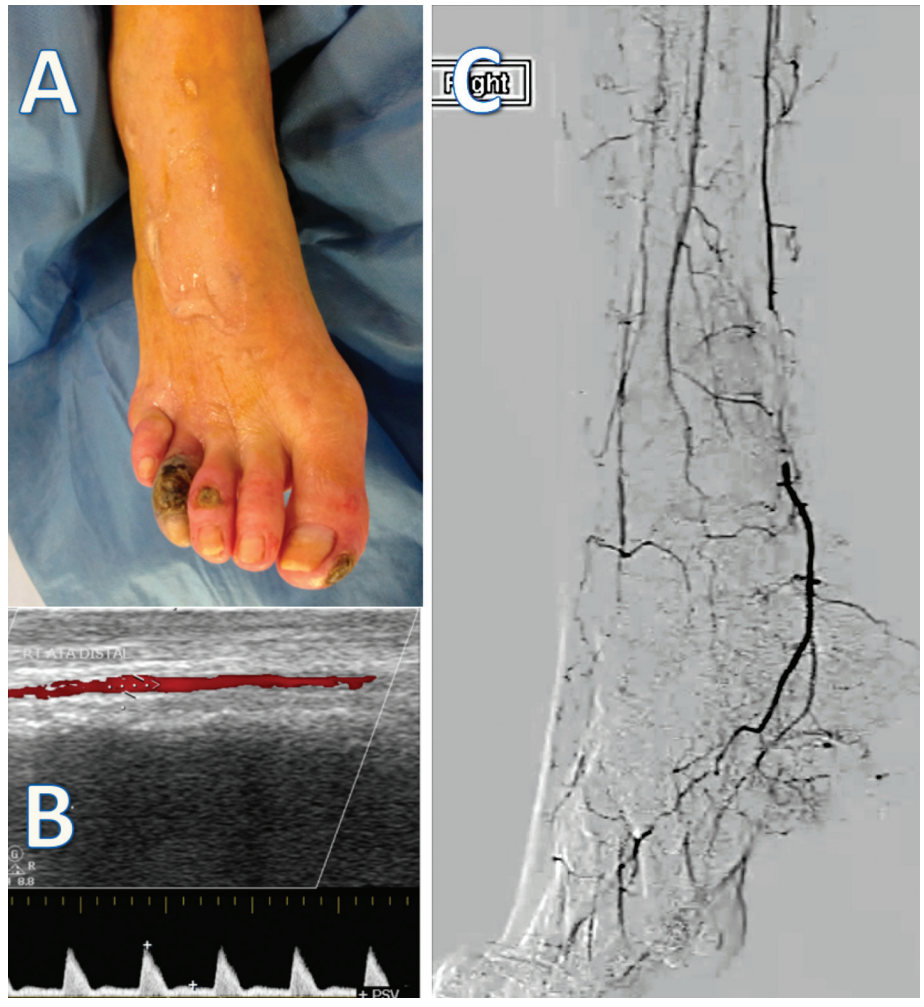


Figure 1. Example of a patient with normal ankle-brachial index and arterial duplex. Wound (A), normal arterial duplex ultrasound (B), selective angiography with plantar disease (C).

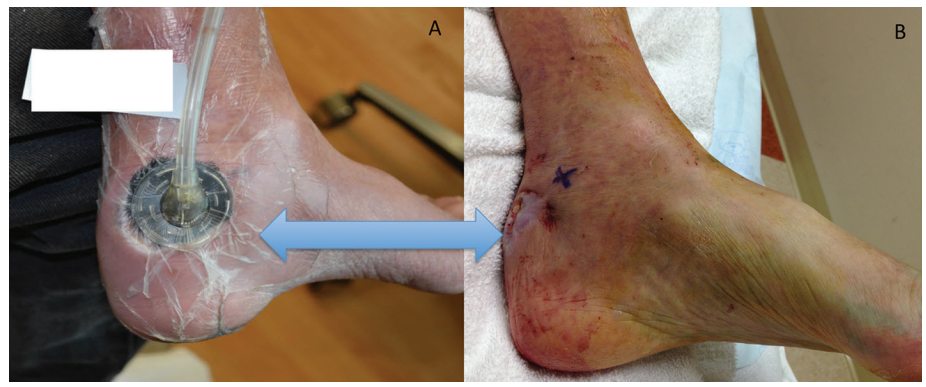


Figure 2. Wound prior to intervention (A) and wound healing post revascularization (B).

