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Treating CLI During COVID-19

Webinar Presented by CLI Global Society Board Members

CLI Global Society President, Dr. Barry Katzen, from Miami, recently moderated an interactive panel discussion with all nine Board Members of the CLI Global Society. Their discussion on treating critical limb ischemia during COVID-19 was attended by 350 individuals globally from five continents.

Dr. Jos van den Berg started off the discussion with a case of a patient who had presented to his institution in Lugano, Switzerland one day prior. A 70-year-old male with a history of diabetes, obesity, and CLI presented with ulceration of the left forefoot with ischemia. His symptoms had been present for several weeks but he had been avoiding a visit to the hospital outpatient clinic due to fear of the COVID-19 virus infection. The patient did present with a fever, but no known exposure or respiratory symptoms. The fever was assumed to be attributed to the infected wound. The patient did have sensory deficit. Following a negative COVID-19 test the patient was revascularized immediately. CT angiography was waived due to a GFR of 27.

Dr. van den Berg and other panelists reported an anecdotal increase in amputation over the last weeks due to patients not seeking treatment for revascularization in a timely manner out of fear of contracting the COVID-19 virus. The panelists discussed how they would have proceeded with patient treatment at their respective institutions.

Dr. Andrew Holden, from New Zealand, shared that his institution does have the ability to test. However, such a case with no history of travel, known exposure, and respiratory symptoms would be revascularized without testing and standard personal protective equipment (PPE) would be utilized for staff and the patient would be masked. With the presence of a fever, they would test and wait 6 hours for results prior to revascularization. Professor Thomas Zeller, from Germany, said his institution would take an approach similar to the one Dr. Holden described.

Dr. Robert Lookstein, from New York City, reported that his institution would

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CLI in Europe: Are There Lessons to Be Learned?

Jos C. van den Berg, MD, PhD
Ospedale Regionale di Lugano, sede Civico, Lugano; University of Bern, Switzerland; Board Member, CLI Global Society

CLI IS UNDERDIAGNOSED, UNDERTREATED, AND DEADLY

Critical limb ischemia (CLI) is an underdiagnosed and undertreated deadly disease that requires proper diagnostic imaging and increased awareness. Between 2000 and 2010, the world's population increased by 12.6%, and the prevalence of peripheral arterial disease (PAD) has increased twice as much over this period.[1] In the United States (US) and the European Union (EU), more than 3.8 million patients suffer from CLI[2] and this number is expected to increase by 23% over the next 10 years.[3] These alarming statistics can be attributed to an explosion in the diagnosis of diabetes and decreasing mortality from cardiovascular disease. A more alarming statistic is that more than 50% of amputations occur without any prior vascular intervention in the year prior.[4]

Efforts to estimate the true prevalence of CLI in population studies are challenging because the CLI diagnosis is clinically established by a constellation of lower extremity features, including ischemic rest pain and non-healing ischemic wounds or gangrene, and requires the objective measurement of ankle or toe pressures. Few prior population-based studies have used such symptom- and examination-based clinical criteria to define CLI incidence or prevalence.[5,6] Validation studies suggest that use of administrative codes for CLI diagnosis may underestimate the true prevalence by 25%.[7] Given these factors, it can be estimated that between 1 million and 3 million Americans have CLI.[1]

Adding to the poor prognosis after diagnosis of CLI, patients with this disease remain underserved with regard to diagnostic evaluation, medical therapy, and utilization of revascularization.[1]

NATURAL HISTORY OF CLI

A recent publication by Conte et al in *the Journal of Vascular Surgery* shows that 12-month outcomes of patients diagnosed with CLI are poor with a 22% mortality rate and a 22% amputation rate. Amputation rates at 4 years as stratified by Rutherford classification are 12.1%, 35.3%, and 67.3% for Rutherford Classification Categories 4, 5, and 6, respectively.[8] When an individual first receives a diagnosis of CLI, the mortality risk is 24% over 1 year and 60% over 5 years.[9] Fewer diseases connote a higher mortality rate. Among 22 different types of malignancy, only six have a 5-year mortality rate higher than that of CLI.[10]

A study by the CLI Global Society showed that mortality rates at 4 years differed by Rutherford Class presentation with 41% (Rutherford 4), 55% (Rutherford 5), and 68% (Rutherford 6), whereas major amputation rates at 4 years were 6% (Rutherford 4), 9% (Rutherford 5), and 30% (Rutherford 6).[9] Overall, the high incidence of CLI in combination

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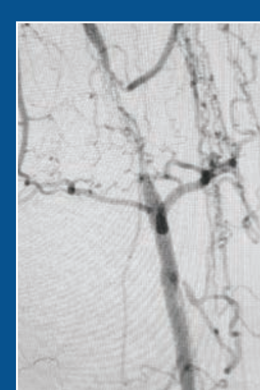

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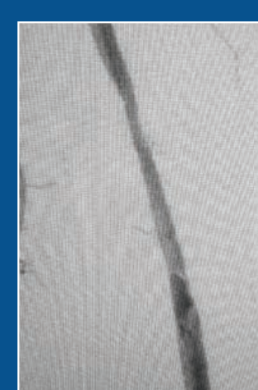

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Treatment of Calcified Common and Deep Femoral Arteries

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UCLA Medical Center, Los Angeles, California

Percutaneous vascular intervention (PVI) is a safe and effective treatment option for symptomatic peripheral artery disease. The ideal treatment strategy for common femoral artery (CFA) disease is controversial. Common femoral endarterectomy (CFE) has been considered the standard of care for over half a century given that the CFA is easily accessible surgically, technically feasible, and provides durable patency.[1] However, CFE may not be a good option in some patients, especially if they have multiple comorbidities or are elderly.[2] A large registry from the National Surgical Quality Improvement Program database reported a 30-day morbidity and mortality rate of 15%, including a mortality rate of 3.4%.[2] Surgery is also associated with infection and paresthesia. Furthermore, CFA disease is commonly accompanied by involvement of the iliac or superficial femoral arteries which are not revascularizable during CFE. PVI represents an alternative for patients who do not want surgery for various reasons, including personal preference or those who are poor candidates for surgery. PVI of the CFA is minimally invasive, non-surgical, and can be performed on an outpatient basis with same-day discharge. In contrast, CFE often requires at least an overnight hospital stay. The large diameter of the CFA makes it an appealing vascular territory to treat with PVI. Compared with CFE, PVI also provides the ability to revascularize other vascular beds including the iliac and superficial femoral arteries. PVI of the CFA can be performed via the radial or brachial artery because of the proximal location of the CFA, which decreases the risk of vascular access complications and bleeding. In the TECCO trial, the stent group provided lower rates of 30-day morbidity and mortality compared with the surgery group in patients with CFA disease (12.5% vs. 26%, odds ratio: 2.5; 95% confidence interval: 0.9–6.6; *P*=.05).[3] The length of stay was also lower in the stent group (3.2 ± 2.9 days vs. 6.3 ± 3 days; *P*<.0001). Delayed wound healing was more commonly observed in the surgery group (16.4% vs. 0%). At 2-year follow-up, there were no differences in sustained clinical improvement and the rates of primary patency, target lesion revascularization, and target extremity revascularization.

Percutaneous vascular intervention of the deep femoral artery is uncommonly performed because angiographic complications may lead to critical limb ischemia if it is the last remaining conduit to the lower limb.

There are several aspects of the CFA which increase the technical complexity of PVI. Osteoid metaplasia, a mature bone structure, was commonly observed in CFA disease.[4] Severe calcification of the CFA decreases the acute procedural success rate. Balloon and stent catheters may not traverse severely calcified lesions. Calcified lesions are also difficult to fully dilate and may require high pressure balloon inflations, which increase the risk of dissection, slow flow, and perforation. Dissection of the CFA may require stenting, which is undesirable at a flexion point

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Editor's note: Articles in this supplement to *Cath Lab Digest* did not undergo peer review.

SAVAL Update: Overcoming Recoil and Restenosis in the Treatment of Complex Tibial Disease

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In patients with chronic limb-threatening ischemia (CLTI), the overarching goal of treatment is successful revascularization of the endangered limb. Prompt restoration of adequate limb perfusion decreases the risk of amputation and maximizes the patient's quality of life by resolving ischemic rest pain and allowing healing of ischemic wounds.[1,2] Surgical bypass and endovascular revascularization (percutaneous transluminal angioplasty, PTA) are the primary modes of treatment for CLTI. Selection of the optimal revascularization method was examined in the BASIL trial, and remains under study in the current BEST-CLI trial.[3-7] The recently published Global Vascular Guidelines offer a surgical perspective on risk stratification and high-yield application of surgical bypass.[2] However, as operator comfort with complex endovascular interventions has continued to increase over time, the use of endovascular intervention for CLTI has predictably continued to grow.

Although CLTI is a predominantly multilevel disease process, the increasing incidence of diabetes mellitus temporally corresponds to a notable increase in the need for complex below-the-knee (BTK) revascularization procedures. Angioplasty remains the gold standard for endovascular BTK intervention, but clearly faces intra-procedural and post-procedural shortcomings in achieving and maintaining optimal patency. In the smaller caliber BTK arteries, even modest recoil or post-angioplasty ingrowth of intimal hyperplastic tissue can rapidly produce a critical restenosis. Drug-coated balloon angioplasty in the infrapopliteal vessels has not shown consistent benefit across the larger randomized trials.[8-11] Multiple studies have suggested that the off-label use of drug-eluting coronary stents in short, proximal tibial lesions provides superior patency.[12-15] However, the applicability of these highly selected trial populations to the more extensive tibial disease patterns treated in everyday CLTI practice is questionable. It is clear that the BTK toolbox would greatly benefit from the availability of a crush-resistant, restenosis-inhibiting scaffolding that is suitable for deployment throughout the tibial vasculature.

The SAVAL drug-eluting stent (DES) system (SAVAL™ DES BTK, Boston Scientific Corp.) was developed to address the aforementioned BTK treatment gaps. In the SAVAL clinical trial (NCT03551496), the primary objective is to demonstrate that the SAVAL DES has a superior patency rate and acceptable safety in BTK arteries compared to PTA. Secondary objectives are the collection of additional data on limb salvage and quality of life for patients participating in this study.

SAVAL DES OVERVIEW

The SAVAL DES is a laser-cut, self-expanding nitinol stent that was purpose-built for BTK use (Figure 1). The SAVAL DES system comprises three parts: the stent, its coating, and the delivery system. Much like the ELUVIA drug-eluting vascular stent system (ELUVIA™ DES, Boston Scientific Corp.), which is indicated for treatment of femoropopliteal disease, the SAVAL coating contains a polymer in addition to the drug itself (PBMA/PVDF:HFP-Paclitaxel). This combination provides sustained release of paclitaxel after stent deployment, with a dose of 0.236µg of paclitaxel per square millimeter of stent surface area. The first part of the SAVAL trial tests only one stent diameter and length (3.5-mm diameter, 80-mm length) to target a reference vessel diameter of 2.5 mm to 3.25 mm. It is anticipated that additional stent diameters and lengths will be added to the second phase of the SAVAL trial as additional safety and efficacy data are gathered.

SAVAL STUDY DESIGN

The SAVAL trial is a two-phase study comparing patency and safety of the SAVAL DES compared with PTA in the treatment of infrapopliteal arteries.

Table 1. Patient Eligibility for SAVAL*
•Chronic, symptomatic lower limb ischemia (Rutherford categories 4 or 5)
•Stenotic, restenotic, or occlusive target lesion(s) in the tibioperoneal trunk, anterior tibial, posterior tibial, and/or peroneal artery(ies)
•Stenosis that is ≥ 70% (based upon visual angiographic assessment)
•Total target lesion length ≤ 140mm.
**Patient must have all 4 symptoms for trial eligibility.*

The first phase of the study is a randomized controlled trial (RCT) with a 2:1 randomization of subjects to SAVAL DES and PTA, respectively (Table 1). The first phase has a target enrollment of approximately 201 patients globally. The trial will include up to 50 study sites across the United States, Europe, and Japan. The primary endpoint for the first phase of SAVAL is primary patency of the DES in comparison to PTA at 6-months post-procedure. Patency assessments will be performed at 1-, 6-, 12-, 24-, and 36-months post-procedure using duplex ultrasound. The primary safety endpoint is major adverse events (MAEs) through 6-months post-procedure (non-inferiority comparison between study arms). MAEs are defined as above-ankle amputation of the index limb, major re-intervention, and/or 30-day peri-procedural all-cause mortality (a combined endpoint also known as "major adverse limb events and peri-procedural death," or MALE-POD).

The second phase of the SAVAL study is a single-armed study to collect ongoing safety and effectiveness data. The second phase aims to treat 100 additional patients with the DES BTK Vascular Stent System, which will include an expanded range of stent sizes. The execution of the second phase is contingent upon effectiveness demonstrated in the first phase. In the second phase of SAVAL, the primary safety endpoint is MAE rate at 12-months post-procedure, with continuing patency-based assessments planned at 1-, 6-, 12-, 24-, and 36-months post-procedure using duplex ultrasound.

PLANNED STATISTICAL ANALYSES

Briefly, analyses will utilize an "adaptive sequential testing hypotheses strategy." Specifically, there is a planned interim analysis when a minimum of 70% of target enrollment of phase one reaches the 6-month post-procedure mark, with an adjusted Type I error for the interim and final analyses. For the second phase, analyses will be conducted when all subjects (pooled from both phases) have reached the 12-month post-procedure mark.

