CLI GLOBAL COMPENDIUM
THE GLOBAL VOICE OF CRITICAL LIMB ISCHEMIA

Long-term Clinical Success in a Diabetic Patient With Multiple Recurrences of In-stent Restenosis Involving Multiple Vessel Segments

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Jos C. van den Berg, MD
Guest Editor

This case report will describe a patient seen for the first time in July 2007 at the Ospedale Regionale di Lugano, a medium-sized regional hospital in Switzerland. At the time of first presentation, the patient was 73 years old. He suffered from type II diabetes mellitus, had visual impairment related to his diabetic disease, and had undergone an above-knee amputation of the right leg 4 years earlier. He presented now with a nonhealing wound on the left foot. He still had a good quality of life, and given his previous right-sided amputation, it was even more important to aggressively treat him when he presented with critical limb ischemia of the left leg, in order to avoid an amputation on the left.

The first intervention involved treatment with conventional balloon angioplasty of a stenosis of the superficial femoral artery (SFA), and of an occlusion of the tibioperoneal trunk extending into the posterior tibial artery and peroneal artery. An excellent angiographic outcome was achieved. One month later, the patient's limb ischemia had not improved. A high-grade restenosis of the tibioperoneal trunk, posterior tibial artery, and peroneal artery was diagnosed and a new endovascular procedure was planned. Bare-metal T-stenting of the distal tibioperoneal trunk/peroneal artery and posterior tibial artery was performed, and the patient's clinical status improved. Three months later, a new occlusion of the SFA and an occlusion of the posterior tibial artery were diagnosed. Recanalization of the occluded stent in the posterior tibial artery was not successful, and the short occlusion of the SFA was treated with plain balloon angioplasty.

Six months from initial presentation, the patient presented with clinical deterioration of the left leg. A restenosis

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Fighting the Good Fight Against CLI

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Critical limb ischemia (CLI) continues to be a challenge on many different fronts. There is no doubt that hospital administrators, health care providers, and device manufacturing companies have the patient at the top of their priority list; however, they all face a unique set of obstacles to providing optimal care. In these pages, we explore what it takes for administrators and clinicians to provide the intricate and expensive care required for the CLI patient.

Over the years, many of my colleagues have expressed to me that their administration and support staff frown on the time it takes to complete a CLI endovascular procedure, that the pre and post care required frustrates staff, and that costs per procedure get the attention of the hospital administration. I happen to be in an institution that has taken a

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Comprehensive Care of the Critical Limb Ischemia Patient From Preprocedure to Long-term Follow-up

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It is important for the critical limb ischemia (CLI) provider to grasp the totality of optimal care for a CLI patient. That is, before embarking on limb salvage, the provider and patient should plan a strategy not only for revascularization, but also for meticulous wound care, diabetic management, foot surgery consultation, detection and treatment of infection, nutrition, secondary prevention of atherosclerotic events, antithrombotic therapy, surveillance for patency, and secondary prevention of CLI following limb preservation. Preoperatively, a frank discussion with the patient addressing the importance of this approach and acknowledging the commitment to optimal CLI care is paramount. Patient motivation is a key component for clinical success, as these marginally ambulatory patients often are best served by attending multiple appointments across several specialties for at least several months, if not years.

Often, revascularization is the most urgent component of care for a CLI patient, because typically appropriate debridement and foot surgery are postponed until revascularization is achieved. Additionally, definitive management of infection may depend on the results of live tissue culture obtained at the time of foot surgery, which may be delayed until revascularization is achieved. As such, an important part of preprocedural care is to minimize unnecessary diagnostic testing that might delay revascularization. Our approach is to use diagnostic testing to identify ideal access sites for revascularization. We reserve catheter-based angiography to delineate the tibioperoneal anatomy, which is nearly always diseased in the CLI patient.

Intraprocedurally, a sound strategy for CLI management is to restore in-line flow to the wound. This approach is a balance between revascularizing what is most technically feasible, even if that arterial conduit is not in the angiosome of the wound, and revascularizing a target that directly supplies a wound. In the common scenario of multivessel, below-knee disease, our approach is to revascularize the more technically straightforward tibioperoneal vessel first and then proceed with the more challenging tibioperoneal vessel, either in the same procedure or in a staged manner. In this high-risk population, strategies to minimize access sites, arteriotomy size, and contrast administration serve the patient well.

In the early postprocedural period, an admission to the hospital can be a convenient opportunity for multiple specialties to assess the CLI patient. The patient can receive appropriate debridement and quantitative live tissue culture in the operating room. This period also provides the opportunity for advanced imaging for infection, diabetes management, creation of nutrition goals, and, if not already established, initiation of a wound care algorithm.

Following hospital discharge, the CLI patient will need meticulous wound care and surveillance for patency at a minimum. Intravenous antibiotics may also need to be managed. It is biologically plausible, even if not yet proven in the evidence base, that ongoing hyperglycemic management likely decreases time to wound healing, an important outcome for the CLI patient. Simultaneously, optimal medical therapy for secondary

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

Should Amputation Still Be Considered Primary Therapy for Critical Limb Ischemia?

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Lower-limb amputations are both common and costly in the United States (US). Approximately 120,000 lower-limb amputations are performed annually in the US[1-3] with nearly 85% above the foot and/or ankle.[4] The prevalence of lower-limb amputation is much higher at 1.3 million.[5] Peripheral artery disease (PAD) is responsible for the majority of these amputations.[5] Critical limb ischemia (CLI) is a serious form of PAD, and the average amputation rate among PAD patients with CLI is estimated to be 25%.[6]

Patients with CLI often have significant comorbidities including diabetes, hypertension, heart disease, and kidney disease.[7] They are also more likely to be 65 years or older and to have a history of smoking.[7] Because of their unfavorable risk profile, many CLI patients receive a major lower extremity amputation (MLEA) as a primary treatment. But limb salvage programs aimed at preventing these MLEAs offer an alternative treatment pathway. Moreover, limb salvage procedures may reduce costs while improving patient outcomes. Herein we examine the evidence on treatment costs and outcomes for primary MLEA vs limb salvage programs for CLI patients.

Is Amputation Cheaper?

To address this question, we developed a simulation model that estimates the potential lifetime economic savings to a national payer from implementing a limb salvage program for CLI patients in the US. The key clinical outcome was the reduction in MLEAs associated with a limb salvage program. Cost parameters included lifetime amputation burden and limb salvage program cost estimates. All parameter values were obtained from the published literature and adjusted to 2016 dollars using the Medical Care Component of the Consumer Price Index.[8]

The estimated lifetime direct health care cost for an MLEA patient is $794,027 (2016 USD).[9] This implies an expected lifetime cost for all MLEA patients (1.3 million) of more than $1 trillion. In the published literature, comprehensive limb salvage programs have been shown to reduce the rate of amputations from 36% to 86%.[10] Using the midpoint of this reduction (61%) and accounting for the estimated per patient cost of a comprehensive limb salvage program ($23,152) yields a cost savings of approximately $600 billion. The reduction in amputations from a formal limb salvage program is expected to save from $342 billion (assuming a 36% salvage rate) to $858 billion (assuming an 86% salvage rate). Thus, we conclude that the lifetime economic burden of amputees is very substantial and that a national limb salvage program may reduce this burden by hundreds of billions of dollars.

Do Major Amputations Lead to Poor Clinical Outcomes?

In addition to its enormous economic cost, amputation also imposes a very substantial human burden. As noted, an estimated 1.3 million Americans were living with a lower extremity amputation in 2015.[5] Subsequent amputations are often required; following an initial amputation, 27% of patients will have one or more reamputation(s) within a year.[4,11] For those patients that have a minor amputation, 40% progress to a higher level of limb loss within a year of an initial toe, foot, or ankle amputation.[4] Among diabetic patients this rate rises to 62%, and 55% of diabetic amputees get an opposite limb amputation within 2-3 years.[12]

Post-amputation mortality rates are poor, with perioperative mortality at 4.2% to 10.4%,[13-15] 1-year mortality at 9.1% to 33%,[4,11] and the 5-year mortality at 25.6% to 81.5%.[11,16] Quality of life (QoL) suffers due to an increase in pain, anxiety, and depression.[17-20] People with amputations make significantly poorer psychosocial adjustments to their domestic and social environments, and report lower overall QoL.[18,21-22]

Why Is Amputation Still Considered Primary Therapy for CLI?

Given the enormous cost and poor health outcomes associated with primary amputation, it seems puzzling that MLEAs remain quite prevalent and are still considered a primary therapy for CLI patients. In part, this reflects a lack of consensus on primary amputation vs limb salvage for target populations such as CLI. For example, TASC II 2007 guidelines leave the physician considerable discretion in deciding whether or not to amputate. The guidelines state that while limb preservation can be achieved through a multifaceted treatment, primary amputation is favored if it offers an expedient return to a useful QoL, while avoiding an aggressive vascular reconstruction with little likelihood of healing.[7] Given the absence of clear guidelines and lack of consensus among key opinion leaders, physicians may tend to adhere to older, more familiar approaches, such as primary amputation.

In addition to its unfavorable economic and clinical profiles, amputation as a primary therapy makes little logical sense given the availability of a less invasive option such as revascularization. Simply put, one can follow a failed limb salvage effort with amputation, but the reverse is not possible. Some researchers have argued that revascularization should be preferred to primary amputation based upon improved QoL, but a systematic review of this literature reports that the evidence on QoL is inconclusive.[23]

What's the Takeaway?

Clearly, a more nuanced, patient-oriented approach that considers clinical factors and patient functional status would seem more appropriate than preferring either amputation or revascularization a priori. Recent efforts to use the Lower Extremity Grading System (LEGS) as a guide to deciding whether revascularization or primary major amputation is appropriate is a step in the right direction.[24,25] Such approaches hold the promise for enhancing patient satisfaction and outcomes while containing costs. Preliminary investigations involving hospital-based, physician-led, comprehensive programs indicate that a multidisciplinary team-based approach to PAD management may lead to reduction in unnecessary amputation procedures.[26-28] A holistic amputation prevention program needs comprehensive pre- and postrevascularization procedures and wound care in order to guarantee quality and improved outcomes.

Furthermore, because early intervention is the key to success, government and regulatory agencies need to make age-based PAD screening mandatory. Extensive patient education and physician outreach efforts will also need to be expanded. Finally, policy makers should be particularly focused on reimbursement for preventive and early recognition/intervention programs, as well as aggressive limb-salvage procedures.

