CLI GLOBAL COMPENDIUM

THE GLOBAL VOICE OF CRITICAL LIMB ISCHEMIA

How Can Measuring Foot Perfusion Be So Difficult? One Person's Perspective

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In the summer of 1992, I began my first day as a fellow in vascular medicine at the Cleveland Clinic Foundation. Joined by a few other eager graduates of internal medicine residencies, and surrounded by some of the brightest minds in this emerging field, I was both excited and nervous. Finally entering my chosen specialty, being able to concentrate on a field that, as a first- and third-year medicine resident, seemed so poorly understood, with such great opportunities, just seemed like the culmination of a great medical training career.

On July 1, 1992, I received my first consultation as a brand spanking new fellow. I will remember this event as if it were yesterday — not because the patient was so interesting, but rather because of my first real lesson. The patient was a man in his mid 60s with diabetes, on dialysis, who was admitted for volume overload. We were consulted for progressively worsening right-leg discomfort with walking. The patient had been scheduled for an outpatient consultation, but the team felt that they might as well cover this base while the patient was undergoing aggressive dialysis.

To cut to the chase, the patient had multilevel peripheral artery disease (PAD), quite disabling claudication of the right calf, and, if he pushed himself, tightness in the arch of the foot. Over the previous 6 months, his functional ability had rapidly deteriorated, with a pain-free walking distance shortening from 6 blocks to what he now states limits him

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What's Beyond Revascularization for the Rutherford V Patient?

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Critical limb ischemia (CLI) patients who present with Rutherford class V signs and symptoms can be described as suffering a "non-ST-elevation MI of the foot," as tissue loss is still limited but the underlying vascular situation can be very compromised.[1,2] Early, aggressive (and almost invariably) endovascular revascularization is the mainstay of modern treatment for Rutherford V patients,[3,4] and we at our diabetic foot clinic have recently been able to show that among patients who presented in the last 2 years with severe symptomatic ulcers, ischemia is found with a very high prevalence (around 65%). Figures 1-5 depict treatment of one such case.

We are firm believers in a team-based approach and integrated amputation prevention programs for optimal CLI care, and our post-revascularization care for Rutherford V patients, as well as the general approach to CLI, is centered on a multidisciplinary medical and surgical team.[5,6] A high-volume diabetic foot clinic with dedicated personnel and surgical competencies, a daily collaborative interaction with interventional cardiologists (mainly in charge of the endovascular approach), vascular surgeons (mainly responsible for the surgical approach, but also involved in endovascular procedures), infectious diseases specialists, orthopedic surgeons, and radiologists

Francesco Liistro, MD

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Do We Have Enough CLI Devices at Our Fingertips?

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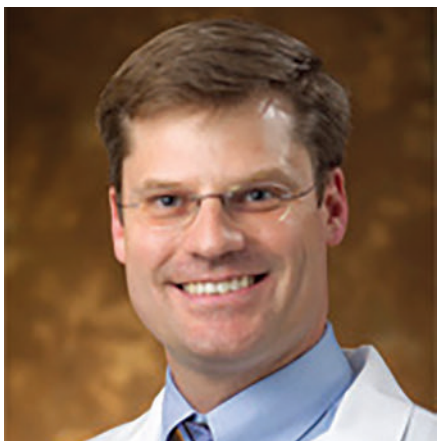

George L. Adams, MD, MHS

Approximately 8 million Americans have peripheral artery disease (PAD), including 12% to 20% of Americans over the age of 65.[1] One to two percent of this population has critical limb ischemia (CLI), defined as peripheral arterial insufficiency causing rest pain and/or nonhealing wounds. CLI can be devastating, with a reported 50% 5-year mortality rate.[2] In fact, 25% of CLI patients at 1 year have undergone amputation while another 25% have died.[3] At 2 years, the mortality for the amputated group is 40%.[3] CLI patients are a high-risk group, typically being older, diabetic, and smokers, and having concomitant cardiovascular and/or cerebrovascular disease, as well as renal insufficiency.[4,5] These are the patients that would derive the greatest benefit from restoration of blood flow to the affected limb, thus preventing amputation. The endovascular approach to restore blood flow has become the preferred strategy not only for CLI patients, but also for PAD patients as a whole. This article focuses on the paucity of devices that effectively address calcified vessels, chronic total occlusions, and below-the-knee disease, all of which constitute the typical phenotype of the CLI patient, along with multilevel arterial involvement.

Calcified Arteries

Atherosclerotic calcification is a significant challenge in the treatment of CLI. Common clinical factors associated with CLI such as diabetes and renal insufficiency increase the risk of calcification of the arterial wall.[6,7] Crossing and treating calcified lesions requires advanced techniques and specialized tools, of which there are only a few available on the market. The problem is compounded as catheters and wires have a tendency to deflect toward the arterial wall, resulting in subintimal entry and perforation while the operator attempts to cross the lesion. Devices that allow the operator to engage the proximal cap and find microchannels (i.e. higher gram tip wires and coil-tipped wires) may allow for a higher procedural success rate.

Once the lesion cap is crossed, the treatment of calcified arteries requires modification of the plaque by atherectomy or other specialty devices in order to reduce the risk of dissection and recoil. Plaque modification is typically followed by percutaneous transluminal angioplasty (PTA). Without plaque modification, balloon angioplasty in calcified vessels is associated with an increased risk of flow-limiting dissections, which may require bail-out stenting.[8] In an unmodified calcific plaque, stenting is less effective because of poor apposition and asymmetric expansion, which may lead to higher rates of stent strut fracture and restenosis. Intraluminal calcium is effectively modified by atherectomy. However, the highest concentration of calcium resides mainly in the medial layer of the arterial wall, where atherectomy devices cannot reach. Recently, drug-coated balloons (DCBs) have emerged as a new interventional tool to reduce rates of restenosis. However, DCBs display the same limitations of other devices when it comes to treating calcified lesions, as the presence of calcium in the medial layer[9] limits the delivery of the antiproliferative drugs to the smooth muscle cells (responsible for the hyperplastic response that leads to restenosis) located in the adventitia.[10] An ideal device would allow us to effectively modify the medial calcium, which in turn would lead to a decrease in arterial recoil and allow the delivery of pharmacotherapies into the medial and adventitial layers.

Chronic Total Occlusions

Treating chronic total occlusions (CTOs) remains a major challenge with reported success rates that vary widely between 34% and 91%.[10,11] The lack of angiographic visualization of the lesion is a significant obstacle in treating CTOs that has led interventionalists to explore retrograde access and transcollateral approaches. Furthermore, the lack of specialized tools for accessing smaller vessels limits the options available to cross and treat these lesions.

While treating CTOs, interventionalists cannot visualize the chronically occluded lesion using standard angiographic techniques, and this inherently increases the risk of subintimal penetration. To

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Beyond Revascularization

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are the foundations of our approach. A podiatrist and two specially trained nurses are essential members of the team.

After angiosome-targeted revascularization is attempted and often obtained,[7] a scheduled follow-up system ensures that no crucial step is missed, with the goal of obtaining complete ulcer healing. The foot clinic team (headed by a diabetologist) coordinates all the aspects of care in this period. A foot clinic visit is invariably scheduled the day after the revascularization, when the patients is still hospitalized, to check for the presence of positive signs of tissue perfusion (post-revascularization edema, hyperthermia, turgid veins) and the absence of negative signs of tissue perfusion (skin whiteness, cyanosis, hypothermia, pain). Usually, at this time, ulcerations or gangrene are not modified from their pre-revascularization appearance.

A second visit with the foot clinic team is generally planned within 1 week, in which, again, positive and negative signs of tissue perfusion are controlled, but also initial modifications of the lesion (such as the appearance of granulation tissue from the bottom or from the borders, the reduction in fibrin coverage and necrosis, or, in case of gangrene, the demarcation of the necrosis plane) are noted. In some cases, nonviable tissue at the bottom of the lesion at this time changes from pink to red (meaning viable) and bleeding is observed. The patient at this time is instructed to report any sign of recurring infection or ischemia.

The third scheduled visit is at 1 month after the vascular procedure, when we perform a new transcutaneous oxygen pressure measurement ($TcPO_2$). During this visit, we again check for positive or negative signs of tissue perfusion and we inspect the lesion and the features of the perilesional tissue. In particular, we search for the integrity of the borders, the absence of maceration and the absence of infection signs in order to schedule and plan the surgical procedure for the foot, respecting foot anatomy and cleavage plans.

In our practice, we generally wait 30 to 75 days (mean of 37±14 days in the last 2 years) after the revascularization procedure to proceed with surgery, which reduces the risk of surgical dehiscence and infection. We usually perform all the minor amputations, like phalangectomy, digit amputation, ray amputation, sequestrectomy, escharectomy, and application of dermal substitute or skin graft, as outpatient procedures. In cases of transmetatarsal amputation, Lisfranc amputation, or Chopart amputation, we prefer to hospitalize the patient for a few days, to ensure strict bed rest.

After surgery we usually evaluate the patient once a week, until surgical sutures are removed (usually at 3 weeks). Each visit includes a routine check for positive and negative signs of tissue perfusion as well as for the presence of infection. After surgical suture removal, if the lesion is completely healed, we check patients every 3 months or more often, depending on general and local conditions. In case of partial healing, but with superficial lesions, we reassess the patient monthly until complete epithelialization occurs.

Patients, relatives, and other caregivers are trained to call our clinic immediately in case of recurrence of pain, discharge, edema, or erythema, and we can ensure a visit within 72 hours. Every time signs of ischemia appear, we plan an intervention-oriented vascular exam within 48 hours, performed by either the interventional cardiologist or the vascular surgeon who will be responsible for any possible reintervention and, in case of restenosis or new vascular lesions, a repeat angioplasty usually is performed within a few days.

