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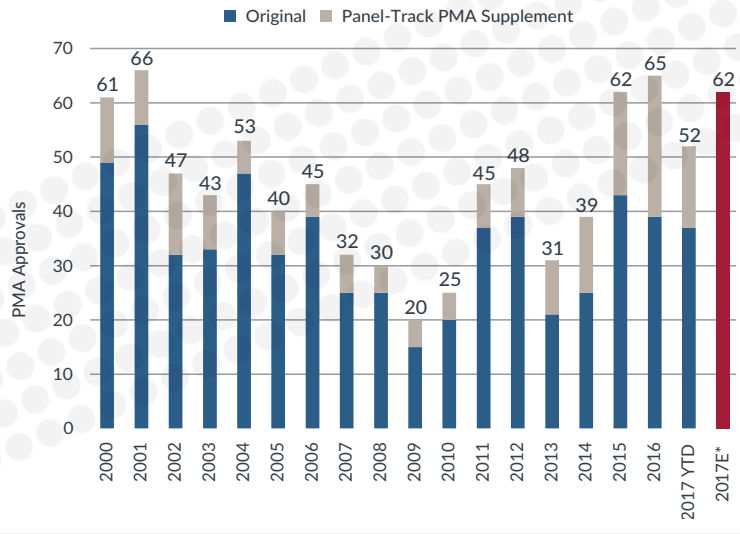


New Interventions for Critical Limb Ischemia

by
MARY STUART

KEY POINTS

- Critical limb ischemia is gaining increased scrutiny because these patients are expensive. One million of them account for $3 billion in Medicare expenses, including the costs of treating their chronic, non-healing wounds, repeat revascularization procedures, and the lifetime costs of limb amputation.

- As a disease of occluded arteries, revascularization is the primary treatment strategy and clinicians have gravitated to the endovascular tools of peripheral artery disease, of which CLI is most severe type.

- Below the knee, where much of CLI needs to be treated, these devices are less effective. Device companies are developing new endovascular interventions purposely designed for the unique requirements of CLI.

- There is no consensus on how to treat CLI patients, because they haven't been recruited into large, randomized controlled trials studying peripheral artery disease. The first of these are in progress, and they aim to answer both clinical and economic questions about this emerging space.

Peripheral artery disease (PAD), or atherosclerosis in arteries in the limbs, is on the rise worldwide, driven by rapidly aging populations and a combination of well-known risk factors, including diabetes, smoking, high cholesterol, kidney disease, obesity, and a sedentary lifestyle. Approximately 18 million people in the US suffer from PAD, many of whom are in need of interventions to restore blood flow from clogged arteries in the legs to reduce pain, restore mobility, and prevent amputation due to the death of ischemic tissue in the lower leg or foot.

The minimally invasive treatment of peripheral vascular disease began as an offshoot of interventional cardiology, borrowing angioplasty balloons, stents, and other devices designed for the coronary arteries. However, in the last ten years or so PAD has gained recognition as a disease with its own specific set of needs, including medical devices purposefully built for the dynamics of arteries in limbs and the challenging long and diffuse lesions that occur in the lower extremities. Now, critical limb ischemia is at the beginning of a similar evolution.

Critical limb ischemia (CLI), which affects 3.2 million people globally, is severe atherosclerosis in leg arteries that causes chronic pain at rest. If left untreated, CLI results in the development of non-healing wounds leading to infection and even gangrene, which, in turn, leads to amputation. The estimated yearly incidence of CLI in Western society is 500-1,000 new cases per one million individuals. Ten percent of CLI patients require treatment in the near term to prevent infection and amputation.

That's only one definition of CLI, though, and those statistics are not hard and fast since for so long CLI has been regarded simply as the most

severe kind of peripheral artery disease—that is, it's had an identity problem. There is no standard definition of CLI that embraces hemodynamic and other objective parameters, no standardization in diagnosis, and no specific DRG reimbursement code that would help build bodies of data on treatments and outcomes. And, since CLI patients are seen as the sickest type of PAD patients, they have often been excluded from clinical trials of new endovascular therapies.

But now CLI is emerging as its own specialty and as a focus of research and innovation on the part of biopharma and medical device companies, due in part to the fact that health systems are looking closely at the patients that cost the most money. Indeed, CLI occurs in almost one million Medicare patients per year and treating them costs an estimated $3 billion per year (according to an article by Goodney, PP et al, in a 2013 issue of the *Journal of Vascular Surgery*, 57(6) 1471-1480).

Those costs take into account that 50% of patients diagnosed with CLI will eventually undergo an amputation and 25% will die within in one year (*see Figure 1*). The prognosis for a patient that loses a leg to CLI is poor: only 47-67% of these patients return to mobility, and post-amputation mortality rates are 40% at one year, rising to 80% at five years.

Thus, while CLI is an ischemic disease that, like coronary artery disease and PAD, is treated by removing blockages in occluded arteries to restore tissue perfusion, it is also a disease of chronic wound care, infection, pain management, and limb salvage, and needs to be looked at differently than other ischemic diseases.