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Six of One, Half a Dozen of Another: Lower-Extremity Bypass or Peripheral Endovascular Intervention for Critical Limb Ischemia

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If your vascular clinic is like mine, you are seeing an ever-increasing number of patients with critical limb ischemia (CLI). Patients are often octogenarians with multiple comorbidities and chronic nonhealing lower-extremity wounds. As many of these patients lose their independence, family members often escort them to the clinic with their walkers or push them in their wheelchairs. Consultations are often urgent, limb salvage becomes a priority, the wound trajectory worsens, and digit amputations are contemplated in the setting of possible osteomyelitis.

Every day, clinicians in the trenches face this reality as the population ages. The numbers are staggering. Peripheral arterial disease (PAD) is present in 12% to 29% of the elderly and as many as 8 million to 10 million Americans, of which an estimated 10% will progress to CLI within 5 years, with the annual incidence of CLI ranging between 500 and 1000 cases per 1 million individuals.[1,2] Historically, treatments for CLI have yielded poor results. At 1 year, 25% of patients will be dead, 30% will have undergone amputation, and only 45% will remain alive with both limbs.[2,3] Just as importantly, health status outcomes (symptoms, function, and quality of life) are extremely poor in patients with CLI, with lower scores than patients with cancer, congestive heart failure, and chronic kidney disease.[4] Thankfully, these patients with the lowest quality of life impairment have the most to gain from our revascularization procedures.

In stark contrast to the evidence that supports revascularization procedures in the treatment of coronary artery disease, there is a paucity of data supporting the treatment of symptomatic PAD. For example, there are 44 level I or IIa recommendations in the ACC/AHA guidelines for percutaneous coronary interventions (either general agreement of benefit or consensus in favor of a treatment with robust evidence).[5] In 2005, there were 6 level I or IIa recommendations in the guidelines for the treatment of PAD, increasing to a total of 8 recommendations 6 years later with the updates to the guidelines in 2011.[6,7] This demonstrates the enormous evidence gap in the PAD arena. Although we look forward to the updates later this year to the ACC/AHA PAD guidelines as well as the consensus AUC (Appropriate Use Criteria) document for peripheral interventions, will it be practice changing? In the meantime, relatively small, single-center retrospective, observational analyses have shown that peripheral vascular intervention (PVI), in comparison to lower-extremity bypass (LEB), has lower procedural morbidity and mortality,[8,9] reduced costs, and shortened hospital lengths of stay.[10,11] In this context, PVI has become the dominant revascularization strategy for treating symptomatic PAD, increasing 1,000% over the last 10 years.[12]

The foundation for an endovascular-first strategy emanated from the BASIL (Bypass versus Angioplasty and Severe Ischemia of the Leg) randomized, controlled trial published 10 years ago, which demonstrated similar amputation-free survival in patients with CLI suitable for both LEB and PVI, with higher short-term morbidity with surgery (mainly due to myocardial infarction and wound infections).[13] To date, the BASIL study remains the only completed randomized, controlled clinical trial directly comparing angioplasty to surgical bypass for CLI. Many important post hoc clinical caveats should be emphasized: (1) in post-hoc analysis after 2 years, there was improved amputation-free survival with surgical revascularization; (2) in the percutaneous arm, only balloon angioplasty was studied (with a 20% 1-month failure rate) prior to the development of many of the endovascular devices and techniques currently being used today; (3) patients were a lower-risk selective cohort with approximately 90% of patients screened for the study excluded for unsuitable anatomy, comorbidities precluding surgery, or physician belief and preference for a specific revascularization strategy; (4) only 10% of distal bypass anastomoses were located distal to the popliteal artery and only 40% of patients had angioplasty performed distal to the superficial femoral artery; (5) 20% of patients in the endovascular treatment arm could not be treated due to an inability to cross a chronic total occlusion; and (6) only 46% and 34% of patients were treated with antiplatelet drugs and statins, respectively. Therefore, the only randomized clinical trial evaluating LEB vs endovascular angioplasty is almost an anachronism in the context of CLI treatment in 2016. Specifically, our patients have more advanced medical and anatomic complexity compared to the patients treated in the BASIL trial. Also, the endovascular techniques (e.g., pedal/tibial access, pedal loop revascularization, and angiosome-directed therapy) and devices for revascularization (e.g., crossing technologies, ablative therapies, drug-eluting stents, drug-eluting balloons) have evolved at a much faster pace than LEB techniques. Therefore, most vascular specialists would consider the BASIL trial to be antiquated, with little relevance to decision-making in contemporary practice.

Interventionalists are looking forward to seeing the results of the BEST-CLI trial, a prospective, multicenter, randomized study comparing "best endovascular" vs "best surgical" options for treating patients with CLI and infrainguinal PAD, which began enrolling in the fall of 2014.[14] This trial is funded by the National Institutes of Health and is designed to compare treatment efficacy, functional outcomes, and cost in 2,100 patients at 140 centers in North America over the next 4 years. All currently available endovascular therapies and all surgical bypass techniques and conduits will be allowed. Nearly 80% of these sites have multidisciplinary CLI teams that are collaboratively working to identify and enroll patients into their trial. Additionally, recently approved protocol modifications will allow for more complex anatomic disease such as severe femoral artery disease and aortic and iliac artery occlusions, as well as more medically complex patients such as those on immunosuppressive medications and with hypercoagulability. Broadening the inclusion criteria is an effort to be more inclusive of the "real world" patients seen in clinical practice and to facilitate enrollment with a goal completion time in 2017. Pragmatic clinical trials like BEST-CLI are randomized clinical trials that are designed to determine the risks, benefits, and costs of interventions as they would occur in routine clinical practice. Pragmatic features of the study include enrollment of a broad range of patients as well as inclusion of a broad range of treatment options (including nonstandardized wound care) by a broad range of providers within each comparator group. By study design,

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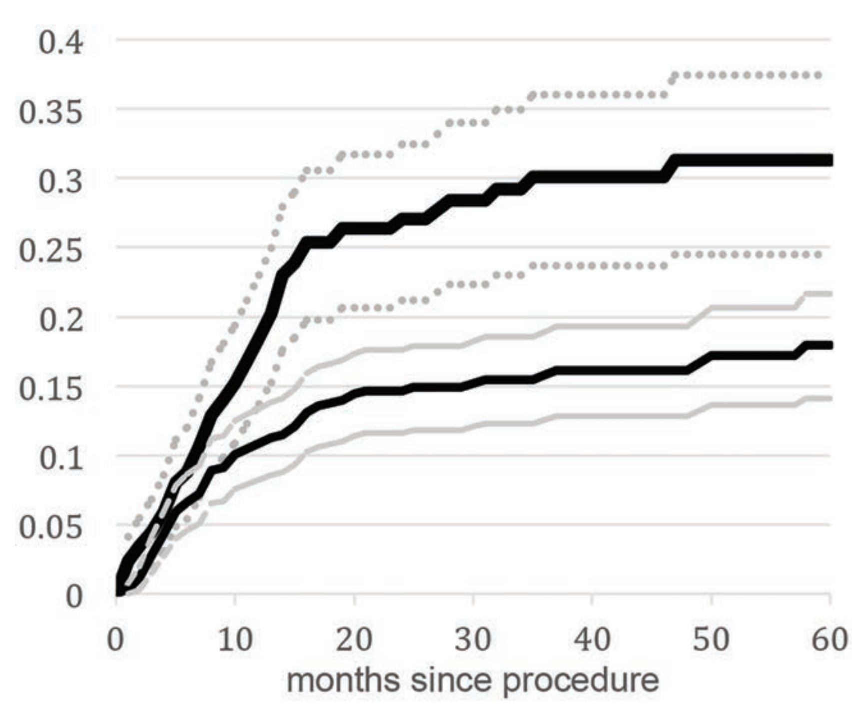

Figure 1. Cumulative incidence of target lesion revascularization. Solid line (95% CI dotted lines), peripheral endovascular intervention; long dashed lines (95% CI smaller dashed lines), lower-extremity bypass.

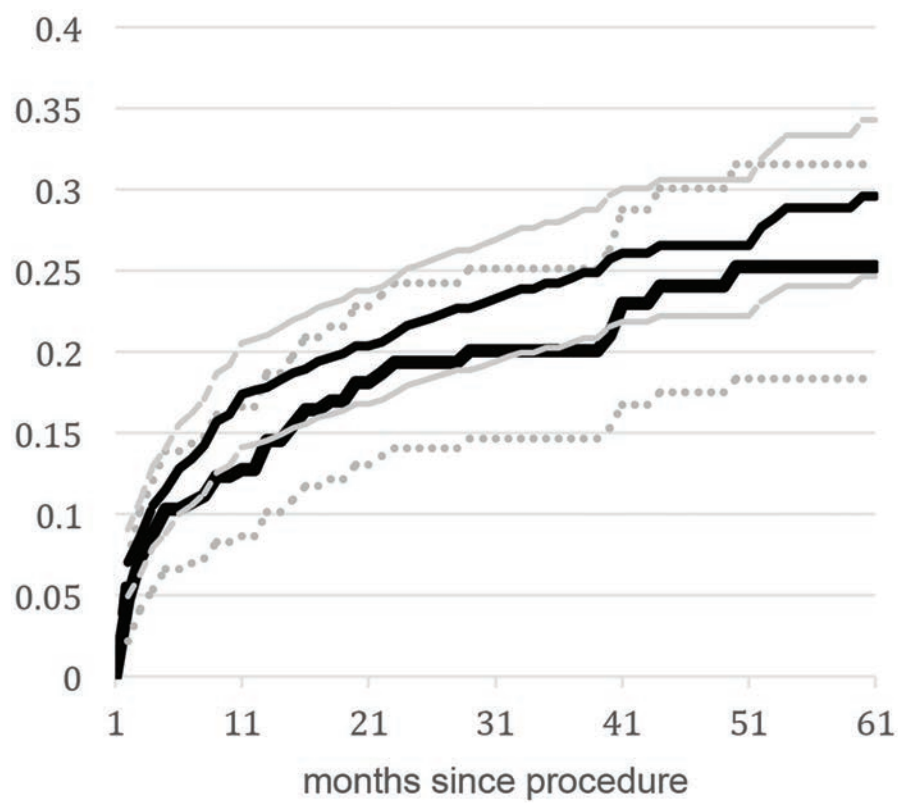

Figure 2. Cumulative incidence of major amputation. Peripheral endovascular intervention = solid line (95% CI dotted lines); lower-extremity bypass = long dashed lines (95% CI smaller dashed lines).