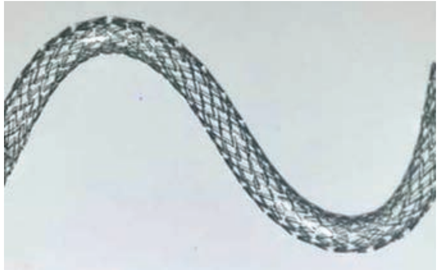

Figure 1. **The DES BTK Vascular Stent is a laser-cut, self-expanding nitinol stent coated with an inner PBMA primer layer and an outer Paclitaxel/PVDF-HFP active layer.** *Image provided courtesy of Boston Scientific.*

WHAT MAKES THE SAVAL TRIAL UNIQUE?

The SAVAL clinical trial is the only large study investigating a purpose-built, self-expanding, sustained-release paclitaxel BTK DES. It is the first study of peripheral vascular intervention granted the FDA Breakthrough Devices Program designation (formerly the Expedited Access Pathway program). The randomized study design will provide a rigorous comparison of this novel BTK device to the current standard of treatment (PTA). Of note, patient recruitment for SAVAL was designed to be international from the outset, with a goal of enrolling patients in the United States, Japan, and Europe. ■

Study Status: The SAVAL trial is actively enrolling subjects in its first phase.

Acknowledgement: I thank Alexandra J. Greenberg-Worisek, PhD, MPH, (Boston Scientific) for providing medical writing assistance.

Disclosure: Dr. Geraghty reports Consulting/Advisory Board: BSCI, BD/Bard; Equity Holder: Euphrates Vascular.

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Utilization of Tibio-Pedal Artery Minimally Invasive Approach to Treat Complex Below Knee Disease in a High Transfemoral Risk Patient

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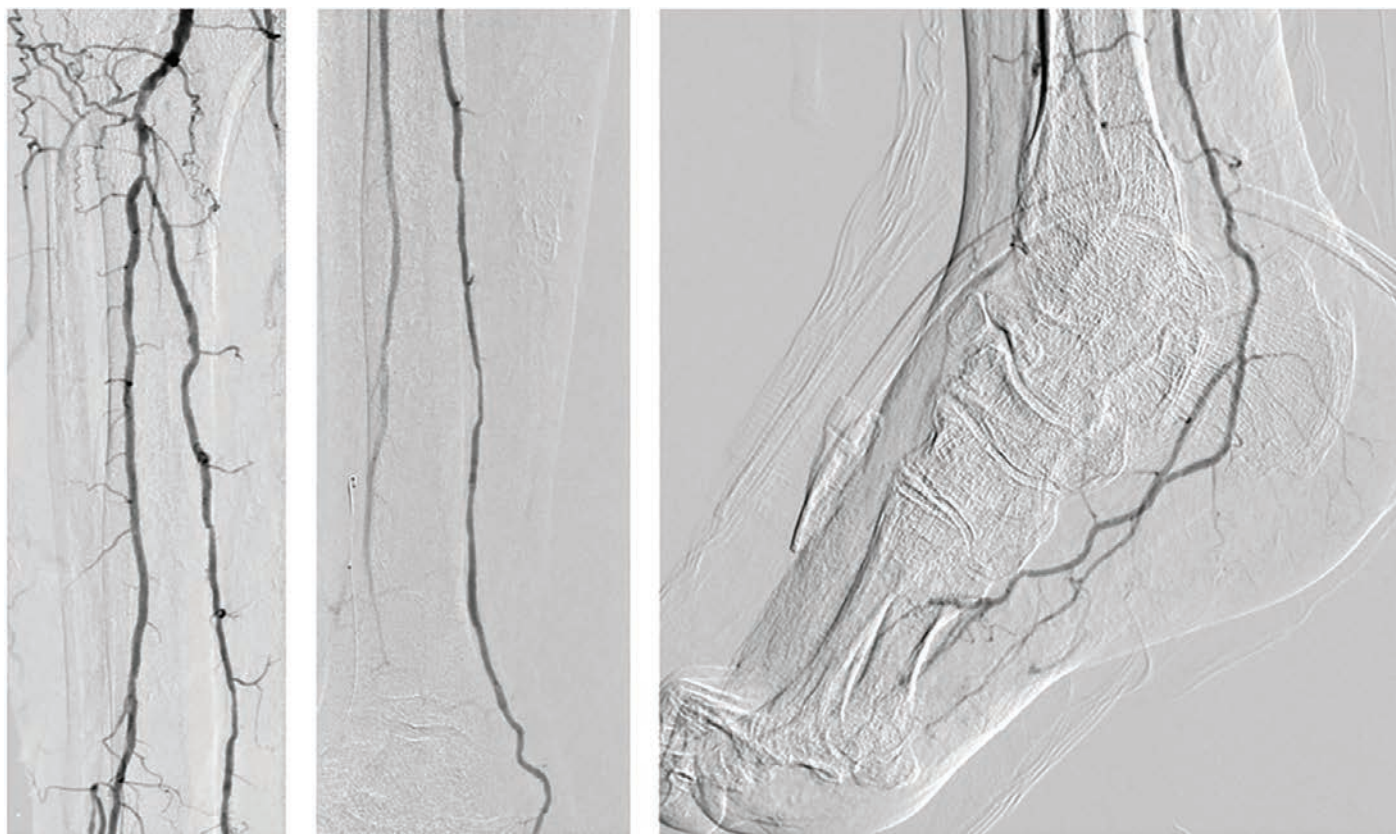

Figure 1. Diagnostic angiogram: ATA CTO, patent PTA, patent PER, and patent LPA. ATA = anterior tibial artery; CTO = chronic total occlusion; PTA = posterior tibial artery; PER = peroneal; LPA = lateral plantar artery.

With the evolution of endovascular techniques, historically untreated patients have options. Tibio-pedal artery minimally invasive (TAMI) approach is safe and feasible when avoiding transfemoral access complications.[1-3]

CASE REPORT

A 66-year-old male with a past medical history of hypertension, hyperlipidemia, insulin-dependent diabetes mellitus Type 2 for more than 20 years, coronary artery disease previously treated with multivessel percutaneous coronary intervention (PCI), ischemic cardiomyopathy with ejection fraction of 35%, morbid obesity with body mass index (BMI) of 52, and sleep apnea presenting with chronic limb threatening ischemia (CLTI), presented with necrotizing fasciitis requiring an urgent debridement for infection control. His non-invasive vascular workup included an abnormal ankle brachial index (ABI), an abnormal arterial ultrasound, and tissue oximetry.

He had a right transradial aortogram with selective right leg angiogram. His angiogram revealed adequate inflow with patent aorto-iliac, common femoral, superficial femoral, profunda, and popliteal vessels. Distally he had a chronically occluded (CTO) right anterior tibial (ATA) with a hibernating dorsalis pedis artery (DPA), which faintly filled from a peroneal (PER) collateral, 90% tibial peroneal trunk (TPT) stenosis, multiple 75% lesions in the proximal and mid posterior tibial artery (PTA), and a patent lateral plantar artery (LPA) (Figure 1).

Anticipating a high risk of complications related to transfemoral access, we decided to proceed with TAMI approach with transradial guidance. A 4- to 5-Fr Glidesheath Slender (GSS) (Terumo Medical) was inserted in the right radial artery for visualization of the proximal vessels. We placed a 2.9-Fr Cook pedal (Cook Medical) sheath in the ATA and advanced a 0.018-inch CXI (Cook Medical) support catheter over a 0.018-inch Command ST (Abbott Vascularl) wire. The CXI catheter and wire were advanced through the course of the ATA intraluminally except for the ostium of the ATA where the wire entered a subintimal

Anticipating a high risk of complications related to transfemoral access, we decided to proceed with TAMI approach with transradial guidance.

Figure 2. Retrograde 2.9 Fr ATA and 4-5 Fr PTA sheaths. ATA = anterior tibial artery; PTA = posterior tibial artery.

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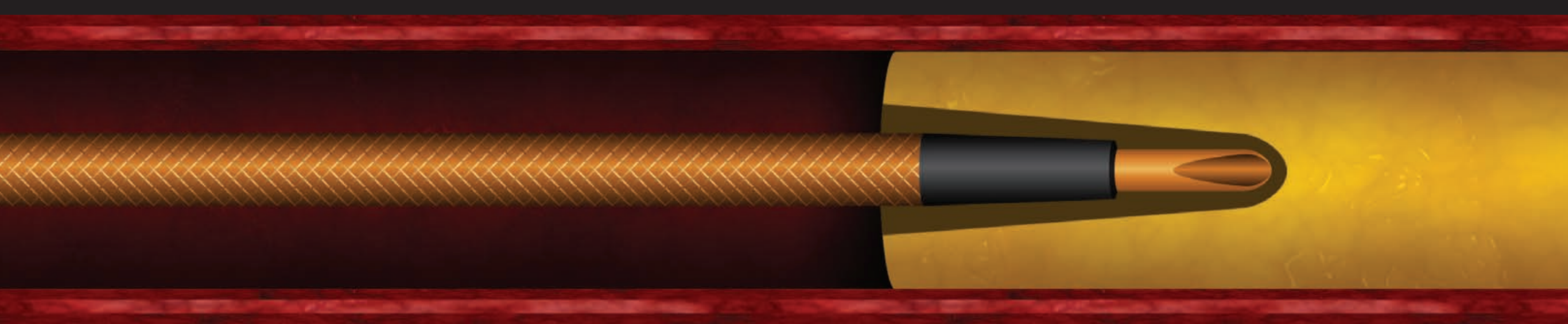

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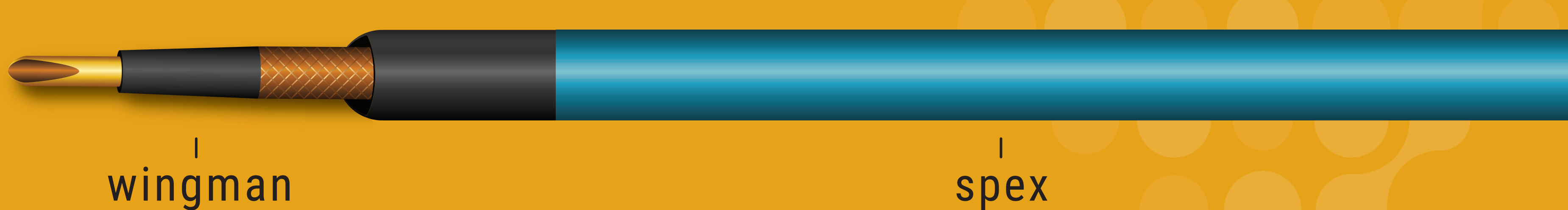

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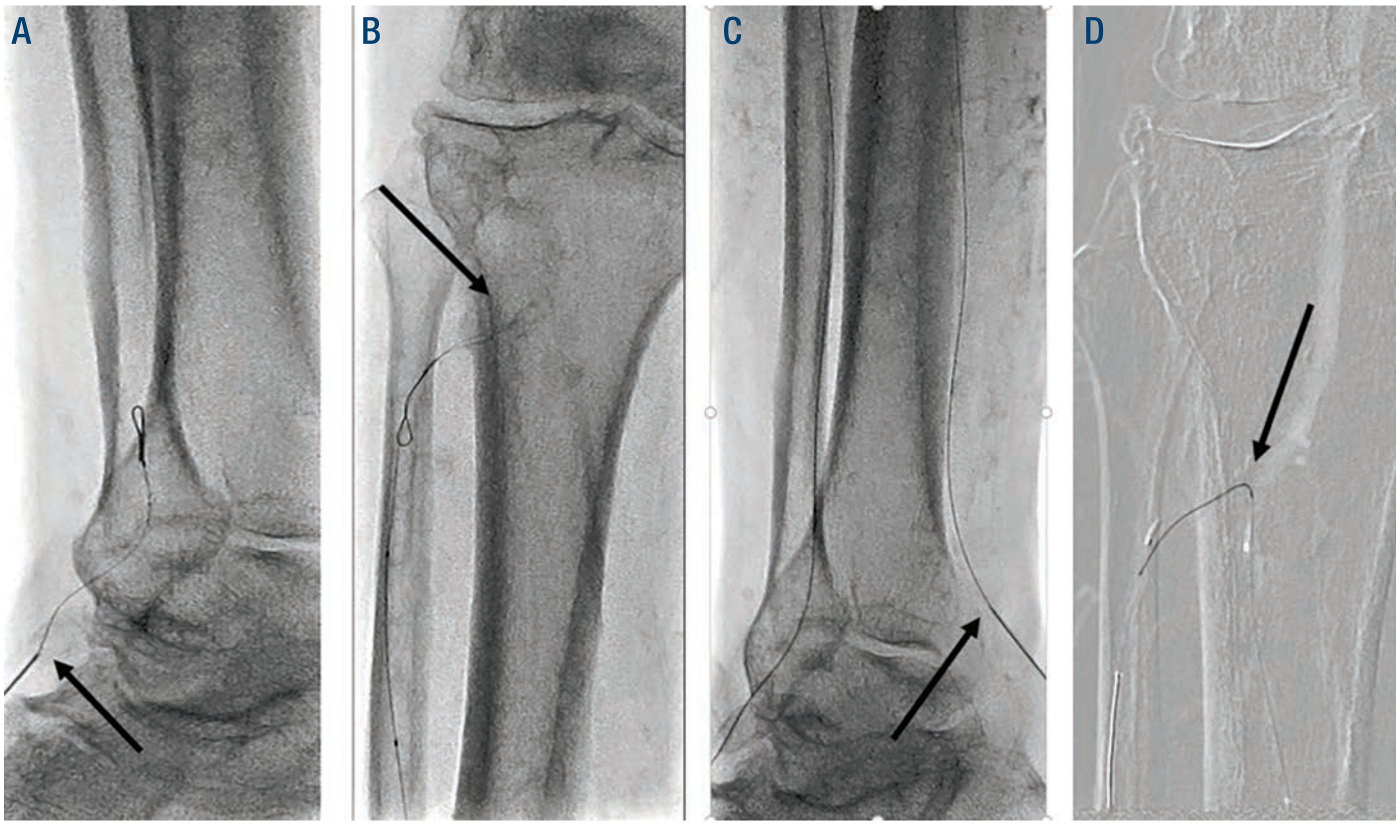

Figure 3. Arrow (A) retrograde ATA access, (B) retrograde wire looped at ATA ostium, (C) retrograde PT access, (D) retrograde PTA crossed into proximal ATA. PT = posterior tibial; PTA = posterior tibial artery; ATA = anterior tibial artery.