In cases of acute deep infection signs (discharge, pus, erythema, edema, pain, dehiscence, abscess or phlegmon) we perform surgical debridement within 24 hours and, after collection of a microbiological sample, we start an empirical broad-spectrum antibiotic therapy. In case of moderate to severe infection, the patient is immediately admitted to the hospital. During the hospitalization, we perform debridement and drainage daily (if needed), until complete resolution of the infection is achieved.

Another factor that could compromise healing is inappropriate pressure relief that can occur at the ulceration site or the surgical lesion. In the last few years, many devices designed to improve pressure relief while walking or resting in bed have been developed to this aim. At every visit, we also ensure that the patient is being compliant with wearing the devices and we reinforce the educational message.

Follow-up is coordinated by a dedicated Foot Clinic, which is run by the endovascular specialists (mainly cardiologists). The goal is to schedule consistent clinical follow-up with a surveillance Doppler ultrasound: all patients are asked to return at 1 month and then every 3 months after revascularization. This dedicated clinic also forms the

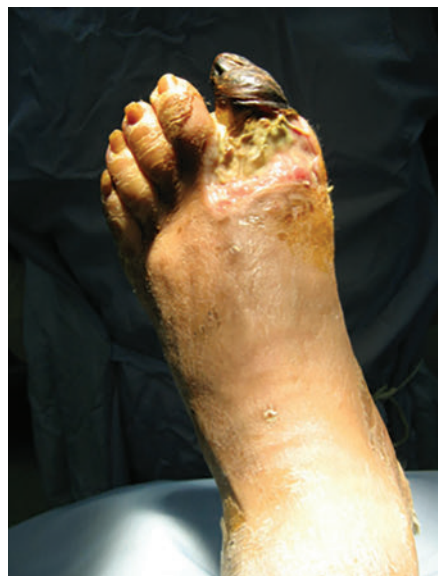

Figure 1. A 65-year-old diabetic patient presents with Rutherford class V claudication in the left limb and a University of Texas Wound Classification System 3D lesion with limited gangrene of the first toe as well as dorsal ulceration at the base of the toe that is partially covered with fibrin. No acute signs of infection exist.

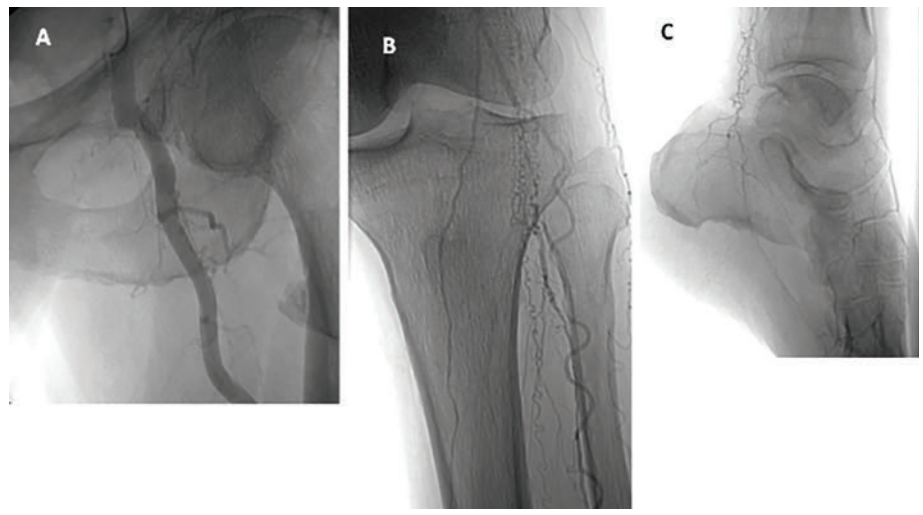

Figure 2. Angiographic anatomy baseline imaging shows ostial occlusion of the superficial femoral artery (A), with partial recovery of flow at the popliteal level and subsequent, severe below-the-knee atheroma with occlusions of the tibioperoneal trunk, anterior tibial artery, posterior tibial artery, and peroneal artery (B). Several collaterals are visible, with indirect flow reaching both the anterior and posterior circulation of the foot (C).

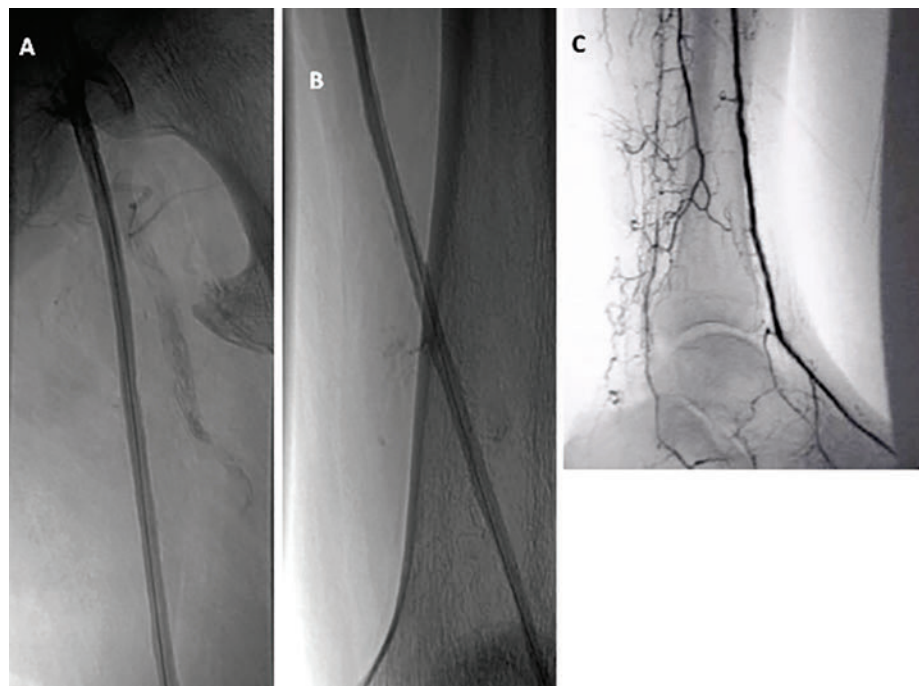

Figure 3. After revascularization, angiography shows that after reopening and ballooning of the superficial femoral artery (A, B), angiosome-oriented revascularization of the foot has been performed, with reopening and ballooning of the entire anterior tibial artery and re-establishment of direct flow to the foot. Peroneal flow has also increased markedly.

We are firm believers in a team-based approach and integrated amputation prevention programs for optimal CLI care, and our post-revascularization care for Rutherford V patients ... is centered on a multidisciplinary medical and surgical team.

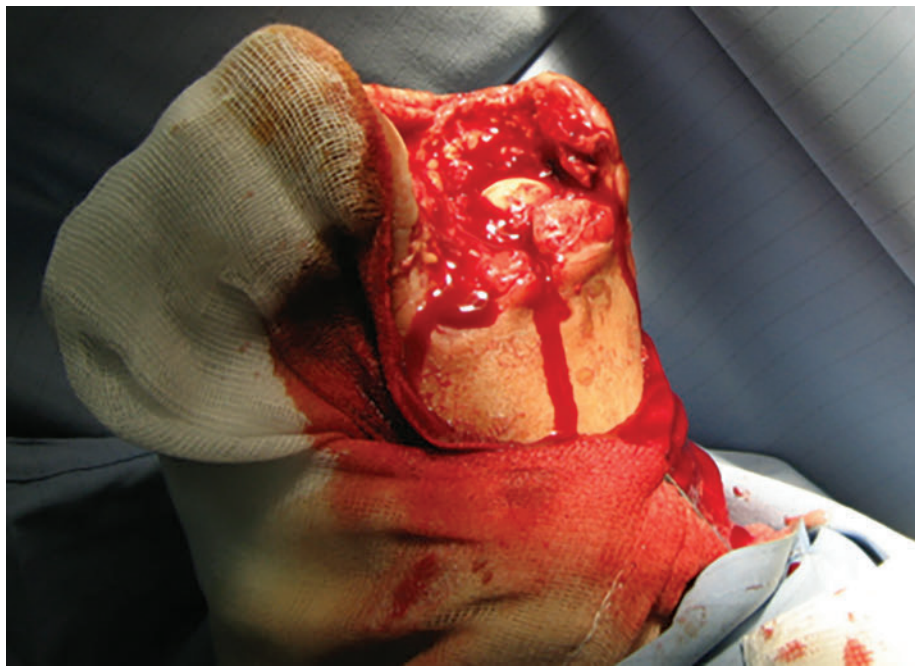

Figure 4. Forty days after revascularization, amputation of the first toe with first metatarsal head salvage has been performed, with debridement of all unviable, necrotic, or fibrinous tissue until active bleeding tissue can be seen. Because of the poor availability of good tissue suturing, we waited for healing for secondary intervention.

backbone of our clinical research activity, which has so far produced several randomized, industry-independent trials that have been published in high-impact journals.[3,4,8,9]

In our experience, this fast-track, team-based approach is linked to a low incidence of major amputations, which remain confined to patients with absence of pedal and digital arteries such as those receiving dialysis.

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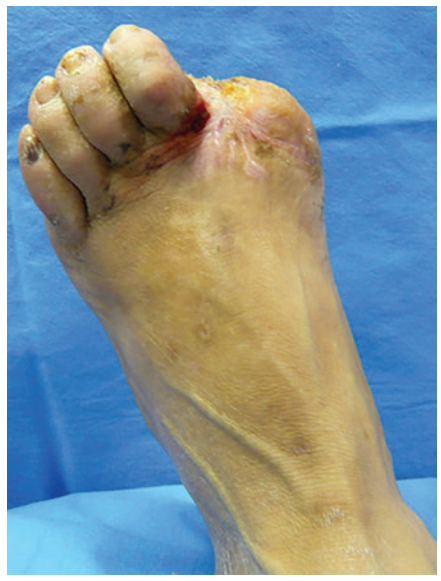

Figure 5. After 60 days of strict follow-up and local wound care, the lesion has completely healed.