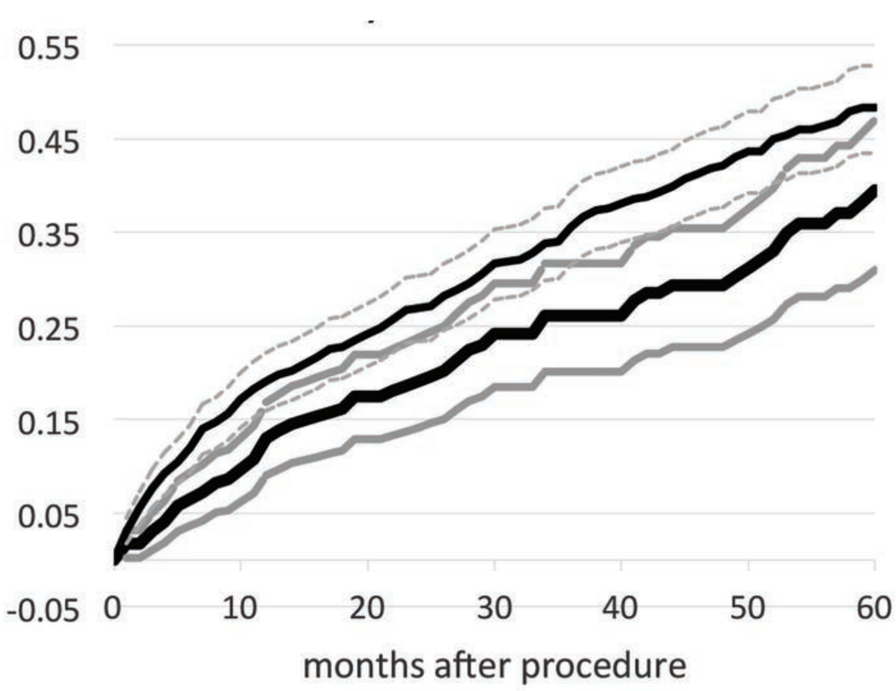

Figure 3. Cumulative incidence of mortality. Peripheral endovascular intervention = solid line (95% CI dotted lines); lower-extremity bypass = long dashed lines (95% CI smaller dashed lines).

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there will be substantial heterogeneity of treatment effect that may dilute any potential differences between LEB and PVI. Nonetheless, the BEST-CLI will provide critical information on the real-world outcomes of "best endovascular" vs "best surgical" options in treating PAD patients with CLI. With trial results expected in 2018, vascular specialists must continue to build on comparative effectiveness analysis applied to population-based registries to provide guidance on the treatment CLI.

In 2009, the American Recovery and Reinvestment Act stimulus package, enacted by the United States Congress and signed into law on February 17, 2009, by President Obama, included $1.1 billion for comparative effectiveness research to identify which interventions are most effective for which patients under specific circumstances and to assist stakeholders in making informed decisions. The Institute of Medicine then released its top 100 priorities for comparative effectiveness research. Second only to "Health Care Delivery Systems," "Cardiovascular and Peripheral Vascular Disease" was recognized as a high-priority area for further research to eliminate waste and shift practice away from low-yield, high-cost interventions. In September 2010, our institution was awarded a $2.4 million Comparative Effectiveness Research and Evidence Development Grant through the Agency for Healthcare Research and Quality to better inform current practice regarding the treatment of symptomatic PAD in community-based settings and to address limitations in prior PVI studies. Our grant focused on comparative effectiveness of surgery vs endovascular therapy, comparative effectiveness of treatment within endovascular therapy (stent vs other adjuncts) and a prospective study on patient-centered health status in revascularization procedures, exercise, and medical therapy. We leveraged the existing healthcare infrastructure at 2 large integrated healthcare delivery systems (Kaiser Permanente Northern California and Kaiser Permanente Colorado) representing over 3.5 million patients cared for by a medical group of over 7,000 physicians. Unique features of our study include the following:

1. Patients were cared for in an integrated health care system with comprehensive specialty care and comprehensive multidisciplinary collaborative vascular therapy and wound-care teams in a non–fee-for-service structure.
2. Detailed chart abstraction was conducted to obtain key clinical variables (history and physical, diagnostic testing reports, procedure reports, discharge summary and follow-up visit within 30 days of discharge, procedure notes for all cases through December 2012) using a standardized abstraction tool by a 6-member, multidisciplinary clinical abstraction team of vascular therapy physicians from interventional cardiology, interventional radiology, and vascular surgery. The goal of this step was to allow for a more robust assessment of the comparative effectiveness of PVI vs LEB. Longitudinal data of clinical events (e.g., reintervention) were obtained from the electronic data sources at each site, including hospitalization and procedures performed at non-Kaiser facilities.
3. Two different propensity methods were utilized to balance the covariates among patients undergoing the revascularization strategies. This was done to reduce potential confounding by indication bias in observational retrospective studies. Inverse probability of weighted models (IPTW) and matched propensity score analyses allowed for comparable results. The similar results imply that patterns seen in the study did not depend on the patient population selected and minimized the impact of unmeasured confounding in nonrandomized studies.

In 2015, we published our paper, titled, "The Contemporary Safety and Effectiveness of Lower Extremity Bypass Surgery and Peripheral Endovascular Interventions in the Treatment of Symptomatic Peripheral Arterial Disease" in *Circulation*.[15] In a community-based clinical registry, we compared 883 patients undergoing PVI for symptomatic PAD and 975 patients undergoing LEB between January 1, 2005, and December 31, 2011. The average patient was 70 years of age, and half of the patients were treated for CLI.

1. Rates of target lesion revascularization were greater for PVI compared to LEB in patients presenting with claudication (12.3%±2.7% and 19.0%±3.5% at 1 and 3 years vs 5.2%±2.4% and 8.3%±3.1%, log-rank P<.001) and CLI (19.1%±4.8% and 31.6%±6.3% and 1 and 3 years vs 10.8%±2.5% and 16.0%±3.2%, log-rank P<.001) (Figure 1).
2. Compared to PVI, LEB was associated with increased rates of complications up to 30 days following the procedure (37.1% vs 11.9%, P<.001).
3. In patients with CLI, there were no differences in amputation rates between the 2 groups (Figure 2).
4. Mortality rates were higher for LEB than for PVI patients presenting with CLI (19%±3.1% and 35.9%±3.9% at 1 and 3 years vs 13.4%±4.0% and 26.9%±5.9%, log-rank P=.003) (Figure 3).

In our study, contemporary rates of revascularization for both LEB and PVI were excellent, with favorable long-term patency rates that were comparable to or better than recent trials or meta-analyses and depict real-world practice patterns in a large, integrated health care system.[16,17] Although PVI was associated with higher target lesion revascularization rates in comparison with LEB, there was no difference in the rate of major or minor amputations. Furthermore, compared to the historic literature, where 30% of patients with CLI undergo a major amputation within the first year, our CLI cohort undergoing revascularization procedures had much lower amputation rates of 15.5% with PVI and 18.6% with LEB. Although we would like to think it is due to targeted revascularization in an angiosomal distribution, it may be related to improved and comprehensive wound-care programs. Even CLI patients who are not suitable for revascularization ("no option" patients) enrolled in gene and cell therapy trials have a 1-year limb salvage rates of >75% to 80%.[18-20] Finally, in comparison with PVI, patients undergoing LEB were more likely to have ≥1 complications from the time of procedure to 30-day follow-up (37.1% vs 11.9%). Intraprocedural complication rates were similar for PVI and LEB, whereas after the procedure, predischarge and postdischarge complications were significantly higher with LEB than with PVI. The majority of the complications occurred early (before discharge or within 30 days following the procedure). The most common complication in patients receiving PVI was worsening ischemia (2.8%) during the post discharge phase compared to surgical site infection (11.0%) for LEB. How procedure-specific complications (apples vs oranges) are weighed against the benefit of decreased reintervention requires judgment by both patients and treating physicians.

However, one must ask, is this a case of "six of one, half a dozen of another"? With limb-salvage rates at 1 year exceeding 85% in most CLI trials evaluating all types of treatments such as PTA (cryoplasty, cutting balloons, scoring balloons), drug-eluting stents for focal tibial disease, atherectomy, ablation, cell therapy and no-option control patients, is limb salvage really the end game? Furthermore, with up to 80% of the BEST-CLI sites having multidisciplinary CLI teams, I would suspect the limb salvage rates will be high and statistically similar in the LEB and PVI strata. If the ultimate endpoint is limb salvage, then revascularization with either LEB or PVI will likely be sufficient (six of one, half a dozen of another). However, the Institute of Medicine envisioned a more patient-centered health care system focused on patients' functional status and health-related quality of life (defined as patient's perceived physical, emotional, and social well-being and function). Although vessel patency and limb salvage are logical, and laudable endpoints to consider and differences in complication rates will continue to be an apples-to-oranges comparison, cumulatively, it will be the patients' functional status and health-related quality of life that will win the day. We eagerly await the results of the BEST-CLI trial and will share the results of our prospective study on patient-centered health status in revascularization procedures, exercise, and medical therapy later this year.

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Current Real-World Practice and Evidence-Based Therapies for CLI: Is the Gap Narrowing?

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The prevalence of peripheral arterial disease (PAD) continues to increase at an alarming pace worldwide. Large-scale studies indicate that there will be 22 million PAD patients by 2030. Critical limb ischemia (CLI) patients represent 1% to 2% of this population and their number is also expected to rise thanks to the aging population, and the uncontrolled epidemics of obesity, diabetes mellitus, and tobacco abuse.[1,2]

Femoropopliteal Segment

Atherosclerotic plaque is omnipresent in CLI. Approximately 65% of obstructive lesions are located in the femoropopliteal (FP) space, and they are characterized by their complexity (length and degree of calcification), which qualifies most as TASC "C" or "D" lesions. Endovascular techniques have continued to evolve and have slowly and progressively replaced the once ubiquitous surgical bypass. Despite this evolution and reported technical success rate of more than 95% for percutaneous transluminal angioplasty (PTA) to revascularize the superficial femoral artery (SFA), restenosis rates of 20% to 65% have been reported after 6 to 12 months. These unacceptable results led to efforts designed to mimic what many years ago took place in the field of coronary interventions. When faced with the elastic recoil, undilatable calcified lesions and complications such as dissections and perforations, interventional cardiologists started to use bare metal stents and later drug eluting stents with remarkable success.

However, the SFA presents significant challenges to achieving long-term results after endovascular intervention secondary to the unique forces to which it is subjected. Proximal continuity with the common femoral artery and distal continuity with the popliteal artery exposes the SFA to elongation with ambulation. Due to its superficial course and intimate interaction with the surrounding musculature, the SFA is subject to compressive and torsional forces, which can result in metal fatigue and stent fracture, which have been associated with restenosis. In addition, the SFA responds to stent implantation with a more potent inflammatory response than other vessels due to micromovements of the stent alongside the vessel wall, which lead to activation of the endothelium and inflammation. When stent segments are overlapped (often done while treating long SFA lesions), hinge points are created, potentiating the likelihood of stent fracture.