N'DANDU *from page 6*

space. Thereafter, we gained access in the right PT with a 4- to 5-Fr GSS sheath to serve as an antegrade access to cross the ATA CTO (Figure 2). A 0.018-inch CXI support catheter was telescoped within a 4-Fr Berenstein (Boston Scientific) catheter with a 0.018-inch Command wire advanced into the proximal ATA (Figure 3). The antegrade equipment was advanced into the distal ATA. The retrograde CXI catheter was pulled back in the distal AT where the antegrade wire was inserted for externalization. Subsequently the antegrade CXI catheter was externalized through the retrograde 2.9-Fr sheath placed in the distal ATA (Figure 4). The 0.018-inch Command wire was exchanged for a 0.014-inch ViperWire (Cardiovascular Systems, Inc.) guidewire to perform atherectomy using a 1.5 mm Classic CSI Diamondback 360 catheter in the PTA, TPT, and ATA (Figure 5). Thereafter, based on extra vascular ultrasound (EVUS) measurements, we performed balloon angioplasty of proximal DPA, ATA, and PTA with a 3.5- x 300-mm balloon (Ultraverse BD Bard), and TPT with a 4.0- x 60-mm Lutonix

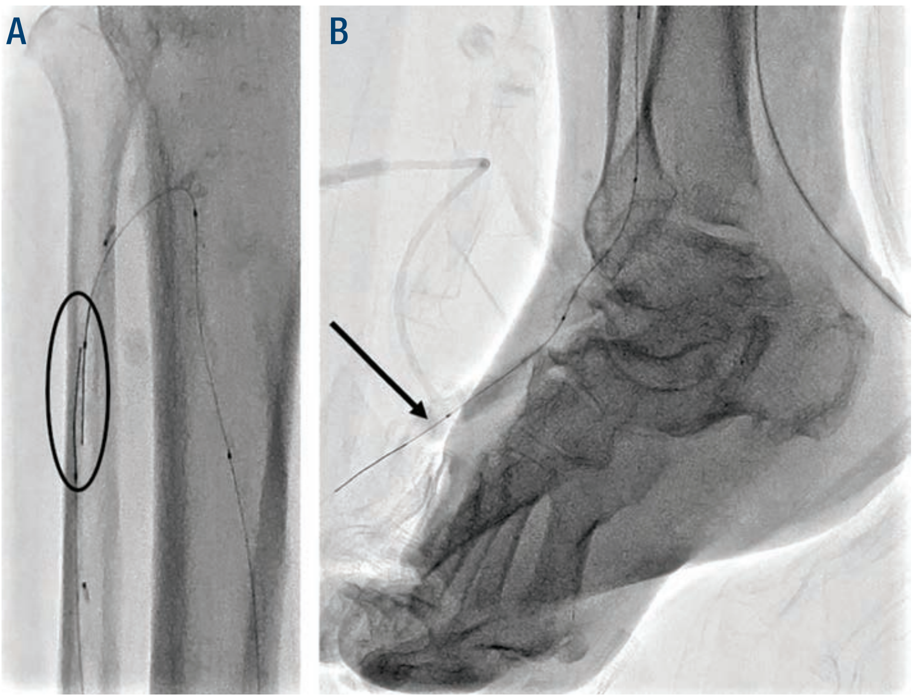

Figure 4. Oval (A) antegrade and retrograde wires in ATA and arrow (B) externalization of antegrade wire through the retrograde ATA access. ATA = anterior tibial artery.

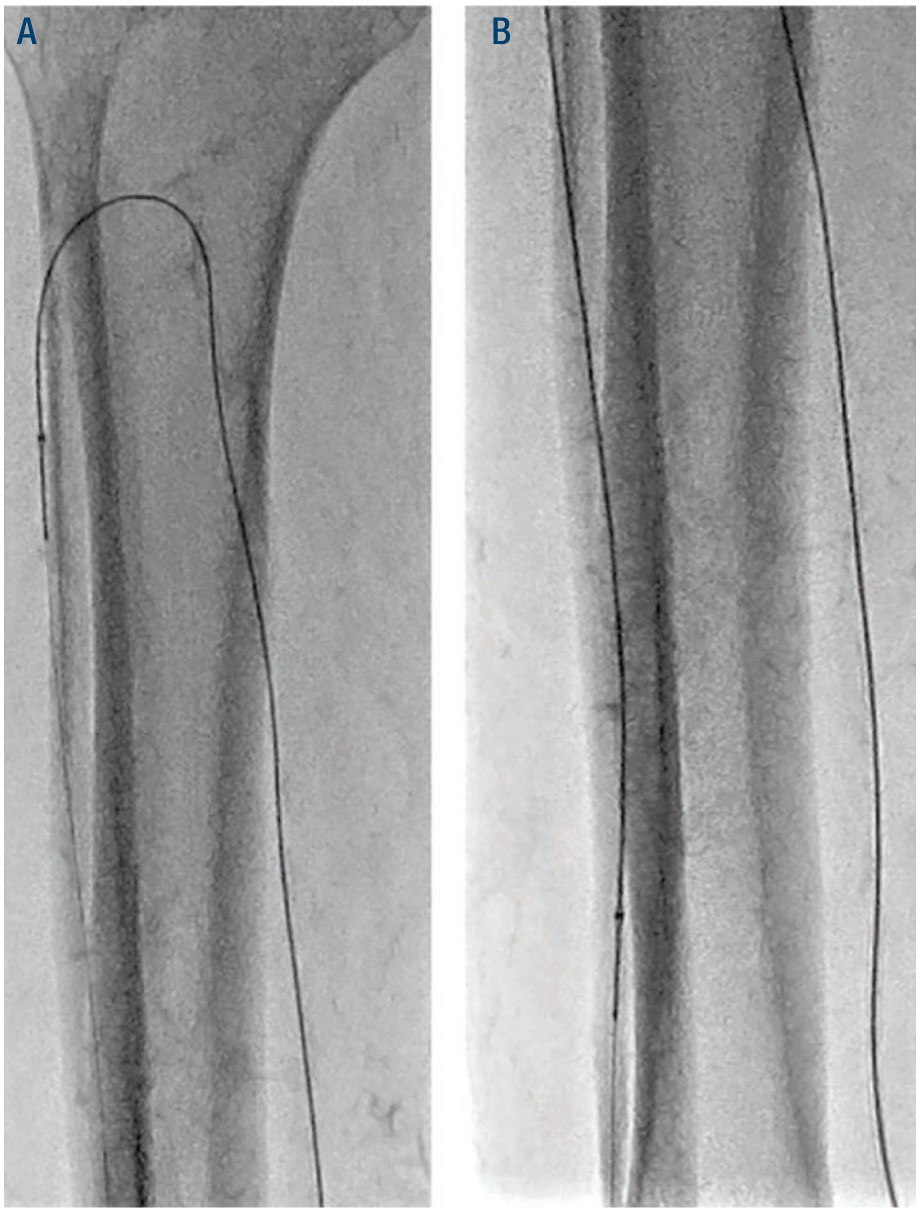

Figure 5. Atherectomy of ATA through PTA access with 1.5 Classic CSI catheter. ATA = anterior tibial artery; PTA = posterior tibial artery; CSI = Cardiovascular Systems, Inc.

With the evolution of endovascular techniques, historically untreated patients have options. Tibiopedal artery minimally invasive (TAMI) approach is safe and feasible when avoiding transfemoral access complications.

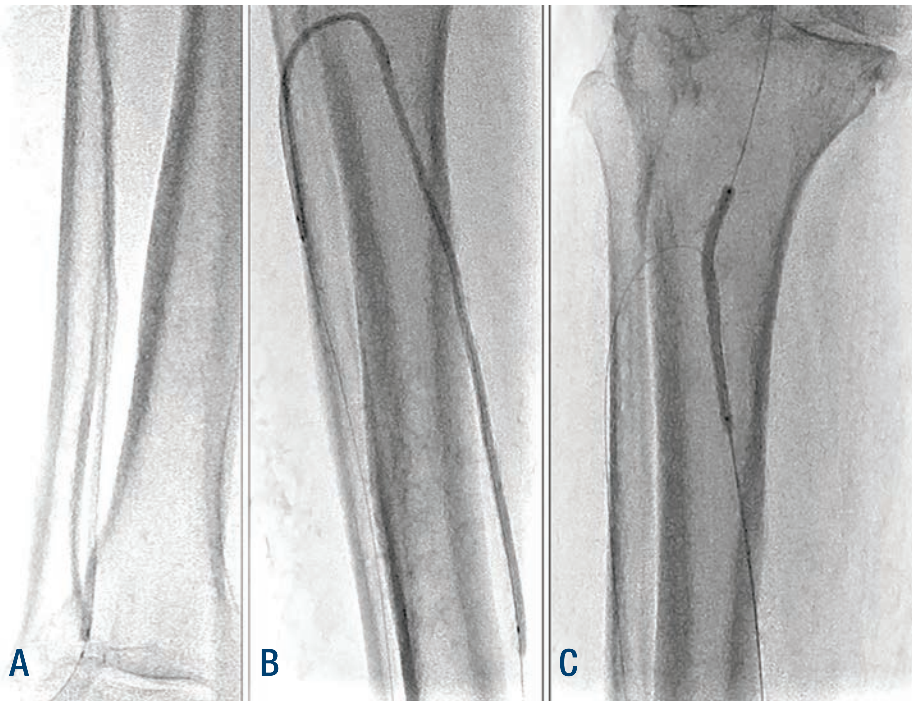

Figure 6. Angioplasty of ATA, PTA, and TPT. ATA = anterior tibial artery; PTA = posterior tibial artery; TPT = tibial peroneal trunk

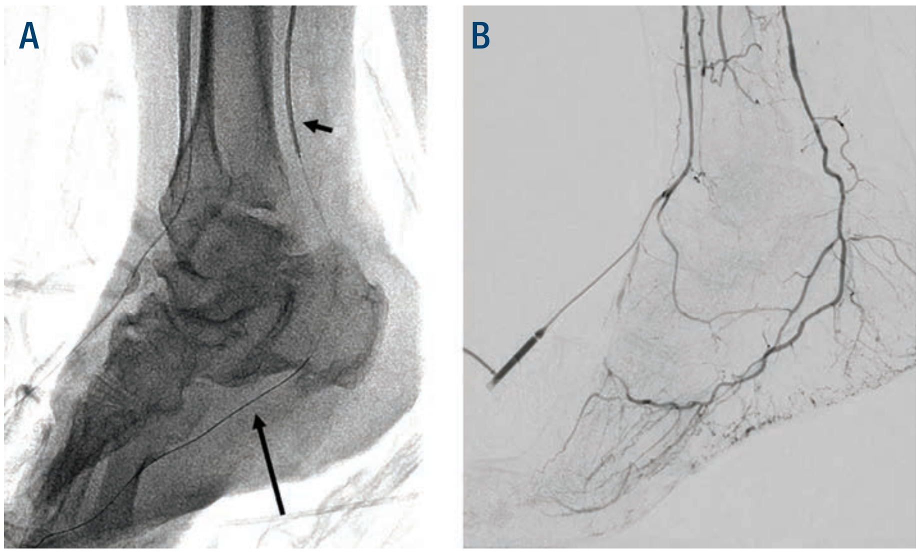

Figure 7. (A) Short arrow points to PTA access balloon tamponade, long arrow is pointing at Fielder XT. (B) Successful hemostasis.

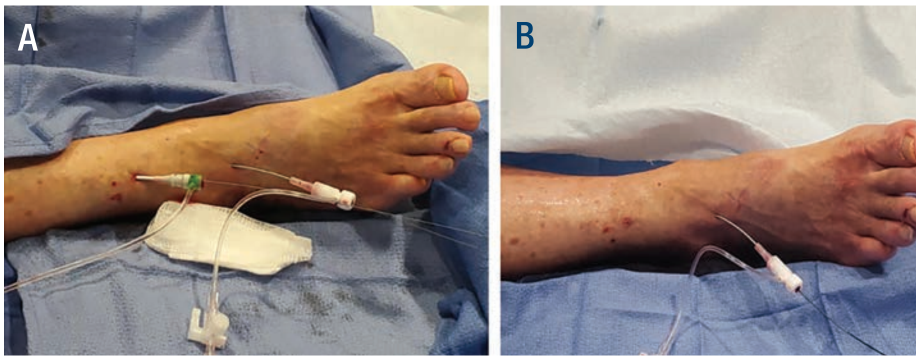

Figure 9. TAMI with a 5-6 Fr GSS and a distal 2.9 Fr sheath inserted at the end of the case for balloon tamponade of the 5-6 Fr sheath with 3.0 mm Advance Micro (Cook) balloon. GSS = Glidesheath Slender (Terumo Medical).