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Approach to Tibial CTOs From Access to Crossing: What Are the Best Tools and Modalities?

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Critical limb ischemia (CLI) is related to multilevel and multivessel, diffuse peripheral artery disease with prevalent involvement of below-the-knee (BTK) and below-the-ankle (BTA) arteries.[1] The distribution of peripheral arterial obstructive disease involves the superficial femoral artery (SFA) and/or the popliteal artery in 55% of cases, the tibial arteries in 93% of cases, and the pedal vessels in 71% of cases. Of patients with CLI, 77% present with disease in 2 or 3 tibial vessels, and 50% have disease in 2 or 3 pedal vessels.[2]

Revascularization is the cornerstone of treatment for patients with CLI, with the goal of re-establishing adequate blood flow to the foot.[3,4]

Crossing long chronic total occlusions (CTOs) in the BTK and BTA territories remains challenging and for this reason, a step-by-step algorithmic strategy can be utilized in an attempt to increase success rates. Endovascular revascularization can be achieved by means of endoluminal, subintimal, and retrograde techniques (Figure 1).[5,6]

Technical Modalities and Tools: Antegrade Approach

Ipsilateral antegrade common femoral artery access is the preferred access for treatment of CLI.[5,6] Endoluminal approach is the first choice, and it is the preferred technique in calcified arteries. The preferred wire to start is a soft-tip, 0.018″ or 0.014″ hydrophilic guidewire, such as the V-18 or V-14 ControlWires (Boston Scientific), the Hi-Torque Pilot 200 (Abbott Vascular), the Hi-Torque Command ES (Abbott Vascular), or the Fielder (Asahi-Intecc), in combination with a support catheter or balloon catheter. These wires allow shifting from the endoluminal to the subintimal approach if needed.

In heavily calcified vessels or short CTOs, the endoluminal approach once again is preferred, and the parallel wire technique with dedicated CTO guidewires such as Astato 30 or Astato XS 20 (Asahi-Intecc), Winn 40 to 200 (Abbott Vascular), or Approach CTO (Cook Medical) can be used for this purpose.[5,6]

In long CTOs that are not considered by fluoroscopy to be heavily calcified or that only have moderate and focal areas of calcification, it may be necessary to shift to the subintimal approach if the endoluminal strategy fails.

The subintimal approach can be safely and effectively adopted to achieve a successful tibial and pedal revascularization.[7] It is performed using 0.035″ half-stiff 1.5 J-Tip Glidewire (Terumo) or 0.018″V-18 guidewire in the tibial and pedal arteries, or a 0.014″ Command ES guidewire in the pedal arteries. The wire is supported by a support catheter, such as NaviCross (Terumo), CXI (Cook Medical), and Total across (Medtronic), or by a balloon catheter (Figure 2).

In this approach, the subintimal space is dissected by pushing the guidewire into a small loop shape in front of the support catheter, and both are advanced as a unit to the re-entry point. The re-entry site can be managed in different ways: the looped wire can be pushed toward the patent distal lumen, in cases of a favorable re-entry site (when the patent distal lumen is straight, far from collaterals or away from a potential bypass target, and without calcium).

Otherwise, in order to avoid the risk of damaging the distal patent artery in cases of unfavorable re-entry sites (calcified areas, sites close to a main collateral, or at a patent distal vessel that represents a good bypass target), it is preferred to approach it by using a new hydrophilic or dedicated CTO wire to reach the distal lumen. More recently there has been an increased use of shifting to a retrograde tibiopedal approach in these cases.

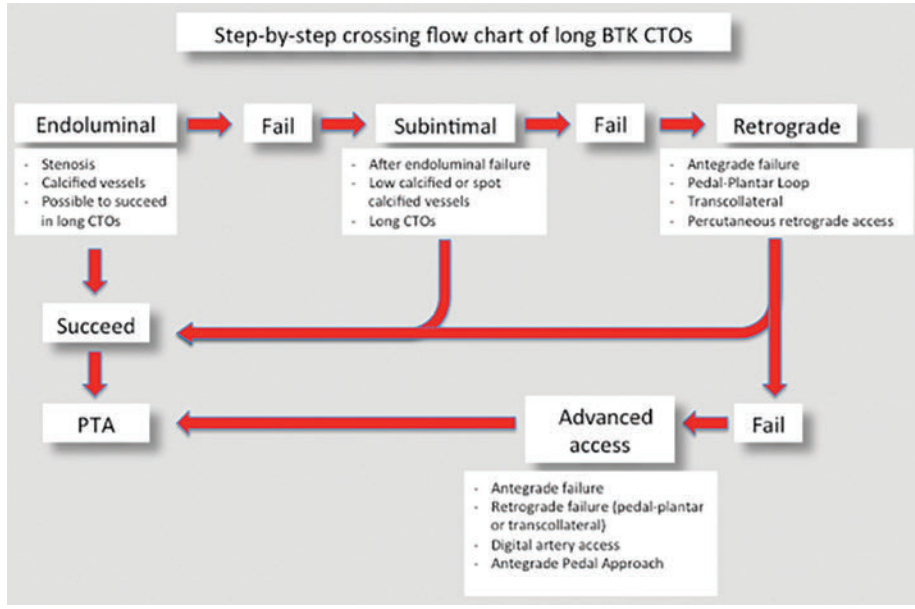

Figure 1. Step-by-step crossing strategies.

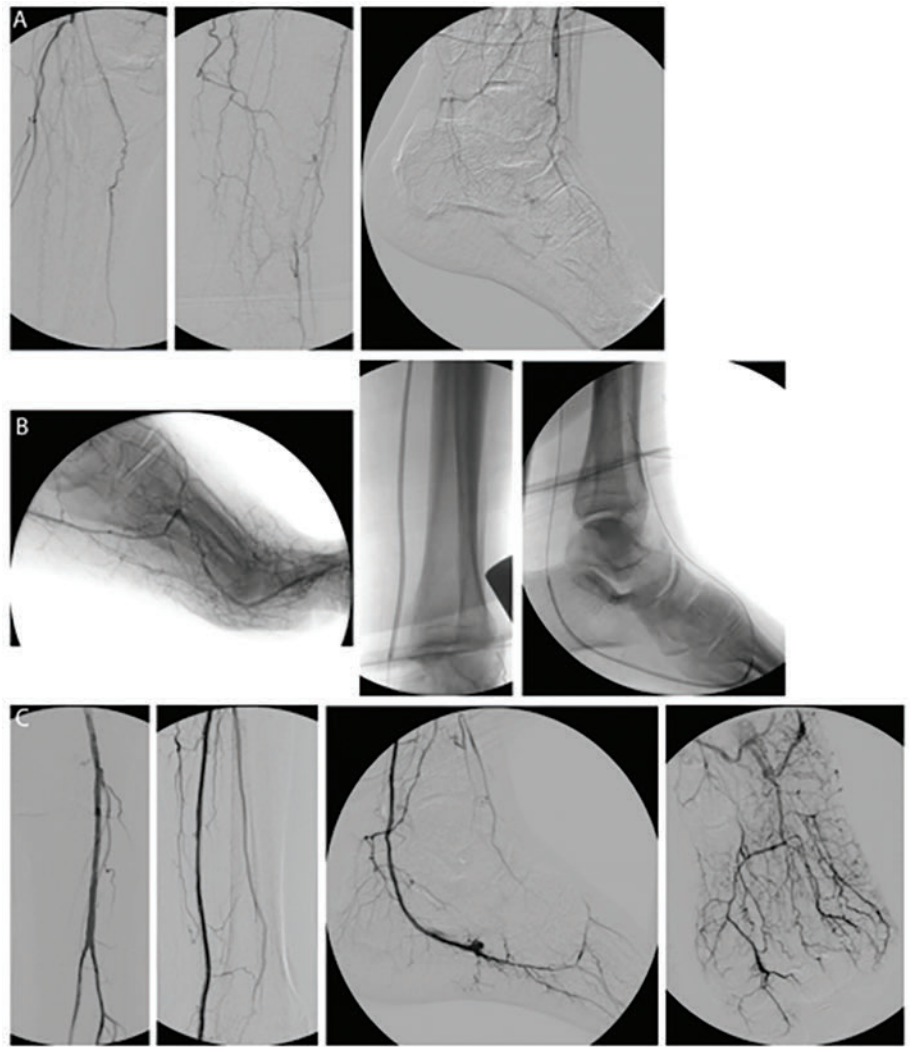

Figure 2. Multilevel and multivessel disease in a CLI patient who presented with wounds on the heel and the fifth toe. Diagnostic angiography shows occlusion of the popliteal artery, occlusion of all tibial arteries, and slow flow through the collaterals in the distal tract of the anterior tibial artery. Occlusion is present in the plantar circulation and dorsalis pedis. The lateral tarsal branch is patent (A). Subintimal recanalization was performed on the posterior tibial (PT) and lateral plantar artery. Super-selective angiography via a 4 Fr NaviCross (Terumo) confirmed re-entry in the plantar arch. Percutaneous transluminal angioplasty was performed to 2.5 and 3 mm of the lateral plantar and PT arteries. Peroneal and popliteal arteries were then dilated (B). Angiographic results showed patency of the popliteal artery, tibioperoneal trunk, and PT and peroneal arteries. Patency was also achieved for the lateral plantar artery and plantar arch with excellent blood flow for the heel and the forefoot (C).

Retrograde Approach

Retrograde recanalization is considered after antegrade approach failure, although some operators are challenging this paradigm by suggesting that this approach should be instituted from the beginning of the case.[8] The options for retrograde approach are detailed in the following sections.

