Supplement to

Sponsored by Inari LimFlow

Endovascular TODAY

February 2024

DANIEL CLAIR, MD

MEHDI H. SHISHEHBOR, DO

ANAHITA DUA, MD

PETER A. SCHNEIDER, MD

MIGUEL MONTERO-BAKER, MD

BRIAN LEPOW, DPM

ROBERTO FERRARESI, MD

RICHARD POWELL, MD

Transforming CLTI

New data and current best practices for limb salvage using Inari LimFlow's TADV

CLariTI and PROMISE II | Procedural Tips & Postprocedure Care | Health Care Economics

Transforming CLTI

Q&A: PROMISE II Experience and Data Overview

Coprincipal Investigators from PROMISE II discuss the uniqueness of the recently published study, patient population characteristics, key highlights from the data, and more.

With Daniel Clair, MD, and Mehdi H. Shishehbor, DO, MPH, PhD

Daniel Clair, MD
Professor and Chair
Department of Vascular Surgery
Vanderbilt University Medical Center
Nashville, Tennessee
dan.clair@vumc.org
Disclosures: Advisory and consultant to Boston Scientific, Bard Peripheral Vascular, Medtronic, and Inari LimFlow.

Mehdi H. Shishehbor, DO, MPH, PhD
President, University Hospitals Harrington Heart & Vascular Institute
Professor of Medicine, Case Western Reserve University
Cleveland, Ohio
mehdi.shishehbor@uhhospitals.org
Disclosures: Consultant to and advisory board for Medtronic, Abbott Vascular, Boston Scientific, Terumo, Philips, ANT, and Inquis Medical.

How did you get involved in the PROMISE II trial, and what were some of the unique aspects of PROMISE II compared to other lower extremity studies you have participated in?

Dr. Clair: I was involved in the PROMISE I trial and was impressed with the success in limb preservation with Inari LimFlow that I saw in the patients I enrolled. For these patients, amputation would have been the only option. They all had wounds and previous revascularization attempts into "dead-end" vessels that did not perfuse the foot directly. Wound care alone had been unsuccessful, and the size and depth of their wounds were increasing. I believe they all would have come to amputation within 4 to 6 weeks of the time of enrollment, and our limb salvage mirrored that of the entire trial. I was looking forward to participating in the next phase of this trial and am very thankful to have been chosen to lead the trial along with Dr. Shishehbor.

Dr. Shishehbor: It's been emotionally difficult to tell our patients that there are no options and they need an amputation. For years, I have been seeking alternative therapies that we could offer our no-option patients, and I was honored to be chosen to be part of the PROMISE I trial. Given our success in that trial, it was very exciting for me and my organization—but more importantly, for patients in Northeast Ohio—to continue with PROMISE II.

How would you describe the patient population included in the PROMISE II trial?

Dr. Clair: The PROMISE II patient population was an adjudicated group of no-option chronic limb-threatening ischemia (CLTI) patients. They were, in my view, one of the sickest patient groups ever enrolled in a trial. Having spoken with most of the investigators, the consensus was that the only other option available to these patients was a major amputation. They are likely some of the sickest patients we see in our practices.

Dr. Shishehbor: As a limb salvage operator, I am used to seeing a lot of sick patients with a number of comorbidities, but in my 20 years of experience in clinical trials, patients in this clinical trial were some of the sickest of the sick. Most trials exclude these patients, particularly the Rutherford class 5 and 6 CLTI patients with gangrene. Three-quarters of the patients had diabetes, a significant portion had some degree of chronic kidney disease, and we included patients with end-stage renal disease. It was rewarding to work with these chronically underserved patients.

How do you define procedural and longer-term success for these patients?

Dr. Clair: The definitions within the trial are noted in the paper[1]; however, for my practice and for practical purposes, I defined success during the procedure as the ability to establish a communication from the arterial system in the leg to the veins of the foot, with a well-perfused venous segment in the distal portion of the foot. In my opinion, seeing this in conjunction with maintenance of antegrade arterial flow similar to what existed preprocedure assured we had achieved procedural success. Longer-term success was defined by limb salvage, wound healing, and pain resolution, and we were able to achieve this in a significant majority of these patients.

Dr. Shishehbor: We know that CLTI has a poor prognosis, meaning that once patients have this condition, they don't live for many years unless we aggressively treat the risk factors,

get them to be mobile, and treat their comorbidities. We also know that when it comes to CLTI, healing the wound is paramount, and many of my patients have had their ischemic ulcers for months or even years. Healing wounds after transcatheter arterialization of deep veins (TADV) does require patience, as it takes time to mature the newly established circuit to allow for nutrient delivery to get us to a point of a healed wound. For that reason, my expectation for the therapy was that we would get enough benefit to heal the wounds. The trial obviously showed that TADV is a viable option for healing these nonhealing ulcers. I am particularly interested in the network of digital collaterals and small arteries we visualize in the foot as the arterialization matures.

What are the key highlights from the latest data from PROMISE II?

Dr. Clair: Some critical findings from this study include the ability to save limbs in patients who truly had no other method to preserve a limb that was threatened. Additionally, a "threatened limb without option" for me now means uncontrolled infection, not absence of a means of revascularization. It is also important to note the minimal learning curve since for most investigators, this was their initial experience with this procedure and the devices and techniques involved. There were no "roll-in" patients for any site, and despite this, outcomes were very favorable. This initial experience likely means we will continue to see improved outcomes for this group of patients with this technique over time. Publication of this study in *The New England Journal of Medicine (NEJM)* highlights the innovative nature of this technique and the value it provides for patients who previously were destined for amputation.[1]

Dr. Shishehbor: PROMISE II was groundbreaking research with a paradigm shift in therapy for patients who had no option. It's a big deal to show an alternative therapy that has a 69% limb salvage rate at 12 months and a 99% technical success rate. I am particularly proud that we have refined a procedure that is so reproducible—we only had one failed procedure out of 105, and that was across operators who were learning this procedure. We also observed impressive pain resolution, with an average pain score at 1 year of 1.4 out of 10, and wound healing, with an average wound size at 1 year of 0.2 cm^2.

It gives me satisfaction that *NEJM* recognized that this was groundbreaking. I'm glad it was published in *NEJM* to give this technology the attention it needed because I believe strongly that the technology will address disparities in the CLTI population. I believe one of the reasons we see higher rates of amputations in African American or Hispanic patients is because they often present later in the stage of disease than White patients. By having tools like this, a benefit may be that we can save some of those patients who present in later stages of disease where there are no targets for traditional revascularization.

What impact does this therapy have on patients facing amputation?

Dr. Clair: This therapy will provide an option for an entire group of patients who previously had no therapeutic method to provide limb salvage. These are often patients who had been living independently and would lose this ability with major amputation. For many patients, it is a light in the darkness and hope for an independent and ambulatory future.

One of the patients initially enrolled in the trial was a patient I had cared for some time ago, who had undergone a digital amputation. At the time of his initial problems (6 years earlier), I informed him that there was no further revascularization option for the foot. I felt we were fortunate to heal his foot at that time. He presented with a severely ischemic foot and no option for any standard procedure. He was enrolled in the trial, and while his progression to healing took time, we were able to heal his wounds and maintain his foot. He is now > 1 year out and walking better than he had been for several years before this event. This was a very gratifying result for this patient who traveled quite a distance to receive the procedure.