These limitations highlight that despite improvement in stent-related data for the SFA, there was still a need to improve outcomes. This led to the development of drug-coated balloons (DCBs). Several studies have been conducted in de novo and restenotic FP lesions comparing DCBs to regular uncoated balloons showing significant improvement in restenosis rates and Rutherford class at up to 24-month follow-up in lesions with mean lengths of 80.8 mm. These trials demonstrated that incomplete balloon expansion and geographic miss resulted in a significant decrease in primary patency and an increase in TLR rates at 12 months. A meta-analysis of the DCB trials showed improved results with DCBs at a median follow-up of 10.3 months with significant reduction in TLR, late lumen loss and angiographic restenosis without an increase in adverse events. More recently, the LEVANT-2 study was released, showing a 12-month primary patency rate of 65.2%.

Infrapopliteal and Inframalleolar Segments

In the infrapopliteal and inframalleolar segments, the data are not much different. Approximately one-third of patients with CLI have isolated below-the-knee (BTK) disease, which is characterized by diffuse, multilevel, and multivessel calcific involvement. Due in part to the heterogeneous complexity of these patients, there is a drought of generalizable scientific evidence to support the use of percutaneous revascularization, and the optimal treatment modality remains controversial. Currently, PTA is the endovascular modality utilized as the standard of care, despite suboptimal outcomes. Infrapopliteal PTA has been shown to result in inferior procedural and short-term outcomes relative to other endovascular modalities. Recent meta-analyses show that outcomes of PTA for infrapopliteal disease have not changed over the last decade, despite newer techniques, approaches, and available technologies.

Over the last 10 years, there has been an exponential increase in the body of knowledge and understanding of the pathophysiological processes governing CLI. The Society of Cardiac Angiography and Interventions published their Expert Consensus Statement for Infrapopliteal Arterial Interventions in 2014 and in 2015; the latest iteration of the TASC guidelines included an entire infrapopliteal segment. These advances span the spectrum from enhanced disease awareness, to screening and diagnosis, to the implementation of standardized protocols for clinical and noninvasive follow-up, wound care, and concomitant risk factor treatment, as well as to the design of novel and disruptive technologies (atherectomy, cryoplasty, focal force balloons, crossing and re-entry devices), which have provided operators with an unprecedented ability to revascularize lesions in patients who were previously thought to be no-option cases.

Despite these advances, the outcomes of PTA as standard of care treatment for BTK disease remain the same. It seems that PTA results have reached their zenith, and adjunctive modalities deserve to be systematically studied to analyze their likely superior results. Appropriate study design can potentially shine a different light on outcomes of endovascular therapies for BTK disease. Although single center, retrospective studies add value to the growth of medical knowledge, they should not be the driving force behind paradigm shifts that dictate practice standards due to their inherent limitations. There is a need for large-scale, multicenter, prospective studies with inclusion criteria that encompass the real-world CLI patient and currently available and future disruptive technologies to generate relevant and generalizable data that can be used as the best source of evidenced-based standards to treat this complex disease.

Multidisciplinary Approach

Extant management of CLI should include a combination of endovascular or surgical revascularization as the mainstay of therapy (as noted in the preceding paragraphs), complemented by a host of noninterventional therapies, which should be carried out by a cohesive multidisciplinary team. Although interventional therapies are blamed for the relatively dismal outcomes, it is becoming clear that the Achilles heel of CLI therapy is overlooked weaknesses of our current practice workflow, whereby different specialists treat CLI patients in isolated fashion and miss the big picture represented by the need of a simultaneous, transitionless, passionate, and dedicated multidisciplinary approach.

When CLI patients are cared for by a dedicated multidisciplinary team, the patient is evaluated by a series of providers, including a primary care physician, endocrinologist, infectious disease specialist, wound care specialist, podiatrist/orthopedist, orthotics specialist, vascular rehabilitation specialist, and the vascular specialist (vascular surgeon, an interventional cardiologist, an interventional radiologist, or an angiologist [Europe]). The patient then undergoes a series of noninvasive imaging and physiologic tests in order to diagnose the extent of disease, plan the therapeutic revascularization strategy, and serve as baseline for follow-up studies. Once complete revascularization is achieved, surveillance should be continued by all members of the team to ensure complete healing and maintenance of tissue integrity.

One commonly unrecognized link in the continuum of care is long-term care facilities. The care provided in this setting can cause a break in the chain of care. Often, patients are transferred to a rehabilitation facility (transiently or permanently), and due to lack of awareness, knowledge, staff, and equipment, the appropriate care is not delivered, jeopardizing the effort previously put forth by the rest of the team. A high index of suspicion and an aggressive approach should be maintained, with prompt referral for repeat revascularization to minimize potential complications and increase the likelihood of permanent positive outcomes. This is of paramount importance because of the delicate balance of perfusion in these patients, which can become insufficient if there is additional insult to the skin barrier. Unfortunately, in the real world, only a very small fraction of these patients returns for follow-up with the vascular specialist or with any of the other members of the team. Many times patients follow up with a wound clinic that is not affiliated with the system where the vascular specialist performed the intervention and therefore is not familiar with the latest techniques. Overall, there is a widespread lack of knowledge and an attachment to old ways that needs to

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[1]McKinsey JF, Zeller T, Rocha-Singh KJ, , et al. Investigators DL. Lower Extremity Revascularization Using DA: 12-Month Prospective Results of the DEFINITIVE LE Study. JACC. Cardiovascular Interventions. Aug 2014;7(8):923-933.

[2]Tepe G, Laird J, Schneider P, et al. DCB Versus Standard PTA for the Treatment of Superficial Femoral and Popliteal PAD: 12-Month Results From the IN.PACT SFA Randomized Trial. Circulation. Feb 3 2015;131(5):495-502.

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be overcome. Unfortunately, data-driven clinical studies evaluating multidisciplinary team strategies for surveillance, use and duration of antiplatelet therapy, anticoagulants, risk-factor-modifying therapies, noninvasive testing, and indications for repeat revascularization in these patients do not yet exist. Current data have been derived from retrospective studies, with inconsistent reporting standards leading to a paucity of evidence, especially following endovascular revascularization in CLI.

Summary

The pathophysiology of CLI is complex and involves micro- and macro-pathology, so it is not surprising that therapeutic modalities are multifold, spanning many health care specialties and requiring substantial institutional infrastructure to provide optimal patient care. Though challenging, the future of CLI treatment is exciting with increasing focus on optimal wound care and prevention, adherence to proven medical therapies, improving revascularization results with novel techniques, devices and approaches, and, most definitely, with the establishment of CLI centers of excellence with dedicated multidisciplinary teams. There is still a gap between real-world CLI practice and evidence-based therapies, which is fed by the disparity between real-world patients and those enrolled in clinical trials. However, we must acknowledge that the CLI community is spearheading an unprecedented effort in an attempt to bridge this gap. Bringing awareness to the forefront of patients, health care providers, institutions, politicians, industry, and all stakeholders is one of the missions of the recently created CLI Global Society, and its accomplishment will undoubtedly continue to narrow the space. Let's do it!

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prevention of atherosclerotic disease is important. Almost every CLI patient requires mono-antiplatelet therapy, but often, dual antiplatelet therapy is appropriate following revascularization. Emerging clinical evidence even suggests that newer antiplatelet agents prevent acute limb ischemia and decrease repeat revascularizations.[1] And although it is not evidence based, we occasionally allow permissive hypertension until the wound has healed, after which time more aggressive blood pressure management is pursued.

After a patient's wound has healed, the patient should continue to be followed for recurrent CLI in the index or contralateral limb. American College of Cardiology Foundation/American Heart Association guidelines recommend at least biannual follow-up for the stable CLI patient for surveillance of new foot wounds and review of optimal foot hygiene.[2] Titration of medical therapy for prevention of stroke, myocardial infarction, and ischemic limb events should also occur at these visits. If the sequelae of restenosis and occlusion are expected to be recurrent CLI (or acute limb ischemia), then more frequent follow-up visits with patency surveillance seems indicated. However, often the CLI patient with good foot hygiene will not have clinical evidence of restenosis following wound healing.

In summary, comprehensive care of the CLI patient may be one of the the most challenging programs to deliver for multiple reasons. This medical problem is underdiagnosed and under-recognized. The patients have many comorbidities, and major amputation has dire consequences. The number of specialties required to take care of this patient population is great. The demands on the marginally ambulatory patient to attend these various appointments can be unreasonable. These challenges are not present in the care of many other disorders, such as isolated coronary artery disease or in populations with claudication but not CLI. Comprehensive care of CLI calls for "CLI Centers of Excellence" staffed by passionate providers from all CLI specialties to achieve optimal outcomes. Institutions that can offer these services in a coordinated fashion in the same physical space are desired to reduce patient visits, allow CLI specialists to collaborate side by side and thereby facilitate care of CLI patients. In fact, the concept of CLI Centers of Excellence has been eloquently described previously in the CLI Global Compendium.