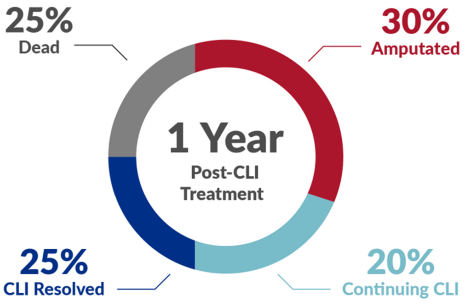
Critical Limb Ischemia Emerges from the Shadows

Professional societies have begun to coalesce around CLI—for example the Critical Limb Ischemia Global (CLIG) Society, formed in 2016, the mission of which is to address unknowns in the clinical approach to these patients and bring resources to the disease. As a starting point, the CLIG Society came up with a specific list of challenges in the field, starting with a lack of definition of the disease; no standard means of diagnosing and staging patients; no consensus on how to treat patients; and the absence of adequately powered, randomized clinical trials in the space (*see Figure 2*).

Figure 1

Critical Limb Ischemia:

Current treatments fail most patients



Source: LimFlow SA

At present, there's not much data to guide clinical decision-making in CLI. Revascularization is the primary therapeutic strategy, so clinicians have naturally gravitated to the less-invasive endovascular tools of peripheral vascular disease—atherectomy, angioplasty, and stents—even though no studies have definitely proven whether endovascular approaches or surgical bypass procedures are equally efficacious.

That data is on its way, though. BEST-CLI (Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia), which is funded by a $24.9 million grant from the National Heart, Lung and Blood Institute of the National Institutes of Health, is enrolling 2,100 patients at 120 sites in the US and Canada to compare FDA-approved endovascular devices to bypass surgery (with either a native or synthetic graft). The trial will measure clinical outcomes in terms of time to major adverse event, amputation rates, time to re-intervention, and numbers of interventions, as well as costs. A CLI registry, sponsored by VIVA, the society for Vascular Interventional Advances, will collect data on 5,000 patients in the study. As of July 2017, BEST-CLI enrollment was at 775.

Another landmark trial, Liberty 360°, is sponsored by **Cardiovascular Systems Inc.**, a leading manufacturer of atherectomy systems for PAD. Liberty 360° will look at the acute and long-term clinical and economic outcomes of PAD patients treated with any FDA-approved peripheral vascular intervention (including angioplasty balloons, atherectomy devices, stents, and CTO crossing devices). The study completed enrollment of 1,200 patients at 51 sites in 2016 and will follow them for five years, looking at procedural success, the percentage of stenosis in target lesions, rates of major adverse events, quality of life, 6-minute walk test, and economic outcomes, among other endpoints.

Patients across all the entire spectrum of PAD were enrolled, including 603 patients with CLI (with a Rutherford Classification [RC] of 4-5) and 100 patients with the most severe form of CLI (RC 6).

One-year results were presented at the Amputation Prevention Symposium in Chicago in August 2017, showing the benefits of peripheral vascular interventions in CLI patients. At 12 months, those in the less severe group (RC 4-5) enjoyed 96% freedom from amputation, and 81.7% of patients in the most severe group (RC 6) also kept their limbs. CLI patients all improved in terms of their Rutherford classification, wound healing,

and quality of life. As noted, these are the types of very sick patients that, in the past, were typically excluded from clinical trials, so the results of studies like these will be important to the development of the field.

A Toolbox Approach

As the trials above indicate, the clinical community is hard at work to establish some basic strategies for CLI—endovascular therapies, or surgery, broadly speaking. But the results of the trials will still leave it up to clinicians to judge the best devices to use on individual patients, while facing complex procedures that often take hours to complete. Many describe the need for a "toolbox" approach to CLI.

Critical limb ischemia is particularly difficult to treat because much of it must be treated below the knee (BTK), which limits device options. (Drug-coated balloons [DCBs], for example, are not yet approved for that indication, and the CR Bard division of **Becton Dickinson**, which is developing the *Lutonix 014* is the only company with an approved IDE trial for a DCB for the treatment of the arteries below the knee. *See "Drug Coated-Balloons: Market Ramps Up as Market-Share Battle Intensifies,"* The MedTech Strategist, *March 30, 2017*.)

Figure 2

Why is CLI a Challenge?

1. Lack of consensus on definition (no good way to correlate patient types with treatments and outcomes)
2. Lack of awareness within healthcare community and general public
3. CLI morbidity and mortality are akin to the most aggressive cancer diagnoses
4. Limited research (bundled in with peripheral artery disease, underpowered, uncontrolled studies)
5. Lack of consensus on best methods to prevent, diagnose, treat, and rehabilitate
6. Limited number of CLI specialists
7. No diagnosis code for CLI (no basis for correlating treatments with outcomes)
8. Costs for the treatment of CLI are among the greatest healthcare expenditures challenging the US today
9. Even now, in 2017, amputation often remains a first-line treatment

Source: CLI Global (the official publication of the Critical Limb Ischemia Global Society), September 2017

Below the knee, vessels are smaller, lesions are long, diffuse and present in many vessels, and they're often fibrotic and calcified. Clinicians need a variety of tools to drill through them, to navigate through and around them with different antegrade, retrograde, and subintimal access approaches, and they need endovascular devices that do a better job than today's tools, because rates of repeat revascularization procedures in CLI are high.

Nevertheless, new companies are beginning to accept the challenge of offering dedicated devices to the interventional cardiologists, interventional radiologists, and vascular surgeons who treat CLI. For example, **Micro Medical Solutions**, which was founded in 2013, has raised $3.6 million for the development of an integrated system of tools for treating CLI below the knee. Its *Microvascular Integrated Platform* has CE mark approval, and the *MicroBalloon* and *MicroGuide* components have FDA 510(k) clearance in the US. The company's *MicroStent* is currently in an IDE trial.