Dr. Shishehbor: Although we had great successes in the PROMISE II trial, the person I think about most often is a patient of mine from the PROMISE I study; she is now 5 years out from her index procedure and doing so well, showing the durability of outcomes from TADV. She came to me having already had a major amputation on her left leg because she had no options for revascularization. She had developed an ulcer on her right leg and had two unsuccessful revascularization attempts, leaving her in the same situation and facing amputation of her only remaining leg. She responded beautifully to TADV and is doing fantastic, walking and living independently. It's difficult to not have tears in your eyes when she tells you her story.

How is PROMISE III progressing?

Dr. Clair: We are actively enrolling in PROMISE III, initiating sites and evaluating patients. With the results we have seen from PROMISE II, I am sure we will continue to see increased experience and improved outcomes for patients moving forward.

Dr. Shishehbor: The site principal investigators across the country are all very excited to be able to continue offering TADV with the LimFlow System (Inari Medical, Irvine, CA) to their patients, and we look forward to continuing to learn from one another and help patients! ■

1. Shishehbor MH, Powell RJ, Montero-Baker MF, et al; PROMISE II Investigators. Transcatheter arterialization of deep veins in chronic limb-threatening ischemia. N Engl J Med. 2023;388:1171-1180. doi: 10.1056/NEJMoa2212754

TADV Treatment Effect

Results of a propensity stratification against the CLariTI study, a prospective cohort study of the natural history of patients with no-option CLTI.

By Anahita Dua, MD, and Richard Powell, MD

Anahita Dua, MD
Associate Professor of Surgery
Co-Director, MGH PAD Center
Director, MGH Vascular Lab
Associate Director, MGH Wound Care Center
Clinical Director of Research
Division of Vascular and Endovascular Surgery
Massachusetts General Hospital/Harvard Medical School
Boston, Massachusetts
adua1@mgh.harvard.edu
Disclosures: Educational consultant to Abbott, Boston Scientific, and Penumbra.

Richard Powell, MD
Director
Dartmouth Health Heart and Vascular Center
Lebanon, New Hampshire
Disclosures: None.

By 2045, every single country in the world will have a > 15% increase in diabetes.[1] People with diabetes are living longer and hence have complications that we as a medical community have yet to overcome. Specifically, for those of us who care for patients with chronic limb-threatening ischemia (CLTI), the difficulty of managing a patient with no named vasculature of the foot due to microvascular dissemination is daunting. The typical armamentarium of open bypass, advanced endovascular revascularization, and hybrid techniques are not useful when facing a patient with severe calcification of the foot arterioles coupled with loss of all capillaries to the distal foot. These patients, who often also have severe atherosclerotic tibial disease, are relegated to the "no-option" category and almost always end up with a major amputation below or above the knee. Up to 50% of this patient population will die within 1 year of their major amputation[2]; therefore, quickly identifying a solution for limb salvage in this cohort is key. But before we can begin the process of "making things better," it is imperative to define the current state of affairs in the United States.

It is surprising that with all the data we have about the incidence of peripheral artery disease and its impact on our society, we have yet to define (1) the natural history of CLTI and (2) the classical practice patterns of interventionalists treating this disease in our country. Because the approach to CLTI has never been standardized and is heavily dependent on provider skill, patient compliance, and logistical support, it has been long known that which part of the country a patient resides in has a direct impact on their likelihood of amputation. However, the objective evaluation and quantification of this phenomenon has not been previously described.

This makes it difficult for us as physicians to get an idea of what is happening to this population in terms of outcomes, particularly in disparate regions of the country. We often resort to generalizing based on our own experiences and fail to see the bigger picture. For example, up to 50% of patients who undergo amputation have never had an angiogram, and while there are indeed patients who have septic presentations that require an immediate source control procedure, there are undoubtedly patients in that statistic who may have had their limb salvaged if seen by a different provider in a different part of the country. It is important to quantify what the actual amputation rate is in the United States, who is undergoing those amputations, and what the true root cause of amputation is in real-world patients to be able to look at a potential solution like transcatheter arterialization of deep veins (TADV) and see a real benefit. This lack of natural history context can make interpreting the impact of TADV using Inari LimFlow in the PROMISE II single-arm study less intuitive because if we say that TADV can save X% of patients facing amputation, we must show that a similar patient cohort would have gone on to amputation if they did not have TADV as an option.

Given the practical and ethical unfeasibility of randomly assigning patients destined for major amputation, we undertook an alternative approach to providing the important information that a control arm can offer and simultaneously enrolled the largest study of the natural history of no-option CLTI patients to date.

The CLariTI registry was designed to capture the standard of care across the country for this patient population. The registry tracked the natural progression of this patient population across both sites in the PROMISE II study and those not participating in PROMISE II.

At the 1-year time point, the outcomes of CLariTI demonstrated a low limb salvage rate of 48.4% with the current standard of care. Additionally, the survival rate at the end of the first year stands at 66.6%, and the amputation-free survival rate is only 32.6%.

Within the CLariTI registry, we were able to illuminate the real-world outcomes faced by CLTI patients who are deemed "no-option" or have experienced multiple failed revascularizations. This benchmarking allows us to contextualize the results of the PROMISE family of trials within a comprehensive and granular study of the natural history of the disease state and current standard-of-care practice for no-option CLTI patients.

Given the parallel nature, both temporally and in population, of the PROMISE II and CLariTI studies, we were able to evaluate the treatment effect of TADV with Inari LimFlow by utilizing patient-level data from each.[3] This propensity stratification allowed us to address the limitation of the single-arm nature of PROMISE II. We adjusted for potential differences in significant comorbidities, such as gender, age, race, and diabetes status. The propensity stratification demonstrated a significant improvement for those patients who underwent TADV as part of the PROMISE II study. These "treatment arm" patients had a 29% improved ($P < .0001$) propensity-adjusted risk difference in amputation-free survival, and a relative event rate reduction of 45% compared to the CLariTI no-option "control arm" patients. The treated patients also had a 29% improved ($P = .0003$) propensity-adjusted risk difference for major amputation.

The real-world patient-level data in the same patient population afforded by the CLariTI study allowed us to utilize it as an external control group to further prove TADV as an appropriate therapy in patients with CLTI. ■

1. Saeedi P, Petersohn I, Salpea P, et al; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843. doi: 10.1016/j.diabres.2019.107843
2. Kristensen MT, Holm G, Kirketerp-Møller K, et al. Very low survival rates after non-traumatic lower limb amputation in a consecutive series: what to do? Interact Cardiovasc Thorac Surg. 2012;14:543-547. doi: 10.1093/icvts/ivr075
3. Powell RJ, Mullin CM, Clair DG, et al. Comparison of transcatheter arterialization of deep veins to standard of care in patients with no-option chronic limb threatening ischemia. Ann Vasc Surg. 2024;99:50-57. doi: 10.1016/j.avsg.2023.08.010

Health Economics: Inari LimFlow Procedure

Highlights from a recent study demonstrating the cost-effectiveness of TADV for no-option CLTI patients.

