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An Overview of the Current Mortality State of CLI: We Must Keep the Awareness Alive

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Despite the high number of patients dying from critical limb ischemia (CLI), awareness of this horrific disease is still lacking. Lack of awareness contributes to the cascade of events that are triggered when a patient develops CLI.

Multiple publications over the years have discussed the high mortality associated with CLI. What makes CLI interesting to discuss is that when the patient is diagnosed with the disease, there is often no sense of urgency to do what must be done to prevent the disease from progressing to its final stages. CLI is associated with one of the highest percentages of mortality, even when compared to many cancers. In one study reviewing approximately 36.5 million Medicare beneficiaries enrolled in 2011, 116,000 were given the diagnosis of CLI. Of those, 96,628 had no CLI-related claim over the previous year.[1] What is bothersome when reviewing these data is the likelihood that many patients with severe forms of peripheral arterial disease (PAD) were excluded from this diagnosis; those that represent a milder (early) form of CLI, patients with pre-CLI, and patients with advanced forms of PAD were likely not counted. This would mean that this subset of patients did not receive the proper diagnostic evaluation and care that should be initiated following a diagnosis. The emphasis on diagnosis is important because it has been shown that if CLI is found and therapy is provided, whether it be surgical revascularization or endovascular revascularization, the outcome is better in regard to lowering mortality.[1]

Clearly one can see the value of raising awareness to identify patients with CLI as early as possible. Data exist showing that patients presenting with Rutherford 4 have a lower 4-year mortality level than patients who present with Rutherford 5. Of course, it is not surprising that the patients presenting with Rutherford 6, representing gangrenous changes, have the worst outcomes.[1] This is a serious consequence and should cause us to encourage earlier patient presentation and treatment. In addition to patient-level consequences, there is also an associated higher clinical burden and cost.

We now know that a patient presenting with Rutherford 4 has a higher mortality than a patient presenting with claudication (Rutherford 3). So why aren't we treating patients with Rutherford Class 3 early and aggressively and maintaining optimal medical therapy as long as possible to prevent either the earlier recurrence of the disease or progression of the disease? Despite society and thought leaders discussing the good likelihood that we might be able to reduce the claudicant from progressing to CLI, there are no randomized controlled studies to support the claim. I am confident that it is absolutely necessary to be aggressive with medical therapy as early as possible and to be continued as long as possible. But I would say that medical therapy alone in patients hovering around Rutherford 3, or early CLI, is likely not enough. Some form of revascularization must be done in conjunction with optimal medical therapy. Lack of revascularization can be associated with sudden onset in Rutherford class change, anywhere from 4 to 6 in a matter of weeks to months. The sudden change a CLI patient may experience could lead them astray. Not knowing what to do, they may wait until their illness progresses to a systemic level, at which point they might seek treatment in the emergency room. Now, the advanced disease progression makes them a candidate for a primary major amputation. Studies have shown that primary major amputation portends a poor prognosis even when adjusted for demographics, medical history, and disease severity.[1-3]

Compared with revascularization, primary major amputation is associated with

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CLI Global Society Organizes Coalition

A coalition of cardiovascular medical and interventional specialty societies support the CLI Global Society's initiative to improve tracking and reporting of CLI disease, starting with refining the ICD-10 Diagnosis Code Set.

The Society for Vascular Surgery (SVS), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), and Society for Vascular Medicine (SVM) have appointed representatives to CLI Global Society's multispecialty Workgroup with the goal of a consensus-based proposal to the ICD-10 Coordination & Management Committee for Medicare's 2021 Fiscal Year, starting in October 2020 for inpatient admissions and January 2021 for outpatient and other services.

This effort is a first step to build awareness of the complexity associated with caring for patients who experience critical limb ischemia – both among public payers such as CMS and commercial payers. ■

Coalition to improve tracking and reporting of critical limb ischemia includes representatives from

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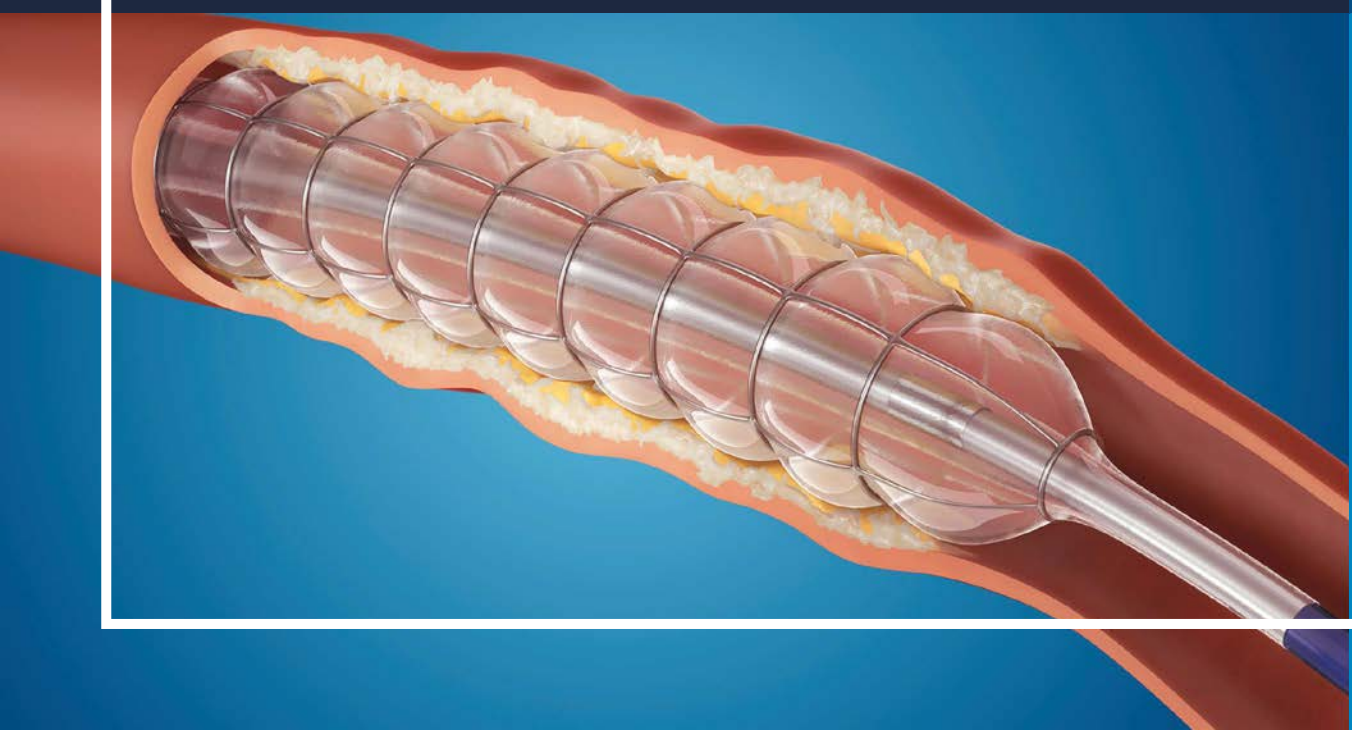

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Why is CLI So Costly?

Mary L. Yost, President, The Sage Group

Mary L. Yost

Medicare pays approximately 75% of the critical limb ischemia (CLI) bill.[1] In 2016, the annual cost of treating a Medicare patient with CLI was almost eight times higher than the cost of treating the average Medicare beneficiary ($93,800 versus $12,046, respectively).[1,2] One recent study estimated that CLI cost Medicare $6.5 billion.[1]

Why is CLI so costly? A number of factors increase the cost of treating CLI. Many of these are modifiable.

PRIMARY AMPUTATION DRIVES UP COSTS

Treatment with primary major amputation rather than revascularization is one important factor that increases costs.[1,3] The direct cost of the 65,000 to 80,000 major amputations employed to "treat" CLI in the US exceeds $11 billion annually.[3] In addition to these direct treatment costs, unreimbursed patient costs add $9 to $10 billion, resulting in total amputation costs of $20 billion.[4]

Numerous studies of hospital costs in different countries, covering varying time periods, all show that amputation is more costly than revascularization with either endovascular or surgical bypass.[5-8] Although initial procedure costs are similar for amputation, surgical bypass, and endovascular revascularization, the total costs of amputation are considerably higher due to the increased frequency of costly procedural morbidity, mortality, and revision amputations.[3]

While treatment with major amputation is more expensive than revascularization and is associated with suboptimal patient outcomes, it is just one of the factors that increases CLI costs.[1,3]

TREATMENT COSTS INCREASE WITH DISEASE SEVERITY

Peripheral artery disease (PAD) treatment costs increase with disease severity. A recent German study demonstrated that average inpatient costs for CLI treatment are higher than for PAD patients in Rutherford Category 1–3.[9] US data show a similar pattern of cost increases with disease severity. Furthermore, as CLI increases in severity from rest pain to gangrene, hospital treatment costs rise.[1,9] These data suggest that earlier diagnosis accompanied by appropriate treatment of PAD and CLI at less severe stages could decrease total costs.

Amputation and mortality increase with disease severity.[1,9] The German study found that 4-year amputation rates for Rutherford 1–3 patients were about 5%.[9] Amputation rates increased with severity of ischemia, so that, in Rutherford 6 patients, for example, amputation rates reached 67%.[9] In US Medicare patients, 4-year amputation rates increased from 6% for CLI with rest pain to 30% in CLI patients with gangrene.[1] Mortality rates followed the same pattern in both studies.[1,9] Once again, these data suggest that earlier diagnosis and treatment at less severe stages could reduce treatment costs, morbidity, and mortality.

MOST COSTS ARE INPATIENT

The majority of CLI costs (62%) are inpatient. Outpatient costs account for 20% and physician/supplier costs for 18%.[1] In comparison, inpatient hospital costs account for one-third of total U.S. healthcare expenditures and 40% of Medicare expenditures.[10,11] The high incidence of hospitalization of CLI patients most likely reflects delays in diagnosis and treatment until the disease has progressed to more advanced and severe stages.

In the U.S. healthcare system, inpatient treatment is significantly more expensive than outpatient. According to a recent study conducted by the University of Washington, the average cost of an outpatient visit in the U.S. in 2016 was about

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Interim Results of the PROMISE I Trial to Investigate the LimFlow System of Percutaneous Deep Vein Arterialization for the Treatment of Critical Limb Ischemia

J.A. Mustapha, MD[1]; Fadi A. Saab, MD[1]; Daniel Clair, MD[2]; Peter Schneider, MD[3]

ABSTRACT: Objective. To investigate the feasibility, safety, and effectiveness of the LimFlow stent-graft system in performing percutaneous deep vein arterialization (pDVA) for treatment of critical limb ischemia (CLI) patients ineligible for conventional endovascular or surgical revascularization procedures. **Methods.** Ten no-option CLI patients (mean age, 67 ± 11 years; 30% women) were enrolled. All patients were classified as Rutherford class 5 or 6 and were deemed by a committee of experts to be ineligible for endovascular or surgical procedures to restore blood flow. Eighty percent were categorized as stage 4 (high risk of amputation) based on Society for Vascular Surgery wound, ischemia, and foot infection (SVS WIfI) scoring index. The primary safety endpoint was amputation-free survival (AFS) at 30 days. A secondary safety endpoint evaluated AFS at 6 months. Other secondary endpoints included primary patency, wound healing, and technical success. **Results.** Amputation-free survival was achieved in 100% of patients, with no deaths or index limb above-ankle amputations observed at 30 days and 6 months. Technical success rate was 100%. No procedural complications were reported. Primary patency rates at 1 month and 6 months were 90% and 40%, respectively, with reintervention performed in 30% of patients. By 6 months, 30% of patients experienced complete (100%) wound healing, half of patients had 84%-93% wound healing, and 20% of patients experienced 60% healing. **Conclusion.** pDVA using the LimFlow system is a novel approach for treating patients with no-option CLI and may reduce amputation in this population for whom it would otherwise be considered inevitable. Initial findings from this early feasibility trial are promising and additional study is warranted.