The Pedal-Plantar Loop Technique

The pedal-plantar loop technique aims to restore direct arterial blood flow to the dorsal and plantar circulation of the foot, achieving a complete BTK and BTA revascularization, but it can also be used for crossing through the opposite patent circulatory pathway to obtain a retrograde recanalization of the occluded tibial or pedal vessel. It is based on the wiring and balloon tracking through the plantar arch, creating a loop from the dorsal to the plantar (or vice versa) pedal circulation (Figure 3).[9] It provides a high rate of acute success, achieving adequate angiographic results without periprocedural complications.[10] The pedal-plantar loop technique is usually performed combining endoluminal and subintimal approaches, using the previously described devices. It is important to avoid damaging the plantar arch by using low-profile and 0.014″ platform devices to cross the arch.

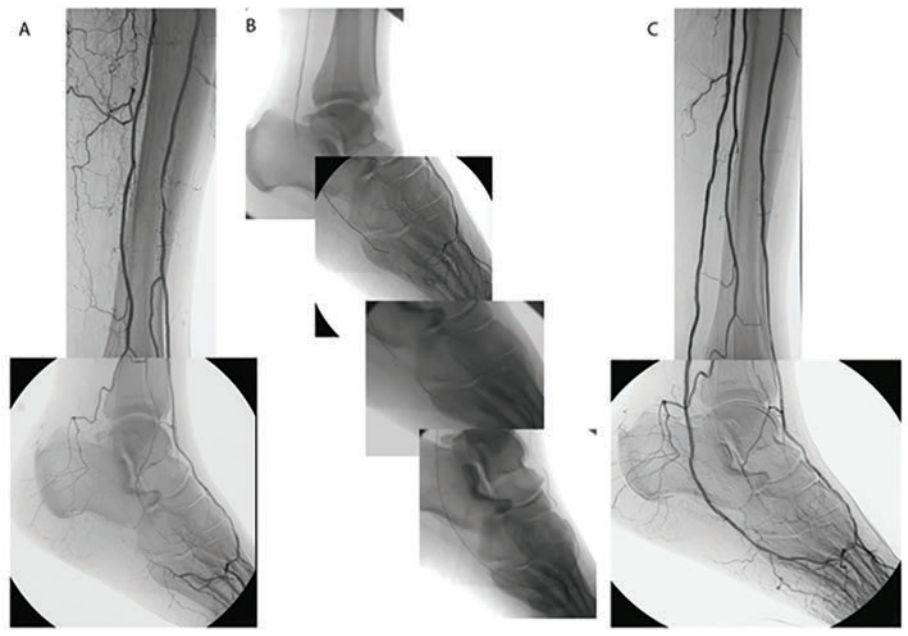

Figure 3. In this example of pedal-plantar loop technique, diagnostic angiography shows occlusion of posterior tibial (PT) artery and stenosis of anterior tibial (AT) artery, as well as occlusion of lateral plantar artery (A). Subintimal recanalization of PT and lateral plantar arteries failed re-entry in the plantar arch. Antegrade crossing was performed of the AT and dorsalis pedis arteries and the plantar arch, followed by retrograde subintimal recanalization of the distal lateral plantar artery. This image shows antegrade wiring of the lateral plantar artery, plantar arch, and dorsalis pedis, after re-connection of dorsal and plantar circulation (B). Angiographic results depict patency of AT, PT, and peroneal arteries. Patency of dorsalis pedis, lateral plantar artery and plantar arch are visible (C).

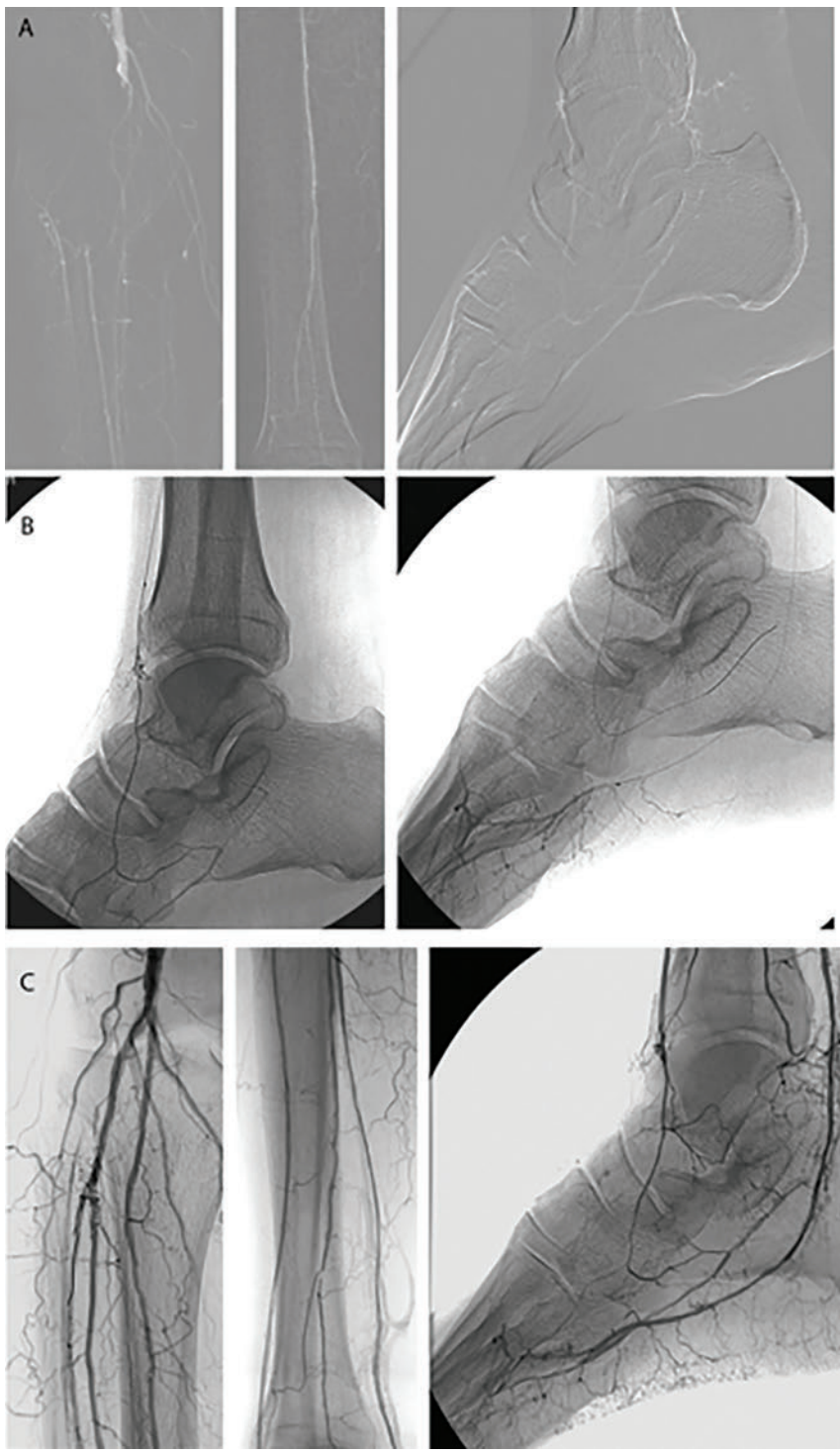

Figure 4. In this example of the transcollateral technique, CO2 angiography shows occlusion of P2 and P3, occlusion of the anterior tibial (AT) artery, the posterior tibila (PT) artery, and the tibioperoneal trunk with patency of the peroneal artery only. There is patency of the lateral tarsal branch, medial plantar artery, and the "deep arch" (A). The origin of the PT could not be found, so antegrade recanalization of the AT, wiring of the deep arch, and retrograde recanalization of the PT artery was performed, followed by antegrade wiring of the PT artery, lateral plantar artery, and plantar arch (B). Angiographic results show patency of the popliteal artery with anatomical variation and high origin of PT through the P2 segment. Patency is visible of the AT, PT, tibioperoneal trunk, and peroneal arteries. Angiography also shows patency of the lateral tarsal branch, medial plantar, and lateral plantar arteries as well as the plantar arch (C).

Transcollateral Recanalization

The transcollateral approach involves using the natural anastomoses to recanalize tibial and pedal arteries.[11,12] Different anastomoses can be used. The deep pedal arch, which communicates the medial plantar artery with the lateral tarsal branch, can be used to recanalize the dorsal or plantar circulation, or as a conduit to reach the pedal arch, through the tarsal branch (Figure 4). Distal peroneal artery branches (anterior and posterior communicating arteries) can be used to reach the distal anterior and posterior tibial arteries respectively. The imperative is to avoid damaging the collateral circulation during crossing. Low profile and 0.014″ platform devices are preferred for this purpose.

Retrograde Percutaneous Puncture

The retrograde percutaneous puncture technique consists of a percutaneous puncture of the distal patent vessel followed by retrograde recanalization, with the aim of reaching the proximal patent lumen of the target vessel.[6]

The steps for retrograde access are as follows:

1. **Choice of puncture site.** Accurate angiographic evaluation using the correct radiologic projection is necessary. In specialized centers, ultrasound guidance has been used with reported success.[13]
2. **Spasm avoidance.** Vasospasm can compromise the puncture and wiring of small vessels, therefore pharmacologic support is essential. The use of a vasodilator (nitroglycerin, verapamil) is mandatory.
3. **Puncture technique.** The puncture is performed with a 21-gauge, 4 cm needle such as the Micropuncture Set (Cook Medical) under fluoroscopic guidance with contrast medium injection and at maximum magnification, or under ultrasound guidance.
4. **Retrograde crossing strategy.** An 0.018″ guidewire, such as the V-18, is preferred, because of the enhanced support it provides. The guidewire is used in combination with a low-profile support catheter such as the CXI (Cook Medical).
5. **Reconnection with the antegrade approach.** After retrograde crossing of the distal cap of the occluded vessel, the goal is to reach the proximal patent arterial segment, in order to perform the rendezvous with the antegrade catheter. After reversal of the retrograde access, treatment is delivered and final hemostasis is obtained by advancing a balloon catheter beyond the puncture site and inflating it to nominal pressure.