Foster a multidisciplinary team approach. Learn the options of care and appreciate the value of each member of the multidisciplinary team, including, but not limited to, primary care, vascular surgery, infectious disease, endocrine, wound care, podiatry, and nutrition.

Know the data. Document your outcomes. Contribute to the data. The importance of knowing the data and knowing your outcomes cannot be underestimated. Document your outcomes in great detail. This will assist you when you contribute to quality initiatives and outcomes research, which is critical not only to track your outcomes but also to help advance this body of knowledge. Documentation is crucial in the care continuum. For example, documentation of wound status before and after revascularization is an important step in measuring your patient's response to therapy (Figure 2).

CLI therapists should feel compelled to participate in meaningful research efforts to help fill in these gaps. CLI patients are complex with multiple comorbidities and complex anatomy and tend to be under-represented in randomized trials. As we stand right now, there is no dedicated scientific body to address the current shortage in data and establish best practices. This need has prompted the creation of the Peripheral Registry

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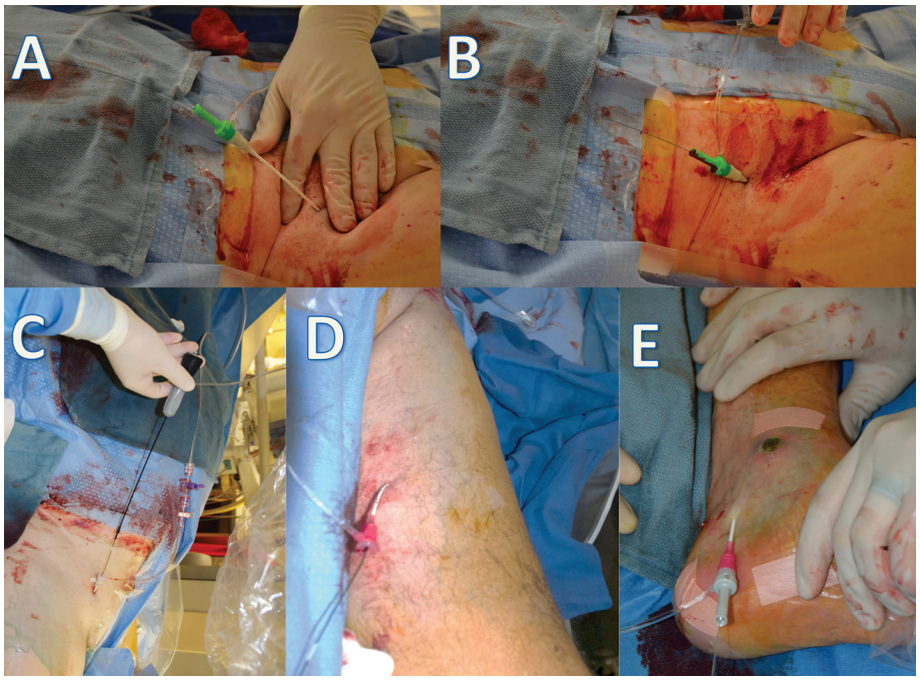

Figure 3. Alternative access. Antegrade common femoral artery (CFA) access (A, B). Antegrade CFA access closure with Mynx closure device (AccessClosure) (C). Retrograde Schmidt (occluded superficial femoral artery) access (D). Tibial access with sheath placement (E).