To reduce the risk of access-related complications, we usually perform balloon tamponade with 2.5- or 3.0-mm Advance Micro 14 2.5-Fr balloon through a distal 2.9-Fr sheath which can safely be closed with minimal manual pressure.

DCB (BD Bard) with an excellent result (Figure 6).

A 3.0- x 80-mm Advance Micro 14 2.5-Fr (Cook Medical) balloon was inserted through the retrograde ATA 2.9-Fr sheath over the ViperWire guidewire which was exchanged for a 0.014-inch Fielder XT (Asahi Intecc) and advanced distally to the 4- to 5-Fr GSS PTA access for intraarterial balloon tamponade to obtain hemostasis (Figure 7). Finally, the retrograde 2.9 Fr ATA sheath was removed, and hemostasis was achieved with manual pressure (Figure 8). He tolerated the procedure well and ambulated an hour later. He underwent additional debridement and placement of a wound vac.

The TAMI approach has been well documented. It can be utilized as an alternative in patients with high risk of complications related to transfemoral access. In other cases, we used up to 5 to 6 and 6 to 7 GSS sheaths. To reduce the risk of access-related complications, we usually perform balloon tamponade with 2.5- or 3.0-mm Advance Micro 14 2.5-Fr (Cook) balloon through a distal 2.9-Fr sheath which can safely be closed with minimal manual pressure (Figure 9). We always utilize a hockey stick ultrasound probe to obtain access. We maintain an ACT greater than 250 seconds during the case. We inject between 200 or 400 mcg of intra-arterial nitroglycerin for vasodilation and repeat the same process every thirty minutes. ■

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Disclosure: None.

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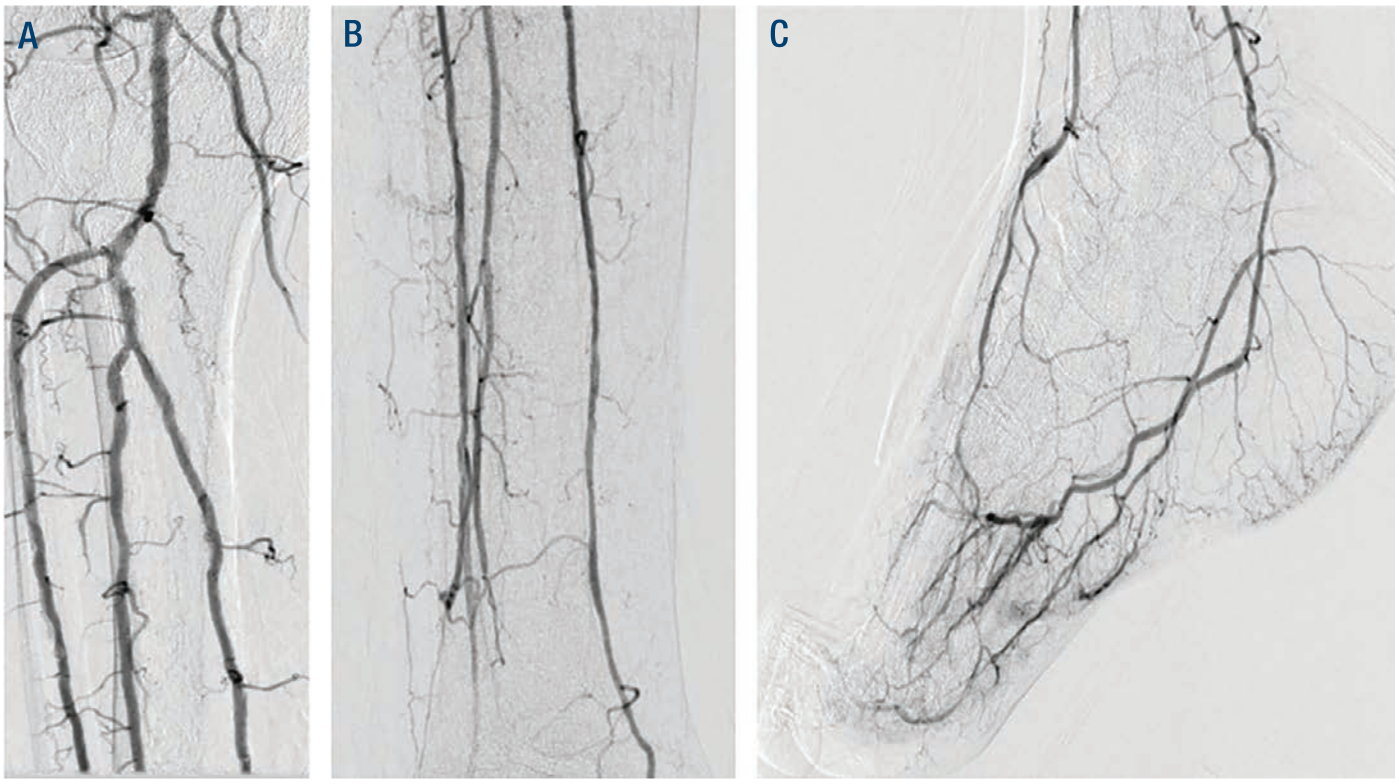

Figure 8. Final result revealed 3-vessel run-off with an intact plantar loop.

The STAND Trial: How the MicroStent® Attempts to Break Through Barriers in Below the Knee CLI

Omosalewa Adenikinju, MD; Michael Patel, MD; Adam Zybulewski, MD; Brandon Olivieri, MD; and Robert E. Beasley, MD

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CLI OVERVIEW

Peripheral arterial disease (PAD) remains a critical, independent predictor of coronary artery disease, cerebrovascular disease, and mortality.[1] A subset of PAD patients progress toward a malignant form of disease known as critical limb ischemia (CLI).[2,3] Vascular specialists and other providers alike cringe when the term 'CLI' is used, as the numbers '20/50' come to mind: 20% of patients with CLI die within 6 months, while 50% of patients die within 5 years. MicroMedical is researching how to flatten this curve by changing outcomes at 6 months and beyond.

The goal of CLI treatment is direct: relieve pain, augment wound healing, improve quality of life, and prevent amputation and mortality. Unfortunately, comorbidities such as diabetes, renal failure, tobacco smoking, heart failure, and infection tend to accompany CLI, leading to major amputation and subsequently, increased mortality.

In order to understand the intent behind the pivotal STAND (Clinical Evaluation of the MicroSTent PeripherAl Vascular SteNt in Subjects with Arterial Disease Below the Knee) trial, it is important to comprehend the barriers of clinical success in below-the-knee (BTK) revascularization.

BARRIERS TO SUCCESSFUL BTK TREATMENT

BTK disease is commonly composed of complex tandem, long-segmented lesions that require complicated revascularization techniques. Currently, there is no U.S. Food and Drug Administration (FDA)-approved stent for primary treatment of BTK disease. Thus, treatment of these complex, diseased vessels has been limited to angioplasty, recent atherectomy, and off-label use of drug-eluting coronary stents in the setting of matched luminal diameter and previously revered drug-coated technology. These treatment modalities, which are sometimes used as bailout options in limb salvage cases, do present challenges.

Despite angioplasty after optimal nominal balloon diameter selection, Baumann et al[4] state that up to 97% of cases have a significant amount of vessel recoil in complex BTK lesions, thus only temporizing the luminal gain and inline flow achieved shortly after procedure completion. It is also well established that the microtrauma exhibited by plaque during angioplasty can lead to non-flow and flow-limiting dissections in approximately 20% to 30% of cases.[5-7] Dissections often go untreated as many are underreported or missed, especially in the absence of intravascular ultrasound (IVUS). These tend to become a nidus for restenosis or occlusion.[5-7]

Atherectomy devices, including laser and orbital atherectomy, can decrease plaque burden in tibial vessels. However, their utility can be limited to vessel size compatibility and true lumen use depending upon the debulking method chosen. Even then, these therapies may need adjunctive therapy from percutaneous transluminal angioplasty (PTA) or stenting.

The use of off-label drug-eluting coronary stents BTK has been employed in complex limb salvage cases for years. Historically, size compatibility and drug-eluting technology made this a viable option to improve and maintain inflow in the BTK vessels, with favorable outcomes as demonstrated in the ACHILLES trial, which showed high patency rates at 1 year with balloon-expandable drug-eluting stents in BTK vessels compared to PTA.[8] However, in lieu of the recent paclitaxel conundrum set forth in 2018, application of the once-prized chemotherapy agent in the treatment of PAD/CLI must now be evaluated on a case-by-case basis due to the possible increased mortality signal. In addition, due to their intended use, coronary stents are typically short (<4 cm in length) and are typically applied only to the proximal tibial vessels when feasible. Since they are balloon-expandable, these stents tend to have limited flexibility and have less radial strength than self-expanding stents, thus bringing a higher risk of extrinsic compression.

With the present challenges, it is imperative to use evidence-based medicine when forming a treatment algorithm for BTK revascularization. Historically, the BASIL trial simulated equal amputation-free survival at 6 months between patients undergoing PTA versus infrainguinal saphenous vein bypass to an above-the-knee or BTK arterial segment. The BASIL trial proved that an endovascular approach is as efficacious and less expensive than a surgery-first strategy for the treatment of infrainguinal disease in CLI.[9]

Subsequent studies, such as the meta-analysis by Caradu et al,[10] demonstrated no significant advantage in off-label use of balloon-expandable bare metal stents versus PTA in patency or wound healing, but highlighted good results with self-expanding stents for PTA bailout. However, no direct comparison was made to PTA in that analysis.

The randomized YUKON-BTX and DESTINY trials have demonstrated higher rates of freedom from target lesion revascularization (TLR) when comparing bare metal and drug-eluting stents BTK, but a clear clinical benefit has yet to be shown.[11] There are conflicting conclusions on improvement in Rutherford class, a query on the economic benefit of drug-eluting stents, and no significant difference in major amputations or survival has yet to be demonstrated between bare metal stents and drug-eluting stents.[12-14]

Thus, in the U.S., use of BTK stenting has traditionally been reserved to combat recoil and dissections in complex CLI cases, especially in patients that are poor surgical bypass candidates.[10] Although some of the trials that have led to such employment may have been limited by statistical power and short-term assessments, their findings may also be reflective of the existing technology and comprehension of CLI (from vessel histology to the pathological implications of this systemic disease) at that time, both of which have vastly evolved.

The current BTK revascularization outcomes thus far, in addition to the paclitaxel conundrum, suggests that the challenges in treating BTK disease in CLI have yet to be met. The meta-analysis of Romiti et al[15] demonstrated more than 90% of patency failures and amputations occurred within 6 months after endovascular infrapopliteal treatment. This timeline parallels the average wound healing time seen after complex BTK revascularization.[16,17] Keeping '20/50' in mind, along with the poor outcomes described throughout this article, the efficacy that can flatten CLI mortality is apparent by 6 months. By establishing primary effectiveness and safety endpoints at 6 months, the STAND trial seeks to break down the barriers that have held us back from successful BTK treatment.

THE MICROMEDICAL SOLUTIONS MICROSTENT®

The MicroMedical Solutions MicroStent® is a self-expanding nitinol stent designed with the intent to treat BTK vessels in CLI and combat the alarming amputation

CASE EXAMPLE

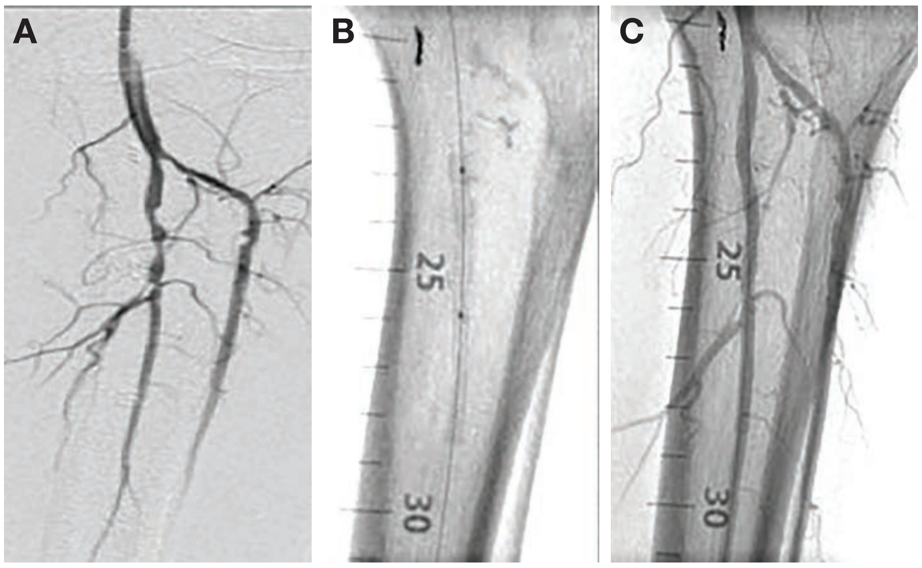

Figure 1. 59-year-old patient with history of smoking, hypertension, dyslipidemia, stroke, and PAD with debilitating RC IV left lower extremity pain with ankle-brachial index indicative of moderate PAD. Digital subtraction angiography demonstrates (A) 5.1 cm (length) target lesion in the 3 mm (diameter) tibioperoneal trunk with multiple tandem significant stenoses on angiography and IVUS (not pictured), with sluggish flow distally. (B) Successful deployment and post dilation of a 3 x 40 mm MicroStent® with post deployment length of 5.8 cm, providing adequate lesion coverage. (C) Completion angiography demonstrates less than 10% residual stenosis with improved flow.

and death rates. With the goal of limb salvage, the stent has been tailored to meet the challenges that come with diseased tibial vessels. The woven nitinol composition makes the scaffold highly conformable without excessive outward force. This is advantageous as it allows for the following:

(1) **Precise deployment.** The lesion length is matched to the predicted stent length upon deployment based on vessel diameter. With help from the 3 French (Fr) MicroGuide® catheter, this ensures reliable and accurate stent selection by the operator and precise delivery.