Mercator MedSystems Inc., discussed below, aims to cut down on the need for repeat revascularization procedures with an adjunctive adventitial drug delivery platform. **Soundbite Medical Solutions**, also profiled below, is advancing a crossing system suitable for chronic total occlusions below the knee. Finally, **LimFlow SA**, with a percutaneous deep vein arterialization system, is entering the space with a strategy of improving the direst situations—CLI patients whose next therapeutic option would otherwise be amputation—by embracing the multidisciplinary nature of the care CLI patients need.

LimFlow Gives "No Option" Patients a New Lease on Life

There are signs that the time has come for investors, payors, and health agencies to focus on critical limb ischemia, and indeed, it's clear that the FDA, for one, recognizes the public health problem the disease represents, and wants to help get valuable treatments onto the market. In September 2017, FDA granted biopharma company **Pluristem Therapeutics Inc.** a Fast Track designation on its cell-based therapy for CLI, now in a Phase III clinical trial in patients facing amputation who have run out of options. On the device side, the equivalent designation, which is referred to as the Expedited Access Pathway (EAP) or Breakthrough Devices Program, was recently granted to endovascular device company LimFlow, for its *Percutaneous Deep Vein Arterialization (pDVA) System*, a minimally invasive system for restoring blood flow to the foot. Both Fast Track and EAP are designed to

expedite the review of treatments for serious conditions and unmet needs.

CLI has proven to be a challenging area for surgical and endovascular therapies. Only 25% of patients experience relief from CLI one year after treatment, even after multiple endovascular procedures such as angioplasty, atherectomy, and stenting, and finally, invasive bypass surgery. Without adequate perfusion, even the most advanced wound care treatments can be ineffective. When CLI patients have exhausted all other options, they face a stark choice: a brief life of immobility and pain, or amputation. Each year in the US and Europe, 160,000 new people join the ranks of CLI "no option" patients (*see Figure 3*). LimFlow is in business to give them a third and better option: an endovascular treatment that restores perfusion to the foot so that wounds like diabetic foot ulcers have a better chance of healing.

LimFlow was founded in 2012. It was one of the first companies of the Paris-based medical device accelerator MD Start, which offers the expertise of two strategics (**Medtronic plc** and **LivaNova**), two venture capital funds (Sofinnova Partners and BPI France), and seasoned medtech entrepreneurs (like Partner/Entrepreneur-in-Residence Tim Lenihan, who has launched many new medical device products over a 28 year career) to shepherd early-stage medical device concepts to the point where they can be handed off to a dedicated CEO and external funding.

The idea for the company's platform came from interventional cardiologist Martin Rothman, MD, now VP of Medical Affairs for Medtronic Vascular, and previously an interventional cardiologist at Barts Health in London, UK. He is an inventor with many patented cardiovascular devices to his credit. (*See "The Future of Cardiovascular Innovation: An Insiders' View,"* The MedTech Strategist, *March 30, 2015.)* Josh Makower of TransVascular Inc. (which Medtronic acquired in 2004) had explored, several years earlier, cardiac venous arterialization—the process of using a vein on the heart to carry arterial blood, with a percutaneous connection technique to connect artery and vein.

TransVascular's technique was not successful in reliably achieving myocardial perfusion. But when Martin Rothman sought to create a reliable revascularization technique for CLI patients that couldn't benefit from other interventions, he recognized the potential of percutaneous deep arterialization to play an important role below the knee in increasing limb salvage rates.

MD Start thus helped found LimFlow based on Rothman's original development work, with Tim Lenihan as acting CEO and funded by early-stage investment from MD Start and a private investor. BPI France invested subsequently: to date, the company has raised €19.4 million, or approximately $22.8 million.

After completing preclinical studies, Lenihan and Rothman enlisted a vascular and endovascular surgeon focusing on CLI—Steven Kum, MD, at the Changi General Hospital in Singapore—who led a seven-patient pilot study in "no option" CLI patients. The results were promising: 100% procedural success, no deaths at 30 days, complete wound healing in four patients at six months (and five at 12 months), and limb salvage rates of 85.8% at six months and 68.5% at 12 months.

These encouraging results were achieved in people who were classified as "high risk" patients using the WIfI (Wound Ischemia foot Infection) clinical classification and were facing certain amputation within a one-year timeframe. The successful first cohort of patients led to a Series A financing round in September 2014, supported by a private investor, to help the group finalize the system and prepare a CE mark submission.

Figure 3

Situation Critical

The impact of critical limb ischemia on patients and payors.

- 3.2 million worldwide suffer from critical limb ischemia
- 25% of patients with CLI will undergo amputation, but that number rises to 50% for "no option" CLI patients
- 160,000 new "no option" CLI diagnoses each year (US and Europe)
- Once amputated, $794,000+ Lifetime Direct Healthcare Costs per patient, and 19+ hospital admissions per year

Source: LimFlow SA

Dan Rose joined as CEO in 2016 (his credentials include executive positions at the transcatheter valve company Direct Flow Medical; Sequana Medical, the developer of an implantable fluid pump; and eight years in leadership roles in cardiovascular businesses at Medtronic). When Rose joined, he says, "The CE mark trial was completed and the CE mark was anticipated in the next month. All this work had been done on only €3.5 million, which is incredible for a Class III device." Rose's first job was to build the team, and he brought in 14 people, four in the US and ten in Europe. CE mark was achieved in November 2016 and commercialization began in Europe in January 2017.