By Peter A. Schneider, MD

Peter A. Schneider, MD
Professor of Surgery
Division of Vascular & Endovascular Surgery
University of California, San Francisco
San Francisco, California
Disclosures: Consultant to Medtronic, Philips, Boston Scientific, Surmodics, Silk Road, Inari LimFlow, and Cagent.

Major shifts in treatment algorithms such as the introduction of transcatheter arterialization of deep veins (TADV), while clearly dependent upon the clinical results, must realistically provide health economic value to be viable. The efficacy of the TADV procedure with Inari LimFlow in chronic limb-threatening ischemia patients with "desert foot" occlusive anatomy was proven in the PROMISE family of trials. My colleagues and I undertook a study to explore the potential cost-effectiveness of TADV in the United States health care system to complete the picture of the value of this paradigm shift. That study was published in *Journal of Critical Limb Ischemia*, and the highlights are summarized herein.[1]

COST-EFFECTIVENESS ANALYSIS

A model was developed to project costs and outcomes over patients' lifetimes and calculate the incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted life-year (QALY) gained. We used 1-year data from the PROMISE I early feasibility study and will soon publish an updated model using results from the PROMISE II pivotal trial.[2] Within this model, amputation-free survival, reintervention, and wound healing data for both TADV and status quo historical control for treatment of no-option patients were utilized, and associated costs were obtained from Medicare and published rates. We conducted extensive sensitivity and scenario analyses, including various worst-case scenarios where survival benefit beyond 1 year was not assumed.

The decision-analytic model demonstrated that in comparison to status quo, which involved major amputation events per historical control data, TADV added 1.45 QALYs and incurred $23,903 in additional costs in the base case analysis, resulting in an ICER of $16,522 per QALY gained. The model also projects an approximate lifetime survival gain of 3 years for TADV patients over the status quo.

Willingness-to-pay thresholds are the standard parameters by which the cost-effectiveness of a given procedure is judged. American College of Cardiology/American Heart Association has defined an intervention costing $50,000 per QALY as "high value" and an intervention costing $150,000 per QALY gained as "intermediate value."[3] The observed $16,522 per QALY for TADV in the base case scenario places it well within the high-value range, indicating that TADV with the Inari LimFlow System (Inari Medical, Irvine, CA) is highly cost-effective. Even after assuming the addition of an add-on payment for the TADV procedure, TADV remained highly cost-effective in the medical care of these highly vulnerable patients.

As a comparison, the life-year gains, QALY gains, and ICERs projected for TADV are more favorable than what has been projected for transcatheter aortic valve

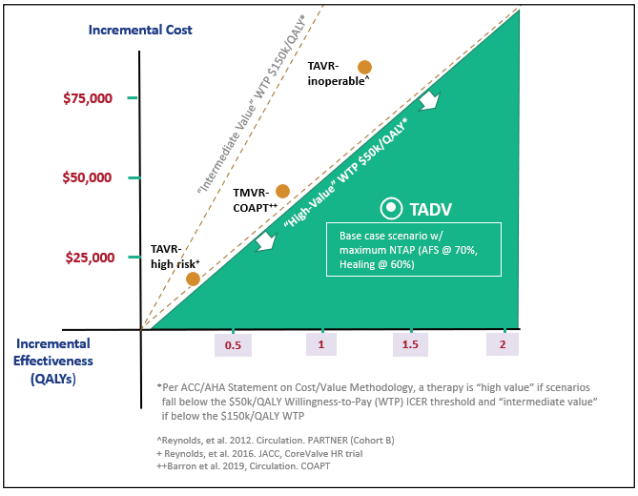


Figure 1. TADV'S cost-effectiveness profile relative to well-established therapies. NTAP, New Technology Add-On Payment; TAVR, transcatheter aortic valve replacement; TMVR, transcatheter mitral valve repair.

replacement versus surgical aortic valve replacement for high-risk and inoperable patients and for transcatheter mitral valve repair (now also referred to as transcatheter edge-to-edge repair) versus medical therapy (Figure 1).

CONCLUSION

We anticipate an update of this cost-effectiveness evaluation with the inclusion of the 12-month data from PROMISE II. The updated analysis plan includes site-of-service considerations and a variety of alternative assumptions about long-term amputation event incidence. It will provide additional data to further assess and corroborate the health economic value proposition of TADV for no-option patients. ■

1. Pietszch JB, Ederhof M, Geisler BP, Schneider PA. Cost-effectiveness of percutaneous deep vein arterialization for patients with no-option chronic limb-threatening ischemia: an exploratory analysis based on the PROMISE I study. J Crit Limb Ischem. 2021;1:E148-E157.
2. Clair DG, Mustapha JA, Shishehbor MH, Schneider PA, et al. PROMISE I: early feasibility study of the LimFlow system for percutaneous deep vein arterialization in no-option chronic limb-threatening ischemia: 12-month results. J Vasc Surg. 2021;74:1626–1635. doi: 10.1016/j.jvs.2021.04.057
3. Anderson JL, Heidenreich PA, Barnett PG, et al; ACC/AHA Task Force on Performance Measures; ACC/AHA Task Force on Practice Guidelines. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329–2345. doi: 10.1161/CIR.0000000000000042

An Overview of the Inari LimFlow Procedure

A case example and step-by-step guide to TADV with Inari LimFlow.

By Miguel Montero-Baker, MD

Miguel Montero-Baker, MD
CEO/Medical Director
HOPE Vascular & Podiatry Innovation Center
Houston, Texas
mmontero@hcic.io
Disclosures: Consultant to Inari LimFlow, Bard, Boston Scientific, Veryan, and Cook Medical.

Within the last decade, significant progress has been made in refining transcatheter arterialization of deep veins (TADV), progressing what was proposed as an open surgical procedure more than a century ago into a consistent and reproducible fully percutaneous treatment option for patients with no-option chronic limb-threatening ischemia (CLTI). The purpose-built products of the Inari LimFlow System (Inari Medical, Irvine, CA) obviate some of the largest hurdles that are otherwise present when attempting to reroute nutritive blood flow to a limb we are unable to revascularize using traditional open or endovascular techniques.

INARI LIMFLOW PROCEDURE

The Inari LimFlow procedure can be summarized into the following steps: pedal venous access in the lateral plantar vein, arterial access in the common femoral, arteriovenous crossing from the donor artery (the artery chosen to be the conduit of oxygenated blood to the vein to the foot by way of the TADV circuit) into the donor vein that will be arterialized, valvulotomy, extension stent graft deployment, and crossing stent graft deployment.