(2) **Optimal stent opposition.** The stent adheres to varying eccentric plaque morphologies as seen on IVUS, permitting luminal gain in lesions that normally recoil after angioplasty, for example. Notably, the integrated platinum core provides unequivocal visualization on follow-up intra- and extravascular ultrasound. Outcomes are enhanced with the use of IVUS, considered "best practice" in the ongoing STAND trial. IVUS helps to characterize the lesion in three dimensions, and evaluate flow and optimal stent apposition post deployment.

(3) **"Gentle" luminal gain.** As excessive chronic outward force between the intima and stent can propagate inflammation promoting in-stent restenosis (ISR),[18] especially in small-caliber arteries, this stent's self-expanding scaffold negates elastic recoil with gentle outward radial resistive force to decrease the rates of ISR.

Lastly, the stent comes in varying sizes to treat vessel diameters ranging from 2.5 to 4.5 mm, and lengths from 8 to 60 mm, delivered on the 3 Fr MicroGuide® catheter. Catheter delivery lengths are available in 40 cm and 120 cm, permitting retrograde and antegrade deployment. These evolutions in design aim to provide successful long-term outcomes in CLI patients after primary stenting. How does this low-profile, flexible, easy-to-use delivery system translate clinically for our patients?

MICROMEDICAL SOLUTIONS MICROSTENT® FEASIBILITY STUDY

Here we provide a brief overview of the results from the feasibility study performed in 2018. The study consisted of 15 patients of Rutherford classification IV-V with tibial disease. Average lesion length was 40.6 mm (42.7 mm on core lab analysis), with an average of 93% stenosis (74.8% on core lab analysis). One hundred percent technical success (defined as stent full expansion, deployment without deformation, and lesion coverage as intended) was achieved in all cases, based upon independent analysis from a core laboratory. Clinical Events Committee and core lab-adjudicated primary patency was 91.7% at 30 days in device-related analysis. The safety endpoint, a composite of freedom from major adverse limb events (MALE) and freedom from perioperative death at 30 days, was 100%. At 6 months, the gold standard in order to ensure optimal wound healing was 90.9% primary patency and 100% primary safety.

STAND TRIAL

After promising results from the initial cohort, the FDA approved the pivotal STAND trial to evaluate the MicroStent® for primary instruction-for-use stenting in tibial vessels. STAND is a randomized, multicenter, clinical study of the MicroStent® device versus PTA in up to 177 patients across 25 sites in the United States. Cadaver lab training was provided to operators. The study aims to demonstrate that the MicroStent® is superior to PTA alone in achieving and maintaining vessel patency and improved blood flow.

Primary efficacy endpoint: Primary patency at 6 months. Primary patency is a composite of freedom from occlusion, clinically driven TLR, and major amputation.

Primary safety endpoint: Freedom from perioperative death and MALE at 30 days and 6 months, respectively, based on the FDA primary safety endpoint for CLI trials adopted from Conte et al.[19]

Hypothesis-tested secondary endpoints include the reduction in size of ischemic wounds at 6 months.

As mentioned previously, outcomes success for endovascular treatment of infrapopliteal lesions is largely apparent by 6 months post procedure. The STAND trial's primary endpoints are 6 months, but long-term follow-up will continue for 3 years.

The STAND trial is in the early enrollment phases with the first patient enrolled in early April 2020. Figure 1 describes this case, which mirrors the high-risk demographic #CLIFighters evaluate and treat to prevent amputation and thus reduce mortality. We look forward to the 30-day follow-up, which is pending at the time of authorship.

HEAL REGISTRY

As our globe battles the challenges brought forth by COVID-19, enrollment in the STAND trial has been temporarily paused to ensure the safety of physicians and patients. The MicroStent® is also under investigation in Europe through the HEAL registry, which began enrollment in October of 2019. The HEAL registry is an open-label, all-comers registry in Italy, Belgium, Germany, Netherlands, and Austria, seeking to characterize the real-world use of the MicroStent®, with open inclusion and exclusion criteria. Furthermore, as regards real-world experience, the registry places no parameters on adjunctive therapy, permitting evaluation of the MicroStent® in conjunction with additional treatments. The primary effectiveness endpoint is primary patency at 6 months post procedure, as defined by freedom of target lesion occlusion and clinically driven TLR. The safety endpoint is freedom from major adverse limb events. Additional enrollment and analysis are forthcoming.

CONCLUSION

As our world heals from the impacts of the COVID-19 pandemic and research continues, we remain enthusiastic in our view of how the MicroStent® will contribute to the dynamic limb salvage treatment landscape, with its goal of clinically effective change by 6 months. ■

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Understanding the Tibial-Pedal Arterial Anatomy: Practical Points for Current Clinical Presentations

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The lower limb arterio-venous vasculature has a gradually tapering distribution, with around 91% of cases showing typical patterns of vasculature and 9% with anatomical variations, and is closely related to the muscular components of the leg.[1,2] Arterial vasculature of the calf and foot gathers three main vascular bundles: the anterior, the posterior, and the peroneal arteries. These arteries correlate with four distinct anatomical compartments in the calf, and nine others in the foot, and are associated with roughly sixteen corresponding inframalleolar bundles.[1-3]

In addition to this balanced compartmental distribution, the lower limb arterial tree follows specific areas of tissue framed in characteristic vascular modules, known as "angiosomes."[4] Similar to genuine muscular compartmental orientation, the angiosome partition expresses topographic reproducibility in humans.[4-6] The angiosomal branches are not indivisible, or "terminal" ramifications of the entire arterial tree.[4,5,7] They are millimetric branches that further divide in smaller divisions ("final ramifications"),[4,5] before reaching the arteriolar level with specific, topographically oriented zones of tissues. From the main ilio-femoral flow sources, throughout the angiosome branches, and down to the capillaries, a harmonious "pyramid of gradual limb flow distribution" is created.[4,5] This vascular system is structured in several levels of tapering vessels (Levels I to VI)[7] toward specific angiosomes.[7,8] Each of these levels continuously provides coordinated and dynamic adaptations in regional perfusion, in accordance with various endogenous and exogenous factors.[7-10]

Every bifurcation becomes progressively thinner than its parent trunk.[9,10] Each arterial path progressively branches into inferior degrees of segmentation that ultimately creates a wider cross-sectional area toward peripheral tissues and increases the amount of perfusion to the tissue.[9,10]

It is important to note that even in the presence of sparse arterial anatomical variants (9-12%),[1,2] the limb maintains steady vascular distribution among all compartments, angiosomes, and their collateral networks.[1,5-7] No random flow is observed among the calf perfusion sectors, or between the dorsal and the plantar territories of the foot.[2,6,7] Appropriate knowledge anatomical features of the lower limb is beneficial for the interventionist. Such knowledge facilitates diagnostic solutions in various presentations of ischemic limbs, as well as a better perspective of outcomes when planning revascularization for optimal tissue regeneration.[6-8]

MAIN TIBIAL TRUNKS

The anterior tibial artery (AT) originates at the interosseous membrane of the calf as the first principal infragenicular arterial branch. At this level, it reveals a constant angulation (of changing degrees in individuals), "the hook." Calcifications may commonly be encountered at this anterior crossing point[6-8] between distinct leg compartments. This calcification is thought to be due additional stiffness and turbulences that are induced by the surrounding fibro-tendinous structures.[7] The AT artery courses within the anterior compartment of the lower leg and foot and is associated with relatively uncomplicated interventional and surgical access for revascularization.[5,11-13]

Interestingly, according to the remarkable anatomical description by Taylor, muscles in the anterior compartment of the lower limb, and also in the dorsal foot are only supplied by one specific AT angiosome.[5] This high-value information can assist in better understanding of certain ischemic wound presentations in the presence of stenotic AT flow and related loss of collaterals.[5,7] It also can facilitate better planning for regional revascularization.

At the ankle level and underneath the extensor retinaculum of the foot, the AT transitions into the dorsalis pedis (DP) branch. This zone of flow towards the pedal circulation represents a second area of increased flow turbulences and a higher risk of local atherosclerotic occlusive disease along the course of the vessels.[7,12]

Both the AT and DP provide flow to the superficial and deep structures (DP angiosome) of the dorsal aspect of the foot, up to the toes.[4-6] The AT also supplies the anterior peri-malleolar ankle perfusion.[4-6] The AT terminates at the first dorsal metatarsal space by dividing the arcuate artery, an influential compensatory vessel of the dorsal angiosome that also affects the entire forefoot and distal limb preservation.[6-8,14,15] At the same level, the DP creates the first dorsal metatarsal artery and the deep plantar artery. These three DP-dependent branches are large collaterals (around 1 mm diameter) and provide a weighty local compensatory flow of >80 mL/min.[10,12,16]

Anatomical variations. According to a recent meta-analysis by Kropman and colleagues that included 7671 cases, atypical calf and foot arteries were observed in approximately 7.9% to 10% of individuals.[1] High origins (at the popliteal level) of AT, or atypical tibial trifurcations, were reported in 5.6% to 6.2% of individuals, while abnormal DP origins were found in 4.3% to 6% of cases.[1,2,7] An anomalous first dorsal metatarsal artery origin, associated with atypical first toe collateral perfusion, was described in 8.1% of individuals, concomitant abnormalities of the arcuate artery in 5%, and variants of plantar arches and plantar arteries in 5%.[1,2,7,12] The presence of one atypical tibial or pedal presentation on one leg should alert the interventionalist to a 21% risk of encountering similar abnormalities on the contralateral extremity.[1,2,7] Although it is useful to acknowledge these abnormalities, these anatomical variants may prompt a more detailed local angiosomal flow evaluation, yet only lead to small changes in wound-targeted revascularization.[6-8] This strategy follows and adapts to every available local collateral network, with or without uncharacteristic anatomical features.[7]

Practical issues. Large DP collaterals (±1 mm diameter) on the lateral side of the foot (the "lateral tarsal" or "diagonal arteries") connect the AT territory to the lateral plantar branches that belong to the posterior tibial artery (PT), in an effective regulatory system.[5-8,17] In cases of DP thrombosis in patients with unaffected diagonal vessels, healing of dorsal foot and anterolateral ischemic wounds can be observed as a result of these collateral branches.[6,8,17] Conversely, with thinner (<1 mm) and less available collaterals on the medial aspect of the foot (medial tarsal arteries), the same DP dysfunction seldom allows recovery of dorsomedial CLI ulcers, and wounds improve only via indirect, medial plantar collateral support.[6,7,17]

The posterior tibial artery (PT) bifurcates the tibio-peroneal trunk (TPT),[2-3] cm distally from the AT emergence. The PT courses along the deep posterior compartment of the calf where current surgical[15,18] or endovascular approaches[11,19] for revascularization procedures can be initiated. A higher frequency of long (>15 cm) calcific obstructions in the segment of the PT appears to be more prevalent in diabetic and renal patients.[13,17] At the ankle level, in the retro-malleolar zone, the PT crosses the retinaculum of the flexor muscles of the foot, a transition zone towards the fixed plantar circulation.[10,17] This high shear-stress zone (similar to the adductor ring for the superficial femoral artery, or the extensor retinaculum for the AT),[16,17] equally inflicts local turbulence of flow and chronic endothelial injuries that may lead to a higher prevalence of atherosclerotic disease.[10,13,17] After releasing its medial calcaneal branch, the PT bifurcates at the plantar aspect of the foot, into the medial and the lateral plantar arteries. The lateral plantar vessel represents an important, large caliber (1-1.5 mm) terminal PT bifurcation that further creates the deep plantar arch. Both foot arches share vital compensatory flow via the deep plantar artery, an important trifurcation branch from the DP.[4-6] The PT, via its medial calcaneal branch, and through the medial and lateral plantar source arteries, provides angiosomal topographic flow for the plantar portion of the foot and toes, in addition to providing 70% of perfusion in the heel.[5-7,16]

Anatomical variations. According to the meta-analysis by Kropman and colleagues, PT native variants can be found in about 6.8% of individuals.[1] Among these variations, PT artery hypoplastic, aplastic, or high emergences were observed in 3.3% of cases. TP dominance (absence of the AT artery) was documented in 1.5% of cases,[1,2] whereas atypical plantar arch and plantar arteries were seen in 5% of cases.[1] In atypical cases, the vast majority of the plantar vessels have a peroneal origin.[1]

Practical issues. As mentioned for the dorsal foot and the arcuate artery (DP/AT), the lateral plantar artery (PT) holds a parallel and key role for the plantar side of the foot. Probably among the most difficult ischemic foot lesions to treat by purely hemodynamic means are those located at the hallux level.[6-8] The hallux and the first interdigital space territories are an important collateral hub of the forefoot.[7,10,17] This zone is a watershed area from at least two or three neighboring angiosomal "source arteries." These watershed arteries