LimFlow's *pDVA* system is a fully percutaneous system for patients

suffering from untreatable disease of the arteries below the knee, which reroutes arterial blood through a leg vein in order to restore blood flow. The company has developed a platform of devices designed to get the vein to do something it ordinarily wouldn't do. Arteries carry blood at high pressure to end-organs; low pressure veins carry deoxygenated blood back to the heart and have valves to prevent blood from going in the wrong direction.

To illustrate the concept of LimFlow's *pDVA*, Rose says, "Suppose you're at a standstill in the southbound lane of traffic, and looking over the median barrier, you see that the northbound lane is empty. You think 'why can't I just cross over and get where I need to go?'" Obviously that part of the highway runs in the wrong direction, and the situation is the same for veins and arteries, which carry blood in opposite directions. The *pDVA* system is able to use one of the tibial veins to send blood south, as it were. "We are essentially crossing from the arterial side into the venous side, and pushing blood down through the venous system to provide oxygenated blood where otherwise it can't be supplied, because the arterial side of the vascular tree is heavily diseased."

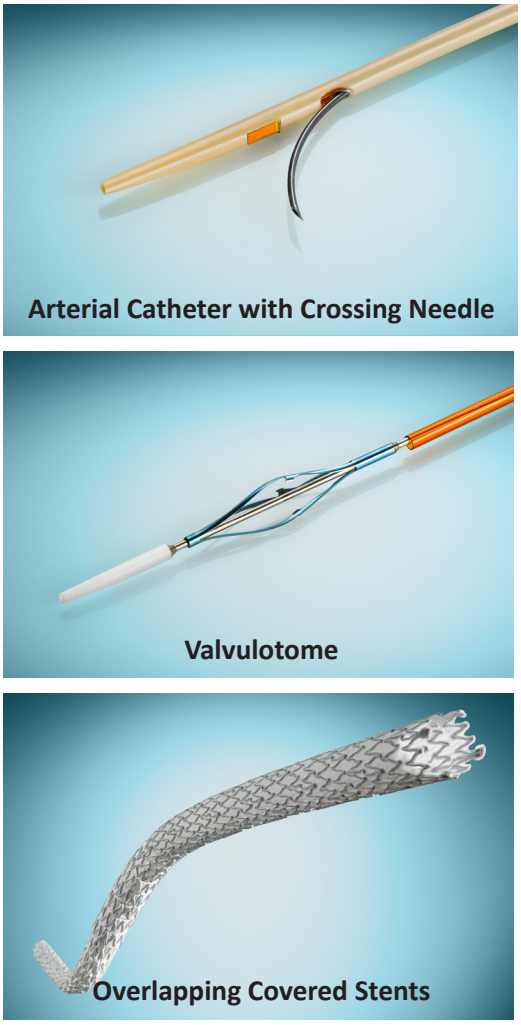
The procedure begins with a small puncture at the ankle to advance a venous ultrasound catheter into the tibial vein. Next, by way of a standard groin puncture, an arterial catheter bearing an ultrasound cathode on its tip is advanced down the tibial artery to the point of the blockage. When the tips of the two catheters (one in the vein, the other in the artery) are aligned, which can be confirmed by fluoroscopy, the ultrasonic signal is used to help orient a hollow crossing needle from the artery into the vein. A micro guidewire is passed through the needle, and a low-profile dilatation balloon catheter is used to slightly predilate the crossing area. A valvulotome is passed into the vein, which is a small flexible basket with inside facing tiny hooks that cut the vein's valves, so they don't interfere with blood flow. While valvulotomes exist for other venous applications, Rose notes that LimFlow offers a "push" valvulotome that is unique and patented (*see Figure 4)*.

Next, a self-expanding covered stent is deployed in the vein, covering the route to the ankle to direct venous blood in the "wrong" direction (to the foot, that is) while blocking off collateral veins that would otherwise take blood back to the heart, in order to prevent loss of pressure and perfusion.

Finally, a tapered covered crossing stent is advanced through the artery and joins with the covered stent in the vein, creating an arteriovenous fistula (AVF). The route is now clear for blood to flow to the foot.

Figure 4

Percutaneous Deep Vein Arterialization System



Source: LimFlow SA

Rose says he's been present at procedures where a foot wound would suddenly begin to bleed after the deep vein arterialization, which might not sound like a good thing, but it's a heartening sign for clinicians that they've succeeded in restoring perfusion. As noted, the native vein is suited for low-pressure blood flow, and it takes some time for maturation to occur (a term borrowed from hemodialysis, where AVFs are commonly created), that is, for the vein to thicken and adapt to high pressure, which happens in about two or three weeks.

The company's US feasibility trial studying ten "no option" patients is just about complete. Rose expects to submit for approval to conduct a pivotal trial before the end of the year and hopes to begin that trial in the second half of next year, in order to support FDA approval.

LimFlow is also about to start a 50-patient study in Europe, following the same protocol that the company will submit in the US, in order to create what Rose says is "a very large, well-controlled and diligent dataset that we can pool for analysis, whether for regulatory or reimbursement purposes." The company is being as rigorous as possible in these studies. For example, the "no option" status

of patients it recruits must be confirmed by an external independent vascular surgeon on a CRO committee.

Revascularization Is Only Half the Battle

"Our goal as a company is to look beyond a great angiogram," says Dan Rose. "While we must have a great revascularization procedure, and we have had great success doing that, as a company what drives us is the clinical objective of healing the wound and that can take up to three or four months."