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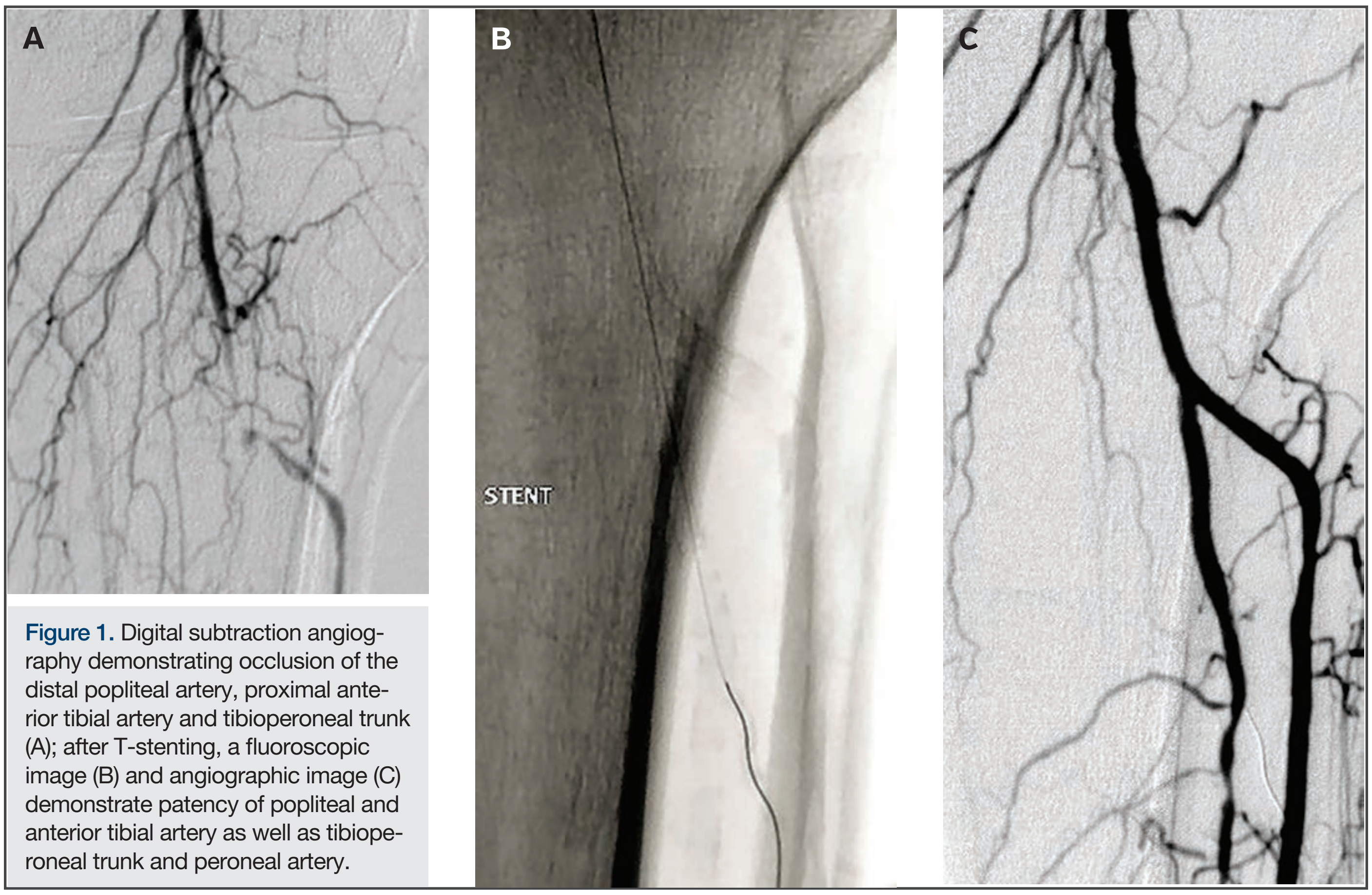

Figure 1. Digital subtraction angiography demonstrating occlusion of the distal popliteal artery, proximal anterior tibial artery and tibioperoneal trunk (A); after T-stenting, a fluoroscopic image (B) and angiographic image (C) demonstrate patency of popliteal and anterior tibial artery as well as tibioperoneal trunk and peroneal artery.

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of the SFA, as well as a new stenosis in the P3 segment of the popliteal artery, was seen during duplex examination. These were subsequently treated with conventional balloon angioplasty with good angiographic outcome. Given the history of restenosis and occlusion in the stented segment, it was decided not to stent the SFA. The anterior tibial artery and fibular (peroneal) artery were still patent at this point.

Although clinical improvement was noted initially, wound healing was not sustained, and 5 months later, restenosis of the SFA was present, and repeat percutaneous transluminal angioplasty (PTA) and stenting was performed. In addition, a subtotal restenosis was seen in the P3 segment of the popliteal artery, as well as a significant stenosis in the proximal segment of the popliteal artery and an occlusion of the tibioperoneal trunk. Recanalization was carried out and bare-metal T-stenting of the popliteal artery/anterior tibial artery and tibioperoneal trunk using small-caliber self-expanding stents was performed. Brisk flow to the peroneal artery and anterior tibial artery was obtained (Figure 1).

The clinical course was uneventful for 5 months. The patient returned with an in-stent restenosis in the popliteal artery and proximal anterior tibial artery as well as an occlusion of the peroneal artery. At this point, drug-coated balloons had become available in Europe and it was decided to proceed with the inflation of a 3 mm

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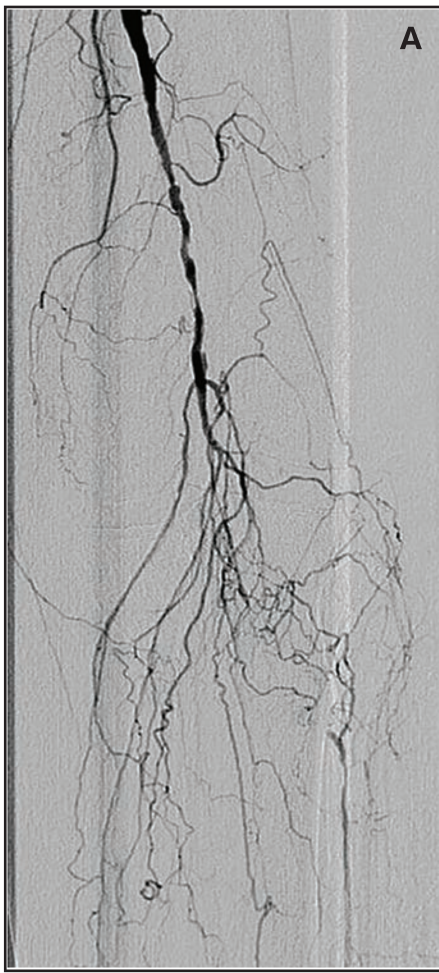

Figure 2. Angiographic image showing occlusion of the P3 segment and proximal anterior tibial artery (A), note occlusion of tibioperoneal trunk and peroneal artery; after laser debulking and DCB angioplasty (B), complete restoration of antegrade flow into anterior tibial artery.

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drug-coated balloon after predilatation of the lesion with a 2.5 mm balloon.

The use of the drug-coated balloon changed the clinical course dramatically and it was not until 9 months later that the patient came back with a restenosis in the SFA (proximal to the previous implanted stent) and an in-stent occlusion of the P3 segment and anterior tibial artery. The SFA was treated with conventional balloon angioplasty, while the in-stent occlusion was treated with excimer laser ablation and conventional PTA.

The patient unfortunately returned with the same arterial lesions as those present prior to the last procedure, and again conventional PTA and laser debulking combined with PTA were used to treat the SFA stenosis and in-stent occlusion of the P3 segment and anterior tibial artery, respectively.

Ten months later, the patient presented again with a reocclusion of the P3 and proximal anterior tibial artery segment. After successful wire crossing, excimer laser debulking was performed, followed by PTA and angioplasty with a drug-coated balloon, with complete reconstitution of flow to the distal anterior tibial artery (now the only run-off vessel) (Figure 2).

Four months after the last intervention, diffuse restenosis of the SFA was detected during duplex follow-up. This stenosis was treated with plain balloon angioplasty. Periprocedural angiography demonstrated good patency of the distal popliteal artery and proximal anterior tibial artery.

Clinical deterioration necessitated another angiographic evaluation after 8 months, revealing a restenosis of the SFA that was treated with another conventional balloon angioplasty. The previously treated P3 and anterior tibial artery segment was widely patent (Figure 3).

It was not until 2.5 years after the last intervention that the patient underwent a target lesion revascularization in the P3 and anterior tibial artery segment that was affected by a focal 60% stenosis (Tosaka class I). No debulking was performed, and instead a drug-coated balloon was used to perform angioplasty.

The patient remained amputation free, without clinical signs of critical limb ischemia for the remainder of his life. The patient died 7.5 years after his first presentation due to a complicated pneumonia.

This case underlines the necessity of perseverance in the treatment of patients with critical limb ischemia and the importance of adopting new technologies whenever they come available and adjusting endovascular strategy whenever necessary. It requires dedication from the interventionalist treating these patients, including unlimited access to resources and absence of issues related to long occupancy of the interventional suite for these kinds of procedures.

Management of these patients also requires active involvement of a team of dedicated specialists, including vascular surgeons, angiologists, diabetologists, and wound care nurses. In our institution, all these requisites are present. One important factor that needs to be mentioned is that the health care system in Switzerland provides a strong incentive for outpatient treatment: all costs of material and equipment used in so-called ambulatory procedures are entirely reimbursed. Even in this category of patients, the majority can be treated on an outpatient basis. In addition, the hospital administration allows us to take on these time-consuming and often costly procedures for patients that are hospitalized; therefore there are no barriers to treatment.

Our institution has become the major referral center in the region, treating patients with critical limb ischemia almost daily who in the past would have been considered "no-option" candidates for either endovascular or open surgical revascularization. As practitioners and physicians from other hospitals in the area have become more aware of minimally invasive treatment options for patients with critical limb ischemia, we have seen continuing growth in the number of patients we are able to treat. In the near future, new endovascular technologies, and further development of new ways of imaging (e.g., CO_2 angiography) will allow for even more of these cases to be performed in an outpatient setting.

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Figure 3. Angiographic image obtained during superficial femoral artery intervention demonstrating patency of the previously treated segment of the popliteal and anterior tibial artery.

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different stance toward the care we provide to our CLI patients. In fact, our hospital administration has and continues to help us build and grow our CLI program. So where does the perception that manifests itself in the aforementioned complaints come from? Drs. Rogers and van den Berg, in their respective articles, detail facts and myths of CLI patient therapy.

The "health care providers" group includes anyone who plays a role in the care process of the CLI patient. Interestingly, I have noted that almost everyone who provides care to these patients loves their work. Of course, as in any profession, there are always exceptions, but generally speaking, health care providers who care for the CLI patient are passionate individuals with the collective goal of prevention of amputation for the complex CLI patient.

Much has been written about the cost of CLI care and the cost of amputation over the last few years. However, conclusive evidence of whether it is more cost effective to provide endovascular or surgical revascularization compared to amputation does not yet exist. Gunnarsson et al and Tsai et al attempt to answer part of this question by addressing whether it is more cost effective to amputate or not to amputation while addressing safety outcomes for those with or without amputations.

The growth of outpatient CLI therapy centers facilitates efficient and effective care for CLI patients. In these centers, patients can receive state-of-the-art CLI care in a warm and inviting environment. Further evidence that these centers can provide cost-effective care will only boost their ability to become a ubiquitous presence in CLI care.