Case Example

This is a case report involving use of the Inari LimFlow System in one of my TADV patients. A woman in her early 70s with type 2 diabetes and a history of stroke, myocardial infarction, hypertension, and dyslipidemia presented for the treatment of nonhealing dry gangrene of the hallux,

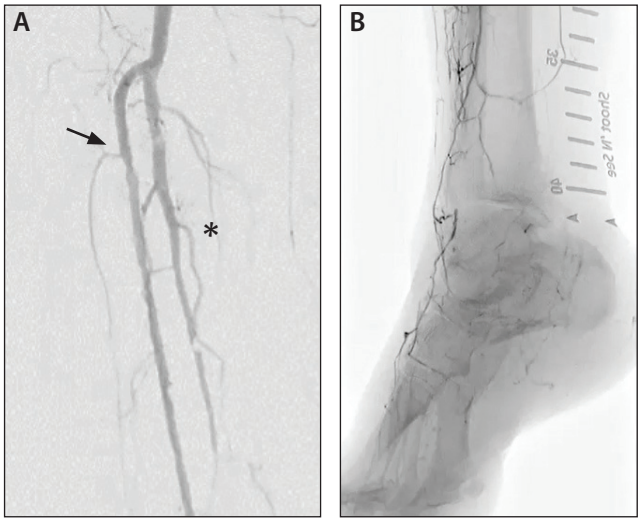


Figure 1. Anterior tibial artery occluded before the foot (black arrow), peroneal—donor artery for TADV (asterisk) (A); collaterals to small irregular perfusion of the foot (B).

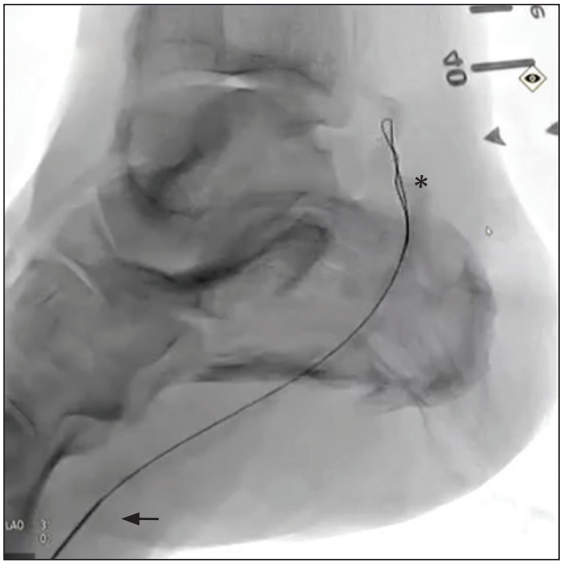


Figure 2. Plantar access needle (black arrow) and 0.018-inch wire through the lateral plantar vein and into the posterior tibial vein (asterisk).

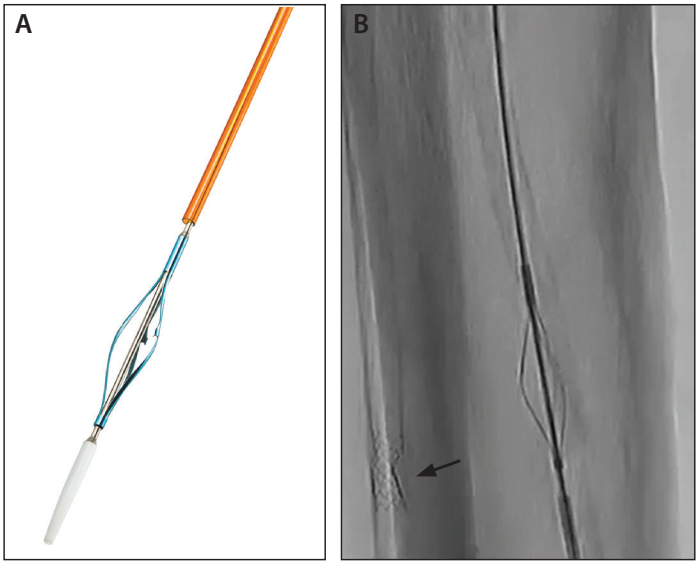


Figure 4. The Inari LimFlow Vector (Valvulotome) (A). Valve lysing with the Vector Valvulotome; deformed balloon-expandable stent in anterior tibial artery (black arrow) (B).

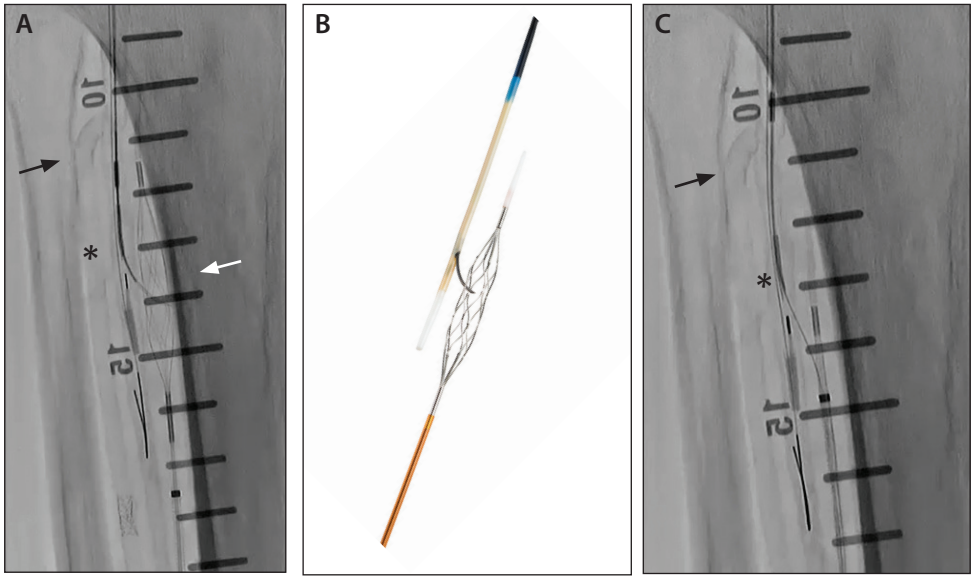


Figure 3. Arteriovenous crossing with the ARC and V-Ceiver; calcium outline of the proximal anterior tibial artery (black arrow), ARC arterial catheter (asterisk), and V-Ceiver (white arrow) (A, C). Image of ARC and V-Ceiver (B).

present for > 6 months. She saw multiple providers for the wound with no resolution and was referred to me for a second opinion after being told she needed a major amputation. She had a history of vascular interventions, including plain old balloon angioplasty and stenting of the anterior tibial artery, all with no resolution of symptoms. This patient had no named surgical or endovascular targets for traditional revascularization (Figure 1).

Over the past several years, my colleagues across the country and I have refined the Inari LimFlow procedure during the PROMISE family of clinical trials. This experience and the learnings garnered in our research have led us to transition venous access from the medial ankle to the middistal plantar surface of the foot.[1,2] Diagnostic imaging learnings have contributed to distal venous access, and we have refined our protocol for ultrasound-based case planning to allow for standardized and reproducible venous access.