That's important, Rose notes, because the vast majority of amputations occur because of infection. "Our goal is to close that window for infection. If the wound itself is closed and the skin is healed, then we will reduce the likelihood that the patient will get an infection that leads to an amputation."

That is the point of treating CLI in the first place, but it's also how payors look at things these days. Patients with critical limb ischemia are already undergoing multiple procedures for revascularization and wound care. "Just adding another interventional procedure isn't creating value. Payors want to see that we have a material impact on the healing of wounds, because wound care costs a lot of money, and we also avoid amputation, which also costs a lot of money." And amputation doesn't put an end to wound care either, says Rose. "You have just created a new wound at the stump." The lifetime cost of caring for a CLI patient following amputation is more than $794,000, in terms of direct healthcare costs, including more than 19 hospital admissions per year. The benefits of limb salvage are clear.

Indeed, says Rose, the cost of the LimFlow *pDVA* system will be incidental in the larger scheme of what's going on with a CLI patient. "If you spare an amputation, you are saving all kinds of money, $50,000 in the first 30 days alone. If you look at the cost of the amputation surgery, extended hospitalization, prostheses, rehab, wound care, it is a very expensive event and all that event has done has bought you a ticket to a terrible prognosis," with post-amputation mortality rates of 40% at one year and 80% at five years for patients with both diabetes and peripheral artery disease.

Thus, the company is very focused on working with sites and the community to promote a multidisciplinary approach to wound care, integrating the vascular surgeon, the podiatrist, the wound care specialists, the diabetologist—all the clinicians who care for the patient who has non-healing wounds due to critical limb ischemia. "It's a little bit different from the normal interventional mentality that says 'We've got good blood flow, we're done.'"

Studies have shown that a team approach to limb salvage results in reductions in amputation rates as high as 83% (according to studies cited in "Limb salvage versus amputation: a closer look at the evidence, costs and long-term outcomes," Mario Ponticello *et al, Podiatry Today*, Volume 29, Issue 3, March 2016). "This is the direction CLI is going. It [a team approach] really doesn't cost more, it's a matter of getting the relevant physicians to look at the patients together, rather than operating in silos. In those cases, limb salvage rates are much higher."

LimFlow has a wound care expert on its team with over 15 years of experience from Smith & Nephew, who calls on the wound care staff in LimFlow sites to communicate, "Hey, we are doing this procedure on the interventional side. You need to be aware that the patient is coming over and his foot is going to look and act a little bit differently than before, and here is the interventionalist you should speak to if you have any issues," says Rose. "We are simply creating the connections, because wound care speaks a different language than interventional cardiology."

Right now, the coordination amongst these disciplines is not great, says Rose, who adds, "There is a tremendous business opportunity for a company that wants to focus on this CLI opportunity between wound care, intervention, and vascular surgery, because of the immense resources that go into these patients. There is a big opportunity to present product portfolios, purchasing patterns, and to track and deliver value to the healthcare system through coordination." LimFlow is at the cutting edge of this trend.

Mercator MedSystems: The Efficiencies of Adventitial Drug Delivery

Mercator MedSystems was founded in 2000 to develop *Bullfrog*, a percutaneous microinfusion device able to deliver drugs into the adventitia and tissue surrounding an artery. It's a platform technology with a lot of potential applications—for a time, it bubbled up to the surface for being able to deliver neuromodulators for renal denervation—but has since been solving unmet needs in peripheral vascular disease, most recently in critical limb ischemia.

Bullfrog is a catheter-based technology that can be advanced through the femoral or other artery (the smallest version can access the pedal artery in the foot) to a disease target for drug delivery. Once at the site, the operator inflates a balloon in order to unsheathe a microneedle that, at 34 gauge, is just about as small as a hollow needle can be, says CEO Trent Reutiman. The needle is inserted through the vessel wall and parked in the tissue surrounding the vessel (beyond the external elastic lamina). The interventionalist delivers a puff of drug that is mixed with contrast agent so the correct positioning can be confirmed on fluoroscopy, and if all looks well, drug is delivered (*see Figure 5*).

Reutiman notes that drug diffuses perhaps 2-3 centimeters longitudinally as well as circumferentially around the vessel, with just one needlestick and one microinfusion. "You get that efficiency of drug delivery because you are delivering into a soft and homogenous tissue, which provides a good reservoir for the drug. Additionally, this is the only technology that provides for diagnostic visualization confirming targeted delivery."

Mercator aims, by the delivery of appropriate drugs to a target vessel following a revascularization procedure, to improve the patency and durability of revascularization and cut down on the need for the repeat procedures that cause CLI patients to be known as "frequent fliers" in the healthcare system. In three quarters of CLI revascularization cases, restenosis occurs within three months.

For peripheral artery disease and CLI, the company's current choice of drug is the generic steroid dexamethasone, which, says Reutiman, is not cytotoxic like the paclitaxel used on drug-coated balloons and drug-eluting stents. "We hope to show that with a more targeted delivery technology, and a less toxic, upstream-targeted drug—upstream of cell proliferation and targeted at inflammation, that is—we can improve the efficacy of mechanical revascularizations." The use of dexamethasone is the first of Mercator's efforts to add durability to the outcomes in CLI by localized drug delivery.

In October 2017, Mercator announced that it had completed enrollment in LIMBO-ATX, a prospective, multicenter, randomized pilot study that's trying to determine the extent to which dexamethasone infused via *Bullfrog* in critical limb ischemia patients enhances the outcomes of conventional atherectomy-based revascularization procedures. The study enrolled more than 100 patients with arterial obstructions below the knee. George Adams, MD, director of cardiovascular and peripheral vascular research at the University of North Carolina, Chapel Hill, and Don Jacobs, MD, at St. Louis University in Missouri, are national co-principal investigators.