Advanced Access

For further improvement in success rates of angioplasty in challenging BTK and BTA cases, a novel revascularization technique has been created.[14,15] When tibial or pedal arteries are occluded and

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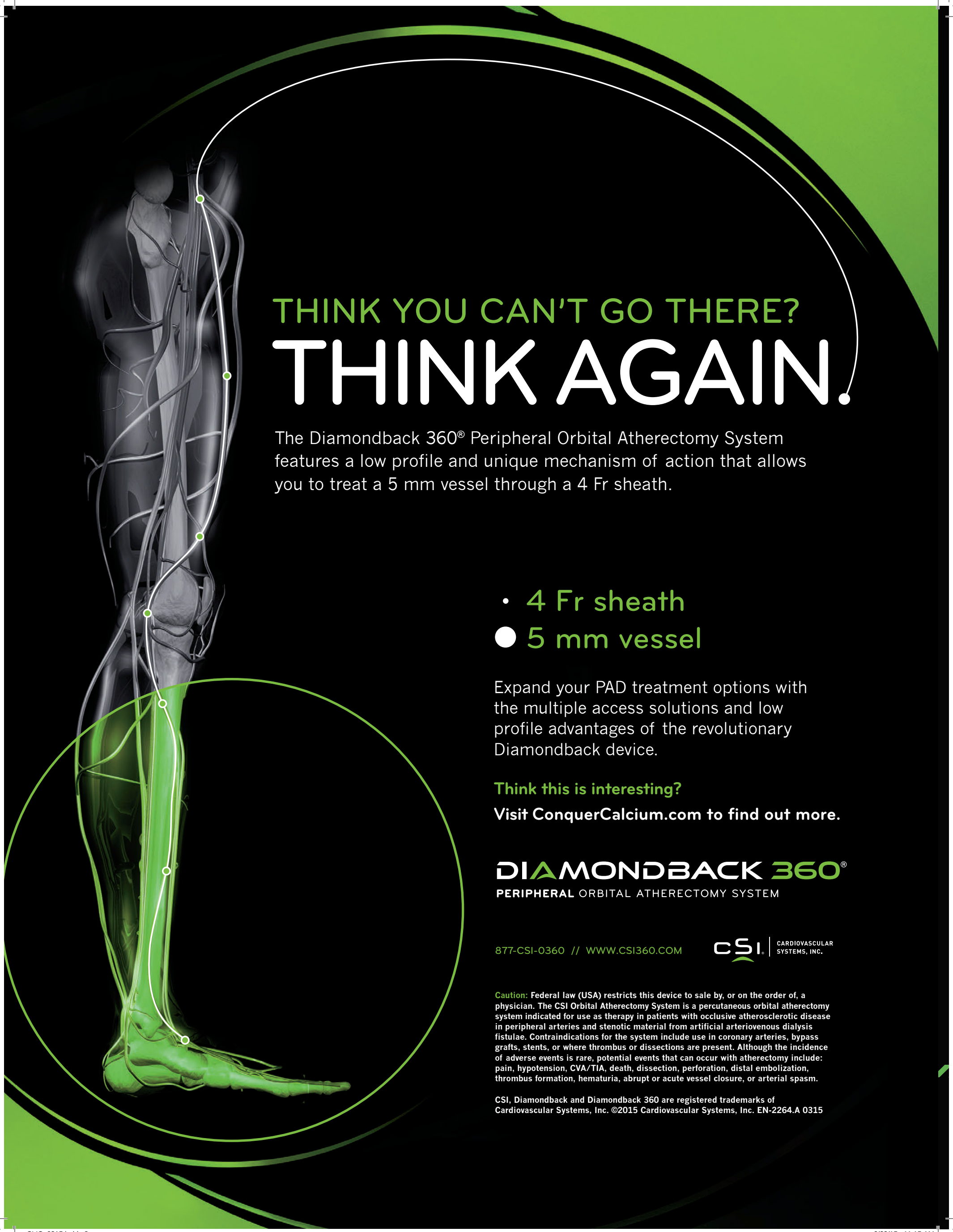

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Drug-Coated Technology in CLI: Will the Promise Deliver?

A look at the potential for drug-coated balloons to improve outcomes in critical limb ischemia patients and the limitations that must first be overcome.

J.A. Mustapha, MD, FACC, FSCAI
From Metro Health Hospital, Wyoming, Michigan.

J.A. Mustapha, MD, FACC, FSCAI

Despite technical success rates of 95% with the use of conventional technologies for the treatment of femoropopliteal lesions, restenosis rates as high as 65% have been reported within a year of follow-up. Recent studies have provided robust evidence to support the use of drug-coated balloons (DCBs) to achieve significant improvements in the durability of positive outcomes obtained with endovascular treatments in the femoropopliteal segment, leading to a unanimous approval by the FDA and the introduction of the Lutonix DCB in the United States in October of 2014. However, DCBs are not perfect as they exhibit the same limitations as their traditional predecessor, plain old balloon angioplasty.

Current Limitations to DCB Techniques and Technology

Limitations include elastic recoil, negative remodeling, dissections and perforations (requiring bail-out stenting), and the inability to treat heavily calcified, "undilatable" lesions. Additionally, DCBs exhibit particular limitations related to the ability to transfer paclitaxel from the balloon surface to the medial arterial layer, which requires an excipient (currently only 10% to 20% of the active drug is transferred into the vessel wall), while at the same time keeping the drug attached to the balloon surface while it is being introduced into the body and placed in the desired treatment area.

The available drug-excipient coatings are unable to achieve the ideally desired level of persistence on the balloon surface during DCB insertion through the sheath and advancement to the target lesion, as well as during balloon expansion. As a result, there is an unavoidable and unintended delivery of the drug downstream into the distal tissues located beyond the target lesion, which could carry uncertain consequences to the wounds of patients with critical limb ischemia (CLI). This has been postulated in the IN.PACT DEEP trial, which had results that turned out to be negative (there was no difference in primary patency rates and a higher, although not statistically significant, amputation rate in the DCB arm) despite two initial successful single-center studies (including the randomized DEBATE-BTK) using the same DCB device.[1]

Two reasons have been postulated to explain the difference in outcomes. The Amphirion DCB (Medtronic) used in IN.PACT DEEP was manufactured differently from the Pacific and the Admiral DCBs (Medtronic). The Amphirion DCB received the drug coating in the deflated state, where as the Pacific and Admiral balloons were exposed to the drug coating in the inflated state. When this happens, most of the drug is preferentially localized between the balloon folds after the coated balloon is deflated and refolded, protecting the drug against the "wipe-off" phenomenon. Also, the polymer materials utilized in the manufacturing process of the balloons are different and therefore have different drug adherence properties.

Attempts to Overcome Limitations

In an attempt to overcome these limitations, multiple potential excipients, drug microspheres, and polymer-like coatings are now under investigation in order to improve DCB outcomes. A different DCB (Lutonix 14, Bard Peripheral Vascular Inc.) is being investigated for below-the-knee (BTK) interventions in patients with CLI, as part of the randomized Lutonix BTK trial. Multiple studies have been launched in Europe, such as EUROCANAL and PICCOLO, but results are not yet available. Also, other balloons such as Dior, Freeway, and Genie (Eurocor) are suitable for potential BTK applications.

The Atherectomy and Drug-Coated Balloon Angioplasty in Treatment of Long Infrapopliteal Lesions (ADCAT) study is looking at an alternate approach to BTK disease by investigating the impact of upfront directional atherectomy before DCB angioplasty compared to DCB alone using the Lutonix 14 DCB. The premise behind the study is the hypothesis that preparation of the vessel bed might improve treatment outcomes of DCB angioplasty and the biological efficacy of the antiproliferative drug by removing the barrier that the omnipresent

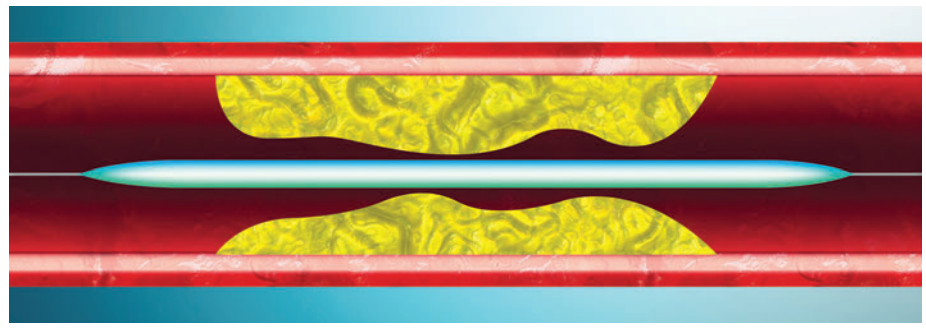

Figure 1. Plain balloon angioplasty positioned in a high plaque burden stenosis to prepare the lesion for DCB delivery. Note that the balloon covers the longitudinal length of the lesion with slight extension proximal and distal to the plaque.