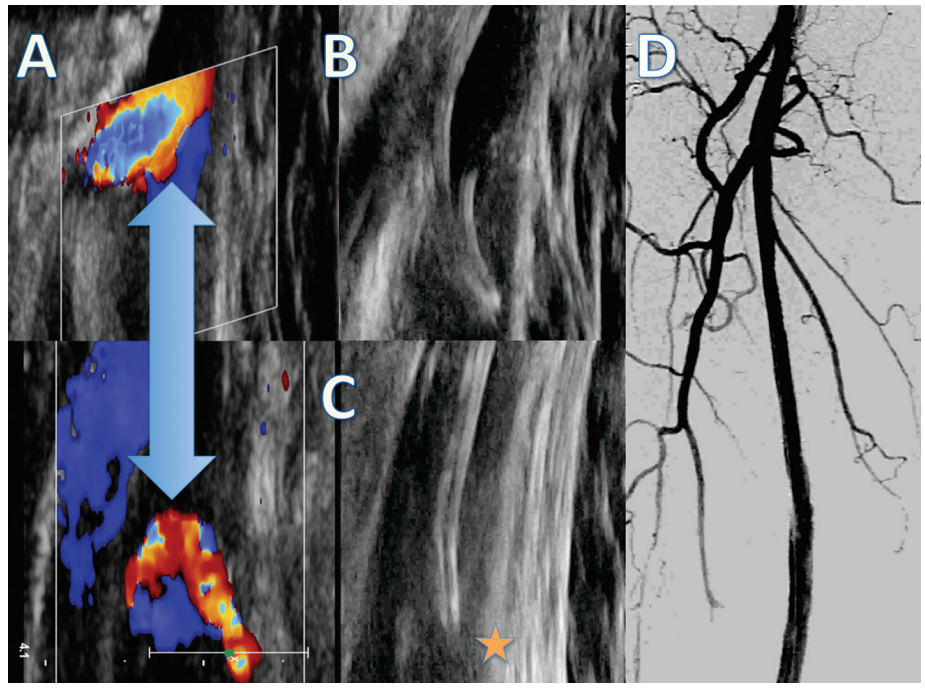

Figure 4. Extravascular ultrasound (EVUS) crossing of chronic total occlusions (CTOs). Flush SFA occlusion with arrow pointing to reconstitution in the popliteal artery (A). Ultrasound-guided crossing of the proximal CTO cap (B). Catheter advanced in the SFA CTO under ultrasound guidance. Tip of catheter (asterisk) (C). Angiogram post CTO revascularization (D).

CLI Operator

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of Endovascular Outcomes (PRIME). This international multicenter initiative is intended to address some of the real-world questions CLI therapists are faced with on a daily basis. Other trials, such as the NIH-funded BEST-CLI, will help expand the limited body of evidence in this sick population.

Revascularization

Perform a baseline selective angiogram. While performing an angiogram with ad hoc revascularization is the norm for the average claudicant, the same does not apply to CLI patients. For example, performing a diagnostic angiogram on a CLI patient allows the physician to plan a successful revascularization strategy. This may include alternative access, such as pedal or antegrade access in complex CLI patients.

Plan your access strategy. Alternative access to traditional CFA access is an important tool to revascularize complex CLI patients. An antegrade approach using an endovascular technique in a CLI patient can also be utilized, especially when treating tibial vessels.[2] Retrograde tibial access will allow access to the targeted region and arguably decrease the length of the vessel treated. Figure 3 shows a variety of alternative access examples a CLI operator must be comfortable performing. New devices for crossing CTOs are becoming available on a more frequent basis. A CLI operator must be willing to adapt newer technologies that can expand the ability to treat complex disease. Extravascular ultrasound allows the operator to use live ultrasound images during the procedure to guide crossing the CTO and delivering therapy. Figure 4 shows an example of a flush SFA occlusion. The CTO was crossed under ultrasound guidance.

Know your exit strategy before you start. Know when to keep going and when to stop. One of the main objectives of treating CLI patients is to improve blood flow to the ischemic limb until the wound is healed. This was a concept that was foreign to me at first and today it is now part of my daily practice. The value of when to keep going and when to stop is very important. This value really comes into play when you're able to revascularize 1 of 3 tibial vessels in a single session and to feel it is okay to stop that day and complete the revascularization on a subsequent day. We are all trained to start and finish a case in one setting. However, CLI therapy often demands cases to be staged to treat the full arterial tree of this multilevel, multivessel disease. CLI patients may require multiple procedures in both lower extremities to establish direct in-line blood flow in patients with ulcers.[3] As much as you want to fix the occlusion, it is equally important to learn when to stop. Sometimes the most effective therapy includes stopping a procedure even when revascularization is incomplete. The potential for multiple, staged procedures requires management of expectations in the patients and their referring physicians. I believe one of the reasons for the high success rate of our CLI program is our team's ability to plan and stage therapy for the complex patient.

Know your treatment options. Critical limb ischemia therapists must learn a variety of techniques as they grow in their practice in order to offer the full scope of therapy to this complex patient population. The CLI operator must display a significant understanding of different revascularization modalities. This starts with being skilled in obtaining alternative access, such as pedal access.