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Tools, Techniques, and Training for the Budding Critical Limb Ischemia Specialist: Skills to Treat Advanced Technically Challenging CLI Disease Scenarios

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The scope of endovascular therapies for the treatment of peripheral vascular disease has evolved over the past decade. Many peripheral endovascular therapies now exist, such as carotid stenting, transcatheter aortic valve replacement (TAVR), percutaneous endovascular abdominal aortic aneurysm repair (PEVAR), aortoiliac interventions, and interventions for critical limb ischemia (CLI). This article will focus primarily on CLI and preparing the budding CLI specialist for the vast spectrum of CLI therapies during the preprocedure, procedure, and post-procedure stages.

The CLI specialist should act as the captain of a team of caregivers to ensure the CLI patient receives the proper preprocedure care. Preprocedure care includes assessing the fragility of the patient and whether it is acceptable to proceed with revascularization. Additionally one must assess and address comorbidities with special focus on renal function, diabetes, anemia, hyperlipidemia, hypertension, and smoking. Critical limb ischemia is a complex disease associated with high morbidity and mortality. The preprocedure evaluation adds quantifiable value to the patient's care, especially when medical adjustments are made to correct off-target disease levels.

The preprocedure stage establishes the platform for the intraprocedure stage. The CLI specialist needs to plan, prior to the procedure, the primary and secondary access points and be prepared for antegrade and/or retrograde access. Also, preprocedure planning must include planning for access closure. Intraprocedurally, the CLI specialist must be prepared to perform a variety of techniques to insure successful chronic total occlusion (CTO) cap crossing, such as Controlled Antegrade and Retrograde Tracking and Dissection (CART), reverse CART, Re-back, subintimal arterial flossing with antegrade-retrograde intervention (SAFARI), and Schmidt techniques. An awareness of the CLI patient's CTO cap morphology lends itself to better treatment decision-making leading to successful crossing.

The immediate postprocedure period is a crucial period for access site surveillance. Additionally, any unnoticed tibial perforations may lead to slow calf swelling. The calf should be measured immediately post procedure and every 15 minutes for 2 hours. Any swelling due to vascular bleeding, if caught early, can be addressed quickly and simply by placing a blood pressure cuff on the calf. Additionally, the use of extravascular ultrasound is helpful to observe color Dopper extravastion of the offending vessel.

Post discharge, following revascularization, the patient should receive optimal medical therapy, regular surveillance for progression of disease, and comprehensive wound care, when applicable. With no large clinical studies to guide postrevascularization care, differing opinions among CLI specialists lead to lack of a standardized approach. Therefore, it is the responsibility of the CLI specialist to apply best cardiovascular postprocedure care until large clinical studies can lead to universal guidelines.

Critical limb ischemia is a growing problem that is known to be associated with high morbidity and mortality. The number of amputations due to CLI is also rising. Treating CLI requires an advanced skill set and multispecialty team strategy. Reducing the number of amputations that are performed can mitigate the huge health care cost burden that CLI brings. Most amputations debatably are unnecessary in the presence of specialized high-volume centers with specialized advanced-skill teams that are able to manage complex disease scenarios.

Specialized Skill Sets

A range of CLI operator skills is very important in planning a complex multilevel, multivessel CLI revascularization procedure. Is there a correlation between high volume CLI centers with low complication rates and better patient outcomes? As much as the authors would like to confirm there is a correlation, there are no data currently available to answer this question. This leads to the second question. Should experienced endovascular specialists dabble in CLI therapy? Critical limb ischemia therapy is not as simple as opening a single vessel with a magical result. The care is complicated and continuous

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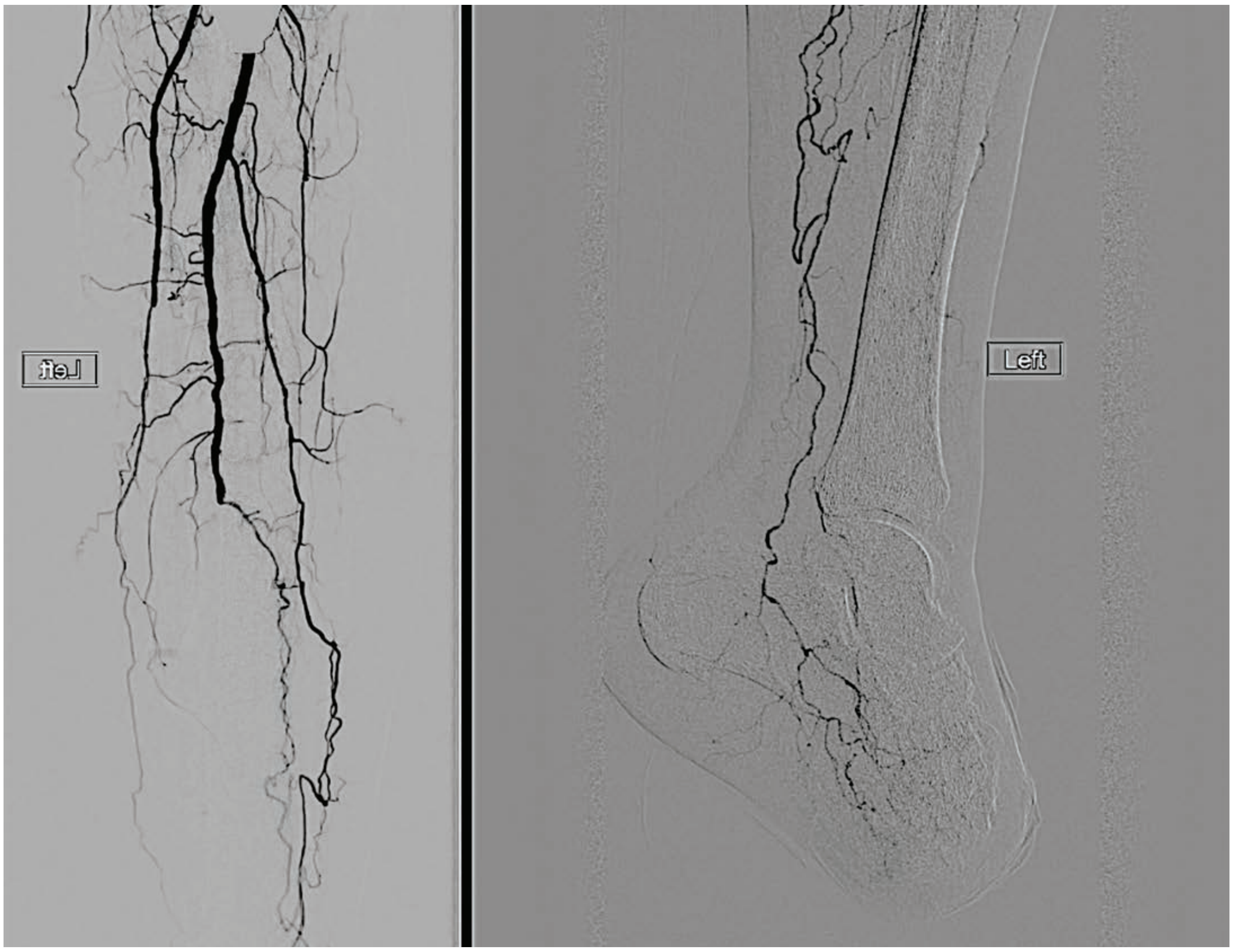

Figure 1. Preintervention angiogram images via antegrade femoral access.

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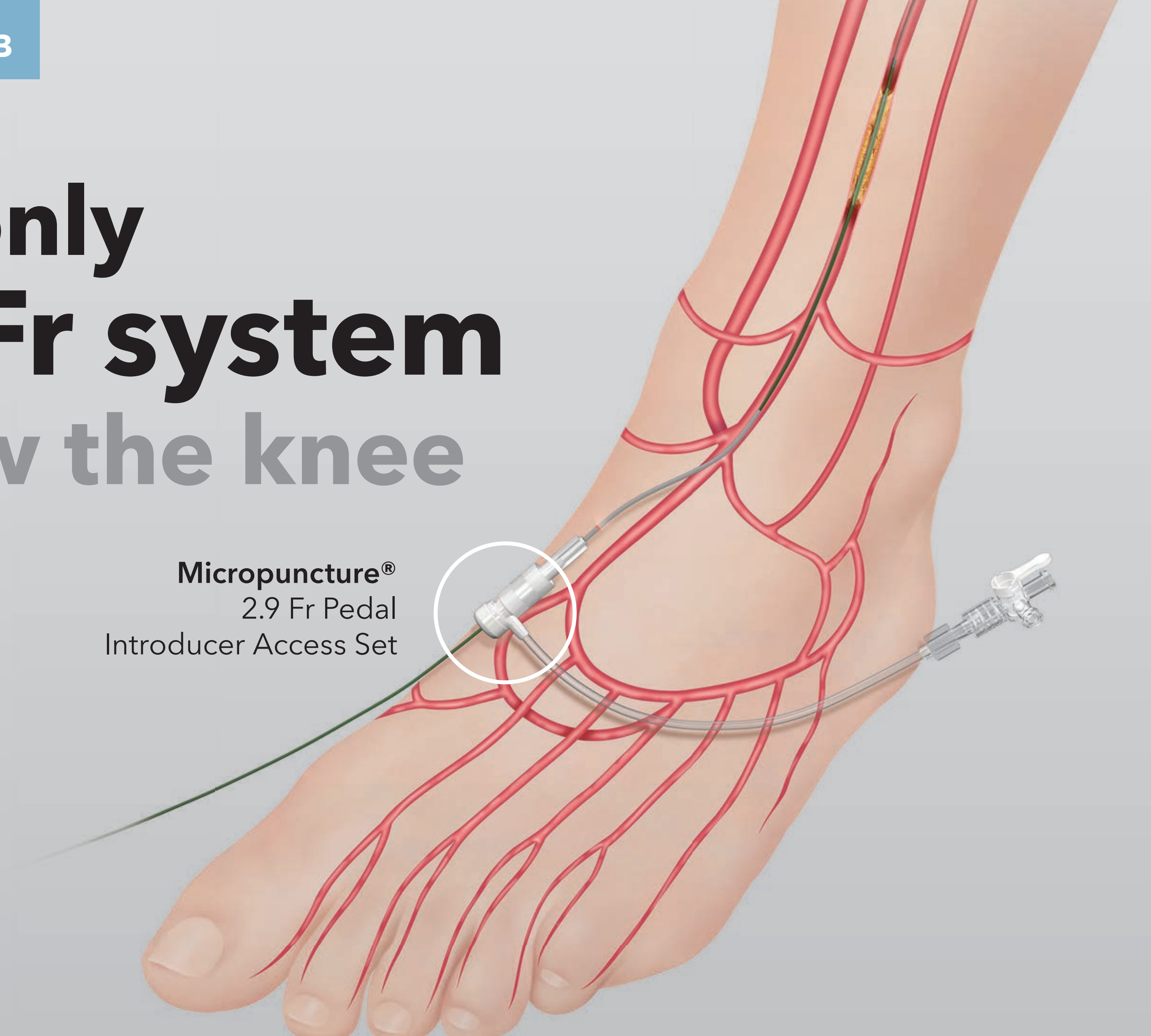