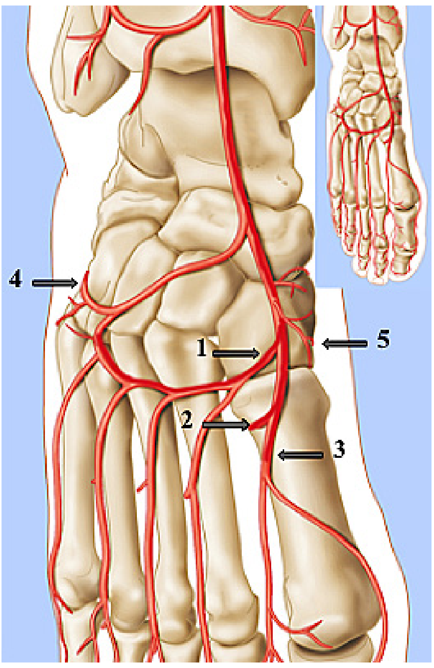

Figure 1. Schematic representation of the dorsalis pedis artery and its main branches:
1. Arcuate artery.
2. Deep plantar artery.
3. First dorsalis metatarsal artery.
4. Lateral tarsal (diagonal) arteries.
5. Medial tarsal arteries.

are the first dorsal metatarsal artery (DP/AT), and the media and lateral plantar arteries (PT).[1,6,17] Critical ischemic wounds/necrosis confined to this level are often expressions of a wider and multilevel occlusive disease, located upstream of the pedal vessels.[6,13] Necrotic lesions detected in this foot territory frequently indicate severe disease of the plantar and forefoot collateral web, and critical injury of more than half of all native compensatory hallux interdigital collaterals.[7,14,17]

In the anterior and posterior tibial-pedal arterial vasculature, specific "high shear-stress" flow zones have been described. These zones seem preferentially exposed to severe atherosclerosis, chronic occlusions, and heavy calcifications.[8,13] Therefore, the "flexor retinaculum" passage (concerning the PT), the interosseous membrane transition point (the AT), and also the "extensor retinaculum" (the AT), all represent constant challenging zones for endovascular techniques,[8,13] via either antegrade or retrograde passages and approaches.[11-13]

The peroneal artery (PA) supplies the lateral compartment of the leg. The PA is often seen as a "rescue" revascularization trunk, as it shows less significant atherosclerotic occlusive disease in the common CLI context. Accordingly, it can support current surgical[15,18] or more demanding endovascular transcutaneous approaches[11,19] for reperfusion. Despite traveling in the deep posterior compartment of the calf, the PA ends superficially by its lateral calcaneal branch, a "terminal-type" branch that provides 30% of the heel perfusion.[10,16]

From a clinical perspective, the peroneal artery provides two important collateral branches at the ankle level: the anterior and the posterior communicants that join

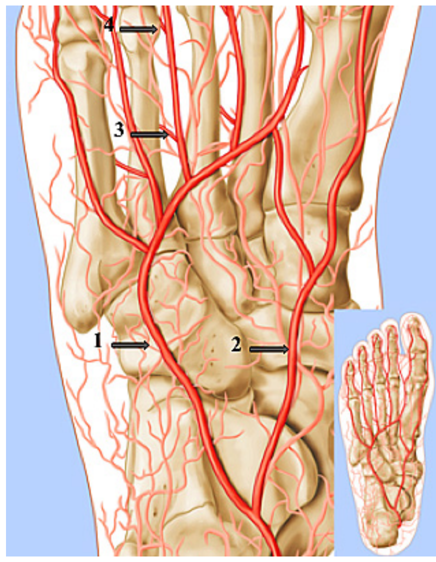

Figure 2. Schematic representation of the main branches of the plantar foot arteries:
1. Lateral plantar artery and plantar arch.
2. Medial plantar artery.
3. Proximal perforating arteries.
4. Distal perforating arteries.

anterior and PT arteries, respectively, in a high-value collateral rescue network.[6-9,15-17]

As an angiosomal "source arteries" provider, the peroneal trunk lends flow to a more narrowed zone of the lateral heel via its lateral calcaneal artery, and also to the anterolateral ankle via its anterior perforating branch and source artery.[4-6]

Anatomical variations. The peroneal artery shares fewer independent abnormal distributions than those described among all tibial trunks. Most cited variants are associated with a high peroneal origin from a dominant calf peroneal trunk in hypoplastic or aplastic PT presentations (± 3%).[1,2]

Practical issues. In the CLI context, the peroneal trunk currently has fewer calcifications than the AT or PT, with higher technical accessibility for surgical or endovascular techniques for limb salvage.[13,17,22] Large-caliber anterior and posterior communicants may provide good filling in the foot arches, although only in isolated collateral patterns.[13,16,17] Accordingly, some authors have labeled the PA as "the best artery to treat," particularly in the multifaceted diabetic foot context.[20-22] Although the PA can provide an effective rescue supply for most CLI Rutherford 4 presentations,[20-22] its usefulness in healing Rutherford [5-6] forefoot or hindfoot complex tissue lesions by unspecific indirect revascularization remains questionable.[14,17,23-25] Meticulous preoperative angiographic assessment may enable us to identify and utilize every individual peroneal flow distribution and collateral partition when planning wound-targeted revascularization.[7,13,17]

For further discussion, including pedal arches, angiosomes of the lower leg, and variations of the ischemic foot, see VASCULAR DISEASE MANAGEMENT 2019;16[7]:E179-E182.

Practical issues. Specific forefoot and hindfoot ischemic wounds or multiple CLI ulcers often reveal severe neighboring collateral deprivation that originates from two or three affected neighboring angiosomes.[6-8] In such cases, routine angiosomal evaluation can be arduous to perform. Advanced macro and microcirculatory CLI conditions perpetuate the destruction of collateral and cutaneous perforators.[7-9] These patterns are frequently encountered in diabetic or renal patients[8,21-23,28] with severely distorted angiosomal landmarks.[7,8,17,28] Clinical representation of the most impressive ischemic ulcer or necrosis zone may not always relate to the lowest perfusion area in CLI feet.[8] Irregular decay of collaterals,[7,8,17,28] the patchy distribution of remnant choke vessels and cutaneous perforators,[5,17,27] local capillary shunting by severe neuropathy,[7,28] sepsis triggering edema, and deep compartment hyperpressure[7,17] may all lead to substantial variations in "real-life" CLI presentations.

Parallel risk factors for tissue recovery such as chronic inflammation, fibrotic scars, recurrent sepsis, extended necrosis, and regional hyper-pressure syndromes, may lead to acute thrombosis of small collaterals, particularly the highly vulnerable interdigital and cutaneous perforator branches.[7,14,17,28] Understanding these elements may help clinicians to better decode the real ischemic burden of each ulcer presentation and more completely assess eventual wound-directed revascularization.

CONCLUSIONS

From main ilio-femoral vascular sources, throughout the angiosome branches, and up to the arteriolar and the capillary vasculature, there is a harmonious pyramid of gradual arterial limb flow distribution. CLI is associated with specific infragenicular patterns of arterial atherosclerotic decay. Compensatory flow pathways are useful for interventionalists to understand for eventual topographic foot reperfusion. Regardless of irregular collateral availability, efficient limb revascularization must involve direct, in-line arterial reperfusion from the level of the iliac down to the foot arches to achieve limb salvage and adequate wound healing. ■

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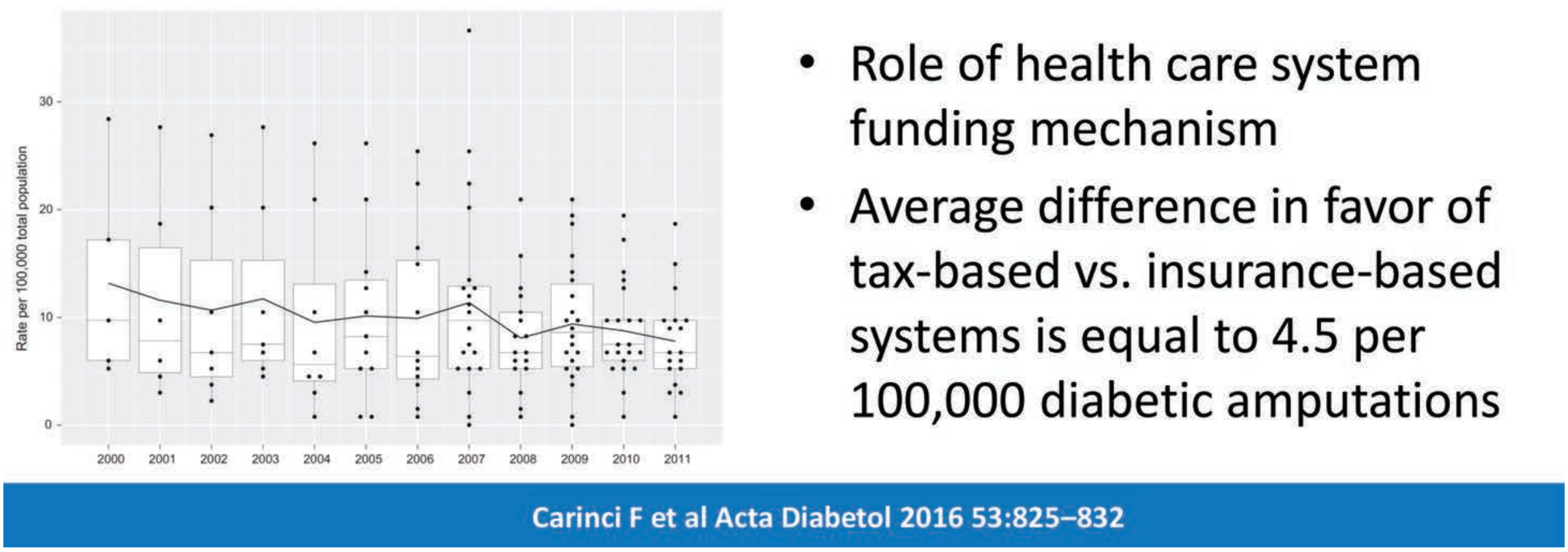

Figure 1. Lower extremity amputation rates in diabetes. OECD 2000–2001.

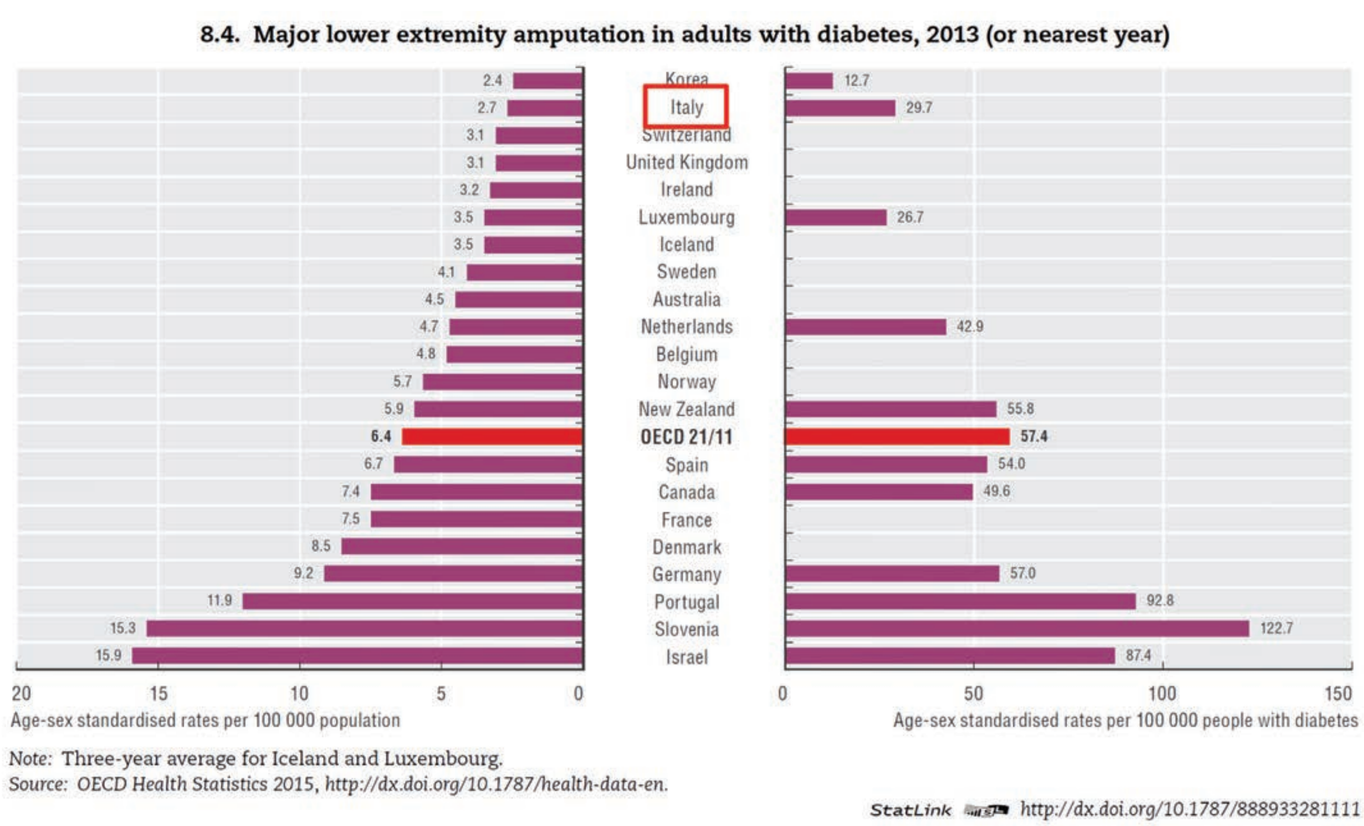

Figure 2. Major lower extremity amputation in adults with diabetes, 2013 (or nearest year).