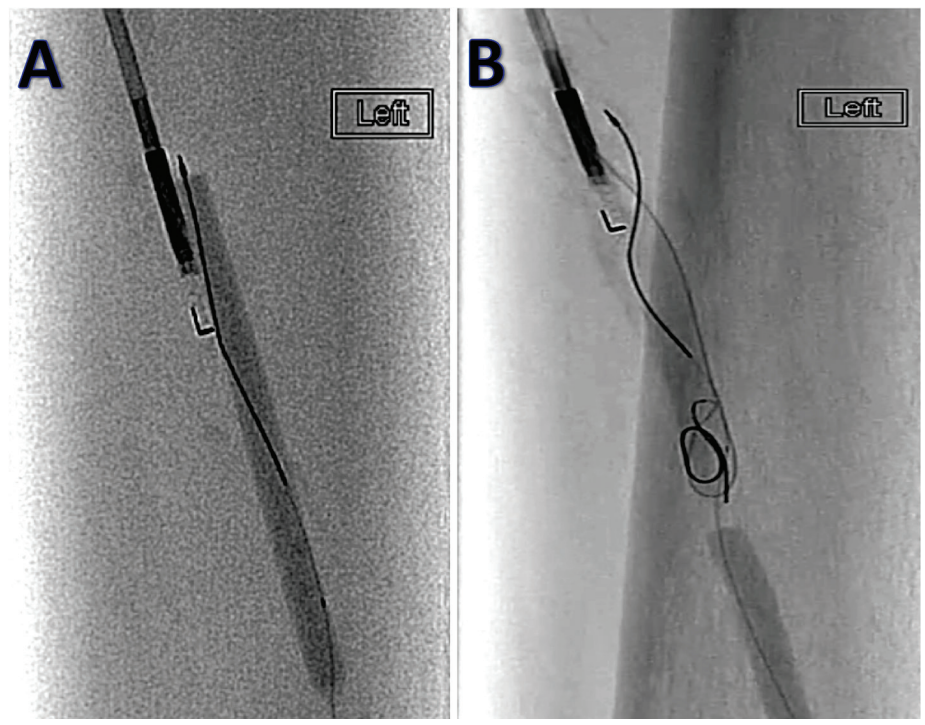

Figure 5. Advanced recanalization (re-back) technique. Outback re-entry device (Medtronic) placed against retrograde tibial 3.5 mm balloon (A). Contrast extravasation after the Outback needle punctures the retrograde tibial balloon. Wire advanced from the Outback into the tibial balloon (B).

The success of retrograde common femoral artery (CFA) access is limited when treating long and complex CTOs with failure rates up to 40%.[4,5] Figure 5 shows an example of an advanced recanalization technique. The term "re-back" refers to re-entry using the Outback re-entry device (Medtronic) in an antegrade fashion. The target of this procedure is to puncture the retrograde tibial balloon. Once the retrograde balloon is punctured via the antegrade Outback, the Outback wire is advanced into the lumen of the retrograde balloon. The balloon is immediately deflated, thus collapsing on the antegrade wire. This approach essentially guarantees crossing the CTO.

Know the tools in your toolbox. Applying the right tool for the right lesion requires understanding of the mechanism of action and design of the different devices available.

Be prepared to treat acute limb ischemia. In addition to treating chronic limb ischemia, the operator must be skilled in treating acute ischemic events. Critical limb ischemia patients tend to have multilevel disease with significant comorbidities, including DM, renal failure, cardiomyopathy, chronic obstructive pulmonary disease, and obesity. These comorbidities

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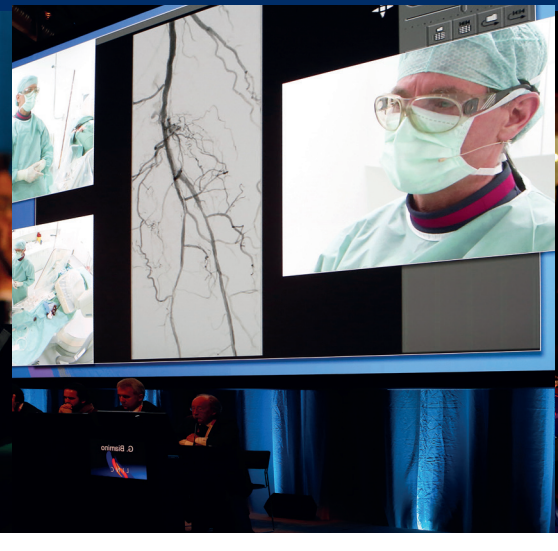

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CLI Operator

Continued from page 24

predispose the patient to acute ischemic events and thrombosis. Having access to a variety of techniques and revascularization strategies will strengthen your ability to care for these patients.