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Key words: critical limb ischemia, desert foot, stent-graft

Critical limb ischemia (CLI) represents the most advanced form of peripheral arterial disease (PAD). Its presentation is characterized by ischemic rest pain, non-healing ulceration, and/or gangrene (Rutherford categories 4 to 6), attributable to arterial occlusive disease.[1] Patients with CLI are heterogeneously complex and frequently endure chronic comorbidities including hypertension, hyperlipidemia, diabetes mellitus, and renal failure.[2] There is a broad spectrum of disease severity and, even with the diversity of contemporary treatment modalities, the therapeutic options for CLI patients are often limited. End-stage CLI pathology results in the occlusion of pedal arteries (desert foot), eliminating suitable targets for distal bypass.This advanced and complex disease also commonly results in failure of conventional revascularization treatment.[3] Even with aggressive local wound care, patients with severe limb ischemia and chronic ulceration who do not, or cannot, undergo revascularization frequently progress to amputation.[4] Up to 20% of CLI patients can face "no-option" situations, eg, due to the complexity or location of atherosclerotic lesions, lack of adequate conduit, or extensive co-morbidities, currently available surgical and endovascular techniques are not sufficient and major limb amputation is considered as the only viable solution.[5] With increasing rates of diabetes and renal failure as well as increasing lifespans, this difficult population of no-option patients may continue to grow, increasing the need for an alternative option for limb salvage.[6]

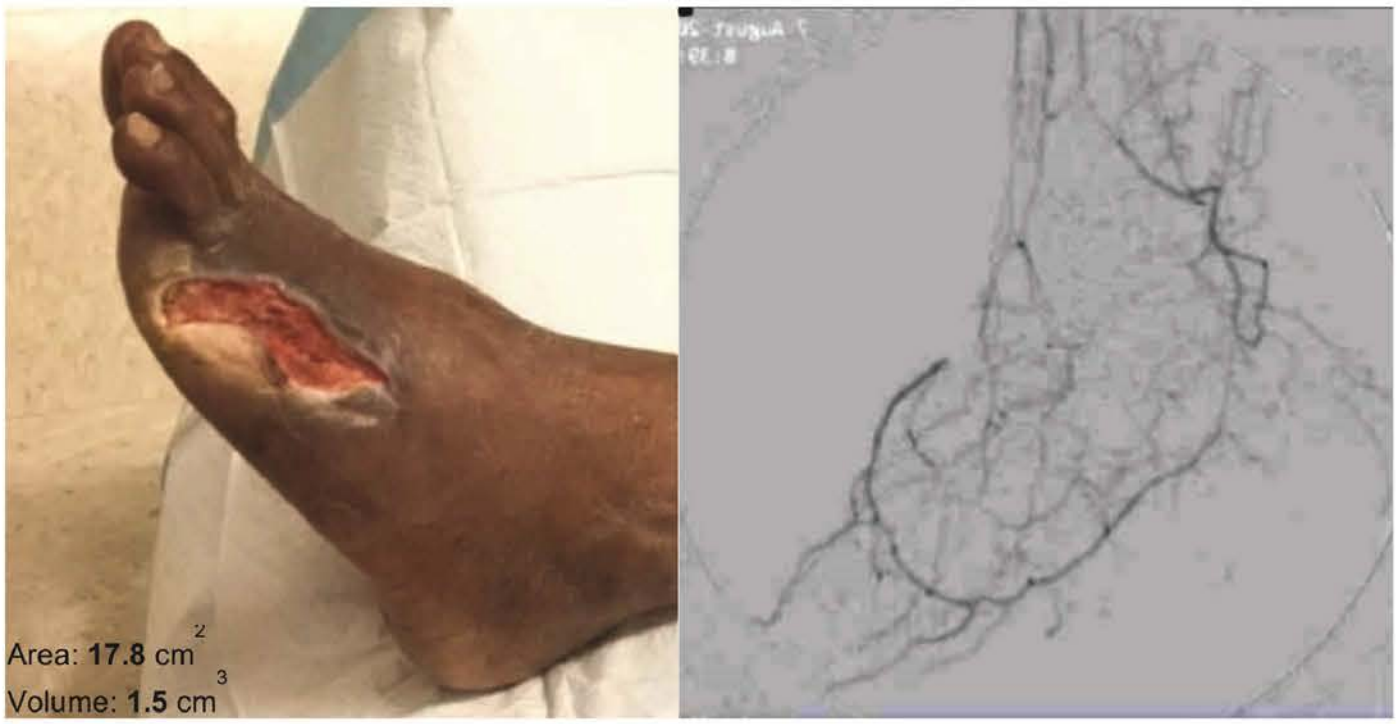

Figure 1. Example of baseline wound and angiographic imaging with limited arterial distal flow.

Increased attention has been focused upon the quality of life (QoL) of CLI patients. A previous study that focused on CLI patients' QoL found that the subset of patients who had no surgical or endovascular treatment option reported inferior overall quality of life when compared to patients with milder forms of PAD, with physical functioning and bodily pain most severely affected.[7] Approximately half of patients who undergo below-the-knee (BTK) amputations are able to regain household mobility, and less than a quarter regain mobility outside of the home.[8] Beyond the loss of functional ability, patients who undergo amputation are at an increased risk of mortality, with rates reaching approximately 25% of patients at 1 month, 50% at 1 year, and 75% at 5 years.[9] Considering the detrimental outcomes of amputation, limb salvage remains the primary goal of contemporary CLI treatment.[10]

The LimFlow percutaneous deep vein arterialization (pDVA) approach to treating CLI is an evolution of the concept of venous arterialization, a procedure that has been performed surgically for many years, with the first clinical surgical cases reported in the early twentieth century.[11,12]

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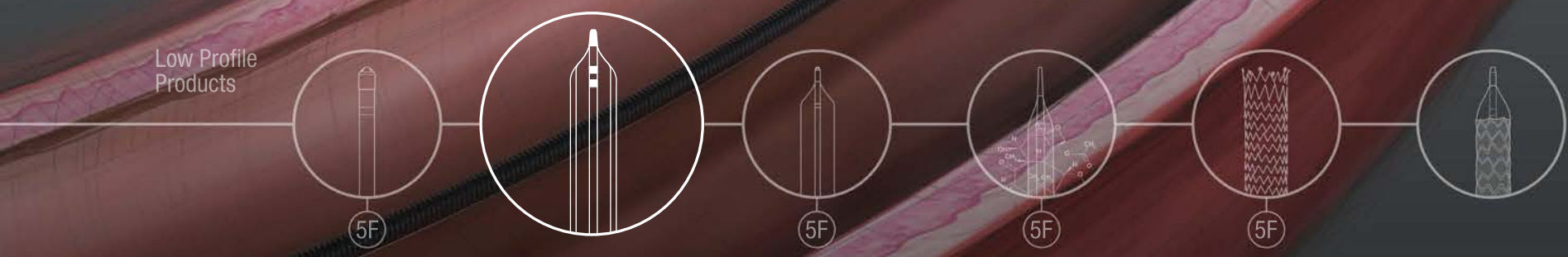

* Yost. Critical Limb Ischemia: Volume 1; The SAGE Group. 2016. Numbers based on The SAGE Group 2016 PAD estimates.
** Based on a simulated finite element analysis. Data on File, Bard Peripheral Vascular, Inc., Tempe, AZ. May not be predictive of clinical performance. Different test methods may yield different results.
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Two High-Volume CLI Operators: Perceptions on Training, and Experience Requirements to Perform Limb Salvage Cases

What's in a Number? Expertise Versus Access: A Complex Balance in Optimizing Management of CLI

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Critical limb ischemia (CLI) represents the most advanced stages of peripheral arterial disease, with impaired arterial perfusion resulting in prolonged ischemia and ultimately a threatened limb. CLI is relatively common in the United States, with an incidence of 3.5 patients per 1,000 and estimated prevalence of 1%, and is incredibly costly to patients and the healthcare system.[1] Clinical outcomes for patients with CLI remain poor, with more than 10% undergoing amputation and survival less than 50% over 4 years in a contemporary cohort,[2] despite increasing attention to the clinical entity and advances in both revascularization and medical therapy. These clinical costs are also reflected in the financial burden of CLI, with estimated mean costs of $35,700 per patient. With up to 10% of patients with peripheral arterial disease expected to develop CLI over a 5-year period, this clinical entity represents a significant threat to individual patients and the healthcare system as a whole.[3]

How is it best to approach this threat? Increases in awareness and urgent revascularization have resulted in reductions in unacceptably high rates of mortality and amputation over time.[4] However, outcomes remain poor despite these evolving efforts. These are complex patients with multiple comorbidities and complex vascular anatomy. Increasing rates of endovascular approaches for revascularization may limit exposing these patients to the risk of open surgical procedures, but in turn require a highly specialized skillset to achieve adequate revascularization for the purposes of limb salvage. Dedicated experience with multi-level anatomic disease, chronic total occlusions, sub-intimal crossing, procedural imaging, and alternative access and techniques for lesion modification are just a small part of the requisite toolbox needed for CLI operators. These skills are acquired through dedicated training in peripheral vascular intervention and through ongoing clinical experience and exposure to CLI care. Prior data have suggested a relationship between both institutional and operator volume in CLI and improved outcomes,[5,6] but what is the "magic threshold," if one exists? And what consequences might setting such a threshold have on CLI care nationally?

Herein lies the dilemma facing the vascular community. Presently, without procedural minimums, there is significant variation in CLI care, with geographic disparities in care and outcomes.[7,8] There are multiple reasons for this possible disparity, with operator inexperience a potential contributor. However, simple access to vascular care may play a significant role as well. A landmark analysis by Goodney et al demonstrated alarmingly low levels of vascular care prior to amputation nationally, but with significant regional variation and an unsurprising inverse association with the intensity of vascular care and rates of amputation rates across regions.[9] This, coupled with well-described associations between race or socioeconomic status (recognized risk factors for poor access to care) and amputation,[10] one can imagine a persuasive argument that access to care may represent as much of a barrier to optimizing CLI care as operator inexperience. While operators need experience and exposure to cases to ensure profiency and quality in their efforts, might there be unintended consequences of establishing a threshold? What would such procedural minimums do to access for CLI care?

On a state level, there may be minimal impact. Medhekar et al evaluated the role of distance to vascular centers on outcomes, and found that institutional volumes were more predictive of outcome

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CLI Intervention: The Importance of Operator Volume

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Critical limb ischemia (CLI) represents a unique challenge in the peripheral vascular arena. Affected patients present with advanced disease coupled with extensive comorbidities. It is not surprising that outcomes in this population remain poor, with amputation rates of up to 40% at 6 months and mortality rates of 50% at 2 years.[1-3] Significant variability exists in the quality of CLI care based on geographic, socioeconomic, and even racial background, leading to delays in treatment with devastating consequences.[4,5] More disturbing are studies demonstrating that a significant number of amputations are performed with perfunctory attention to the patients' underlying vascular status both diagnostically and therapeutically.[6] As a result, there is a strong desire to create dedicated regional CLI programs in which care can be coordinated among a myriad of healthcare providers including primary care physicians, podiatrists and wound care personnel, vascular disease physicians, infectious disease specialists, and endocrinologists. This multidisciplinary approach has clearly been shown to improve wound healing and limb preservation in CLI patients, particularly diabetics.[7]

From a vascular standpoint, surgical revascularization can be limited in CLI patients due to advanced age and concomitant systemic cardiovascular disease, making endovascular therapy the primary option for limb salvage. However, many physicians who comfortably treat peripheral vascular disease in claudicants can struggle in critical limb patients. CLI operators face significant technical challenges including multi-level vascular disease with infrapopliteal lesions characterized by diffuse calcified plaque and long chronic total occlusions. Several techniques have been developed to overcome these challenges including pedal access for antegrade/retrograde luminal or subintimal recanalization, transcollateral angioplasty, and pedal-plantar loop techniques.[8-13] These approaches are coupled with various specialty balloons and atherectomy tools to facilitate optimal angioplasty results. Studies demonstrate significantly improved rates of limb salvage with a 60% reduction in major amputations when applying alternative access techniques.[9] Use of these techniques not only requires specialized training but also an adequate volume of patients upon which mastery can be developed.