VAN DEN BERG *from cover*

Major amputation is associated with shorter survival time, higher risk of subsequent major amputation, and higher healthcare costs.

with its highly fatal course make this disease an underrecognized major threat to public health.[1]

CLI SITUATION IN EUROPE

The Organization for Economic Cooperation and Development (OECD) studied lower-extremity amputation (LEA) rates in people with diabetes from 26 European countries from 2000 to 2011. The study showed a decline in amputation rates of more than 50% from a mean of 13.2 (median, 9.4; range, 4.1–28.1) to 7.8 amputations per 100,000 in the general population. Despite the decline, still in 2011 an amputation attributed to diabetes occurred every 7 minutes (216 amputations per day). Variability between countries exists and is difficult to explain. For example, Germany has a rate of amputation more than 18 times higher than Hungary (18.4 vs 1.1 per 100,000). The result for Germany may be biased by a higher number of minor amputations in the numerator or lack of accurate data, given that there is no national register to verify the precision of these estimates. The data from these 26 countries show lower amputation rates in health systems financed by public taxation. The average difference in favor of tax-based versus insurance-based systems is equal to 4.5 per 100,000 diabetic amputations (Figure 1).[11]

In a similar study that examined a time period between 2000 and 2013, Carinci et al reported a mean reduction of major amputations in the general population from 10.8 to 7.5 per 100,000 (-30.6%). Additionally, a mean reduction of major amputations in people with diabetes from 182.9 to 128.3 per 100,000 (-29.8%) was seen. Interestingly, minor amputations remained stable over the study period. The implementation of standardized definitions, necessary to increase the comparability of multinational data, highlighted remarkable differences between countries. Therefore, these results can help identify and share best practices effectively on a global scale (Figures 2 and 3).[12] An overview of data available from various European countries can be found below.

CLI SITUATION IN BELGIUM

In a nationwide study of 5,438 individuals provided by the Belgian national health insurance funds, covering more than 99% of the Belgian population (approximately 11 million people), the risk of undergoing a major lower extremity amputation in Belgium gradually declined for individuals between 2009 and 2013. Many reports have demonstrated that a substantial decrease in the incidence of major amputations, as well as a decrease in the total incidence of amputations in people with diabetes, is feasible after the implementation of multidisciplinary and trans-sectoral programs for diabetic foot ulcer care and prevention. A new finding of this was the strong decline in the major amputation rate in people with diabetes, but not in people without diabetes. The relative risk comparing people with and without diabetes decreased but remained high. The decline in the amputation rate in those with diabetes was particularly prominent for major amputations above the knee. A weaker, but still significant decrease in the amputation rate for minor lower extremity amputations with and without diabetes was also observed.[14]

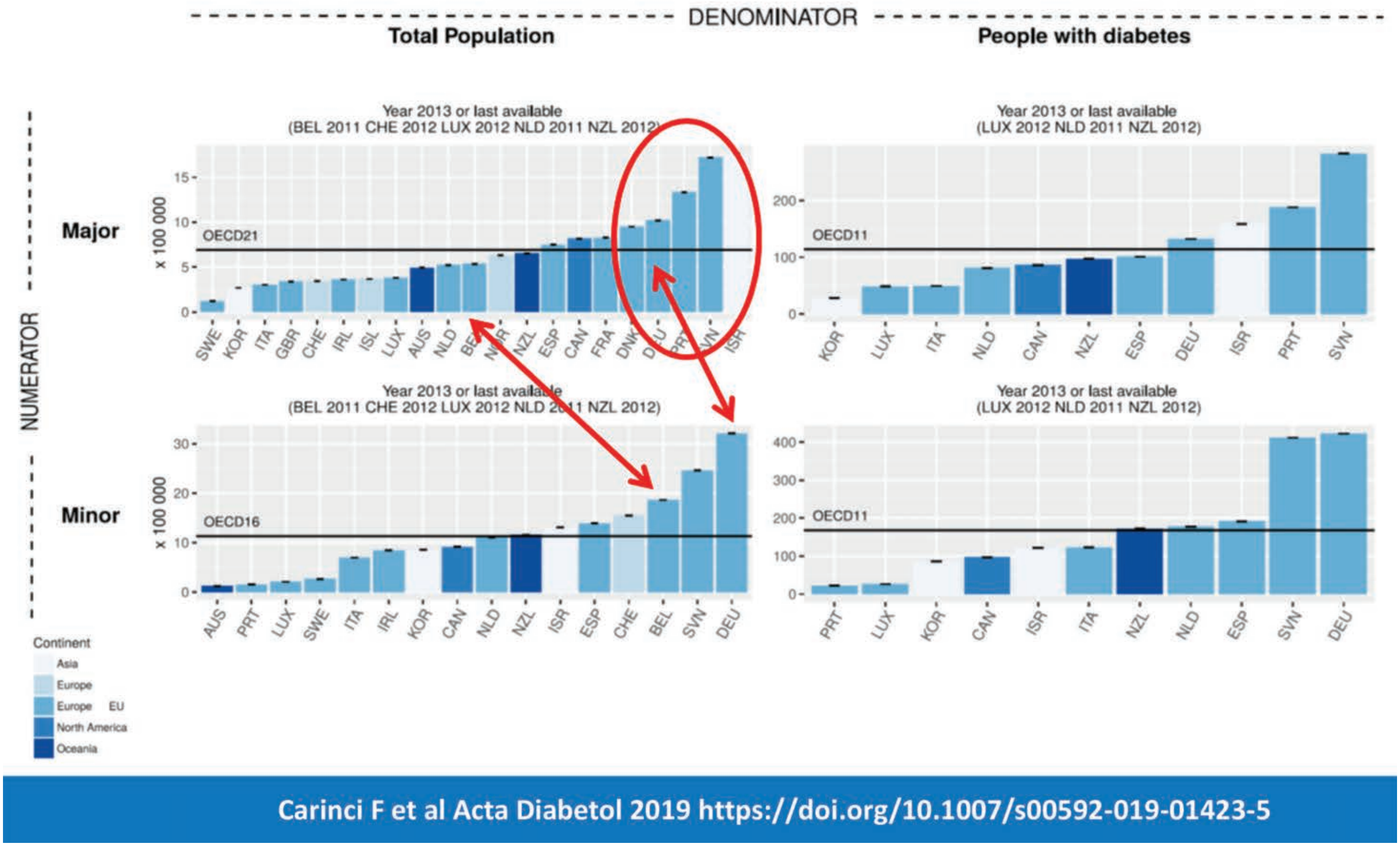

Figure 3. Lower extremity amputation rates in diabetes according to different definitions, year 2013, or last year available, OECD data collection 2013.[12] Used with permission from Springer Nature.

CLI SITUATION IN GERMANY

A study by Heyer et al showed that the amputation rates per patient in Germany have remained stable in the overall population, while a slight decline in patients with both diabetes mellitus and with arterial occlusive disease between 2006 and 2012 was seen. The authors recommend the implementation of intensified preventive measures that are considered crucial to the permanent reduction in the number of amputations of the lower extremities.[15]

In a retrospective analysis of the database of the largest public health insurance in Germany, which included all in- and outpatient diagnoses and procedural data obtained from a cohort of 418,882 patients hospitalized due to PAD during 2009 to 2011, including a follow-up until 2013, it was shown that 44% of amputees with CLI did not undergo a diagnostic angiogram in the hospital prior to their amputation. When taking into account a 24-month time frame prior to the amputation, the number of patients without angiography or revascularization attempt during the index hospitalization, or the 2 years before, was slightly lower, but still 37%.[16]

This information is particularly disturbing as many studies, including one by Henry et al, report that if angiography is performed in order to evaluate the options for endovascular or surgical revascularization, the risk of major amputation can be 90% lower.[17]

CLI SITUATION IN THE NETHERLANDS

A study by van Houtum et al, including data from 1991 to 2000 from the Dutch National Medical Register, showed that in 1991, a total of 1,687 patients with diabetes had been admitted 1,865 times for 2,409 amputations. In 2000, a total of 1,673 patients with diabetes were admitted 1,932 times for 2,448 amputations. The overall incidence rates of the number of patients who underwent lower extremity amputations decreased over the years from 55.0 to 36.3 per 10,000 patients with diabetes ($P<.05$). This rising population with diabetes combined with a decline in major amputations reflects an increased attention toward the diabetic foot. The number of hospitals in the Netherlands with access to podiatrists increased from 32% in 1995 to 72% in 2000. The number of multidisciplinary foot clinics increased from 16% to 40% in the same time frame.[18]

The first striking observation in the study was the decrease in the number of diabetes-related lower extremity amputations in the Netherlands over a period of 10 years. The incidence decreased by 26% in men and 38% in women with diabetes. A clear explanation for the difference in growth in the numbers of individuals with diabetes between men and women is lacking. The prevalence of diabetes diagnoses in the U.S. also showed a greater increase in men than women.[19]

The increase in the prevalence of diabetes in the Netherlands was marked and in agreement with previous reports that predicted an increase in the prevalence of diabetes, resulting partly from demographic changes.[20]

The authors concluded that the incidence of individuals with diabetes who are hospitalized for lower-extremity amputations is decreasing in the Netherlands, but despite this, there is still room for improvement. It is possible that increased use of minor amputations may result in a lower incidence of major amputations, with their impact on patients' quality of life. Therefore, more must be done regarding selection of amputation level, possibly enabling a decrease in high-level amputations.[18]

CLI SITUATION IN DENMARK

A study by Jorgensen et al of a Danish diabetic specialist center from 2000 to 2011 showed an incidence of all lower-extremity amputations in Type 1 diabetes of 87.5% for men and 47.4% for women. It showed in incidence of all lower-extremity amputations in Type 2 diabetes a decrease of 83% for men and 79.1% for women ($P<.001$). No significant change in cadence of minor amputations was noted. Due to improvements in metabolic risk factor and lifestyle factor management, increased emphasis on early and aggressive treatment of foot ulcer and better patient education may have contributed to these results.[21]

CLI SITUATION IN ITALY

A study conducted using the National Hospital Discharge Record database for the period 2001 to 2010 looked at lower extremity amputations in persons with and without diabetes in Italy. The study showed a reduction of major amputations during the study period of patients with diabetes (30.7%) and without diabetes (12.5%). The rates of minor amputations for those without diabetes increased 22.4% and those without diabetes remained stable. These data reflect an improvement in the quality of diabetes therapy as well as in the overall approach to diabetic foot care such as the inclusion of peripheral vascular revascularizations, for example.[22]

Continued on page 18

COVID-19 *from cover*

test immediately upon admission to the emergency room and likely wait to treat until results were known. In the interim, the patient would be started on anticoagulation and antiplatelet therapy. "We have seen an anecdotal change in the last several weeks to a less liberal stance to intubate COVID-19 patients due to the dismal prognosis for those who are intubated. We have adopted an almost never intubate approach to these patients. I think this approach is being replicated around the New York area. Intubation is not considered benign and is really viewed as a high-risk intervention, even for emergent cases."

Dr. Richard Neville, from Virginia, stated that just a couple of weeks ago his institution may not have even intervened on this patient who would have been considered a Tier 2 patient. These patients would instead get treatment after 48 hours. However, over the past couple of weeks, the window has been expanded, and now Tier 2, or urgent, cases are being intervened upon immediately. If the patient has any symptoms, they would be tested. Without symptoms, standard precautions would be followed.

Q AND A

Q: What are your thoughts on testing for everybody?

A: Dr. Michael Jaff responded, "From a staff standpoint, it is reassuring and shows empathy and concern. Anything we can do to reassure staff is of great value. We need to keep in mind the facts regarding acute diagnosis: active viral shedding tests were designed to diagnose sick patients and not designed to screen populations of asymptomatic patients. The false negative rates, in my view, are unacceptable and give people a false sense of security." Dr. Jaff underscored the fact that staff should know you care and are trying to protect them as best you can.

Q: Are patients comfortable being treated in an outpatient setting versus a hospital and what type of protection are you providing?

A: Dr. Jihad Mustapha, who performs CLI revascularization in a busy outpatient CLI center in Michigan, described seeing an increase in patients being referred from the hospital systems to the outpatient center for treatment. "Hospitals are performing fewer non-COVID procedures and patients fear going to a hospital setting. We provide screening of patients and staff and provide adequate PPE for our staff. Patients are comforted by being treated in an environment where they believe their risk of exposure is less."

Q: What are you seeing in the United States regarding urgent versus emergent treatment for patients with CLI needing podiatric surgery?

A: Dr. Driver reports that her experience now on the west coast and her communication with the east coast confirms that CLI patients are being seen in the clinic setting as much as possible and being kept out of the ER. Minor procedures needing to be done urgently are being done in the outpatient setting as much as possible.

Q: There has been a lot of talk of arterial and venous thrombosis in the COVID environment.

What is your opinion of the risk of COVID to patients with CLI and vice versa?

A: Dr. Lookstein reports anecdotally seeing a massive uptick in large vessel strokes in a unique population much younger than typically seen. We are seeing patients who underwent endovascular therapy in the last 6 months coming in with a complete thrombosis of the infrainguinal circulation, where the typical presentation would be a focal restenosis. This is mostly not a chronic CLI population, however, but rather a more ALI population.

Q: Who in hospital administration in the United States came up with the theory that procedures like CLI are not important and urgent procedures to be done? What is the CLI Global Society's statement on this matter?