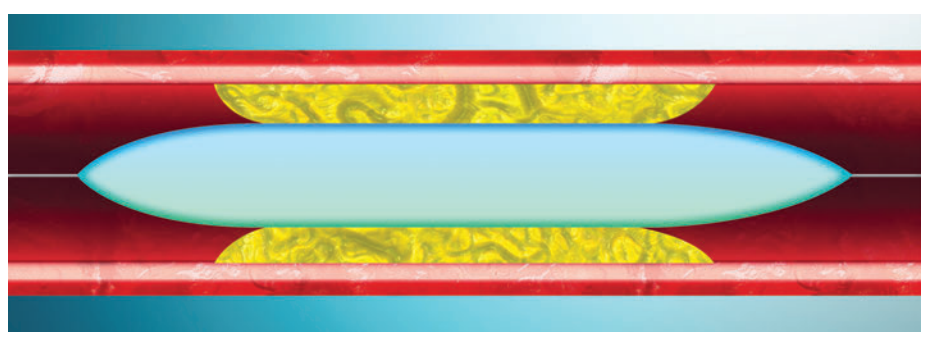

Figure 2. Balloon is inflated with slight undersizing that is noticed by the 50% reduction in the circumferential plaque burden and longitudinal elongation of the compressed plaque.

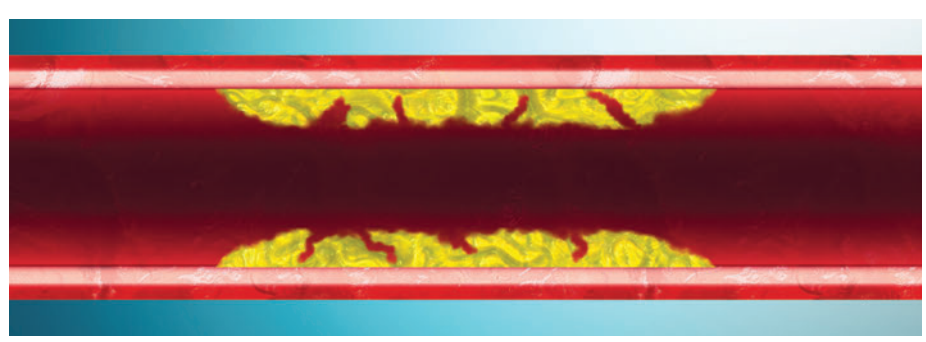

Figure 3. Post plain balloon angioplasty plaque preparation. Note the multiple contained microdissection features, which will be the track for the drug to travel along the microchannels, especially in calcified lesions.

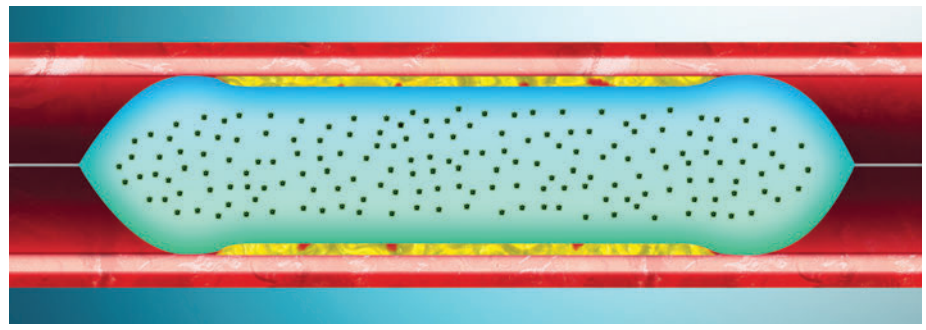

Figure 4. Drug-coated balloon positioned and inflated in the now well-prepared plaque and vessel. Notice the important extension of the balloon proximal and distal to the lesion with excellent contact between the surface area of the balloon, the surface area of the vessel, and plaque, ensuring proper contact to optimize drug transfer from the balloon to the vessel wall.

calcium offers to the drug transfer process. Interestingly, among the many hypotheses postulated to explain the failures of DCBs in BTK vessels, the issue of inadequate sizing has not been discussed.

Nonselective fluoroscopic angiograms characteristically underestimate the true diameters of the tibial arteries, leading operators to undersize balloons when treating this segment of the anatomy. A frequently seen scenario is the use of 2.5 mm balloons when treating proximal tibials, which actually tend to have a 3.5 mm to 4.0 mm diameter. With the use of selective and superselective angiography (injecting from the distal superficial femoral or popliteal artery, or from the tibial artery itself), accurate sizing is more likely to occur. A modality frequently used in our lab is extravascular ultrasound (EVUS), which provides the ability to accurately measure the size of the vessel being treated as well as to evaluate CLI treatment. With EVUS, we have observed that healthy arterial walls are actively involved in the transfer of kinetic energy to the bloodstream, which is perceived as a brisk antegrade expansion of the diastolic wavefront. However, in arterial segments with progressively increasing levels of calcification (typically seen in tibial arteries of patients with CLI) there is a linear progressive reduction of the arterial wall pulsatile wavelet, which abruptly ceases at chronic total occlusion (CTO) caps. The evaluation of arterial wall plasticity is performed by measuring diameters at peak systole and diastole. The difference of these diameters is divided by the maximal vessel diameter during diastole and the result is the vessel contractility index (VCI).

We have observed that measuring the VCI before and after interventions allows us to determine the adequacy of the intervention and to predict 30-day vessel patency. If there is evidence of significant plasticity heterogeneity (as indicated by a wide variation of VCI from proximal to distal vessel), angiography reveals stagnant flow and the 30-day patency decreases. On the other hand, if there is homogeneous plasticity after revascularization (as indicated by brisk and strong vessel wall pulsation without wide variations of the VCI throughout the length of the treated lesion), angiography reveals antegrade brisk flow, with a concomitant increase in 30-day patency.

Summary

There are multiple limitations to current DCB technology. For DCBs to be most effective, operators should strive to achieve the highest surface area contact between the balloon and the arterial wall. If the balloon-to-vessel-diameter ratio is not 1:1, the result is less drug transfer to the target site and a significantly higher risk of drug washout into the distal capillary beds. In CLI patients, this issue is concerning because the capillary beds surrounding nonhealing ulcers are typically hyperemic as demonstrated in late-phase angiography. Theoretically, these hyperemic beds could act as reservoirs for the "washed-out" drug, which would then inhibit cell proliferation and potentially interfere with the wound healing process.

We believe the use of concomitant technologies allows us to address the changes in wall plasticity and pursue a more accurate sizing of the tibial arteries to maximize contact between DCBs and the arterial wall. This approach will likely enhance drug transfer rates while minimizing drug wash-out to the distal capillary beds and ultimately lead to improved clinical outcomes.

Editor's note: Dr. Mustapha has disclosed that he is a consultant to Covidien, Bard Peripheral Vascular, Inc., and Medtronic.

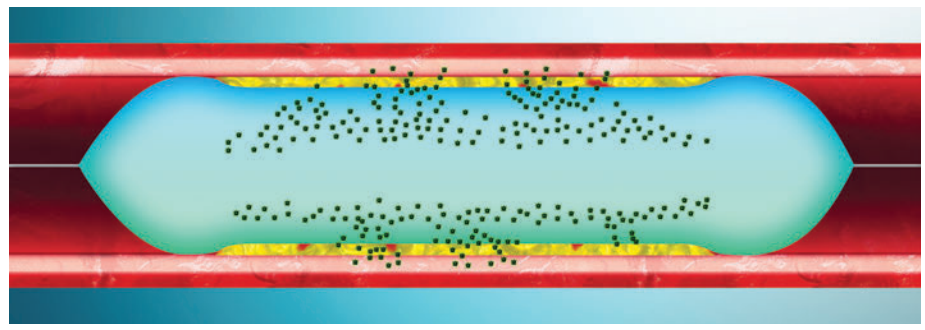

Figure 5. The mechanism of drug transfer from the surface of the balloon to the vessel wall happens immediately after balloon inflation and most of the drug is transferred within 30 seconds to 2 minutes after inflation. This is why it is crucial to perform proper sizing between the balloon and the vessel lumen to achieve optimal transition of the drug from the balloon to the vessel wall. The tight apposition of the balloon to the vessel wall prevents any flow along the surface area of the balloon while inflated, thus minimizing risk of distal embolization.

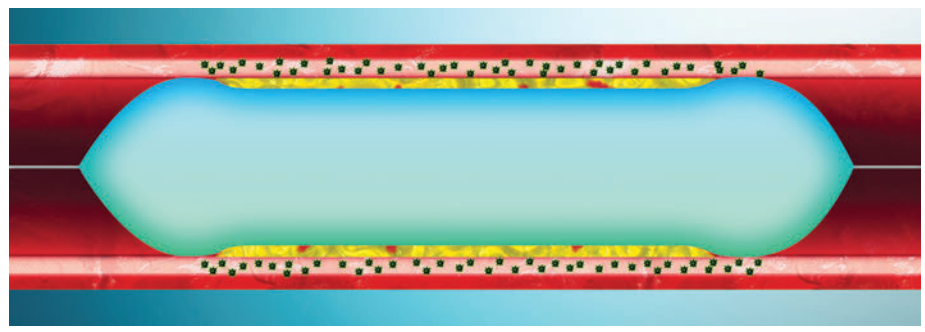

Figure 6. Employing 1:1 sizing ensures delivery of most of the surface content of the drug to the vessel wall, resulting in optimal DCB performance post inflation.

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VIVA 2015: Vascular Interventional Advances
Las Vegas, NV, United States
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www.vivaphysicians.org

VEITHsymposium 2015
New York, NY, United States
Tuesday, November 17, 2015 to Saturday, November 21, 2015
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The VERVE Symposium in Conjunction with LINC Australia
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December 3 to 5, 2015
www.vervesymposium.com

Leipzig Interventional Course (LINC)
Leipzig, Germany
January 26 to 29, 2016
www.leipzig-interventional-course.com/

Foot Perfusion

Continued from page 1

to stay within his home. On exam, I noted a linear fissure along the medial aspect of the right first transmetatarsal head. The center of this fissure was black, and the surrounding skin was heavily calloused and dry. Get the picture?