Volume-outcome relationships have been well studied in the percutaneous interventional literature. Lower volume coronary operators demonstrate greater in-hospital mortality rates compared to their higher volume counterparts, and early carotid stenting trials were plagued by poor outcomes largely due to inexperienced physicians performing stenting in these early trials.[14-16] Poor outcomes can be attenuated by practicing in high volume institutions, presumably from collaboration with more experienced colleagues.[17] Nevertheless, procedural volume standards have been adopted or recommended for numerous advanced percutaneous therapies (Table 1).[17-20]

The complexity of CLI endovascular treatment rivals the procedures mentioned above, therefore it seems appropriate that CLI operators should also have a procedural volume mandate. Setting aside a debate regarding the definition of a "CLI case" and recognizing that an exact number is inherently unsatisfactory, it seems that a yearly volume of at least 75 CLI cases/year is reasonable and comparable to the current standards for complex catheter-based therapies. Coronary intervention has seen a drop in procedural volume requirements as PCI has become safer and more predictable due to advancements in technology. CLI vascular treatment, on the other hand, is still in its infancy and there is a growing need for widespread education to keep up with this rapidly progressing field. Of course, other quality measures are equally important

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Focusing on Amputation Prevention in a Challenging PAD Anatomical Subset

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Hyperbaric & Wound Care Center at Mercy Hospital, Miami, Florida

Enrique Hernandez, MD

The implementation of limb preservation programs has been the response of the medical community to the already significant economic burden of minor and major amputation. Palli and colleagues concluded that nationwide limb salvage programs can potentially save the US healthcare system up to $38.5 billion.[1] Various models of interdisciplinary cooperation exist, and each exemplifies the titanic collaboration efforts needed to decrease the incidence of amputation. In a recent study, higher lower extremity amputation indices were associated with low revascularization volume hospitals.[2] Thus, amputation represents probably the most severe manifestation of critical limb ischemia (CLI), and proper revascularization is likely the most appropriate way to bring adequate perfusion to the affected limb.[3] In an extensive 22-year prospective study, Boyko and colleagues noted the intricate relationship between macrovascular disease and the protagonist role of poor perfusion on the road to amputation.[4]

CASE PRESENTATION

An 82-year-old Hispanic woman was initially referred by her primary care doctor to the Hyperbaric & Wound Care Center at Mercy Hospital in Miami, Florida. She presented with a progressively worsening non-healing painful ulcer for the prior 7 months that now exhibited purulent discharge. Her past medical history included peripheral arterial disease (PAD), chronic obstructive pulmonary disease, hypertension, and 1 pack per day tobacco use for most of her life, though she had quit smoking 4 years ago. The woman described bilateral lower extremity claudication symptoms that had occurred during the prior 3 years upon walking less than a half block.

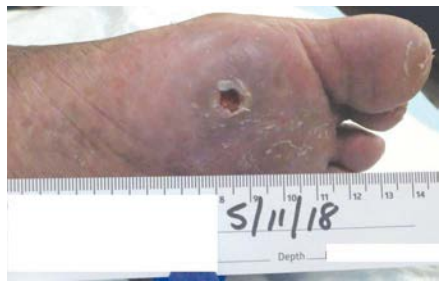

Figure 1. There was a full thickness ulceration of the left plantar first metatarsal with necrotic base and positive probe to bone.

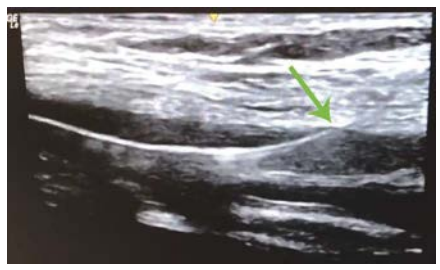

Figure 3. Extra-vascular ultrasound demonstrating direct wire access retrograde into occlusion.

Her laboratory results revealed anemia and an elevated erythrocyte sedimentation rate. On physical examination, she appeared underweight and older than her stated age. There was a full thickness ulceration of the left plantar first metatarsal with necrotic base and positive probe to bone (Figure 1). The peri-wound was dusky in appearance with atrophic changes consistent with chronic disease. The temperature was warm to cool from tibial tuberosity to digits with delayed capillary filling time. Pedal pulses were non-palpable. Lower extremity arterial Doppler revealed extensive left lower extremity PAD with monophasic wave forms in the infrapopliteal vessels with occlusive disease. An MRI of the left foot showed no evidence of osteomyelitis with ulceration of the plantar aspect of the foot superficial to the proximal phalanx of the first toe, and nonspecific minimal marrow within the lateral sesamoid without circumscribed collection, suggesting an abscess and subcutaneous edema. In view of her clinical presentation, lower extremity angiography was recommended. This revealed:

- Aneurysmal infrarenal aorta with moderate atherosclerotic disease
- Left common and external iliac arteries with 30%-40% stenosis
- Left common femoral artery (CFA) with 40%-50% calcified stenosis

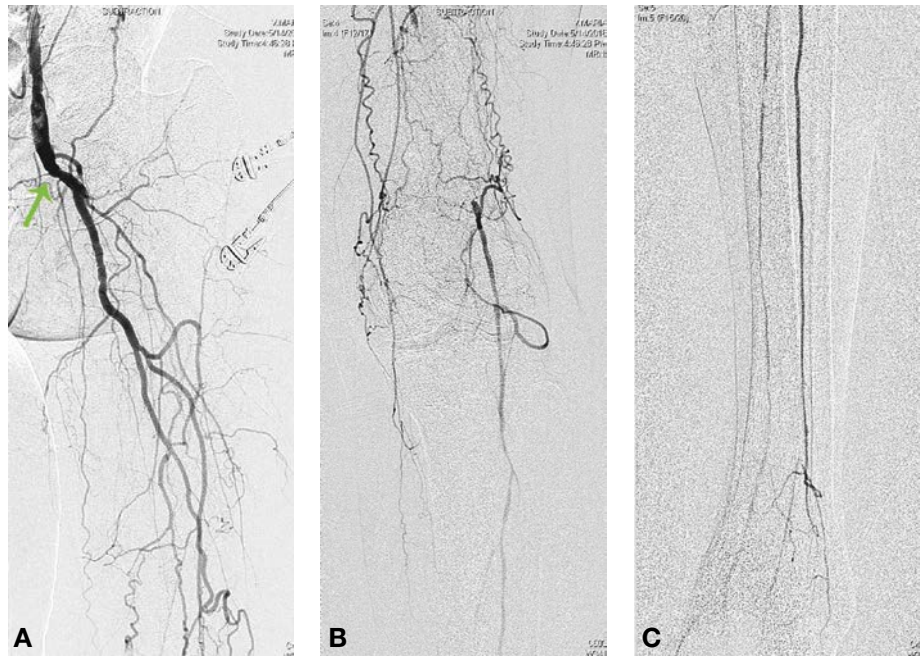

Figure 2. (A, B) Left superficial femoral artery (SFA) with "flush" 100% occlusion at the proximal segment extending distally into the popliteal artery; (C) The left anterior tibial was 100% occluded and reconstituted at the ankle. The left posterior tibial diffuse was the single vessel runoff to the foot 95%-99% segmental stenosis. The left peroneal artery had mild diffuse disease and collateralized the anterior tibial.

- Left superficial femoral artery (SFA) with "flush" 100% occlusion at the proximal segment extending distally into the popliteal artery (Figures 2A and 2B)
- Left popliteal artery was 100% occluded proximally with reconstitution at the mid segment via profound artery collaterals (Figure 2B)
- Left anterior tibial was 100% occluded and reconstituted at the ankle (Figure 2C)
- Left posterior tibial (PT) diffuse was the single vessel runoff to the foot 95%-99% segmental stenosis (Figure 2C)
- Left peroneal artery had mild diffuse disease and collateralized the anterior tibial (Figure 2C)

ENDOVASCULAR TECHNIQUE

A 5 Fr 11 cm sheath that was initially placed in the right CFA was exchanged over a wire for a 7 x 45 cm sheath that was advanced "up and over" and placed antegrade at the ipsilateral left CFA. Brief unsuccessful attempts were made with .018″ and .014″ wires to cross the SFA given calcific proximal "flush" occlusion, with wires favoring the open profunda artery (Figure 2A). Using extravascular ultrasound visualization, a micropuncture needle tip (Cook) was advanced retrograde directly into the proximal left SFA 100% occlusion, and 0.014″ wire was advanced through a needle into the occlusion and across the proximal cap into the left CFA (Figures 3, 4, and 5A).

Initially, a 12g CTO wire (Cook) was used and eventually successfully crossed with a HydroST wire (Cook). This wire was then advanced into the antegrade sheath and retrieved through the contralateral hemostasis valve (Figure 6). A micropuncture needle was then removed (Figure 7). A CXI .018″ microcatheter was advanced over this wire through the antegrade sheath and, using ultrasound visualization, the catheter was advanced into the proximal left SFA just proximal to the wire exiting the vessel out to the skin (Figures 4B and 8). The wire was then removed and manual pressure applied at the ipsilateral retrograde needle/wire entry point for one minute with excellent hemostasis. A therapeutic dose of heparin was given, and we proceeded to intervene through the SFA in standard fashion via the contralateral sheath (Figure 5C). We attempted to advance 0.018″ and 0.014″ wires antegrade through the SFA, but angiographically the wire appeared to progress to the extraluminal space at the mid portion. We therefore gained retrograde left ankle PT access using ultrasound guidance, and a Cook 5 Fr pedal sheath was inserted. The 0.014″ Hydro ST wire was advanced retrograde through the pedal sheath using 0.014″ CXI catheter support across the left popliteal artery reconstitution site and through the distal and mid segments

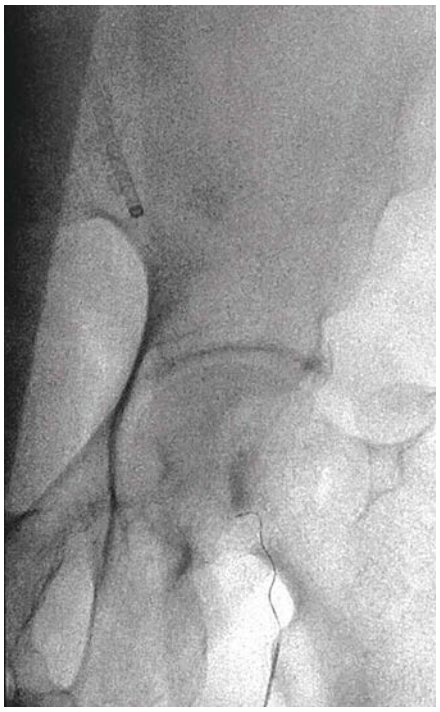

Figure 4. A Cook micropuncture needle tip was advanced retrograde directly into the proximal left superficial femoral artery 100% occlusion and a 0.014″ wire advanced through needle into the occlusion, across the the proximal cap into the left CFA.

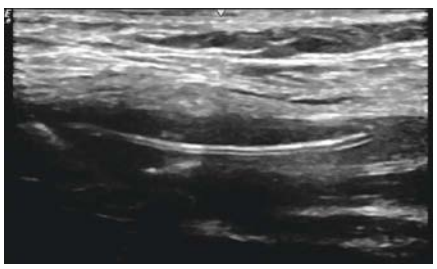

Figure 8. We advanced a CXI 0.018″ microcatheter over the wire through the antegrade sheath and using extravascular ultrasound visualization placed the catheter into the proximal SFA just proximal to the wire exiting the vessel out to the skin.

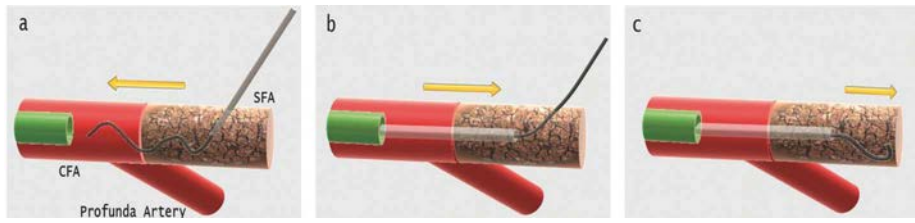

Figure 5. (A) Direct Cook micropuncture needle access retrograde in the proximal SFA occlusion and crossing the proximal cap into the common femoral artery and into the previously placed antegrade sheath. (B) After the retrograde wire is externalized through the contralateral sheath a 0.018″ Cook CXI microcatheter is advanced over this wire antegrade and tip placed within the occlusion just prior to exiting the vessel. (C) Wire is removed and 0.018″ or 0.014″ wire of physician choice to cross the rest of the occlusion advanced antegrade in standard fashion.