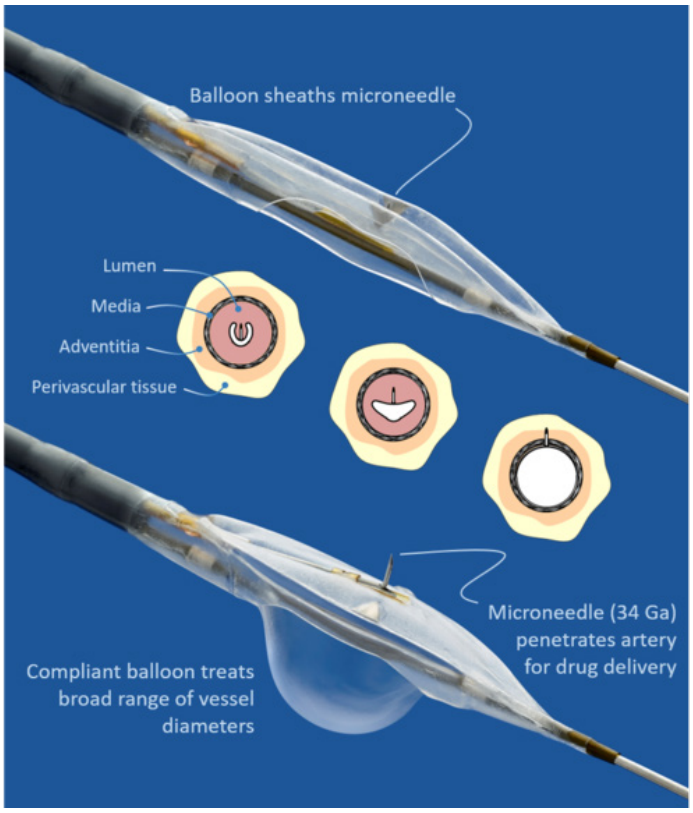
LIMBO-ATX' primary endpoints will be measured angiographically, with transverse-view vessel loss percentage (TVAL) at six months, along with rates of amputation and the need for additional revascularization procedures. The control group will receive atherectomy (with or without angioplasty) but no drug. Six-month results will be available in the second quarter of 2018.

This study follows on Mercator's prior above-the-knee study called DANCE. The primary endpoint of DANCE, which was achieved in early 2017, was one-year primary patency rates in two interventional arms: angioplasty plus the microinfusion of dexamethasone by *Bullfrog* (124 limbs), and, in the other arm, atherectomy and the *Bullfrog* dexamethasone infusion (159 limbs). Thirteen month results reported in 2017 showed a result similar to drug-coated balloons, with primary patency rates of 79.6% in the atherectomy group and 76.2% in the patients who underwent angioplasty. The investigators reported freedom from clinically driven target lesion revascularization of 90% for atherectomy and 89% for angioplasty. The trial sets the stage for the adjunctive use of *Bullfrog* with dexamethasone in both balloon-based procedures and atherectomy above the knee.

As for the below-the-knee treatment, as noted, no drug-coated balloons are yet approved for BTK applications in the US, and if *Bullfrog* proves to be a useful adjunct to atherectomy, it may get to that market before DCBs do.

Figure 5

Bullfrog Micro-Infusion Device



Source: Mercator MedSystems Inc

An Enabler of Combination Drug Strategies

Mercator MedSystems is also studying the adventitial delivery of *Torisel* (Temsirolimus, from **Pfizer Inc**.) for applications below the knee. In April 2017, the company began enrolling in TANGO, a prospective, multicenter, randomized, dose-escalation trial recruiting

approximately 60 patients who have CLI related to arterial obstructions in BTK arteries. *Torisel* will be delivered into the tissue after balloon angioplasty or atherectomy. The study will be the first in the US to look at the local delivery of a limus agent without an implant in lesions longer than 5 cm.

The company has been creating a case for the efficiency and efficacy of its device in many different scenarios, demonstrating the flexibility it enjoys because the drug is not married to the device; the microinfusion platform is capable of delivering any number of small molecule and biologic drugs, says Reutiman.

If drug-coated balloons come to market for BTK applications, *Bullfrog* might enable a combination drug strategy—an anti-proliferative paclitaxel on the balloon, plus microinfusion of an anti-inflammatory drug. Or it might offer the benefit of a limus or a combination of a limus and an anti-inflammatory agent, both delivered by the *Bullfrog* to atherectomy or angioplasty procedures, since that strategy might be more economically efficient and more effective than a DCB. "Our drug delivery is not tied to the shape of a drug-coated balloon or a stent. With one device, you can make a series of microinfusions without having to resort to multiple DCBs or stents." Reutiman notes that the LIMBO trial has recruited patients with lesions up to 25 cm in length. "I would estimate that the vast majority of the time we are able to treat those with just one device."

Mercator MedSystems also continues to work in cardiac disease, and its *Bullfrog* platform is being used by cell therapy company **Athersys Inc.** in its myocardial infarction program, which is currently in clinical trials. Indeed, the ability to deliver biologics is particularly interesting in critical limb ischemia, because biopharma strategies here are focused on regenerative medicine. Cell therapy companies operating in CLI include Pluristem Therapeutics, as noted, as well **Hemostemix Inc.**, **Caladrius Biosciences**, and **VESSL Therapeutics Ltd.** In gene therapy, **Juventas Therapeutics** is in a Phase II exploratory study in critical limb ischemia patients.