Following pedal venous access (Figure 2) and antegrade arterial access, the donor artery is selected and prepped. The V-Ceiver (venous catheter; Inari Medical, Irvine, CA) is advanced into the donor venous target, where the balloon-shaped radiopaque mesh is expanded to fill and distend the vein, allowing for a distinct visualization and alignment of the crossing target. The ARC (arterial catheter; Inari Medical, Irvine, CA) is advanced into the donor artery to the desired crossover

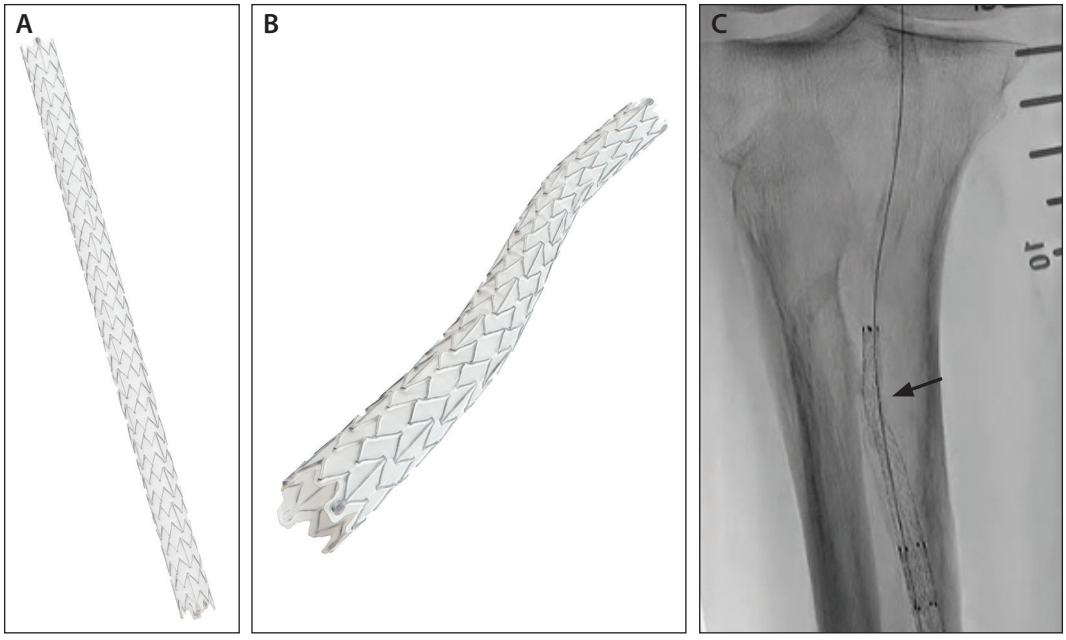


Figure 5. Inari LimFlow stents (A, B); highly calcified anterior tibial artery, tapered Inari LimFlow stent bridging donor artery to donor vein (black arrow) (C).

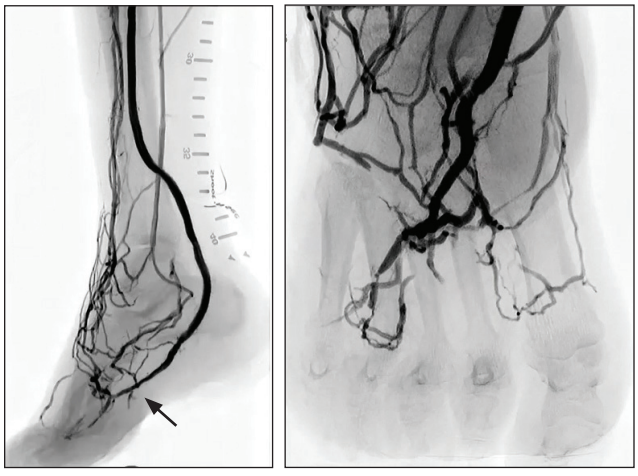


Figure 6. Angiographic results showing the fully opacified TADV circuit flowing into the deep system of the plantar foot to the dorsal superficial venous system. Lateral plantar vein: TADV outflow (black arrow).

point, and the embedded crossing needle (purpose-made to pierce the often-present medial arterial calcification) is advanced into the V-Ceiver mesh (Figure 3). A wire is advanced, the crossing needle retracted, and the wire captured within the V-Ceiver and externalized from the venous access.

After establishing the arteriovenous conduit, the Inari LimFlow Vector (Inari Medical, Irvine, CA), an over-the-wire push valvulotome, is advanced into the vein, and the forward-facing hooks on the valvulotome lyse the venous valves from the tibial crossover point to the distal foot (Figure 4), enabling the forward flow of blood into the foot.

After rendering the valves incompetent, the focalization of arterial flow is accomplished by lining the length of the tibial donor vein with Inari LimFlow nitinol-covered self-expanding stents. To accommodate the size differences between the smaller donor artery and the larger donor vein, the Inari LimFlow tapered crossing stent is then placed in the most proximal segment of the TADV circuit, creating the permanent arterialized venous conduit for blood flow into the foot (Figure 5). This tapered crossing is key to optimizing the flow within the circuit.

Upon completion of stenting, evaluation of the venous loop is performed under angiography to confirm the flow to the metatarsal segment, adequate outflow, and that there is no stagnation (Figure 6). Although immediate angiographic results show flow into the foot, over the coming weeks, this circuit will continue to mature and additional vessels will be recruited as flow dynamics continue to evolve.

CONCLUSION

The TADV procedure, as developed by Inari LimFlow, continues to show a consistent and reproducible endovascular method to treat no-option CLTI patients. And thus, it sets the stage for future studies on the life cycle and mechanisms of the venous arterialization. ■

1. Clair DG, Mustapha JA, Shishehbor MH, et al. PROMISE I: Early feasibility study of the LimFlow System for percutaneous deep vein arterialization in no-option chronic limb-threatening ischemia: 12-month results. J Vasc Surg. 2021;74:1626-1635. doi: 10.1016/j.jvs.2021.04.057
2. Shishehbor MH, Powell RJ, Montero-Baker MF, et al. Transcatheter arterialization of deep veins in chronic limb-threatening ischemia. N Engl J Med. 2023;388:1171-1180. doi: 10.1056/NEJMoa2212754

Latest Postprocedure Wound Care: Best Practices

The first 2 months after TADV are a critical time for monitoring wound progression and infection control.

By Brian Lepow, DPM

Brian Lepow, DPM
Chief of Podiatry
HOPE Vascular and Podiatry
drbdlepow@gmail.com
Houston, Texas
Disclosures: Consultant to Inari LimFlow.

While all the transcatheter arterialization of deep veins (TADV) patients at our institution are cared for by our comprehensive limb salvage team throughout their course, the first 2 months after the TADV procedure with Inari LimFlow are the most critical time for our multidisciplinary team to work together. The arterialized circuit matures over approximately 4 to 6 weeks, and it is critical that we keep a close eye on the wound during that time frame, with particular focus paid to infection control.

Wound management in the revascularized patient can either help or hinder the overall healing process. Proper wound care techniques are a necessary entity when dealing with this high-risk patient population where functional and expedited limb preservation is needed. For some, adequate product selection for best wound management can prove to be a challenging task. It is not a matter of what you are putting on the wound that will assist with patient care; it's more about what's being taken off the wound that will ultimately promote healing, mitigate infection, and lead to a positive outcome. It can be a daunting task given the expansive options for wound care products. The ultimate end goal is to select the appropriate product that will assist with healing and lead to a functional outcome for the patient.