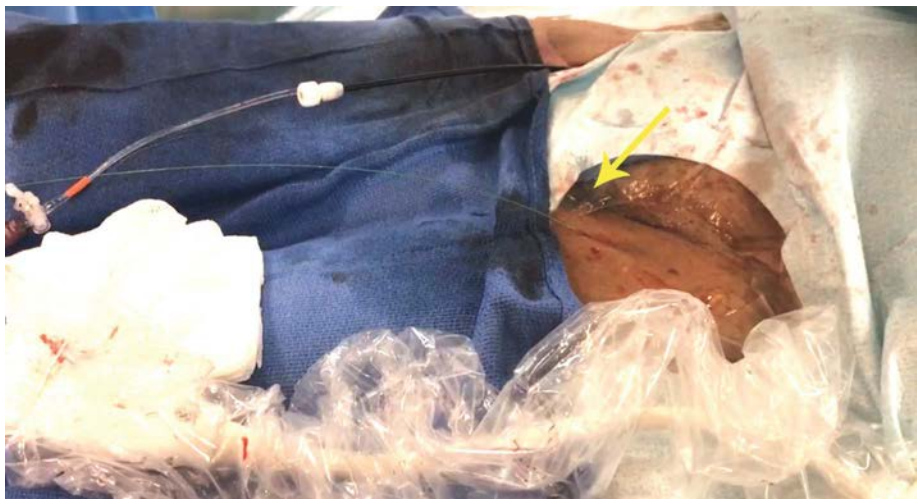

Figure 7. The extracorporeal portion of the wire is seen after the 12g Cook needle used to access the SFA occlusion directly has been removed.

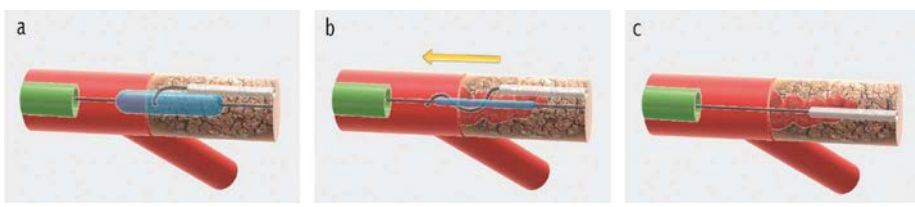

Figure 9. (A) The balloon is advanced over a known intraluminal wire into the proximal "flush" occlusion cap and inflated. (B) During balloon deflation, the retrograde wire with microcatheter support is advanced across the new reentry-able proximal cap into the CFA. (C) If preferring to treat via the antegrade sheath, the retrograde wire is advanced into the antegrade sheath (may use a snare if needed) and externalized. Further treatments could be performed through catheter exchanges.

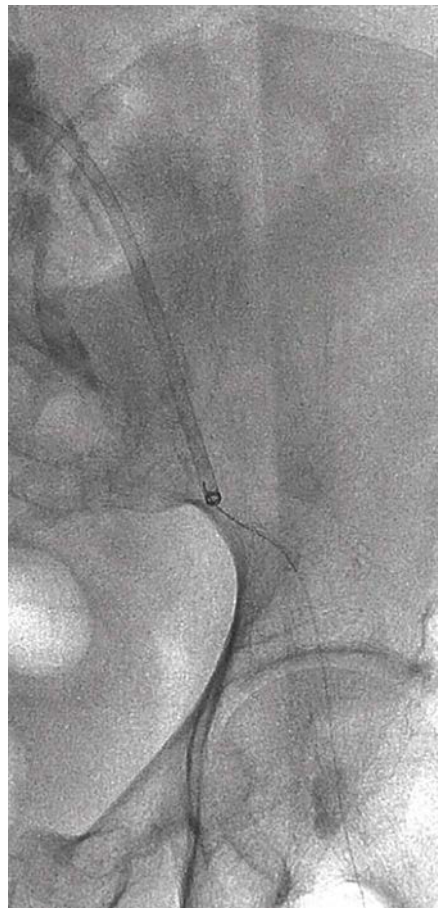

Figure 6. HydroST Cook wire was then advanced into the antegrade sheath and retrieved out through the contralateral hemostasis valve.

Figure 10. A 3 x 40 mm balloon over the antegrade wire into the left CFA/proximal SFA junction and inflated this to nominal pressure to create a new more "reentry-able" proximal cap.

of the SFA, appearing angiographically to stay intraluminal, but unable to reenter the left CFA.

Knowing our initial retrograde left proximal SFA needle/wire access was intraluminal, we advanced a 3 x 40 mm balloon over the antegrade wire into the left CFA/proximal SFA junction and inflated this to nominal pressure to create a new more "reentry-able" proximal cap (Figures 9A and 10). During antegrade balloon deflation, the retrograde HydroST wire was advanced and able to reenter the left CFA (Figures 9B and 11). This wire was then inserted into the antegrade sheath (Figure 9C) and, through microcatheter exchange, we advanced a Grandslam wire (Asahi) antegrade and tip left in the left popliteal artery rather than the PT to avoid being occlusive at the single runoff vessel and reduce the risk of causing slow flow and "trashed foot" during intervention, including atherectomy.

To avoid embolization with this poor distal runoff, the Jetstream device (Boston Scientific) was used to perform aspiration during atherectomy of the entire SFA into the popliteal artery. Post balloon angioplasty was initially performed with a 3 x 220 mm balloon throughout the SFA. The wire was exchanged for a Viper wire (Cardiovascular Systems Inc) and advanced into the left PT, and CSI atherectomy was performed with a 1.25 mm Solid Crown throughout the posterior tibial artery. Post balloon angioplasty was performed with a 2.5 x 220 mm balloon to nominal pressures with excellent results (Figures 12A and 12B). The wire was exchanged for a 0.035″ Glide Stiff wire and post balloon angioplasty of the SFA was performed with a 4 mm Lutonix drug-coated balloon (Bard PV) to nominal pressures with excellent results (Figures 12C and 12D). Throughout both Jetstream and CSI atherectomy we allowed "bleed out" through the pedal sheath to enable any possible distal embolization to exit the body. There was no evidence of distal embolization, despite initial poor runoff.

THE CHALLENGE OF PROXIMAL SFA FLUSH OCCLUSIONS

Proximal caps can be a challenge in general. When the proximal cap is truly "flush" at the CFA bifurcation, CFA vessel size and the patent profunda artery make it very difficult to direct the wire and/or the support catheters that allow for adequate weight to penetrate that cap, particularly convex and/or significantly calcified ones. Additionally, there is always skepticism that the interventionist might be overly aggressive at the CFA/profunda artery, given both a risk of perforation,

Continued on page 10

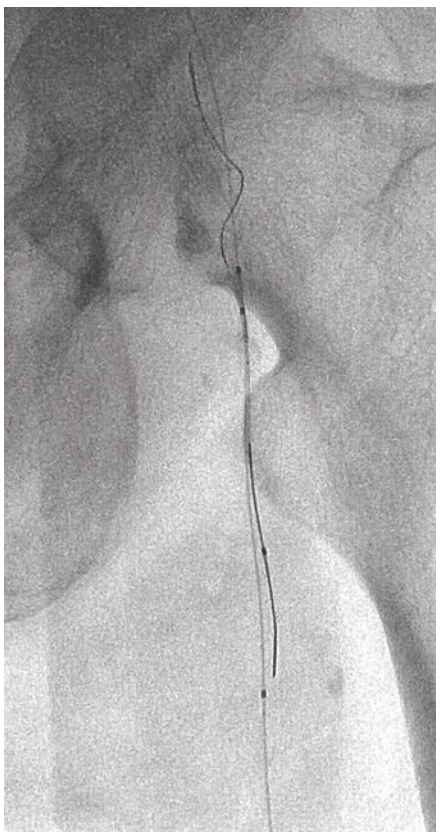

Figure 11. During antegrade balloon deflation the retrograde HydroST wire was advanced retrograde and able to reenter the left CFA.

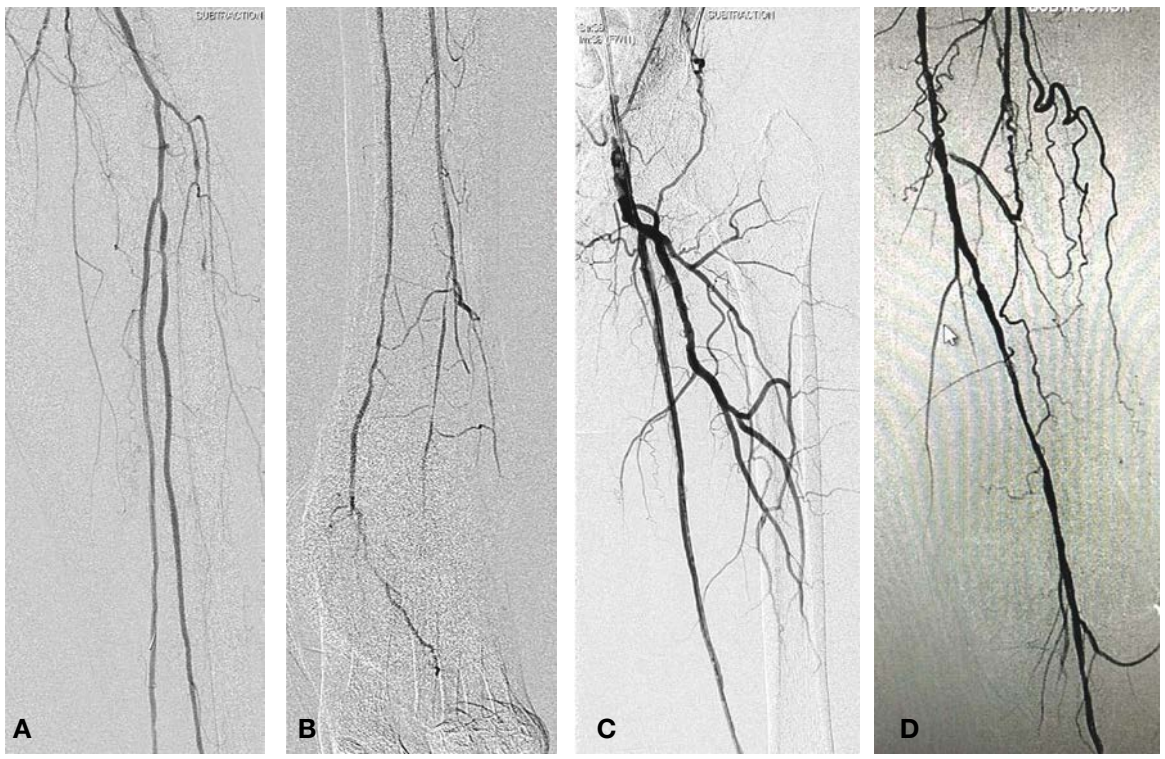

Figure 12. (A, B) CSI atherectomy and post balloon angioplasty performed with a 2.5 x 220 mm balloon to nominal pressures to the posterior tibial artery with excellent results. (C, D) Jetstream atherectomy and post balloon angioplasty of the SFA was performed with a 4 mm Lutonix drug-coated balloons (Bard PV) to nominal pressures with excellent results.

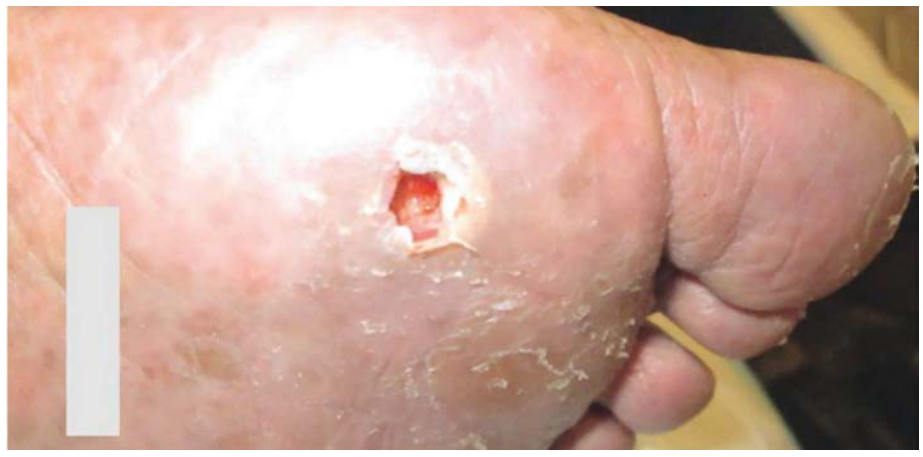

Figure 13. Perfusion markedly improved after the revascularization.