Finally, points out Reutiman, since the device is agnostic as to the drug it delivers, it might provide the platform for precision medicine in critical limb ischemia. "We might be able to show that in some sub-groups of patients certain drugs, like anti-inflammatories, work better. Or an anti-proliferative drug works best in another type of patient. Or a combination of drugs in yet a different patient group. We might be able to deliver on the long-term promise of the personalization of medicine."

Of course, each of these myriad applications requires clinical studies and the resources to fund them. To date, the company has advanced by taking in incremental funding, supported by each positive clinical trial. But Reutiman, who joined as CEO in 2014, leaving stent company IDEV Technology after its acquisition by Abbott Laboratories, is ready to pick up the pace. With the move to BTK therapy and the continual arrival of new opportunities where microinfusion provides a more efficient delivery method, Reutiman says Mercator MedSystems continues to lay out robust clinical development plans. "I think we are in a good position to accelerate the clinical development of solutions for large unmet needs, building a very good return for investors," he says.

> ***"We might be able to deliver on the long-term promise of the personalization of medicine."***
>
> ***—Trent Reutiman, Mercator MedSystems***

Soundbite Medical: Crossing Into New Territory

Up to 40% of patients with symptomatic peripheral artery disease have chronic total occlusions (CTOs), which are complete or almost complete blockages of an artery that has persisted for more than 30 days. If left untreated in peripheral arteries, lack of blood supply to the lower half of the extremity may result in amputation. CTOs are often fibrotic and heavy calcified and specialized devices have been developed to open them up, but heavily calcified lesions still remain a roadblock and account for the high failure rates of revascularization procedures. This is particularly true below the knee, where vessels are small and calcification is diffuse.

In recent years, several CTO crossing devices from major manufacturers have been introduced for BTK applications, including the *Crosser* from CR Bard, *TruePath*, from **Boston Scientific Corp**., *Kittycat*, from **Avinger**, and *Viance* and *Enteer*, from Medtronic. Now, Canadian start-up **Soundbite Medical Solutions Inc.** believes it will offer a novel CTO platform with competitive advantages over predecessors, especially in BTK applications, since its system delivers therapy on a wire (without requiring a catheter) so it's easy to maneuver in small vessels, and its energy source, which is destructive to calcium and not harmful to soft tissue, offers safety advantages.

The scientific founders of Soundbite Medical began their work at the University of Sherbrooke in Quebec. Martin Brouillette, PhD, who is now CEO of the start-up, is an

expert in shockwaves. He (along with his graduate students Steven Dion and Philippe Riel, whom he names as co-founders) was developing a new shockwave lithotripter (to break up kidney stones) and hit upon a novel way to deliver shockwave energy. The project changed direction, however, when, at a scientific conference on shockwaves, a chance conversation set Brouillette on the path of coronary and peripheral artery disease, a large and important clinical target in which unwanted calcium also plays a large role.

There are other medical devices on the market that deliver shockwaves for applications in renal disease or vessel preparation prior to revascularization procedures. Brouillette explains that their shockwaves are generated by a discharge of electricity. "We thought that wasn't the best way to do it, because it is difficult to control and generates a lot of electromagnetic noise."

Such shockwaves are of high amplitude and short duration. But Soundbite generates thousands of low amplitude, short-duration pressure pulses and has found a way to "add" them together, such that the accumulation of short pulses results in a single pulse of high magnitude. "Think of it as an 'acoustic laser,'" says Brouillette. "A laser is very powerful, highly collimated light, but it is produced by the accumulation of many light flashes inside the laser device. We have a similar concept, but in the acoustic realm."

With a research grant from the university as well as some pre-commercial funding (which helped hire medtech consultant Steve Arless, who became the company's first CEO), the team got the technology through proof-of-concept. The first device, which was tested on the bench on CTOs in amputated legs, was a crude guidewire that delivered shockwave energy from its tip. IP was filed, and Soundbite Medical was founded in 2015.

There is one other shockwave company in the vascular space, **Shockwave Medical Inc.** (*See "Shockwave Medical: Cracking the Calcium Code in Cardiology,"* The MedTech Strategist, *March 30, 2017.*) But that company has a different approach. It is focused on vessel preparation, not CTOs, and delivers shockwave energy generated inside a balloon in the lumen of a vessel. Soundbite generates its shockwave pulses using a low-power generator outside the body. It is carried inside the body by a guidewire that looks, feels, and acts like the standard guidewires familiar to interventionalists, and is currently available in two sizes: 0.014" and 0.018".

In Soundbite's system, shockwave energy travels from the extracorporeal generator along the wire to the distal tip, and the tip moves only slightly, but with the force of a jackhammer. The system delivers ten pulses per second, as long as the physician is depressing a pedal. Like a conventional guidewire, it provides tactile feedback, so if the physician suddenly feels a lack of resistance, he can use angiography to see where he is and whether he's crossed the CTO, and stop the delivery of energy, if appropriate.

Asked if there is any danger that the tip of the wire will perforate the vessel, Brouillette notes, "Even though there is a lot of force on the wire, tip displacement is small, on the order of a micron. If it hits something hard, force is applied to the hard surface. But if it hits tissue that is soft and elastic, the tip motion is very short, so it won't break elastic tissue." Brouillette notes that the company has demonstrated that's the case in animal safety studies. And it's just possible that the system might result in fewer perforations than others, he says, simply because the operator doesn't have to use any force to push the device through the occlusion. "The crossing ability is being provided by that jackhammer mechanism of action."