A: Dr. Katzen responded on behalf of the Board with assurance that they believe CLI is an urgent, life threatening disease that needs to be addressed in that manner. The goal is to prevent loss of life and loss of limb. The CLI Global Society supports this type of therapy as needing urgent and emergent attention. Dr. Neville's experience is not necessarily that the administration thinks CLI is any less important, but rather they were dealing with a utilization problem. "We saw what was happening in New York and it scared the heck out of everybody. The response was to shut down at first to reserve resources. We've now backed off on that after having secured resources. However, I do think we potentially are going to see an increase in amputations during this COVID period due to this." Dr. Jaff, as a former hospital administrator, stated that the hospital administrators were not the decision makers. "The truth of the matter is that Medicare, American College of Surgeons, and American College of Cardiology came out with guidelines. Quite frankly, our voice wasn't loud enough."

Q: Do you feel that treating CLI in the COVID era conveys a higher risk for the CLI patient?

A: Dr. Mustapha responded, "CLI patients are fragile. Treating them now in this era to keep them out of the hospital is more important than ever before."

Q: Is COVID less disruptive in New Zealand?

A: Dr. Holden responded, "One of the advantages of living on a couple of islands in the South Pacific may have afforded some protection. However, the New Zealand government went hard and went early on a complete isolation and lockdown that I believe helped us. One of the things we did right from the beginning was to state that any CLI patient presenting acutely would be treated acutely in our hospital system with the kind of protection mentioned earlier. As we open up more of our clinics, we have been swamped with late-presenting CLI patients who have been battling on at home despite huge advertising campaigns urging patients not to wait to seek needed therapy."

Q: As we are starting to look at recovery in various parts of the world, will we see a deliberate attempt to push things more into the ambulatory space than they were before?

A: Dr. Mustapha stated, "Actually, I see the future to be right for CLI centers like ours because the patients can be isolated, you can control who comes in and out, you can deliver the majority of care you need to delivery, and the safety is extremely good. I look forward to a future with more CLI centers. For me, it's been a great experience."

Q: Germany has had the lowest mortality rate of almost any place in the world. Does this translate into a population less fearful of hospitals?

A: Dr. Zeller stated, "This differs from region to region in Germany. In my area we have an infection rate of less than 2% at the moment. In our institution and our area, patients do not seem to fear coming to the hospital. So, we did not have the experience of patients coming in with delayed treatment. We did inform our physicians right from the beginning to refer CLI patients for therapy. We are not experiencing an increase in amputation; I believe due to this.

Q: What is happening in wound centers? How far can telehealth go for this population?

A: Dr. Driver responded, "These are very important questions because patients are being left behind. Programs with good telehealth are critically important. If you have a patient with a CLI diabetic foot with potential sepsis, it is critical to get them in front of a provider. Many wound care centers are completely closed down. Centers of excellence, particularly with combined vascular and podiatric specialists, that are separate from the hospital are being allowed to stay open. But there are not many of them." Dr. Neville reports that his organization has four wound centers. Their volume is down about 50%. "As we protocolize who is to be seen at our wound centers, we are hoping to stretch telemedicine to 80% of all visits. We are currently at about 60%."

LESSONS LEARNED

Professor Zeller: I believe what we've learned during this discussion is that the pandemic is hitting different regions in different severity stages and therefore all recommendations cannot be generalized. In areas with high infection rate, testing is important. However, you may have 4–6 hours to wait for the test. In areas with low infection rates, I believe we can proceed with our standard technique and procedural steps to take care of patients and staff.

Dr. Mustapha: This pandemic forced us to become more efficient and nimbler to address the urgent needs of CLI patients while adapting to the changing environment.

Dr. van den Berg: I think what we have learned from this pandemic is that in addition to all the damage that was done by the virus, there is a lot of collateral damage due to delayed treatment affecting patients with CLI, but also patients who need to postpone oncology treatment among other things. We are bracing for the impact when we can fully reopen our activity. We need to be prepared for longer working days.

Dr. Driver: The bottom line is that we are still fighting for our patients. In the middle of a pandemic, if not treated, these patients are going to lose their limb or their life. We have to keep fighting for them and help them understand the best way to get care from us. We can't back down.

Dr. Holden: Planning and preparation is important. There is a large, silent group of patients who are going to turn up in the next few weeks. I believe there is always a positive and there are opportunities that will come from this, opportunities to be more efficient and improve the way we communicate with patients and educate our colleagues. Take this webinar for example. We should embrace the good things that come out of it.

Dr. Neville: I think the importance of the CLI Global Society is now more important than ever in terms of raising awareness and advocating for our patients.

Dr. Lookstein: I am very proud to say that at our institution none of the staff have become symptomatic despite having done hundreds of cases over the past weeks, with close to 150 of those being COVID positive. I think that is because we've all come together as a dedicated team motivated to do the right thing. This is a testament to how you can be successful and understand you can overcome the challenges we are all facing.

Dr. Jaff: I am heartened by how the scientific community around the world has banded together to share data. As we come out of this, the voice of the physician is going to be even more important. This is particularly new to us because the US is going to have to figure out how to rebuild healthcare again and we need to have a loud and upfront voice. ■

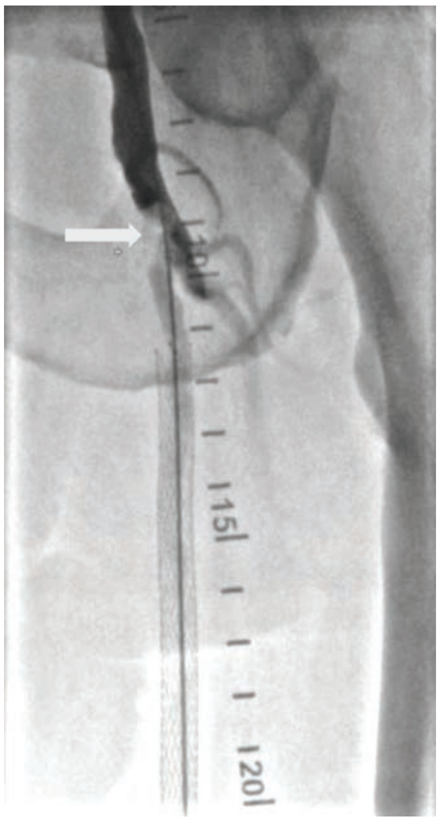

Figure 1. 85-year-old male with Rutherford class 3 claudication with severely calcified CFA disease.

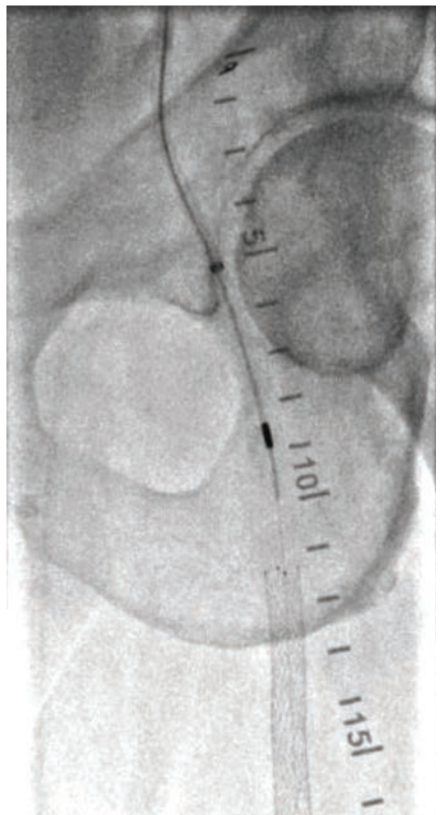

Figure 2. Orbital atherectomy with a 1.5-mm crown.

Figure 3. Balloon angioplasty with a 6- x 40-mm drug-coated balloon.

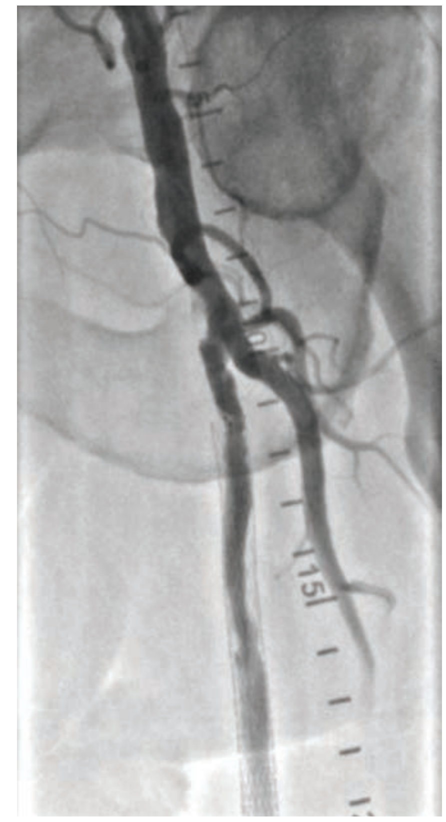

Figure 4. Final angiographic result.

LEE *from page 3*

at the inguinal ligament, as it may lead to stent fracture. An interwoven nitinol stent like the Supera stent (Abbott) is flexible and may lower the risk of stent fracture compared to other nitinol stents. However, the Supera stent strut design is not very conducive to ballooning the side branch. This may pose a challenge in the setting of distal bifurcation involvement of the CFA, which could lead to compromise of the deep femoral artery (DFA). Bifurcation lesions are also associated with increased risk of procedural failure and a trend toward higher 1-year rates of restenosis and target lesion revascularization.[5] The presence of a stent in the CFA could make arterial access and the use of a vascular closure device to achieve hemostasis more difficult. Stenting of the CFA may hinder the option of CFE. The rates of restenosis and target lesion revascularization are higher after PVI of calcified lesions.

Strategies to improve procedural success rates in heavily calcified CFA include the use of athereoablative devices and intravascular lithotripsy (Figures 1–4). We reported that orbital atherectomy appeared to be safe and effective for the treatment of severely calcified CFA.[6] The primary endpoint of angiographic complication, defined as the composite of dissection, perforation, slow flow, closure, spasm, embolism, or thrombosis at 30 days, was lower in the CFA group compared with the SFA group (17% vs. 24%, *P*=.02), driven by a lower dissection rate (10% vs. 15%, *P*=.04).

One of the disadvantages of PVI of the CFA is that it may compromise the DFA, which may be the last vascular conduit providing collateral flow to the lower extremity. PVI of the DFA is uncommonly performed because angiographic complications may lead to critical limb ischemia if it is the last remaining conduit to the lower limb. In 282 patients who underwent isolated DFA disease, the technical success rate was 94%, and the 30-day mortality rate was 1.8%.[7] We reported that orbital atherectomy of the DFA was associated with a low rate of the composite of flow-limiting dissection, perforation, slow flow, vessel closure, spasm, embolism, or thrombosis.[8] However, the number of patients in our study was low and limited to short-term follow-up.

In summary, controversy surrounds the ideal revascularization strategy for CFA disease. Surgery has long been considered the gold standard. However, despite the technical success of surgery, it is associated with complication rates. PVI of the CFA is associated with less procedural mortality and morbidity compared with surgery. PVI may represent a paradigm shift for the treatment of CFA disease. ■

Disclosure: None.

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VAN DEN BERG *from page 15*

CLI SITUATION IN SPAIN

López-de-Andrés et al studied Spanish national data from 2001 to 2008 that included 46,536 minor lower extremity amputations (LEAs) and 43,528 major LEAs. In patients with Type 1 diabetes, the incidence of minor and major amputations decreased significantly from 2001 to 2008 (0.88–0.43 per 100,000 inhabitants and 0.59–0.22 per 100,000 inhabitants, respectively). In patients with Type 2 diabetes, the incidence of minor and major LEAs increased significantly (9.23–10.9 per 100,000 inhabitants and 7.12–7.47 per 100,000 inhabitants). The decrease in LEAs in Type 1 diabetes may be related to more strictly controlled risk factors in these patients. The increased burden of amputations in patients with Type 2 diabetes suggests that diabetic foot care in Spain remains suboptimal.[23]

A similar study in Spain by Rubio et al compared amputation rates in people with and without diabetes during two periods: before (2001–2007) and after (2008–2011) the introduction of the Multidisciplinary Diabetic Foot Unit. A significant reduction in major amputations in people with diabetes was shown, from 6.1 per 100,000 per year (2001–2007) to 4.0 per 100,000 per year (2008–2011) (P=.020).[24]

CLI SITUATION IN THE UNITED KINGDOM

A study published in Diabetes Medicine by Moxey et al showed that the variation in incidence of amputation across the United Kingdom ranges in rates from 3.9 to 7.2 per 100,000 (P <.0001).[25] These differences are mainly related to the variability in implementation of specialized diabetic foot care.

CONCLUSION: CLI IS A GLOBAL SITUATION

Significant global variation exists in the incidence of lower extremity amputation. Ethnicity and social deprivation play a significant role, but it is the role of diabetes and its complications that is most profound. Significant reduction in the incidence of lower extremity amputation have been shown in specific at-risk populations after the introduction of specialist diabetic foot clinics.

Patients initially diagnosed with CLI suffer poor long-term prognosis and generate high healthcare costs. Long-term survival and cost are comparable between revascularization techniques (surgical and endovascular). Compared with each approach, primary major amputation is associated with shorter survival time, higher risk of subsequent major amputation, and higher healthcare costs. It is clear that considerable efforts are needed to raise disease awareness, implement coding to better define and identify the disease, refine diagnostic algorithms, establish evidence-based treatment pathways, and address the high mortality rates associated with this diagnosis.[26]

Please join the CLI Global Society at cliglobalsociety.org to contribute to global efforts to eliminate unnecessary amputations due to critical limb ischemia. ■

It is possible that increased use of minor amputations may result in a lower incidence of major amputations, with their impact on patients' quality of life.

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