Figure 6 shows an example of an acute stent thrombosis in a CLI patient. The patient had limited access points available, with an occluded iliac system and a fresh thrombotic occlusion in the right SFA where only antegrade access is feasible. Leaving a lytic catheter in place will increase the risk of graft infection, which is a catastrophic complication that can threaten the patient's limb and life. Using the Indigo aspirational system (Penumbra), flow was re-established within the same session, avoiding prolonged lytic infusion.

Practice makes perfect. Take it one step at a time to become adept at tibiopedal access, angiosome-directed therapy, CTO crossing, and treating calcified vessels. Make the investment of time and don't become discouraged. Share your failures, as well as your successes, with your mentors and peers to provide growth and learning opportunities.

Be patient. CLI cases are complex and some may take hours to complete. You must be willing to accept failures and embrace your mistakes in order to better yourself and sharpen your skill set.

Conclusion

As a physician, satisfaction comes from many sources. Patient healing and limb salvage is a life saving measure CLI specialists aspire to achieve. Critical limb ischemia therapy requires a passion for amputation prevention and dedication of your professional and personal time to achieve the above-mentioned competencies.

Becoming a CLI specialist requires commitment to a constantly evolving journey and assuming the responsibility of sustaining the highest quality of care for the patients who desperately need it. In order to sustain a high level of technical skills one must continue to perform an adequate number of CLI cases, maintain ongoing education regarding the available data and new technological advances to reduce the burden of CLI.

If you feel today that CLI therapy is difficult, you are not alone. When I first began I feared it wasn't going to be possible to perform the type of cases I do today. Stick with it, as I did, and you will achieve satisfaction in your career. CLI therapy is very rewarding with an absolute unmet patient need that must be filled with physicians who are passionate and committed to the cause of limb preservation. ■

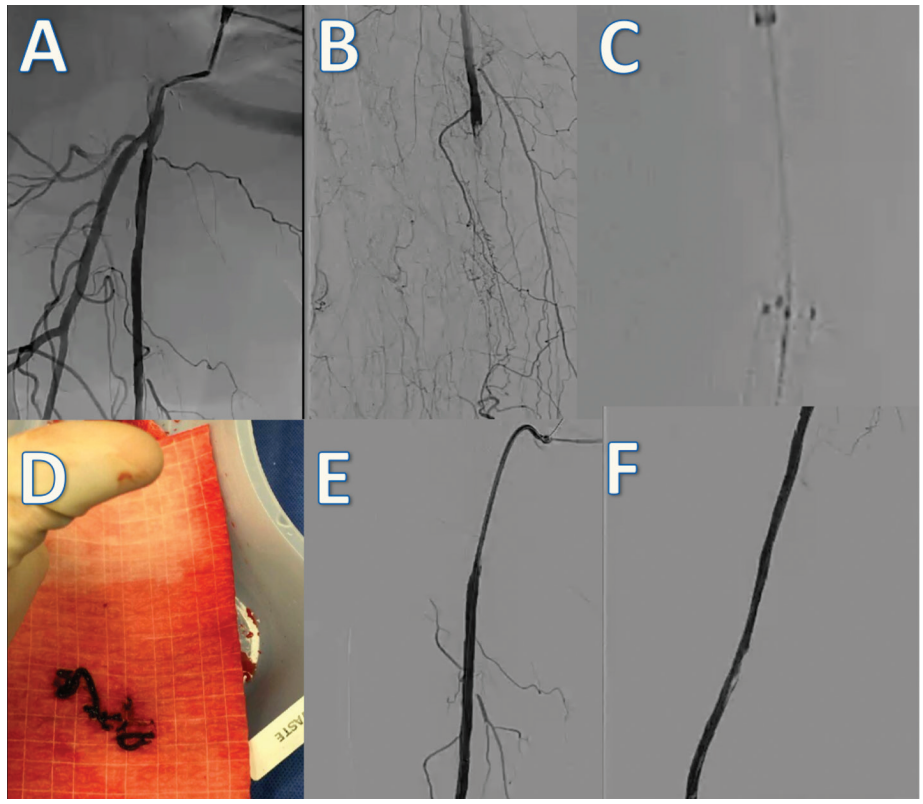

Figure 6. Patient with acute stent thrombosis of a stent. Antegrade access (A), site of occlusion (B), mechanical aspiration with Indigo System (Penumbra) (C), angiogram post aspiration (D), sample of aspirated thrombus (E).