Now comes the point of the story — it was time to present the patient to my attending physician, the legendary chairman of vascular medicine, Jess R. Young, MD. A quiet, brilliant, and terribly intimidating figure, he had an appearance somewhat similar to that of Marcus Welby, MD, with his pressed and sharply creased white lab coat, perfect tie, and laugh lines around his eyes and mouth. However, the similarities ended there. Dr. Young had an encyclopedic knowledge of medicine — not only vascular medicine. He fully subscribed to the Socratic method of teaching, and allowed you — correct that, helped you — to walk down the primrose path of incorrect diagnoses, plans for treatment, and recollection of the medical literature. It was just my fortune that he was my consult attending that sunny summer first day of fellowship in Cleveland.

Picture this — we are walking from his office on S60 to the H ward of the Cleveland Clinic, and I am flawlessly presenting the case. I mention on exam the patient's hairless lower legs and feet, the coolness of the feet, and the dystrophic toenails. Dr. Young softly asked me the value of those physical exam findings in diagnosing advanced PAD. Here was the facilitation of my entrance to the primrose path. I proudly responded about the importance of those findings, almost struggling to pat my own back. Abruptly, Dr. Young grabbed my arm, pulled me to the side of the hallway, took off his right shoe, pulled off his right sock, and asked me to comment on what I saw and felt. (Do you feel for me yet?) Dr. Young had no hair on his lower leg or foot, had a quite cold foot, and some thickening of his great toenail. However, he had an excellent dorsalis pedis and posterior tibial pulse.

I have told this story countless times to trainees and colleagues alike. It is an important lesson about the lack of specificity of these common physical findings in aiding in the diagnosis of PAD. Dr. Young, a huge advocate of the recently established role of the vascular diagnostic laboratory (Dr. Young was a driving force behind the foundation of the Society for Vascular Medicine and Biology and the Intersociety Commission for the Accreditation of Vascular Laboratories, subsequently a component of the Intersocietal Accreditation Commission), repeatedly taught us that the ability to objectively determine the need for amputation, the ability of an ischemic ulceration to heal without revascularization, or the level of amputation at which the site would heal, was challenging.

I was fortunate during my training to also spend time with the emeritus chair of vascular surgery at the Cleveland Clinic, Normal Hertzer, MD, who was quite clear that no objective test was any more accurate in answering these clinical questions than running the back of your hand down the leg to the foot and determining the level of temperature change.

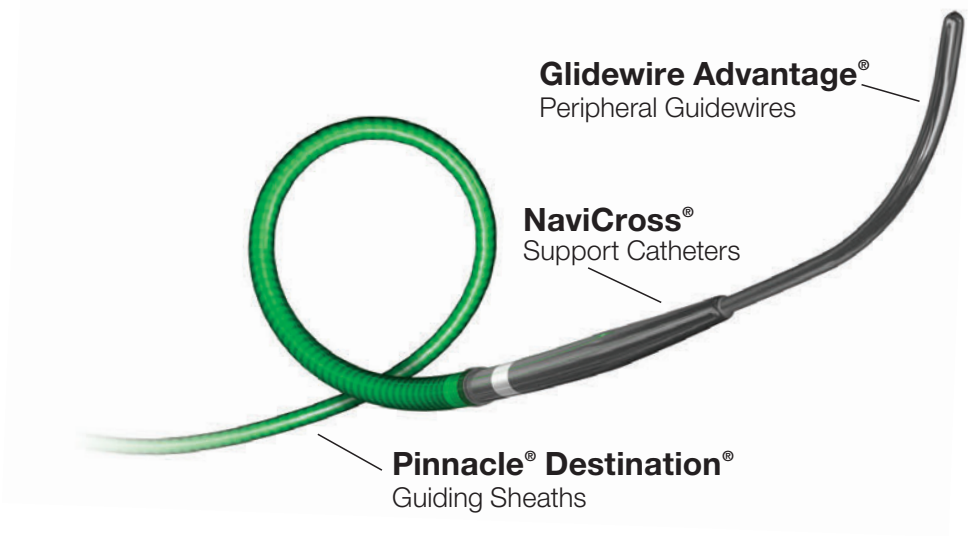
Fast forward to the first quarter of 2015, when the entire field of vascular medicine has changed with the technologic explosion of endovascular therapy, and I would submit that we are no better at objectively determining foot perfusion. All of us have our own perspectives on how to answer these questions. Depending on who you ask, experts will tell you that any one or a combination of these strategies solve the problem:

- Ankle brachial index;
- Toe brachial index;
- Toe pressure;
- Photoplethysmographic waveform amplitude;
- Pulse volume recordings;
- Transcutaneous oximetry;
- Skin perfusion pressures;
- Hyperspectral imaging;
- Duplex ultrasonography;
- Occult runoff vessel imaging on magnetic resonance arteriography;
- Contrast arteriography with intra-arterial vasodilation.

However, reviewing the published literature strips away the thin veneer of each of these modalities, and the limitations become overwhelming. With the more recent attention of the field on the novel and unique methods of revascularizing patients with critical limb ischemia, using smaller profile delivery systems and unique access points to gain entry into tiny pedal and tibial arteries, the question of "when is revascularization enough" becomes very relevant. During an endovascular revascularization procedure being performed for limb salvage, do you need to target the angiosome-related artery and stop there, or would there be advantages regarding wound healing, pain relief, and prevention of limb loss if a second "non-target" artery were treated? We have no idea.

It is exciting to note that this area of vascular medicine is starting to gain more attention with a number of novel noninvasive devices being developed. The extent to which rigorous analysis and testing is done remains to be seen. Unfortunately, at present we are left with our best guesses and the back of the hand.

Approach CLI and PAD with a perfect combination for crossing complex lesions.



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CLI Devices

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successfully cross these lesions, advanced technical skills and patience are of paramount importance. These procedures tend to be long and time consuming, leading to increased radiation exposure to providers and patients. Intravascular ultrasound (IVUS) is an alternative imaging strategy that can be employed to assist in crossing these lesions. It provides direct visualization of the lesion and at the same time can help to reduce the amount of radiation and contrast exposure. However, current IVUS systems only provide a narrow cross-sectional view of the artery and are incapable of imaging the vessel ahead of the imaging catheter. Forward-looking intravascular ultrasound (FL-IVUS) is a promising new technology that is capable of visualizing the lesion ahead of the catheter, thereby providing crucial information needed to successfully cross and treat the lesion. In addition, due to the eccentric plaque distribution in a CTO, a device that allows direct visualization will consequently provide the ability to maintain the catheters and wires in the center of the lumen, therefore minimizing the risk of subintimal penetration.

Interventionalists often resort to employing retrograde access or transcollateral approaches to treat CTOs when traditional antegrade approaches fail. In using such techniques, interventionalists need to access smaller arteries and traverse through tortuous vessels. There are only a few tools available to meet these challenges, such as the ones utilized in neurologic interventions. However, these need to evolve to be used in the peripheral vascular space. In addition to addressing size constraints, devices must also be able to provide support as the catheter and wires are advanced, while being flexible enough to maneuver through the tortuosity of the vessels. Additionally, devices capable of deflecting 180 degrees to gain access to the native vessel from collateral channels are desirable for the treatment of CTOs. Also, pharmacotherapeutic device solutions that reduce vessel spasm and thrombosis in smaller peripheral vessels can improve retrograde and transcollateral procedural outcomes.

Below-the-Knee Disease

Below-the-knee (BTK) interventions are challenging due to the smaller vessel size and increased concentration of calcium in those lesions.[10] Treatment of BTK lesions is therefore associated with higher rates of restenosis, due to vessel size and lack of efficient technologies to tackle the issue. Several studies looking at drug-eluting stents revealed some improvement in long-term patency compared to balloon angioplasty; however, these results have been rather disappointing when compared to the results achieved with these devices in the coronary arteries. There is a remarkable paucity of efficient technologies that are designed to treat BTK lesions, and the currently available devices perform rather poorly in this space.[12] Longer and smaller tools are particularly desirable to treat BTK disease. Current interventional tools have operational lengths of 65 cm to 180 cm, limiting their applicability for treatment of BTK lesions. If transfemoral, transpopliteal, and pedal access is unavailable, a radial or brachial approach must be considered. As the field of endovascular treatment moves forward and transradial vascular access becomes the preferred option, longer devices are needed in order to treat BTK lesions. In addition to length, devices capable of maintaining support as they are advanced distally from the access site are highly desirable for the treatment of BTK disease in CLI.

Conclusion

Significant advances are being made in the development of endovascular devices and pharmacotherapeutics that improve technical success rates as well as long-term patient outcomes. However, there is a paucity of available dedicated efficient devices to successfully treat CLI. Treatment of calcified lesions, CTOs, and BTK disease (all common in CLI patients) remains challenging and outcomes are largely dependent on the skill of the interventionalist, time required to successfully treat, and devices available. New medical devices capable of addressing the challenging clinical needs posed by these pathologies will significantly improve the treatment and management of patients with CLI. Remember, a carpenter is only as good as his tools. ■

Editor's note: Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts or financial relationships related to the content herein.

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Tibial CTOs

Continued from page 7

not available for puncture, retrograde transmetatarsal artery access is a useful alternative for retrograde recanalization of pedal and tibial vessels. Another technique that can be considered is the antegrade pedal approach for revascularizing CTOs in the opposing circulatory pathway of the foot.[16] These maneuvers can improve both technical and clinical results for nonsurgical candidates.

A New Dedicated Crossing Device

Recently a new crossing solution has been presented, the Viance crossing catheter (Covidien). This is an instrument designed to quickly and safely deliver a guidewire via the true lumen or subintimal pathways. Its atraumatic, low-profile tip helps the device remain within the true lumen. In cases where the device tracks into the subintimal space, it creates a very small channel, helping to facilitate reliable re-entry. It appears to be very useful and safe, anecdotally providing good technical results.