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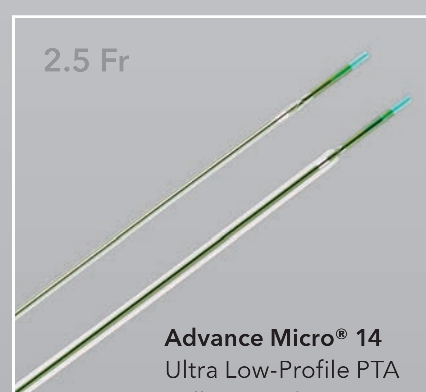

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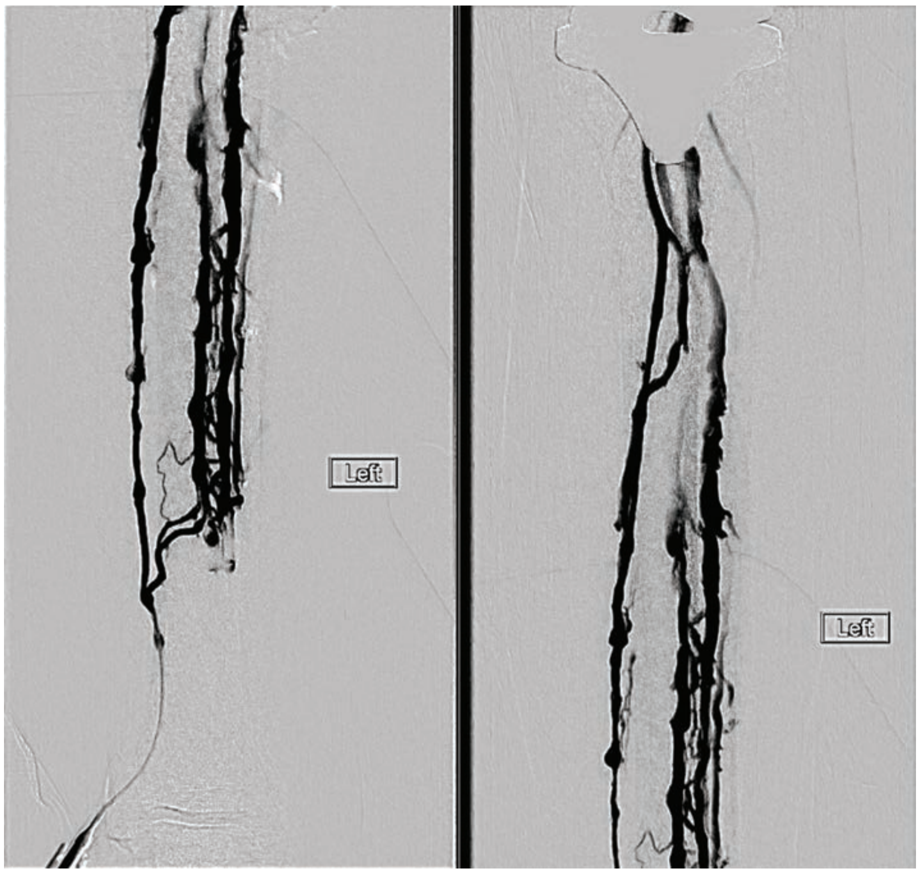

Figure 2. Preintervention venogram images via retrograde posterior tibial (PT) vein access.

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and therefore demands post-procedure involvement of the CLI team.

Much time and training is necessary to bring an operator up to date on the currently available approaches and techniques for CLI therapy. Newly trained operators should be given time to grow and develop mature skills. Hence, the next question comes to mind. Do CLI specialists receive proper training followed with continued medical education to reach and maintain proper knowledge and skill? The authors see value in carving out time for the new CLI operator to focus on CLI therapy because it is a complex disease process associated with a serious rate of mortality, which can not be emphasized enough.

Proper specialized training that can provide adequate case volumes and range of experience allows development of the requisite cognitive skills to competently perform complex CLI interventions. Operators should be provided exposure to the latest technologies available for revascularization. Many newer programs are opening and expanding in order to provide better quality care and offer an array of interventional and surgical procedure options to the CLI population. A CLI specialist is required to be well versed and equipped with a diverse range of procedural skills and comprehensive combinations of different technologies to finish advanced care. Currently, there is a significant lack of tools and devices that are developed primarily for CLI. In general, most operators have learned to improvise, borrow, and combine tools made for other vessels. This is a good indicator of the infancy of the CLI specialty.

The Growing Burden of CLI

An aging population coupled with a high prevalence of serious risk factors creates a ripe environment for cardiovascular events, which tend to be the primary cause of death in the CLI population. To make things worse, CLI now affects 10% of PAD patients over the age of 70.[1] Our ability as CLI specialists to successfully treat more complicated patterns of disease requires sophisticated techniques and the knowledge of endovascular devices needed to perform them.

Operators should become facile with the majority, if not all, of the available endovascular devices starting with atherectomy devices. We have learned over the years that one single atherectomy device does not suffice for all types of CLI disease. Stents are still an excellent tool for below-the-knee disease, especially drug-eluting stents, as were shown to be effective in multiple trials (ACHILLES, PARADISE, and YUKON), especially in the proximal tibial arteries.

Devices for Treating CLI

In the authors' opinion, the most important segue into successful revascularization is to become knowledgeable about when and where to use endovascular devices. Crossing tools and devices are a very complex subject and beyond the scope of this paper. However, the CLI specialist is expected to have current knowledge of the latest crossing tools and to have a high successful CTO crossing rate. As of the writing of this paper, there is no published acceptable CTO crossing rate for the CLI patient. Most likely, this will become a core measure in the future. Also, there are many different types of balloons available to the CLI specialist, and he or she should know each balloon's ability to accommodate the resistant and super-elastic nature of the tibial vessels.

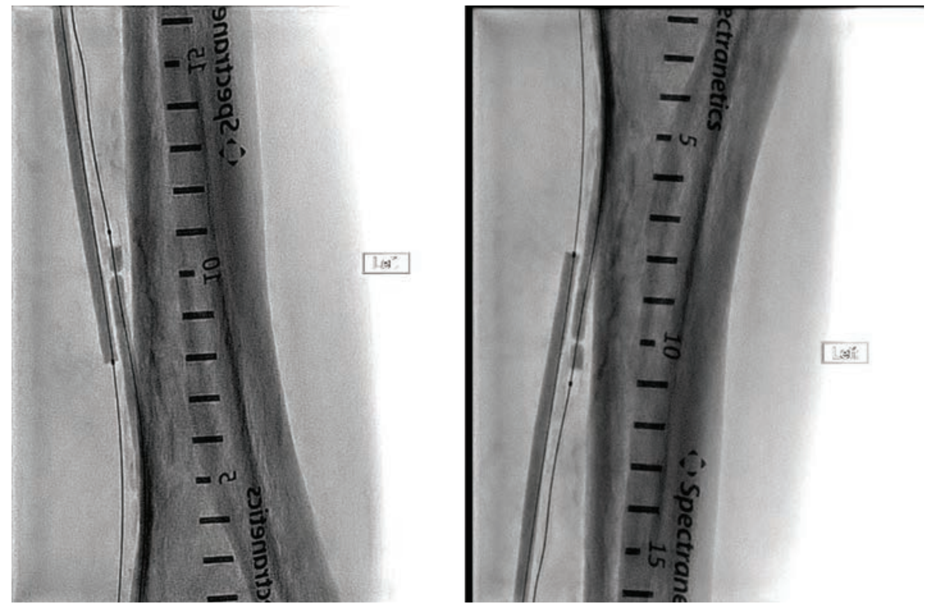

Figure 3. Balloon angioplasty of posterior tibial (PT) artery and (PT) vein.

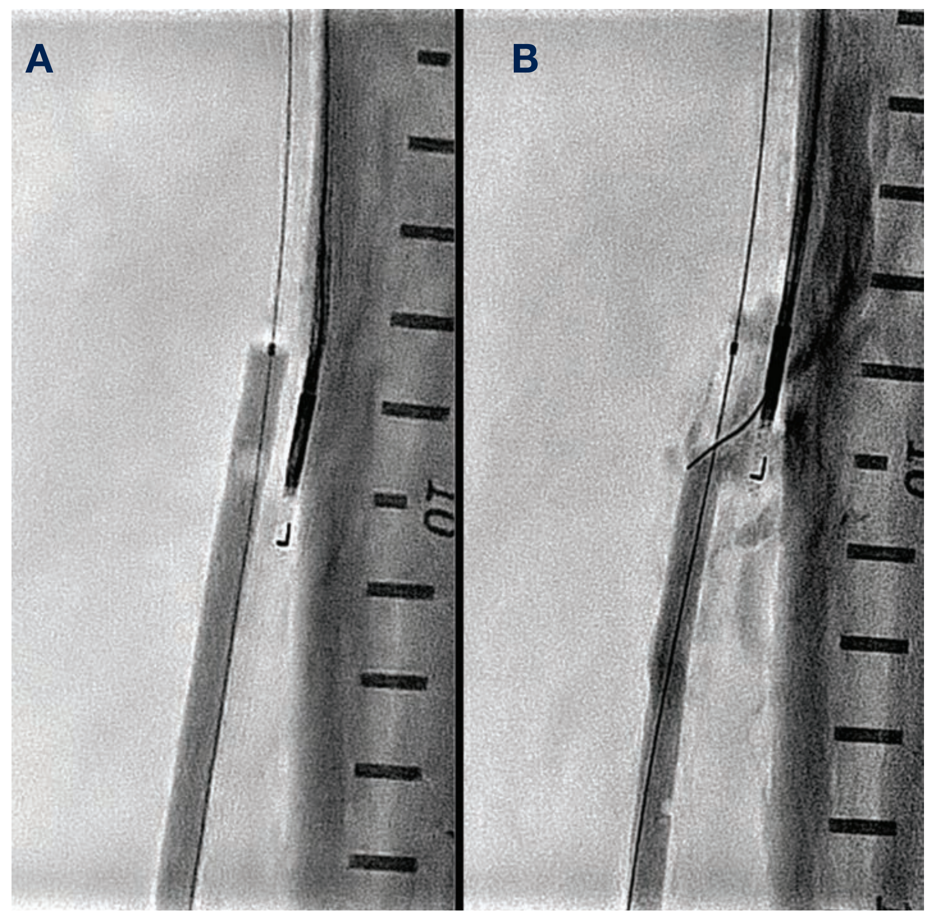

Figure 4. Outback re-entry catheter (Cordis) in position ready to pierce through the artery to the vein containing the dilated balloon (A). Rupture of the balloon and passing of the wire from the artery to the vein (B).