GUILLOTINE TRANSMETATARSAL AMPUTATION

Given the severity of the wound present in many TADV patients, there will be cases in which foot-sparing minor amputations must be performed to remove nonviable tissue. Formalization of any foot surgeries should be delayed until that 4- to 6-week circuit maturation time point, if possible. For patients who require a transmetatarsal amputation (TMA), the traditional option of primary closure is not an appropriate technique for patients with a TADV circuit, as the tension hinders microvascular perfusion, leading to flap necrosis. For TADV patients requiring a TMA, I have instituted the practice of performing guillotine TMA (gTMA), followed by definitive soft tissue coverage within my own practice (Figure 1), as well as in recently published long-term outcomes.[1] We have found great success with gTMA, followed by the application of a dermal substitute and low-pressure negative pressure wound therapy and, after full granulation, application of split-thickness skin graft. Utilizing this approach, we are also able to get our patients ambulating quite quickly, with a median of 2 days to ambulate. ■

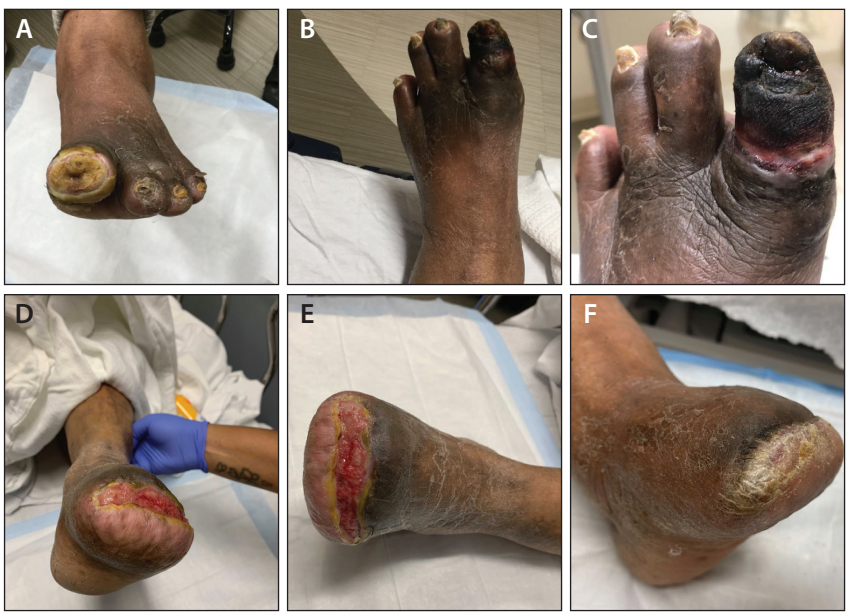


Figure 1. Images of wound progression after gTMA: baseline (A), 2 weeks (B), 1 month (C), 2 months (D), 3 months (E), and 6 months (F).

1. Lepow BD, Zulbaran-Rojas A, Park C, et al. Guillotine transmetatarsal amputations with staged closure promote early ambulation and limb salvage in patients with advanced chronic limb-threatening ischemia. J Endovasc Ther. Published online December 24, 2022. doi: 10.1177/15266028221144587

TADV Circuit Maturation and Pressure Wire Experience

How pressure gradient measurements can monitor remodeling during TADV.

By Roberto Ferraresi, MD

Roberto Ferraresi, MD
Scientific Director
Diabetic Foot Clinic
San Carlo Hospital
Paderno Dugnano
Milan, Italy
ferraresi.md@gmail.com
Disclosures: Consultant to Inari LimFlow.

Transcatheter arterialization of deep veins (TADV) with Inari LimFlow is a promising new technique for saving limbs of patients with no-option chronic limb-threatening ischemia (CLTI).[1,2] The traditional method of diverting blood flow from the diseased arterial system to the healthy vein system is now presented in a new totally percutaneous scenario, without surgical wounds and in a standardized and reproducible procedure across centers and countries.

There is a fundamental difference between traditional revascularization procedures and TADV. After a successful bypass or angioplasty, the functional result of the procedure is immediately visible angiographically and clinically: The reestablishment of distal blood flow achieves sudden relief of ischemia. That is not the case with TADV. At the end of a TADV procedure, we generally observe a roundabout of blood in the foot without any blood flow reaching the tissues. The so-called vein "fortress" is locked by a multitude of small vein valves. In some cases, patient symptoms can worsen in the short term, and pain control is a fundamental part of the postprocedural care.

In their first-in-human study, Kum et al observed the rise of transcutaneous oxygen tension ($TcPO_2$) levels starting 2 to 4 weeks after treatment and reaching > 40 mm Hg only 6 to 8 weeks later,[3] demonstrating a time-lapse between the acute TADV procedure and the physiological effect. Clair et al affirmed that management of the maturation process to achieve maximum effectiveness and minimal ischemic complications will be more frequent in TADV than in conventional open and endovascular arterial reconstruction.[1]

All authors agree that TADV needs time for perfusing the deep tissue—waiting for a remodeling process that relies on the residual biological adaptation capacity of the patient's vascular system, which we should be able to monitor, guide, and promote. In addition to $TcPO_2$, we should have other parameters to detect TADV maturation and guide possible reinterventions.

Looking for this quantitative evaluation of vascular remodeling, we performed intravascular pressure measurements in some TADV patients using a pressure wire (Philips).[4] We recorded the pullback of the wire from the venous plantar arch to the proximal superficial femoral artery (pSFA) and compared it with the pressure recorded inside the sheath in the pSFA. We selected and measured the ratio between the mean pressures because these types of measurements can be easily obtained with a simple 4-F catheter, avoiding the cost of the dedicated equipment.

PATIENT HISTORY AND TADV PROCEDURE

A man in his early 60s with type 2 diabetes, high blood pressure, and previous coronary artery bypass graft was admitted to our hospital with gangrene of the second toe and pain at rest. $TcPO_2$ was 7 mm Hg and the baseline angiographic study demonstrated diffused disease of the foot vessels (Figure 1A), leading to the diagnosis of no-option CLTI.

A TADV procedure was performed, and Figure 1B shows the final result. A good arterialized circuit was achieved with direct blood flow inside the foot vein fortress and outflow in the great saphenous vein (GSV) and deep dorsal vein. The arterialized circuit did not give any blood flow to the tissues. Pressure wire pullback showed a progressive drop of mean value from the pSFA to the plantar arch, with a maximum gradient above the conical stent (Figure 2). The high blood flow due to the low resistance of the fortress vein outflow typically increases the functional effect of mild or moderate inflow stenosis. In the first procedure, we generally stop here because a sudden and extreme increase in foot vein pressure could lead to worsening ischemia, counterbalancing the gradient between the poor arterial inflow (which is still the only tissue flow) and the venous outflow of the capillary system.