Conclusion

Revascularization for CLI patients remains challenging, mainly due to multilevel and multivessel, complex and long BTK and BTA CTO lesions. Multiple technical strategies and dedicated devices are becoming available to improve success for procedures from arterial access to crossing and treating the occlusions of the distal arteries.

The best modality for CLI revascularization seems to be a combination of all the techniques available today, following the step-by-step model and adapting it to each individual patient. ■

Editor's note: Disclosure: The author has completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Palena reports no conflicts or financial relationships related to the content herein.

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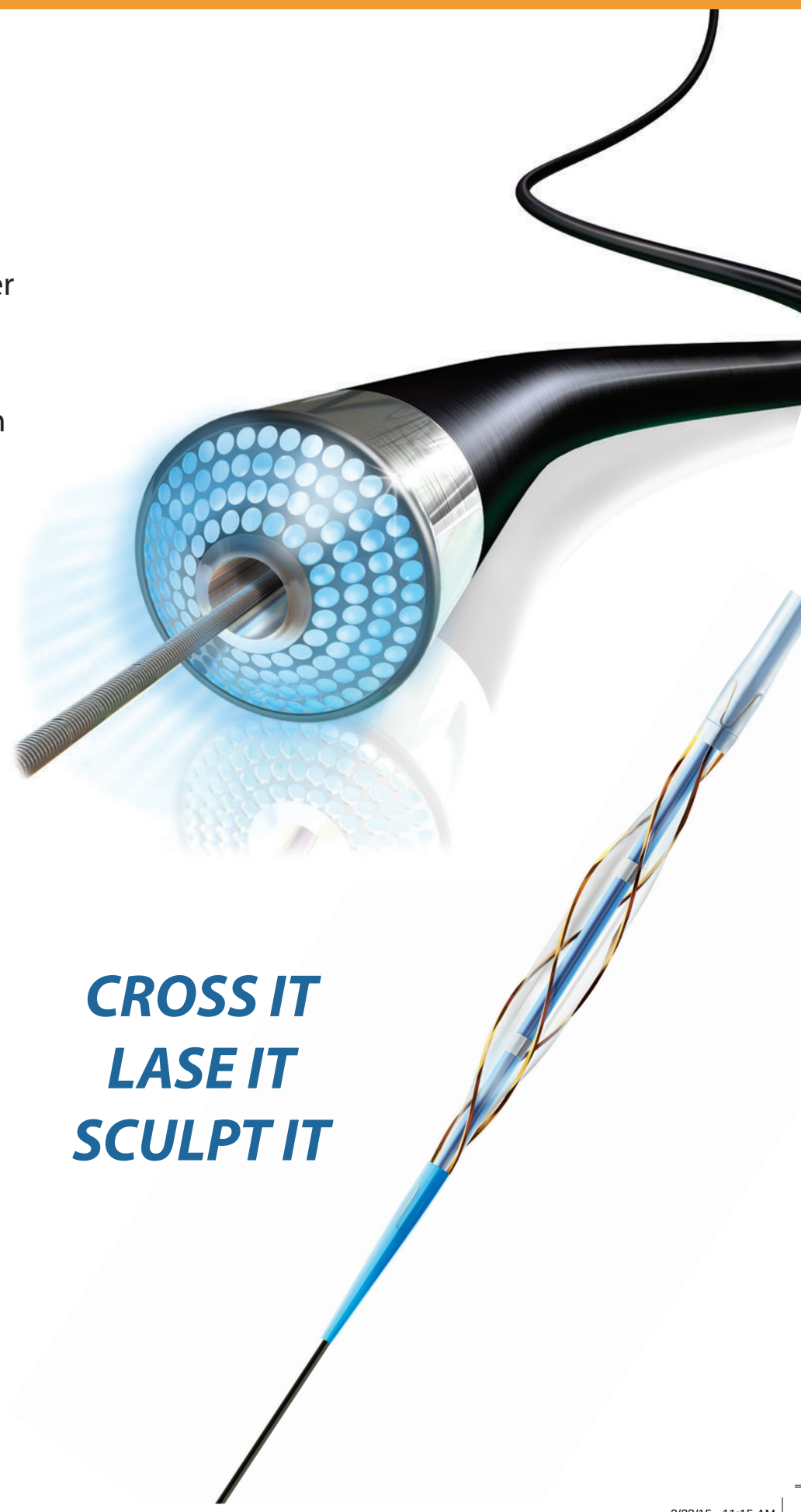

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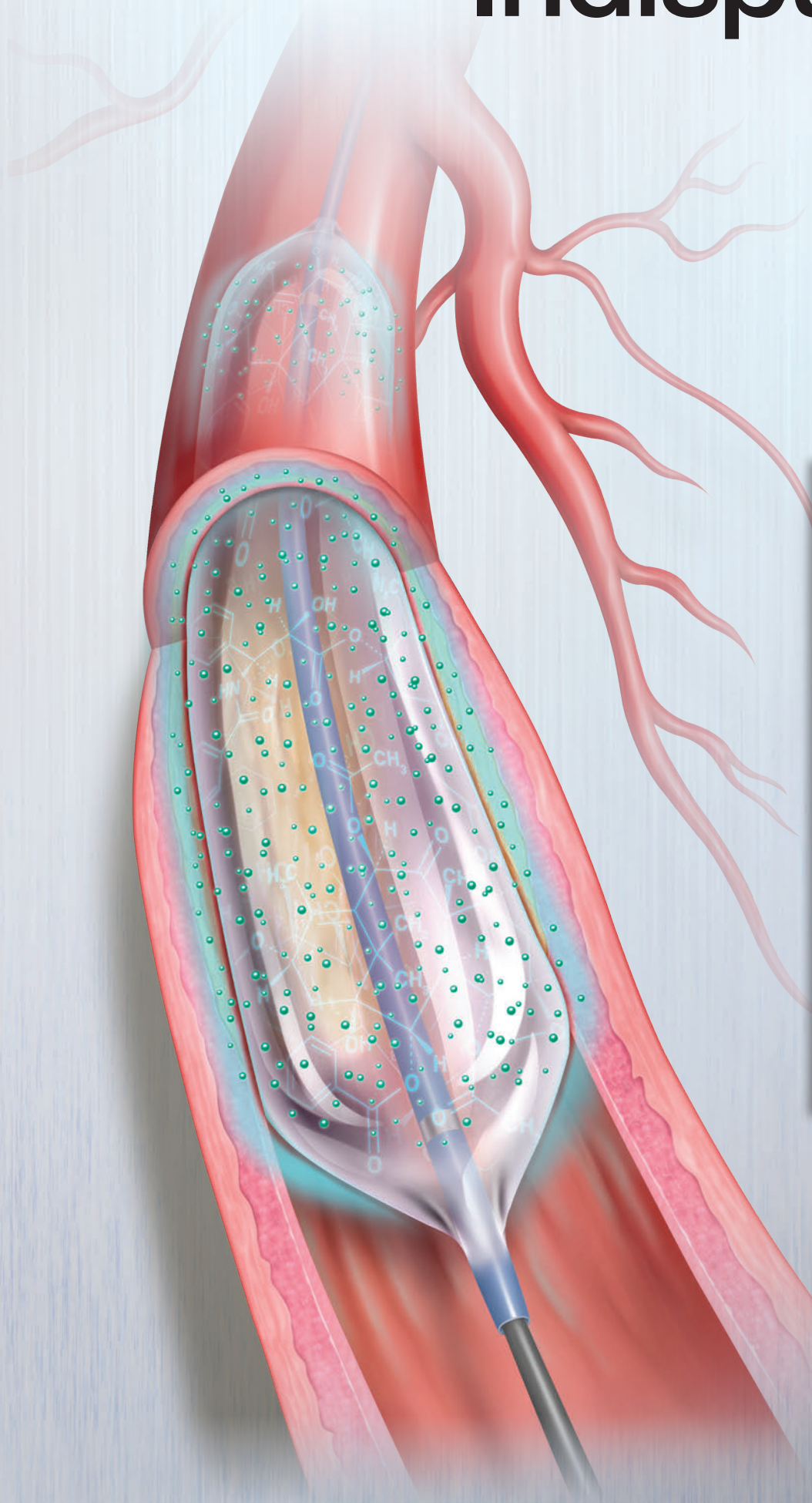

LUTONIX® 035

Drug Coated Balloon PTA Catheter

- **73.5% Primary Patency** at 12 Months[1]
- **89.7% Freedom from TLR** at 12 Months[1]
- Established Safety Record **Comparable to PTA**[1]
  - **No** unanticipated safety events at 12 months in LEVANT 2[1]
  - **No** evidence of systemic or downstream embolic events[2]
  - **Similar risk** for embolic events, amputation and thrombosis **as standard PTA**[1]

This product should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds. Please consult product labels and instructions for use for indications, contraindications, hazards, additional warnings and precautions. ℞ Only

1 LEVANT 2 clinical trial data on file. N=476. At 12 months, treatment with Lutonix® 035 resulted in a primary patency rate of 73.5% versus 56.8% with PTA alone (p=0.001). Primary patency defined as absence of binary restenosis defined by DUS PSVR ≥2.5 and freedom from Target Lesion Revascularization (TLR). At 12 months, treatment with Lutonix® 035 resulted in a freedom from primary safety event rate of 86.7% versus 81.5% with PTA alone (p=0.185). Primary safety defined as composite of freedom from all-cause peri-operative death and freedom at 1 year in the index limb from Amputation (ATK or BTK), Reintervention, and Index-limb related death. Numbers reported are Kaplan-Meier analyses, not pre-specified.

2 Preclinical animal data on file. Animal test results may not be indicative of clinical performance. Different test methods may yield different results.

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