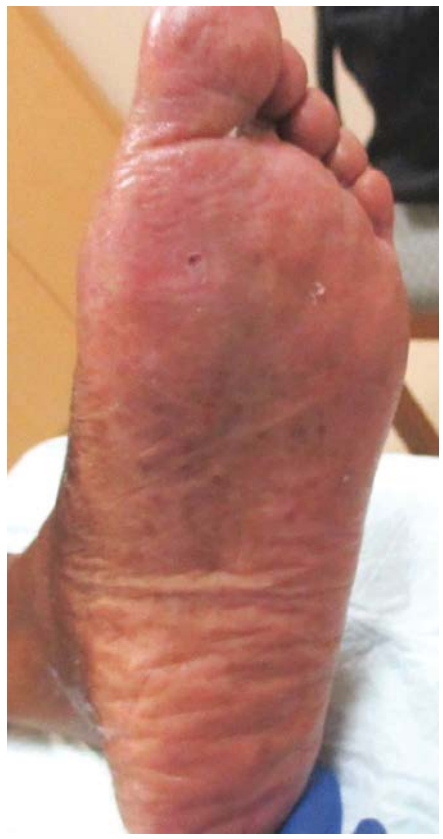

Figure 14. After 6 weeks of local management, the wound was fully epithelialized.

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dissection, and acute closure of the single vessel to the leg. These complications preferably should be treated surgically.

Pedal access techniques have improved the success of intervening in these types of SFA occlusions, as these caps can be approached retrogradely.[5] Despite this improvement, the pedal approach does not guarantee that a retrograde wire can be maintained intraluminally, or even if luminal, that the CFA can be reentered. Approaching the proximal SFA occlusion directly under extravascular ultrasound guidance retrograde with a micropuncture needle (Figures 3, 4, and 5A) gives the ability to visualize the needle tip well enough to ensure that the wire is intraluminal and also provides great support to advance both 0.014″ and 0.018″ wires, both hydrophilic tip and heavy gram wires, with excellent control. The wire can then be advanced into the previously placed antegrade sheath and a microcatheter can be advanced antegrade past the proximal cap and worked via the standard access (Figures 5B and C).

Wiring retrograde into the sheath (Figure 6) may be a challenge, but we have used 5 mm snares to retrieve the wire through the antegrade sheath with minimal effort. The multiple cases that we have performed have taken less than 5 minutes. In this case, we gained pedal access via the antegrade approach, but we were unable to maintain intraluminal position. We were unable to re-enter the CFA retrograde via the pedal wire for which that initial direct needle access technique helped us to know the antegrade wire was intraluminal at the proximal cap. We could comfortably perform balloon angioplasty across the ostial SFA occlusion/cap (Figure 9A), creating a new reentry cap/point in the SFA (Figure 9B).

In other cases, we have been able to work through the SFA without needing pedal access. This technique may be restricted to patients who are not of large body habitus, which limits both adequate visualization of the vessel and on occasion the reach of the micropuncture needle. Particularly in short SFA occlusions or in patients with severe infrapopliteal artery disease where pedal access may not be an option, this approach is an alternative that can be performed easily and quickly, as well as ensure "flush" SFA occlusion proximal cap intraluminal access. This approach can serve as an adjunct in cases in which crossing the proximal cap antegrade or retrograde via pedal access is difficult, and it can also shorten the interventional time.

CONCLUSIONS

We continue to search for endovascular techniques to approach certain traditionally challenging anatomical subsets that technology has not yet been able to tackle in the setting of advanced PAD and CLI. Our patient had a deep wound that had developed within the prior 7 months and had healed within 4 weeks. Immediately after the endovascular procedure, we witnessed markedly improved perfusion (Figure 13). After the revascularization, our patient underwent 4 HBOT sessions in combination with non-cytotoxic agent cleansing and application of Opticell AG as the primary wound dressing. After 6 weeks of local management, the wound was fully epithelialized (Figure 14). Our patient benefited from a team-focused limb salvage and endovascular approach to achieving optimal care. The team approach was in place from early wound care, revascularization, and post revascularization care, which included hyperbaric oxygen therapy (HBOT), through wound care and follow-up, ensuring medical adherence.

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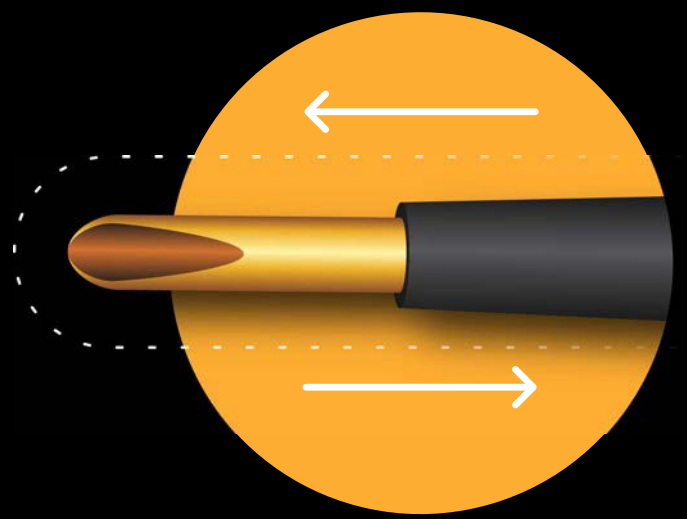

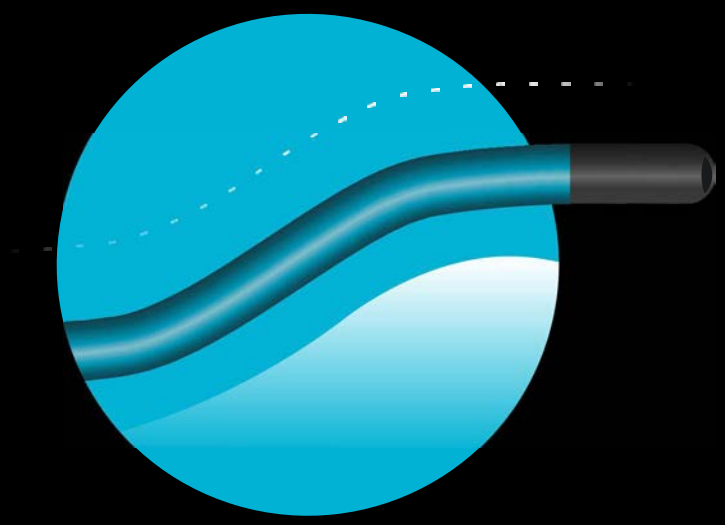

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VALLE *from page 6*

than distance traveled by patients.[5] This would suggest that operator and institutional volumes are important to optimize care. However, more discerning evaluation of this analysis reveals some limitations. First, it was the analysis performed at a single state level (New York). Second, the inverse relationship between patient distance and outcome is suggestive of residual confounding, where healthier patients were able to travel further distances. This begs the question, what happens to those patients who are too sick to travel and never make it to the hospital? Would that change the interpretation of these findings? A compelling argument exists for increasing revascularization volumes, yet the concern of limiting access remains.

The ideal solution would be for the vascular community to focus on both operator and institutional experience and access to CLI care. The intersection of these two concepts is likely to be where optimal CLI care can be achieved, on a national level (Figure 1). Ongoing efforts are being made to increase education and awareness, but there remains much work to be done with rates of revascularization attempts prior to amputation estimated at 60% in the best of cases.[9] Multidisciplinary consortiums and educational efforts to disseminate techniques and approaches to complex peripheral interventions are being formed, with publications offering algorithmic approaches to complex anatomic lesions[11] and the emergence of national conferences focusing on limb salvage and best practices for CLI care (the Amputation Prevention Symposium, https://www.amptheclimeeting.com/; the International Symposium on Endovascular Therapy, https://www.iset.org/). Ultimately, a balance between experience and access must be achieved, with rigorous study of quality in CLI care, as well as availability. These analyses are challenging, as the clinical syndrome of CLI is broadly defined, encompassing presentations ranging from rest pain to ischemic ulceration or gangrene, but are critical. Results of such analyses could carry significant implications for both clinical care and healthcare policy.

Operator expertise is just one piece of the puzzle, with critical gaps remaining in regional access to vascular care. The pathway to optimal CLI care goes beyond just a number. ■

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Disclosures: None.

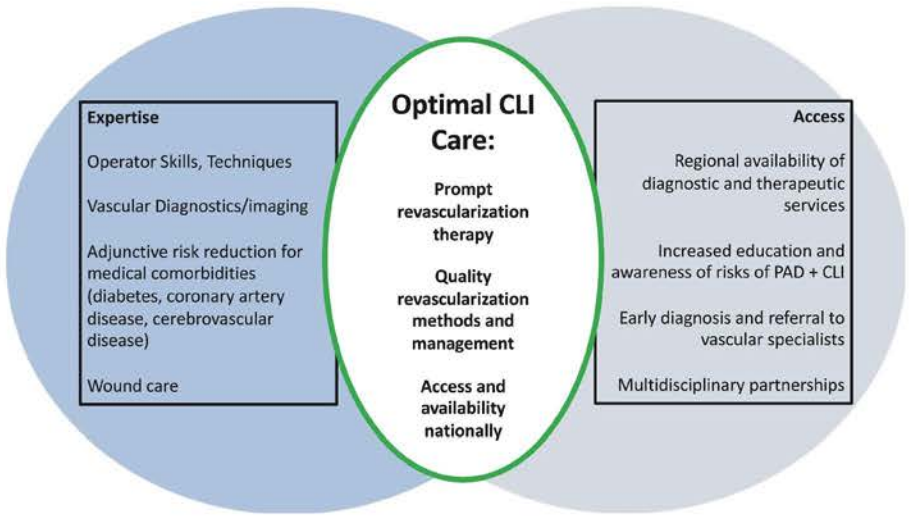

Figure 1. The intersection of the vascular community focusing on operator and institutional experience along with access to CLI care is likely to be where optimal CLI care can be achieved on a national level.

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including number of CLI operators, institutional peripheral volume, and rigorous monitoring of procedural outcomes.

Any establishment of criteria must be balanced with the patients' access to care. Highly stringent requirements will leave few institutions capable of offering "acceptable" CLI care and may require patients to travel long distances to receive treatment. While that may be feasible for one-time surgical procedures, this poses a challenge for CLI patients who often require multiple endovascular procedures and close follow-up to ensure limb salvage. Only an integrated model of treatment as described above can identify and prevent patients from "falling through the cracks." The ultimate solution is to provide advanced training opportunities so more operators can develop the requisite skill set to successfully treat CLI patients at their home institution. Dedicated CLI programs can and do provide these educational opportunities. Moving forward, there will be no scarcity of CLI patients; our challenge is to ensure that they are receiving the best treatment available in this rapidly evolving specialty. ■

Table 1. Recommended and/or Mandated Volume for Various Percutaneous Procedures

Percutaneous coronary intervention (PCI) operator 50 cases/year, averaged over 2 years (previous guidelines were 75 cases/year)
TAVR (transcatheter aortic valve replacement) Interventionalist 100 transfemoral cases/lifetime (50 as primary operator)
Program 50 cases/year averaged over 2 years
Carotid artery stenting (CAS) operator 100 cases as primary operator/lifetime 25 cases/year
Coronary CTO (chronic total occlusions) operator 50 cases/year

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Disclosures: None.