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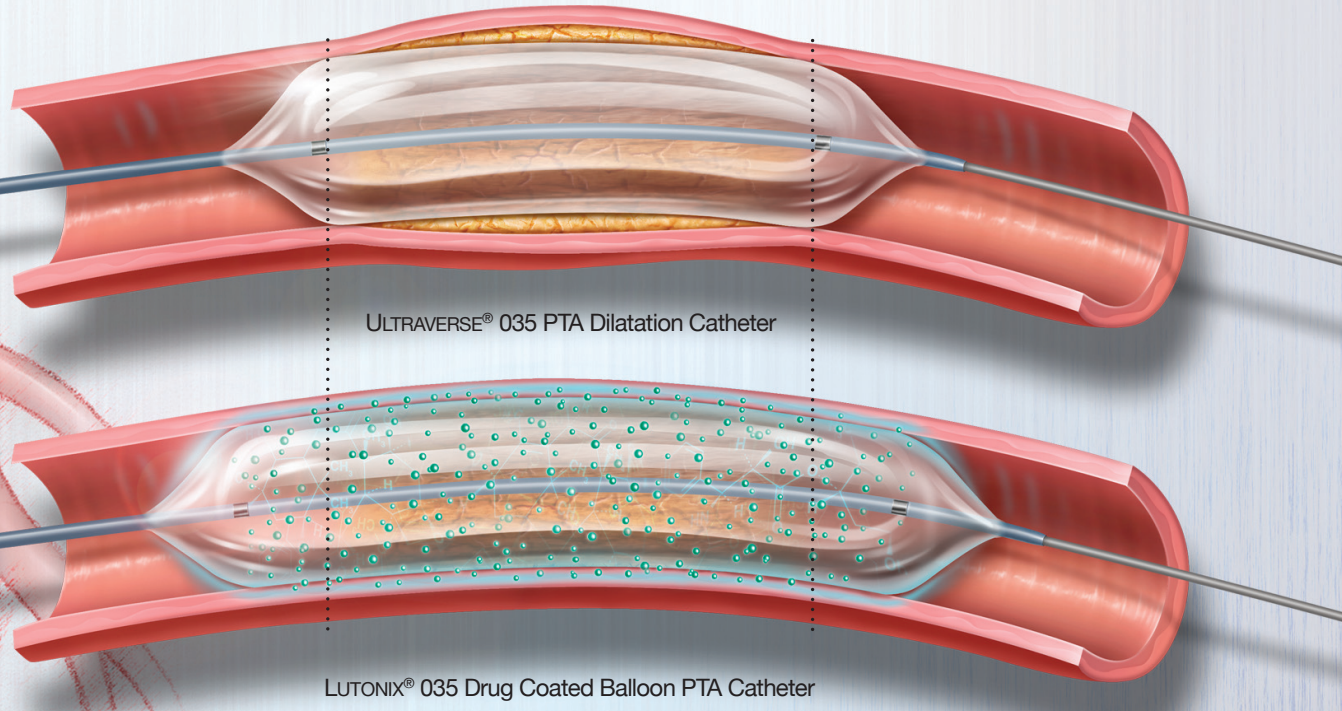

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PTA Dilatation Catheter

GEOALIGN® Markers are not a replacement for fluoroscopy. When the catheter is exposed to the vascular system, the location of the balloon should be confirmed while under high quality fluoroscopic observation.

LUTONIX® DCB should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds. The LUTONIX® Catheter should always be manipulated under fluoroscopic observation when in the body. Please consult product labels and instructions for use for indications, contraindications, hazards, additional warnings and precautions. $R_{x\ Only}$

* Animal study (repeat PTA in swine artery) was performed by 3 physicians who tested the LUTONIX® 035 DCB (no drug) and the ULTRAVERSE® 035 PTA Catheter, both with GEOALIGN® Markers, to POBA with no GEOALIGN® Markers (n=112, test n = 96 (with an average placement time of 66 seconds), control n = 16 (with an average placement time of 90 seconds)). Animal data on file. Bard. Animal test results may not be indicative of clinical performance. Different test methods may yield different results.

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