The company has completed its first-in-human studies on 37 patients, which began in December 2016. Procedures have been successful so far, (92% success rate with no adverse events), in both above-the-knee and below-the-knee applications, says Brouillette. The company is in the process of filing for a CE mark, and is preparing for its 100-patient pivotal trial on peripheral CTOs in the US and Canada.

Without clinical data, it's too early to define Soundbite's position in the armamentarium of treatments for peripheral vascular disease, but Brouillette has outlined the potential value proposition for his company's device. As noted, it potentially offers safety advantages because of its selectivity for hard, calcified tissue. It might offer procedural advantages as well if it allows clinicians to enter from an antegrade approach and go right through the CTO without having to cross the subintima, come back at the CTO from a retrograde approach, or resort to re-entry devices. Because these steps complicate some CTO crossing procedures, many clinicians don't do them. "Our understanding of the field is that only 10% of operators attempt it. Because of the assistance that our energy provides, we might be able to democratize the CTO procedure," he says.

Soundbite has also completed development of a system for crossing coronary CTOs and will start first-in-human trials for that application in the first quarter of 2018. Indeed, while we have focused here on the BTK applications that address critical limb ischemia, Brouillette emphasizes that his company has a platform technology. Next, the company will target vessel preparation with a shockwave atherectomy device by incorporating a bundle of shockwave wires into a catheter.

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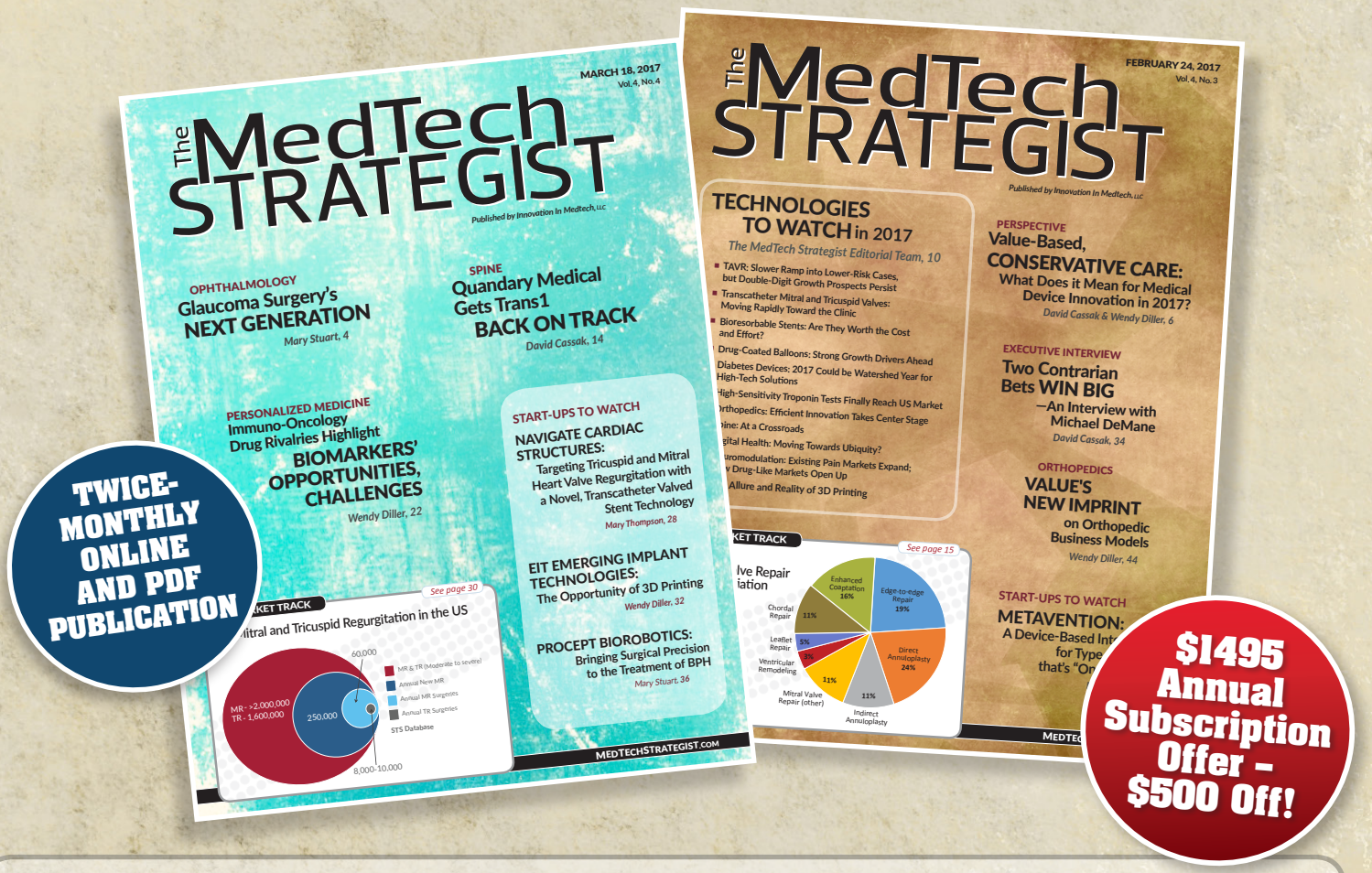

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