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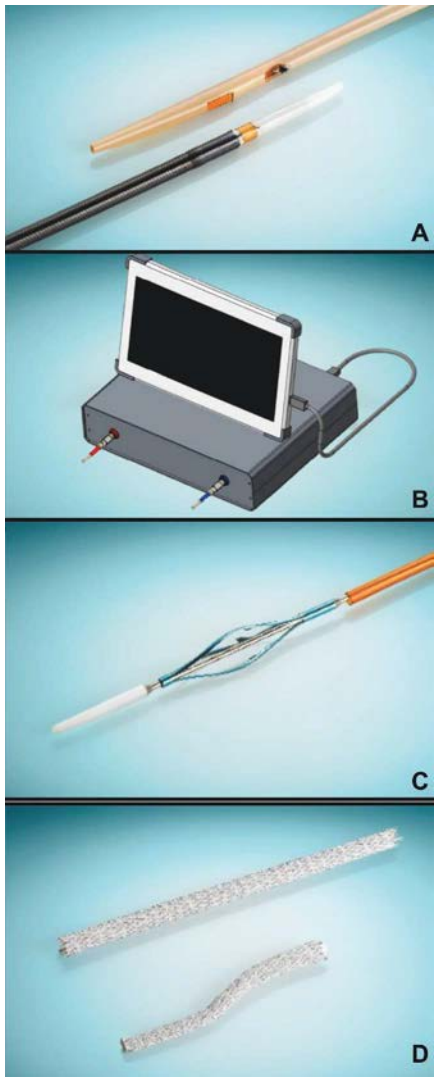

Figure 2. Components of the LimFlow stent-graft system. (A) Arterial and venous catheters. (B) Ultrasound console. (C) Forward-push valvulotome. (D) Electrospun polytetrafluoroethylene stent grafts.

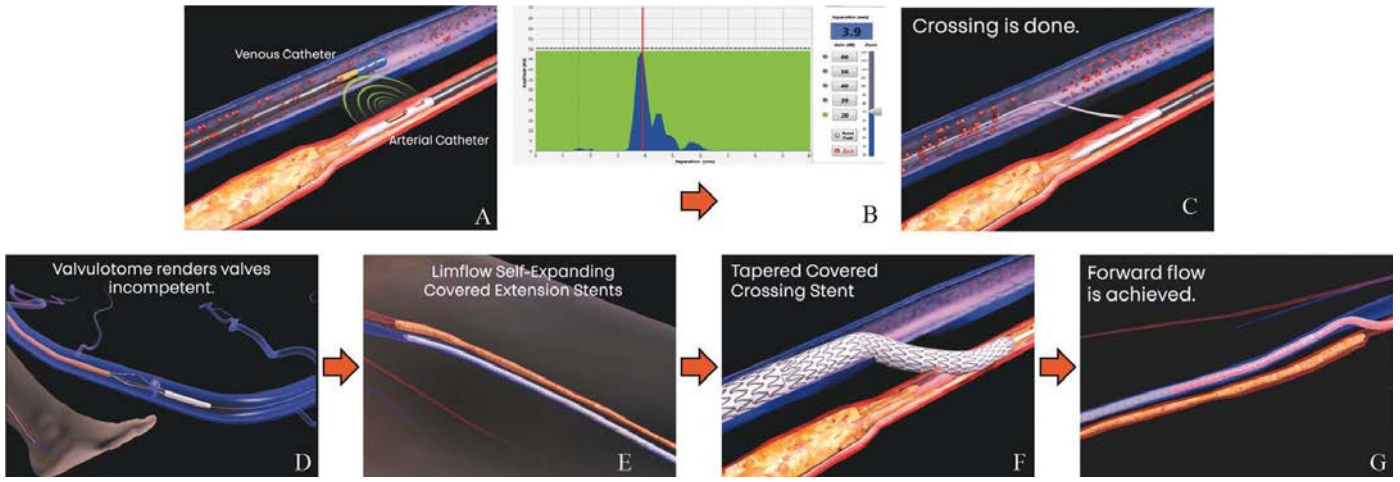

Figure 3. Steps of LimFlow percutaneous deep vein arterialization. (A) Arterial and venous catheters aligned. (B) Signal received by the venous catheter displayed as a waveform, permitting orientation. (C) Crossing needle extension from arterial catheter into target vein and crossing wire advancement. (D) Valvulotome insertion over crossing wire and utilization to render venous valves incompetent. (E) Length of vein from above the ankle to crossover point lined with polytetrafluoroethylene (PTFE)-covered stents. (F) Crossover point lined with conical PTFE-covered crossing stent. (G) Forward flow of blood to foot achieved.

MUSTAPHA *from page 4*

Multiple small clinical trials on a surgical approach have been published, and a recent meta-analysis article summarized this work. Despite the promising initial findings that limb salvage can be obtained with utilization of venous arterialization, the technique has not been widely adopted due to the technical challenges and potential morbidity of the surgical operation.[13]

Clinical studies utilizing LimFlow pDVA for intervention in no-option CLI patients were first performed in Singapore and Europe, with CE mark approval granted in October 2016. Early experiences resulted in promising outcomes in high-risk no-option CLI patients with a 6-month limb salvage rate of 86%[3] and clinical improvement in 60%.[14] In 2017, a pilot study instituted as part of the Food and Drug Administration's early feasibility study program was launched in the United States. Presented here is the first experience of the LimFlow system in the United States.

METHODS

Design and patient population. The PROMISE I trial is a single-arm, multicenter, pilot study conducted to investigate the feasibility, safety, and effectiveness of the LimFlow stent-graft system. Ten patients with no-option CLI were enrolled at three hospitals across the United States (Metro Heath, Grand Rapids, Michigan; Palmetto Health, Columbia, South Carolina; and Kaiser Permanente, Honolulu, Hawaii) between July 2017 and January 2018, with preliminary results through 6 months reported here (follow-up is ongoing through 24 months). Trial enrollment has since been expanded to 35 subjects with additional United States medical centers included.

Eligible patients were ≥21 years old with Rutherford classification (RC) 5 or 6 who were determined to have no feasible option for conventional revascularization. No-option status was defined as the lack of ability to perform conventional distal surgical bypass or endovascular therapy for limb salvage due to the absence of a usable pedal artery target or suitable vein conduit. In addition to the strict no-option definition, key exclusion criteria included immunodeficiency disorder, thrombophlebitis, deep vein thrombus or coagulation disorder, active infection that would preclude graft insertion, elevated creatinine, and end-stage renal disease.

The study was conducted in accordance with the International Conference of Harmonization Guidelines for Good Clinical Practice and prospectively registered at *ClinicalTrials.gov* (NCT03124875). Institutional review board approval was received for each study site. Following signed patient informed consent, all patients were confirmed as no-option by an Independent Safety Committee (ISC) before enrollment in the study. The ISC also participated in ongoing review of study safety data to ensure the rights and welfare of study patients were protected.

Study device and procedure. No-option CLI patients who underwent the study intervention presented with both non-healing wounds and poor arterial run-off (Figure 1). The pDVA treatment approach was utilized to create an arteriovenous fistula and generate an alternative conduit for blood flow to the foot through use of a tibial vein. The system consists of arterial and venous catheters, an ultrasound console, a forward-push valvulotome, and electrospun polytetrafluoroethylene (PTFE) stent-grafts (Figure 2).

During the procedure, an antegrade femoral arterial approach is utilized to insert a 7 Fr sheath and a retrograde tibial venous approach is utilized to insert a 5 Fr sheath. Both access points are placed under ultrasound guidance and used as the working channels for the procedure. The arteriovenous crossover point is located proximal to the total occlusion of the artery and is determined by angiography with consideration of the vascular anatomy. The arterial and venous catheters are then inserted from opposing directions and aligned utilizing ultrasound guidance from the console (Figure 3A). The arterial catheter has a small, single-directed ultrasonic transmitter as its tip and the venous catheter features a 360° ultrasonic sensor, allowing each to detect the other catheter in the neighboring vein/artery. The catheters are connected to an ultrasound console that applies short electrical pulses to the arterial transmit catheter. The signal received by the venous catheter is displayed on the console as a waveform, permitting orientation of the two catheters (Figure 3B). Once complete orientation is achieved, the crossing needle is extended from the arterial catheter into the target vein and a crossing wire is advanced through a support catheter down to the pedal vein (Figure 3C). The crossover point is then ballooned and serves as the working channel for the remainder of the procedure.

After a wire has been advanced from the artery to the vein, it is advanced into the lateral plantar vein. The wire is passed through the venous arch through which outflow will be established once the revascularization is completed. Wire passage through the pedal venous arch creates the support that provides a stable and rigid rail for the delivery of the forward-push valvulotome and the stent-grafts. The valvulotome is then inserted over the wire and is utilized to render the venous valves incompetent in order to allow the retrograde flow of blood into the venous system (Figure 3D). Finally, the length of the vein from above the ankle to the crossover point is lined with electrospun PTFE-covered stents (Figure 3E) and the crossover point is covered with a reverse-conical PTFE stent-graft (Figure 3F), completing the conduit for blood flow (Figure 3G). Figure 4 demonstrates a representative angiographic result.

Study endpoints and follow-up. Clinical evaluations were performed at 1, 3, and 6 months following the procedure. Patient follow-up is currently ongoing, with postprocedure evaluations at 9, 12, and 24 months. Routine surveillance of the wound and index limb is performed during each follow-up visit, in accordance with the 2006 American College of Cardiology/American Heart Association peripheral disease guidelines. Examinations included assessments of pulse, pain, RC, oxygenation, wound-healing status, and any procedures or complications related to the index limb. Patients were assessed for wound healing using quantitative wound measurement and qualitative tissue description.

The *primary endpoint* was amputation-free survival at 30 days, defined as index limb salvage (freedom from above-ankle amputation) and survival (freedom from all-cause mortality). *Secondary endpoints* included amputation-free survival at 6 months, primary patency at 30 days and 6 months (defined as absence of occlusion of the stent-graft without prior clinically-driven major reintervention of the graft), wound healing at 3 and 6 months (defined as complete index wound healing), and deterioration in renal function at 6 months (25% increase in

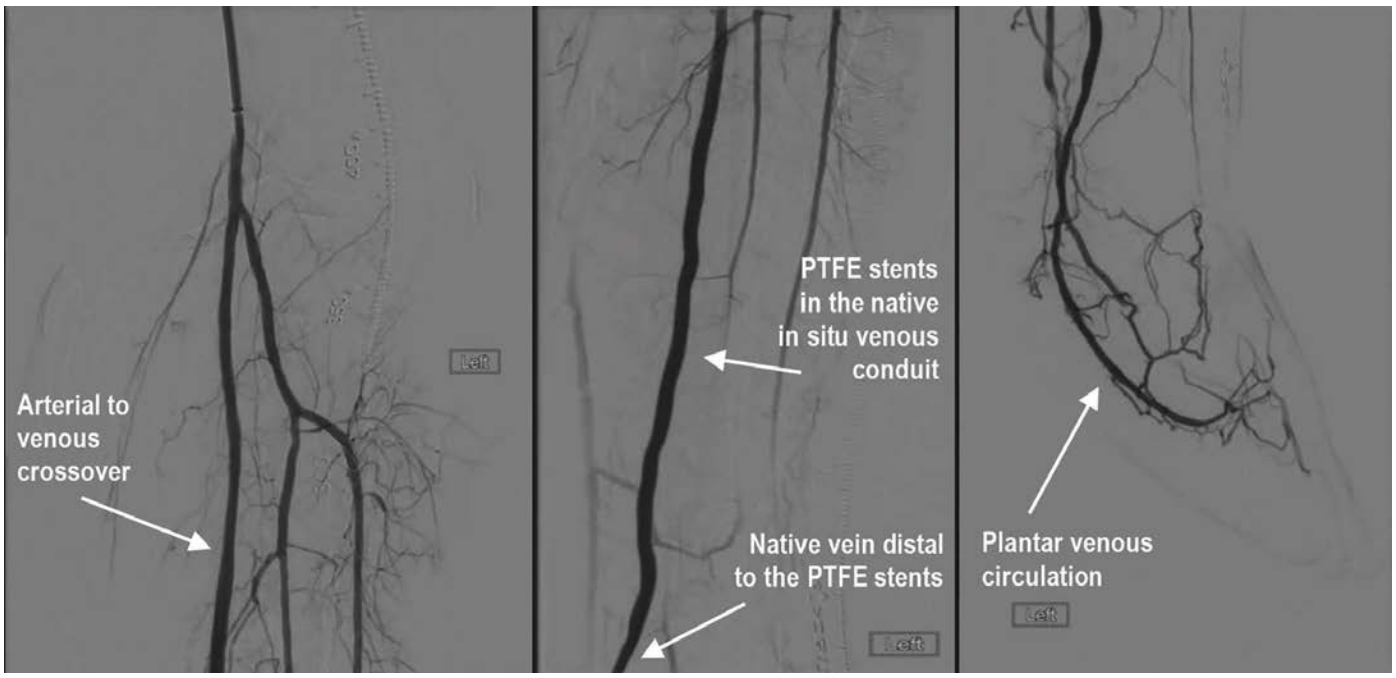

Figure 4. Angiographic imaging of lower-extremity arterial flow post percutaneous deep vein arterialization.