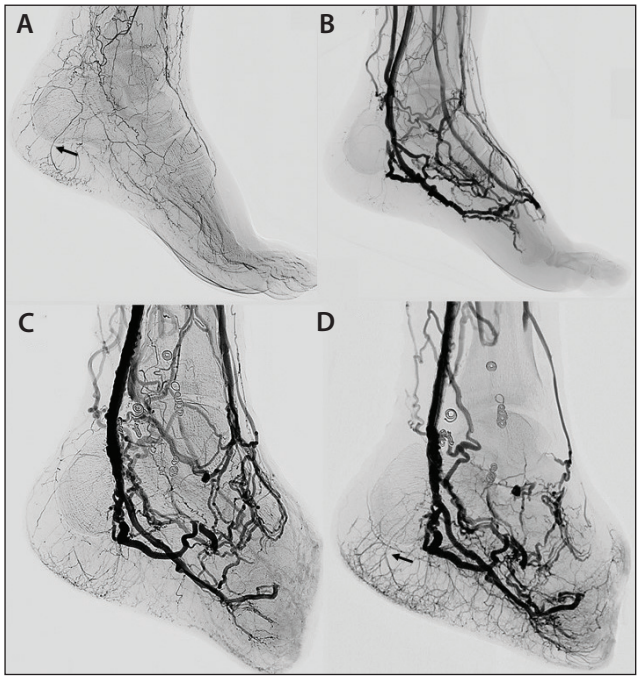


Figure 1. Angiographic images of the foot. Baseline (A); acute TADV result (B); 4 months later, before skin graft (C); 1 year later (D). Black arrows indicate an arterial calcaneal branch.

ONE MONTH LATER: BEFORE TRANSMETATARSAL AMPUTATION

Pain and progression of gangrene continued in the next month. A second angiographic study was obtained before performing a transmetatarsal amputation (TMA). Initially, the inflow was treated by stenting the tibioperoneal trunk; however, that did not result in any particular improvement of the pressure gradient. The vein outflow was then reduced by "pruning" with coil embolization of some posterior collaterals and the root of the GSV. This significantly reduced the gradient (Figure 2).

FOUR MONTHS LATER: BEFORE SKIN GRAFT

In subsequent months, the pain slowly disappeared, the wound presented with good granulation tissue, and $TcPO_2$ increased to 56 mm Hg. Four months after the initial intervention for "pruning," a new angiographic study showed a patent arterialization circuit with recruitment of small distribution vessels and initial tissue blush of the wound (Figure 1C). The pressure gradient improved, with no significant gradient above the covered stent and mild residual gradient in the plantar venous arch (Figure 2).

ONE YEAR LATER: MATURE REMODELING OF THE ARTERIALIZED CIRCUIT

One year post–index procedure, the patient had no pain and showed minimal residual wound dehiscence, and transcutaneous oxygen tension had increased to 65 mm Hg.

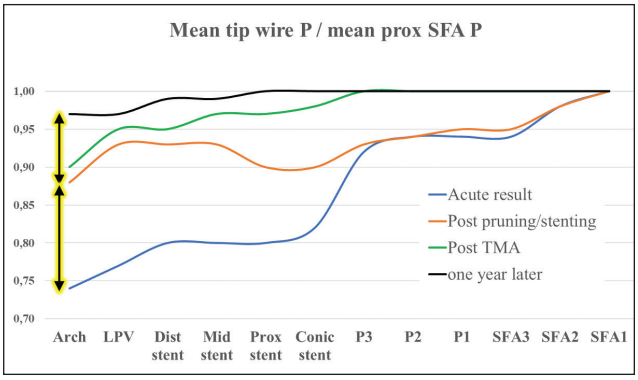


Figure 2. The ratio between mean SFA pressure and tip wire pressure in the arterialized circuit. LPV, lateral plantar vein.

At that point, angiography was performed via injection of contrast dye through a catheter inside the distal covered stent to visualize only the purely arterialized vasculature. The angiogram revealed complete remodeling of the arterialized circuit, with a well-developed arterial distribution system (Figure 1D). Some of these arteries, perfused by connection with the arterialized veins, can be morphologically identified as residual arterial segment and visible and recognizable in the baseline angiographic study (Figure 1, black arrows). Others are impossible to distinguish as preexisting hibernated and recruited arteries or entirely newborn arteries. Remodeling affected not only the arterial circuit but also the venous outflow, as visible in Figure 1B to 1D.

In the acute phase, the vein fortress was filled by the posterior tibial vein and the dorsal systems were a huge outflow. After pruning and TMA, the vein outflow of the circuit was represented by the deep dorsal veins. At 1 year, only a few residual collaterals were stealing blood in some small superficial veins.

Regarding the pressure wire, the last pullback did not show any residual significant gradient (Figure 2).

DISCUSSION

Immediately after the TADV procedure, the arterialized circuit did not have any positive physiological effect; the gradient between the plantar arch and the pSFA was the consequence of the low resistance of vein outflow and consequent high blood flow.

After pruning some of the vein outflow, the blood flow and gradient reduced, as shown in Figure 2 (bottom double-tip arrow). Subsequent remodeling was only due to the adaptability of the patient's vasculature, leading to expansion of the vein-dependent arterial distribution system, further self-pruning of the outflow veins, and progressive normalization of the distal gradient (Figure 2, top double-tip arrow).

In our experience, when an arterialized circuit is completely developed, every gradient disappears, such as in

a healthy arterial segment. This clinical case is an example of how pressure gradient measurements could monitor the remodeling process of TADV, giving important clues on the progress of the spontaneous biological remodeling and the need to potentially help this process with targeted interventions. ■

1. Clair DG, Mustapha JA, Shishehbor MH, et al. PROMISE I: early feasibility study of the LimFlow System for percutaneous deep vein arterialization in no-option chronic limb-threatening ischemia: 12-month results. J Vasc Surg. 2021;74:1626-1635. doi: 10.1016/j.jvs.2021.04.057
2. Shishehbor MH, Powell RJ, Montero-Baker MF, et al. Transcatheter arterialization of deep veins in chronic limb-threatening ischemia. N Engl J Med. 2023;388:1171-1180. doi: 10.1056/NEJMoa2212754
3. Kum S, Tan YK, Schreve MA, et al. Midterm outcomes from a pilot study of percutaneous deep vein arterialization for the treatment of no-option critical limb ischemia. J Endovasc Ther. 2017;24:619-626. doi: 10.1177/1526602817719283
4. Garcia LA, Carrozza JP Jr. Physiologic evaluation of translesion pressure gradients in peripheral arteries: comparison of pressure wire and catheter-derived measurements. J Interv Cardiol. 2007;20:63-65. doi: 10.1111/j.1540-8183.2007.00213.x

How Will TADV Change Clinical Practice?

TADV can offer no-option patients hope for limb preservation and will become part of the armamentarium for vascular specialists.

By Daniel Clair, MD

Daniel Clair, MD
Professor and Chair
Department of Vascular Surgery
Vanderbilt University Medical Center
Nashville, Tennessee
dan.clair@vumc.org
Disclosures: Advisory and consultant to Boston Scientific, Bard Peripheral Vascular, Medtronic, and Inari LimFlow.

Factors such as advancing age,[1] increasing diabetes prevalence,[2] and rates of renal insufficiency[3] are leading to a large number of patients with lower extremity arterial occlusive disease. These disease processes progressively lead to arterial calcification and impair outcomes of revascularizations performed in these patients.[4] The ability of vascular specialists to address an increasing population of patients with chronic limb-threatening ischemia and poor options for revascularization challenges even those with the greatest skill. These patients, who often need amputation despite attempts at revascularization, can be left with no hope and persistent pain.[5]

Transcatheter arterialization of deep veins (TADV) with Inari LimFlow offers patients hope and the opportunity for limb preservation, which for many of these patients offers the chance to continue living an independent life.