Figure 5. Example of wound healing through 6 months post intervention.

serum creatinine after using iodine contrast agent without another clear cause for kidney injury). *Technical success* was also evaluated, and was defined as completion of the endovascular procedure and immediate morphological success with successful placement of the arterial and venous catheters and stent-grafts.

Statistical analysis. This pilot study enrolled a small number of patients to evaluate the device design concept with respect to initial clinical safety and device functionality; as such, the statistics are descriptive in nature. Measures of safety and efficacy were assessed through hospital discharge, at 30 ± 7 days, and at 3 and 6 months (± 2 weeks) post procedure. Patient demographics, baseline characteristics, and medical history are summarized descriptively. Frequencies and proportions are reported for categorical variables.

RESULTS

Ten no-option CLI patients comprised the patient population; a total of 7 patients (70%) were male and 3 patients (30%) were female, with an average age of 67 ± 11 years. Five patients (50%) were African-American. Comorbidity and risk factors included diabetes (80%), hypertension (70%), heart failure (New York Heart Association class I, 60%), history of stroke (20%), history of cardiac event (myocardial infarction or coronary artery disease, 30%), and history of smoking (60%). Average glomerular filtration rate (GFR) was 62 ± 23 mL/min/1.73 m^2 and average serum creatinine level was 1.3 ± 0.4 µmol/L. Six patients (60%) were RC 5 and 4 patients (40%) were RC 6. Eight patients (80%) were categorized as stage 4 (high risk for amputation) according to the Society for Vascular Surgery (SVS) wound, ischemia, and foot infection (WIfI) index (Table 1).

The posterior tibial artery and vein were the most commonly used target vessels (60%), followed by the anterior tibial (30%), and the peroneal (10%). The majority (90%) of procedures were performed under general anesthesia. Most patients (80%) required arterial preparation (including balloon angioplasty and stenting to treat inflow disease) prior to the use of the LimFlow system, and 30% required venous preparation (including balloon angioplasty to treat venospasm).

Among the 10 patients enrolled in this pilot study, a 100% technical success rate was observed in the revascularization of the foot and all maintained amputation-free survival through 6 months. No patients experienced a deterioration of renal function. Postprocedure adverse events included access-site pain and bleeding, edema, and pain in the target limb. There were no procedural complications or postprocedure severe adverse events reported. The only severe adverse events reported through the 6-month follow-up were for reintervention to restore patency. One patient refused in-person follow-up at 6 months, but was followed via phone interview for the primary endpoint.

At 1-month follow-up, primary patency was maintained in 90% of patients; at 6 months, primary patency was 40%. Thirty percent of patients underwent reintervention within the 6-month timeframe, with 1 patient undergoing 2 reinterventions. Two of the 3 patients had a pulse present by Doppler distal to their occluded stent at the time of reintervention. At the 6-month follow-up, only 1 patient had an absent pulse distal to the stent-graft (assessed by duplex ultrasound). Thirty percent of patients required transmetatarsal amputation (1 patient at 1 month post intervention, 2 patients at 3 months post intervention) and 20% underwent digit amputation (1 patient at 3 months post intervention, 1 patient at 5 months post intervention).

At 6 months, all patients experienced progressive wound healing, with complete wound healing occurring in 30% of patients. Half of the patients had 84%-93% wound healing by 6 months and 2 patients were noted with approximately 60% overall healing. Throughout the follow-up, healthy granulation tissue, an indicator of healing,[15] was found in the wounds of all patients. Figure 5 shows an example of target-wound healing. Noted acceleration in healing occurred after the postprocedure 1-month follow-up, which was likely a result of maturation of the arterialization.

DISCUSSION

Since the initial findings reported by Halstead and Vaughan regarding use of venous arterialization for limb salvage,[12] several mechanisms have been noted to support utilization of this technique. Use of the venous bed as a conduit for perfusion has been found to successfully increase flow through existing collateral vessels, improve tissue perfusion and nutrition in the capillary beds, and stimulate angiogenesis.[13,16,17] A meta-analysis of 15 studies that included 768 CLI patients who had venous arterialization performed for lower-limb salvage found that the pooled limb-salvage rate at 12 months was 75%. These findings were promising for patients presenting with no arterial reconstruction options. Within the 15 studies, venous arterialization was performed surgically.[13] Kum et al reported the initial clinical findings of pDVA performed on 7 no-option CLI patients in Singapore. Technical success and primary safety endpoints were achieved in 100% of patients, with no above-ankle amputations, deaths, or major reinterventions required at 30 days. Compete wound healing was noted in 57% of patients at 6 months and 71% of patients at 1 year. Within this small cohort of patients, pDVA appeared to be a safe and feasible approach for limb-salvage treatment.[3] The evolution from surgical to percutaneous venous arterialization offers the benefit of lower procedural risks and eliminates the need to create a surgical wound in the ankle or foot of a critically ischemic limb.[13] In addition, the development of contemporary devices for pDVA enhances the potential for clinical success. Ultrasound-guided dual catheters offer

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a reliable approach for arteriovenous fistula creation, the reverse valvulotome allows for a less traumatic approach than barotrauma to render the valves incompetent, and extension stent-grafts create a large-caliber shunt analogous to a surgical bypass.[14]

The interim findings reported here represent the first 10 patients to be treated with the LimFlow pDVA system in the United States. At the time of screening for the feasibility trial, all patients were evaluated for surgical or endovascular intervention by the treating investigator and the Independent Safety Committee and were deemed to have no feasible options for revascularization. Treatment of the patients' presenting wounds with a minor (toe or transmetatarsal) amputation was not a viable approach in these ischemic limbs without a corresponding intervention to improve wound perfusion. Without the pDVA endovascular procedure, conservative wound treatment, leading most likely to major amputation, was the only medical therapy available to these no-option patients. All patients treated with the LimFlow system experienced successful revascularization of the foot and were alive and amputation free at the 6-month endpoint. Those patients who did not maintain patency and/or required revascularization continued to heal and met the primary endpoint, indicating that occlusion that occurred once the healing process had initiated did not appear to translate to worsening outcomes. It is feasible that the increase in oxygenated flow allowed for collateral growth, but there is additional work to be done to determine the mechanism behind this observation.

The primary goals of CLI treatment are preservation of a functional limb with minimization of tissue loss and promotion of wound healing.[18] Utilization of pDVA endovascular revascularization resulted in a 100% 6-month limb salvage and a progression toward complete wound healing for all patients. Patients diagnosed with CLI face a substantial clinical burden, with 4-year survival rates of 46%.[19] The rates of morbidity and mortality remain substantially higher for patients whose clinical course results in a major amputation (mortality of 13.5% vs 6.9% at 1 month, 48.3% vs 24.2% at 1 year, and 70.9% vs 43.2% at 3 years), and the continued reduction of these amputations could predict continued reduction in overall patient mortality.[20] Although QoL measurements were not included in this pilot study, one can extrapolate that the promising outcome of limb salvage with wound-healing progression would also result in a rise in the patient's functional and overall QoL. Thus, pDVA endovascular revascularization with the LimFlow system appears to offer a promising treatment modality for no-option CLI patients who currently face a poor prognosis.

Study limitations. The initial analysis of the PROMISE I trial was limited to a small sample size with enrollment performed at three medical centers. Despite the small number of medical centers included, the investigators had varied specialties, including endovascular interventionists and vascular surgeons. The current data only extend to 6 months. Patient enrollment is ongoing, with inclusion of additional medical centers, and long-term follow-up will continue through 2 years.

CONCLUSION

The LimFlow stent-graft system is a novel treatment modality for no-option CLI patients. The initial feasibility trial outcomes revealed complete avoidance of major amputation at 6 months with progressive wound healing. The treatment was performed safely, with no instances of procedural complication or decreased renal function in patients. These are promising findings in a subset of patients for whom amputation would otherwise be considered inevitable. Additional study through ongoing enrollment and follow-up in the early feasibility trial, as well as a larger-scale trial, is warranted. In this initial cohort, the LimFlow treatment was technically feasible, safe, and effective for the revascularization of no-option patients suffering from severe CLI. ■

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Table 1. Baseline patient characteristics and outcomes.

Variable	(n = 10)
Demographics	
Age (years)	67 ± 11
Gender, male	7 (70%)
Ethnicity, African American	5 (50%)
SVS WIfI high-risk staging	
High risk (clinical stage 4)	8 (80%)
Moderate risk (clinical stage 3)	1 (10%)
Low risk (clinical stage 2)	1 (10%)
Comorbidities	
Diabetes	8 (80%)
Smoking history	6 (60%)
Body mass index (kg/m2)	26 ± 4
Cardiac event history	3 (30%)
Hypertension	7 (70%)
Stroke history	2 (20%)
Dialysis	0 (0%)
Kidney function	
eGFR (mL/min/1.73 m2)	62 ± 23
Serum creatinine (µmol/L)	1.3 ± 0.4
Outcomes	
Amputation-free survival at 1 & 6 months	10 (100%)
Technical success rate	10 (100%)
Primary patency at 1 month	9 (90%)
Primary patency at 6 months	4 (40%)
Complete wound healing at 6 months	3 (30%)
Reintervention required	3 (30%)
Transmetatarsal amputation required	3 (30%)
Minor amputation (toe) required	2 (20%)
Data provided as mean ± standard deviation or number (%).	

eGFR = estimated glomerular filtration rate; SVS WIfI = Society for Vascular Surgery wound, ischemia, and foot infection score.

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$500 versus more than $22,000 for an inpatient stay.[12] Consequently, based on the general data we believe that inpatient treatment of CLI rather than outpatient drives up costs.

POLYVASCULAR DISEASE

Most PAD patients have polyvascular disease. The U.S. Reduction of Atherothrombosis for Continued Health (REACH) registry indicates that just 30% of PAD patients have PAD alone. The rest have some combination with coronary artery disease (CAD) and cerebrovascular disease (CVD). The largest group, almost 50%, have PAD combined with CAD.[13]

Polyvascular disease increases costs. In the REACH registry, patients with PAD alone cost approximately $11,300 per year. Costs for those with PAD and CAD were $15,600. PAD patients with both CAD and CVD cost approximately $20,000 per year.[13,14]

The majority of CLI patients also have polyvascular disease. In a recent study of Medicare patients, almost half of CLI patients had comorbid CAD.[1] Studies in CLI patients undergoing revascularization found that the prevalence of CAD and CVD is 52% to 73% and 17% to 27%, respectively.[15]

Although we do not have specific economic data for CLI with and without polyvascular disease, an analysis of recent trends in CLI hospital admissions demonstrates that almost half of admissions are due to non-CLI causes, including myocardial infarction (MI), stroke, and congestive heart failure (CHF).[16] In addition, cardiac disease is one of the important causes of the high rate of costly 30-day readmissions for CLI patients.[17]

Consequently, inpatient treatment of CAD and CVD in CLI patients adds to the overall cost burden of those with critically ischemic limbs. As discussed below, appropriate treatment with cardiovascular risk factor modification therapies could reduce these adverse events and the need for inpatient treatment. Similarly, optimal glucose control in CLI patients could reduce some of the diabetes admissions to the hospital.

UNDERTREATMENT OF CARDIOVASCULAR RISK FACTORS INCREASES MORBIDITY AND MORTALITY

PAD is considered a coronary artery disease risk factor equivalent. Guideline recommended risk factor modification therapies include smoking cessation, aspirin, statins, and antihypertensives, as well as optimal glucose control in those with diabetes.[18,19]

Despite these guideline recommendations and the high prevalence of both CAD and CVD, CLI patients are undertreated for their risk factors.[19,20] Statins, antiplatelets, and antihypertensives are underutilized.[19,20] Even when compared to intermittent claudication (IC) patients, fewer CLI patients receive statins and ACE inhibitors.[19] Glucose is inadequately controlled in 40% of CLI patients and smoking persists in up to 50%.[20]

This suboptimal risk factor management increases the risk of amputation and/or death by eight times.[20] The resulting adverse cardiac and leg events drive up costs.

HIGH AND INCREASING PREVALENCE OF SERIOUS COMORBIDITIES IN CLI PATIENTS

Hospitalized CLI patients have a high prevalence of hypertension (75%) and diabetes (57%). Other serious comorbidities included chronic kidney disease (38%), prior amputation (18%), and obesity (15%). Furthermore, between 2003 and 2011 these comorbidities increased and represented an important cause of hospital admissions.[16]

Non-CLI causes accounted for almost half of hospital admissions (46%). These included diabetes, septicemia, procedure complications, cardiovascular events, hypertension complications, respiratory disorders, and kidney disease.[16] Optimal risk factor management has the potential to reduce many of these cardiovascular and diabetes-related admissions eliminating the associated inpatient treatment costs.

By 2011 annual in-hospital mortality and major amputation rates declined to 3.4% and 10.8%, respectively; length of stay also declined. However, the cost of hospitalization among CLI patients did not decline significantly from 2003 to 2011.[16] We believe that the increase in treatment of expensive comorbidities is one of the factors elevating hospital costs.

Several of the non-CLI diagnoses were associated with significantly elevated risk of in-hospital mortality including acute MI, cerebrovascular accident, respiratory disease, CHF, and acute kidney injury. Presence of stump complication also independently predicted in-hospital mortality.[16]

The 2015 cost of an in-hospital death is estimated at almost $24,000.[3] Because in-hospital death is costly, further reductions in mortality could decrease costs. Similarly, substituting revascularization for primary amputations could decrease CLI costs.

UNPLANNED READMISSIONS ADD TO COSTS

At 20% to 27%, 30-day CLI readmissions are high and exceed the 12% and 15% rates for stroke and acute MI respectively.[17,21-24] At 6 months, approximately 60% of CLI patients are readmitted. The majority of these CLI readmissions are unplanned.[21] In addition, readmissions increase with severity of ischemia.[17,25]

High rates of unplanned readmissions increase CLI costs.[17,22] A recent study estimated that CLI readmissions cost $624 million.[17] Unplanned readmissions also increase mortality and major adverse leg events (MALE).[26,27]

Significantly, less than one-third (22%–33%) of readmissions are CLI related.[17,21] The majority are due to non-CLI reasons such as procedure complications, diabetes related non-vascular problems, and cardiovascular events.[17,21,22]

Notably, most of the factors that lead to CLI readmissions are modifiable.[26,28] Modifications include improved risk factor management to reduce cardiovascular and diabetic events. Meticulous surgical technique and peri-procedural monitoring can decrease procedure complications.[26,28] Implementation of these and other actions could decrease readmissions costs.

"The direct cost of the 65,000 to 80,000 major amputations employed to "treat" CLI in the US exceeds $11 billion annually."

Diagnosis and treatment of CLI at less severe stages could also reduce readmissions and costs. Since major amputation is a risk factor for CLI readmissions, replacing amputation with revascularization procedures could favorably impact readmission rates.[21]

CONCLUSION

In conclusion, while utilization of primary major amputation rather than revascularization increases the costs of treating CLI, other primarily modifiable factors add to the economic burden of the disease. These include a delay in diagnosis and treatment until the later stages of the disease, which necessitates expensive inpatient treatment, the high presence of polyvascular disease, suboptimal treatment of cardiovascular risk factors in CLI patients, and high rates of unplanned readmissions. Optimal management of risk factors and comorbid diseases (diabetes, CAD, CVD), as well as improved management of preventable issues such as procedural complications and infections, could significantly reduce the economic burden of CLI.

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AWARENESS *from page 1*

shorter survival time, an increase in the risk of a second major amputation, and significantly higher healthcare costs.[1] These results were generally consistent regardless of patient characteristics and clinical presentation. This goes to show that CLI does not differentiate what type of underlying characteristics the patient has. It seems CLI has its own agenda and its own timeline if left alone and unchecked, hence the need for a strict and consistent follow-up and vasculature flow surveillance.

A recent study showed that CLI is more deadly than many cancers and is truly a threat to not only limb, but life (Figure 1).[2] Twenty-nine percent of CLI patients will die or undergo a major amputation in the first year after diagnosis.[1] This is a significant percentage for patients who just received a diagnosis of CLI. To make a comparison, consider a patient diagnosed with colon cancer who enters the treatment cascade. Treatment decisions are made quickly, often by a multi-disciplinary tumor board. Treatment is initiated quickly and surveillance is ongoing. The same approach is not consistently taken across the country for patients diagnosed with CLI. They often do not receive therapy in a timely fashion and the disease is not taken seriously. I believe this adds to the unfortunately high mortality and amputation rate following the first year of diagnosis. This is unacceptable in 2019 in the US. We can no longer sit back and let patients die from a disease that has treatable options.

For the sake of reducing mortality associated with CLI, we must work together toward a solution that can increase the median lifespan of a CLI patient from 3.5 years after the diagnosis, just like we approach the care of cancer patients. The time has come for us to treat the CLI patient well enough to increase their average life span and provide them with an amputation-free survival. We all know that major amputation is a serious and devastating event. We must reduce the rate of higher-level amputations and contralateral limb amputations. Mortality rates after primary amputations are very high with rates ranging from 9% to 33% in the first year and 26% to 82% at 5 years. Despite devastating results, primary amputation is still one of the primary treatment modalities for CLI today.

The 2016 AHA/ACC guidelines provide statements on the management of patients with lower extremity PAD giving a Class I recommendation on evaluation for revascularization options by a multidisciplinary care team before amputation. Interestingly, recent studies demonstrated an increased utilization of endovascular intervention as first-line approaches for CLI patients in the United States with a corresponding decrease of in-hospital death and major amputation.

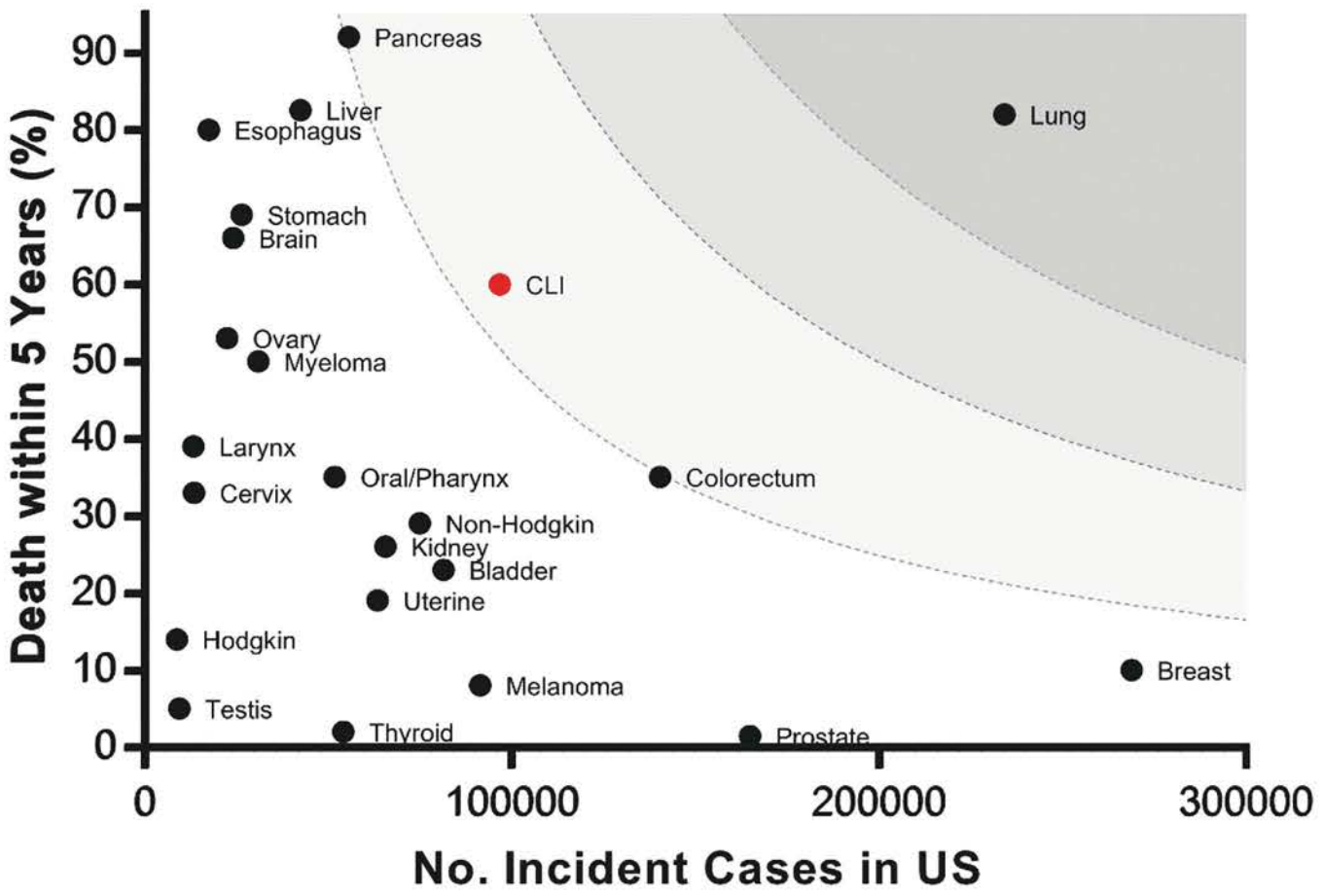

Figure 1. The relationship of 5-year mortality rates with annual incident cases of critical limb ischemia and 22 common cancers. Plotted is the absolute number of deaths within 5 years among US patients receiving first diagnosis during a 1-year period. Number of deaths is > 150,000 for diagnoses plotted in the dark gray background, > 100,000 in the gray background, > 50,000 in the light grey background, and < 50,000 in the white background.[2]

"To make a comparison, consider a patient diagnosed with colon cancer who enters the treatment cascade. Treatment decisions are made quickly, often by a multi-disciplinary tumor board. Treatment is initiated quickly and surveillance is ongoing. The same approach is not consistently taken across the country for patients diagnosed with CLI."

CLI patients, in particular, Rutherford class 5 and 6 patients with ischemic ulceration or gangrene are often excluded or under-represented in endovascular intervention clinical trials given the multiple comorbidities and advanced peripheral arterial disease burden. A recent LIBERTY 360 observational study manuscript discussed a sub-analysis to investigate the outcome through 1 year of patients with Rutherford class 5 and 6 who underwent endovascular interventions. These patients showed a marked improvement from baseline up to 12 months. Importantly, it showed a significant improvement in quality of life baseline to 12 months. The LIBERTY 360 study was designed to assess the real-world outcome of CLI patients in whom endovascular revascularization was performed. The analysis of the Rutherford 5 and 6 patients demonstrated that peripheral vascular intervention can be successful in CLI patients, with low rates of major amputation and improvement in wound healing and quality of life through 1-year follow-up. The study showed significant value in early treatment, especially in those patients with advanced Rutherford classification such as Rutherford 6 and 5. Not only were survival improvements shown, but also the study showed significant improvement in the quality of life, which can be translated into more opportunity for the CLI patient to remain a productive member of society.[4]

Let us not stand on the sideline watching CLI kill our patients. Instead, we ought to increase collaboration by enhancing the multidisciplinary team approach and providing the best possible care for CLI patients, because now we have the means to make a difference and alter the historic poor outcome to a better one. The cascade of treatment for the CLI patient can start with any specialty and lead to CLI recovery. We CLI specialists all have the same goals and vision to provide good care for CLI patients, save them from major amputations, and increase their life span. I am confident that one day, we will have a pathway that leads to good outcomes for patients with CLI and pre-CLI. ■

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