Results from the PROMISE II trial reveal that not only can limb salvage be achieved, but a competent vascular specialist working in conjunction with meticulous wound care can quickly learn to repeat these results.[6] In some patients, recognition of the poor circulation in the foot and the lack of adequate "collateral circulation" may allow this procedure to be offered prior to revascularization into a "dead-end" vessel that does not adequately provide circulation to the diseased area of the foot. Currently, patients with no distal target or no usable vein for revascularization are managed with wound care alone until pain is too severe, the wound becomes infected, and tissue infection leads to amputation or, in a minority of patients, until healing can be achieved.

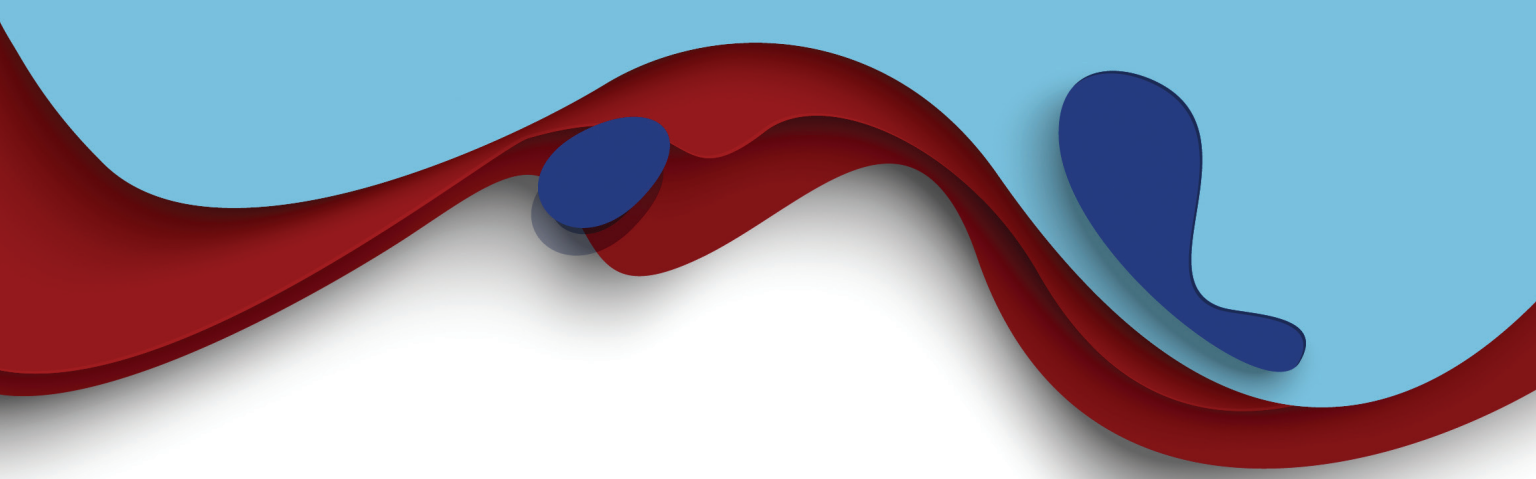
This technique changes the paradigm in a way that nothing else to date has done. Revascularization can be achieved through the venous system with a percutaneous intervention in most situations; while limb salvage success is not as high as might be expected were the patients to have arterial revascularization options, it is clearly improved from the alternative expectant management.

Based on these results, I have been able to redefine what a "threatened limb without option" means for my practice. Whereas it used to mean the absence of a means of revascularization, that barrier has been lifted and it is now defined as uncontrolled infection.

Moving forward, this technique will become a part of every vascular specialist's armamentarium for limb salvage, and facilities aiming to be centers for limb salvage will need to have this option available for their patients. ■

1. Wetrogan SI. Projections of the population of states, by age, sex, and race: 1988 to 2010. Curr Popul Rep Popul Estim Proj. 1988:1-124.
2. Lovic D, Piperidou A, Zografou I, at al. The growing epidemic of diabetes mellitus. Curr Vasc Pharmacol. 2020;18:104-109. doi: 10.2174/1570161117666190405165911
3. Eggers PW. Has the incidence of end-stage renal disease in the USA and other countries stabilized? Curr Opin Nephrol Hypertens. 2011;20:241-245. doi: 10.1097/MNH.0b013e3283454319
4. Lanzer P, Hannan FM, Lanzer JD, et al. Medial arterial calcification: JACC state-of-the-art review. J Am Coll Cardiol. 2021;78:1145-1165. doi: 10.1016/j.jacc.2021.06.049
5. Liu IH, Wu B, Krepkiy V, et al. Pedal arterial calcification score is associated with hemodynamic change and major amputation after infrainguinal revascularization for chronic limb-threatening ischemia. J Vasc Surg. 2022;76:1688-1697.e3. doi: 10.1016/j.jvs.2022.07.009
6. Shishehbor MH, Powell RJ, Montero-Baker MF, et al; PROMISE II Investigators. Transcatheter arterialization of deep veins in chronic limb-threatening ischemia. N Engl J Med. 2023;388:1171-1180. doi: 10.1056/NEJMoa2212754

Endovascular TODAY



LimFlow System Intended Use/Indications for Use: The LimFlow System is indicated for patients who have chronic limb-threatening ischemia with no suitable endovascular or surgical revascularization options and are at risk of major amputation. **Contraindications:** Patients with deep venous thrombus in target vein; Patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy **Warnings and Precautions:** Use in patients with concomitant hepatic insufficiency has not been evaluated; Use in patients with poor cardiac output, e.g., NYHA Class IV, has not been evaluated; Use in pregnant and breastfeeding women has not been evaluated; Implanting the device in the distal half of the calcaneus may result in stent fracture **Adverse Events:** Acute renal impairment requiring dialysis; Cardiac arrest; Death; Embolization; Graft rupture, trans-graft leak, site leak; Hematoma; Insufficient blood flow to foot; Ischemia; Myocardial infarction; Occlusion; Pain; Peripheral edema; Procedural bleeding; Restenosis of stented segment; Sepsis / Infection; Stent damage, implant migration; Stent graft fracture; Stent graft misplacement, deformation, or migration; The need for surgical or endovascular interventions to rectify an access site problem; Thrombosis; Vessel dissection, perforation, injury; Vessel spasm. Please reference product Instructions for Use for more information regarding indications, warnings, precautions, contraindications and adverse events. **LimFlow ARC Intended Use/Indications for Use:** The LimFlow ARC is intended to facilitate placement and positioning of guidewires and catheters within the peripheral vasculature. **LimFlow V-Ceiver Intended Use/Indications for Use:** The LimFlow V-Ceiver is intended for use in the cardiovascular system to manipulate and retrieve guidewires specified in the IFU. **LimFlow Vector Intended Use/Indications for Use:** The LimFlow Vector is intended for the treatment of vascular disorders and more particularly for excising or disrupting venous valves. **Important Information:** Prior to use, refer to the Instructions for Use for indications, contraindications, suggested procedure, warnings, adverse events, and precautions. **Caution:** Federal (USA) law restricts these devices to sale by or on the order of a licensed healthcare practitioner.