The CLI specialist should consider using ultrasound for all access and closure. Ultrasound assists in finding a good segment in the access target area that is less hostile than other segments for successful sheath placement. Ultrasound-guided access can contribute to a successful exit strategy with low access complication rates.[2]

Pharmacomechanical thrombolysis techniques are a crucial treatment modality that an operator treating CLI must become expert at performing. In addition, the CLI specialist should have advanced skills in coiling, flossing, tunneling, snaring, and retrieval of broken parts of devices. Competency in a full range of techniques will aid the CLI specialist during complex procedure scenarios.

Training the CLI Specialist

There are multiple routes to achieving the same goal of high-level knowledge and skills necessary to deal with all three stages of the treatment pathway of the CLI patient. The most common path is on-the-job learning with the aid of a senior partner. This is a feasible path as long as operators self-govern and track both success and failure to continue proper growth until reaching independent status as a CLI specialist. Increased skill and knowledge will naturally lead

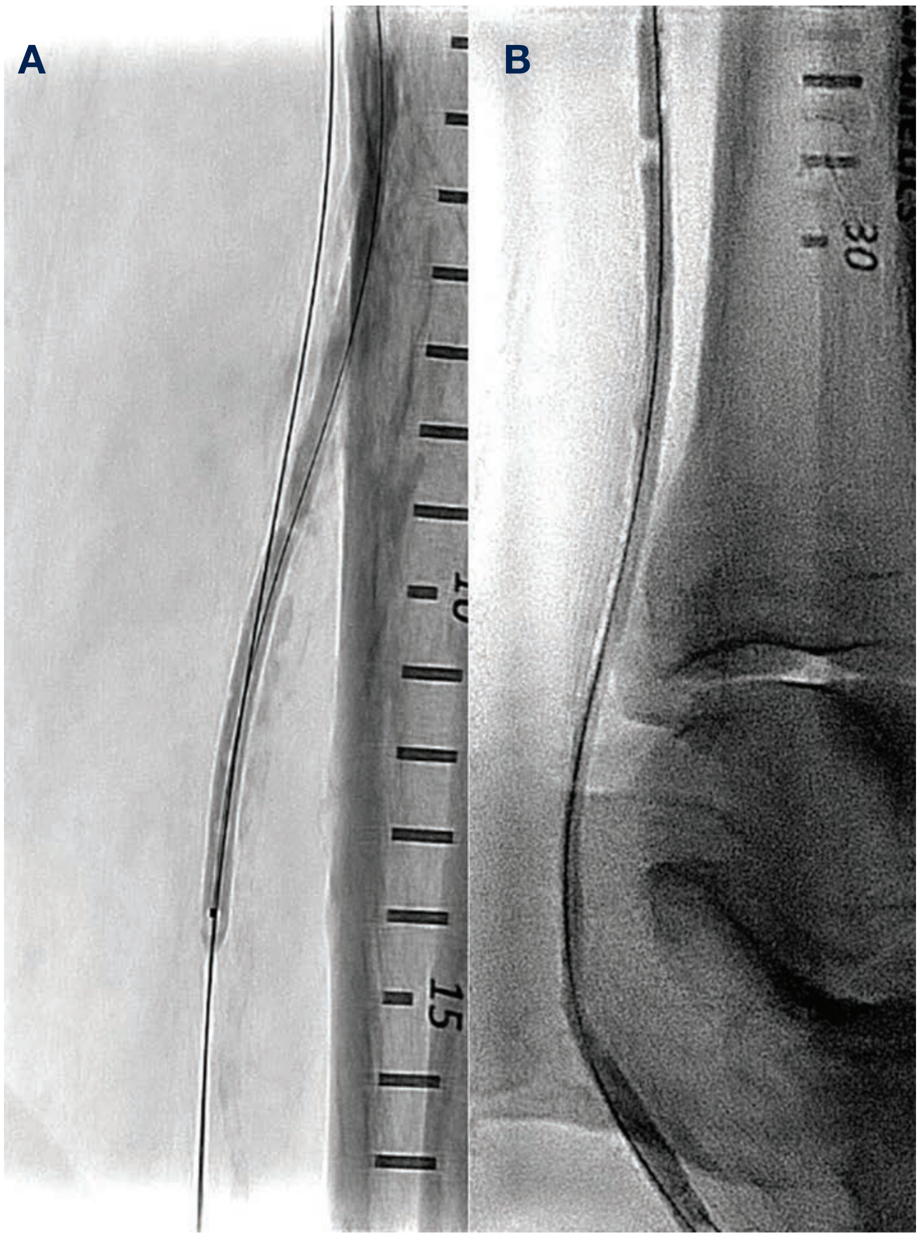

Figure 5. Transarteriovenous balloon angioplasty (A). Balloon angioplasty of the entire posterior tibial vein (B).

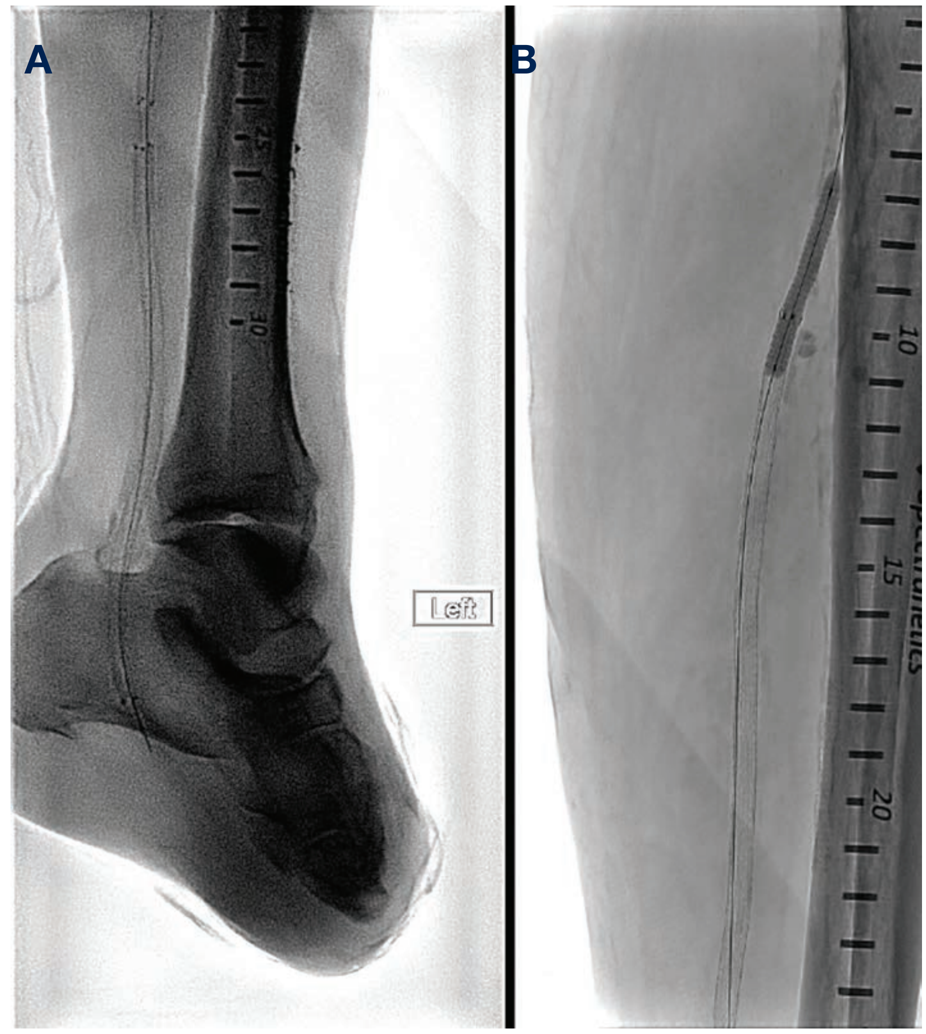

Figure 6. After Viabahn stents (W. L. Gore) in posterior tibial (PT) vein and deploying the Xience drug eluting stent (Abbott Vascular) across from the PT artery to the PT vein.

Figure 7. Final run showing brisk flow from posterior tibial (PT) artery down the PT vein distally to foot.

to better procedure success, safety, patient care, and outcomes.

Conclusion

Critical limb ischemia therapy is becoming its own specialty due to the broad spectrum of associated clinical and procedural demands. Also, the nature of the disease tends to be associated with a large number of risk factors that are known to be associated with high morbidity and mortality.[3] Because CLI patients often present late in the disease process, the treating CLI team faces significant challenges. In cases where the blood flow to the foot is nearly absent, referred to as "desert foot," treatment is limited to two methods. The first and most preferable is arterial revascularization and second is arteriovenous flow reversal, as described in the case below.

Finally, and very importantly, CLI awareness continues to be lacking at a critical level. Sadly, CLI awareness is not only lacking in the general population, but also within the health care community. The CLI Global Society (www.cliglobal.com) calls to action the need for CLI awareness, education, training, and data.

The following case is an example of the ability of advanced techniques allowing successful revascularization and clinical outcomes even in the most challenging cases. This case was chosen to demonstrate that thinking outside the box is crucial. When there is a lack of approved devices for CLI in the United States and other countries, operators must use tools designed for other vessels to perform limb-saving procedures.

Case Report: Arteriovenous Reversal Procedure Performed as Last Resort to Prevent Amputation

Arteriovenous (AV) reversal is an advanced procedure performed as a limb salvage procedure in patients with desert foot. In this case, an 89-year-old patient presented with CLI and a nonhealing ulcer (Rutherford Class VI) involving a transmetatarsal amputation site with interrupted pedal loop distally. He was referred following multiple unsuccessful revascularization attempts, including an earlier attempt via a retrograde Schmidt access technique to provide subintimal recanalization. Options for revascularization were limited considering the interrupted pedal loop. Arteriovenous reversal was chosen as a final attempt to prevent a major amputation.

After informed consent was obtained, the patient was brought to the cardiac catheterization lab. Ultrasound-guided access was obtained through the left common femoral artery via antegrade approach. Initially a 5 Fr, 10 cm Glidesheath Slender (Terumo Medical) was inserted, which was later exchanged for a 6 Fr, 45 cm Destination sheath (Terumo Medical). The posterior

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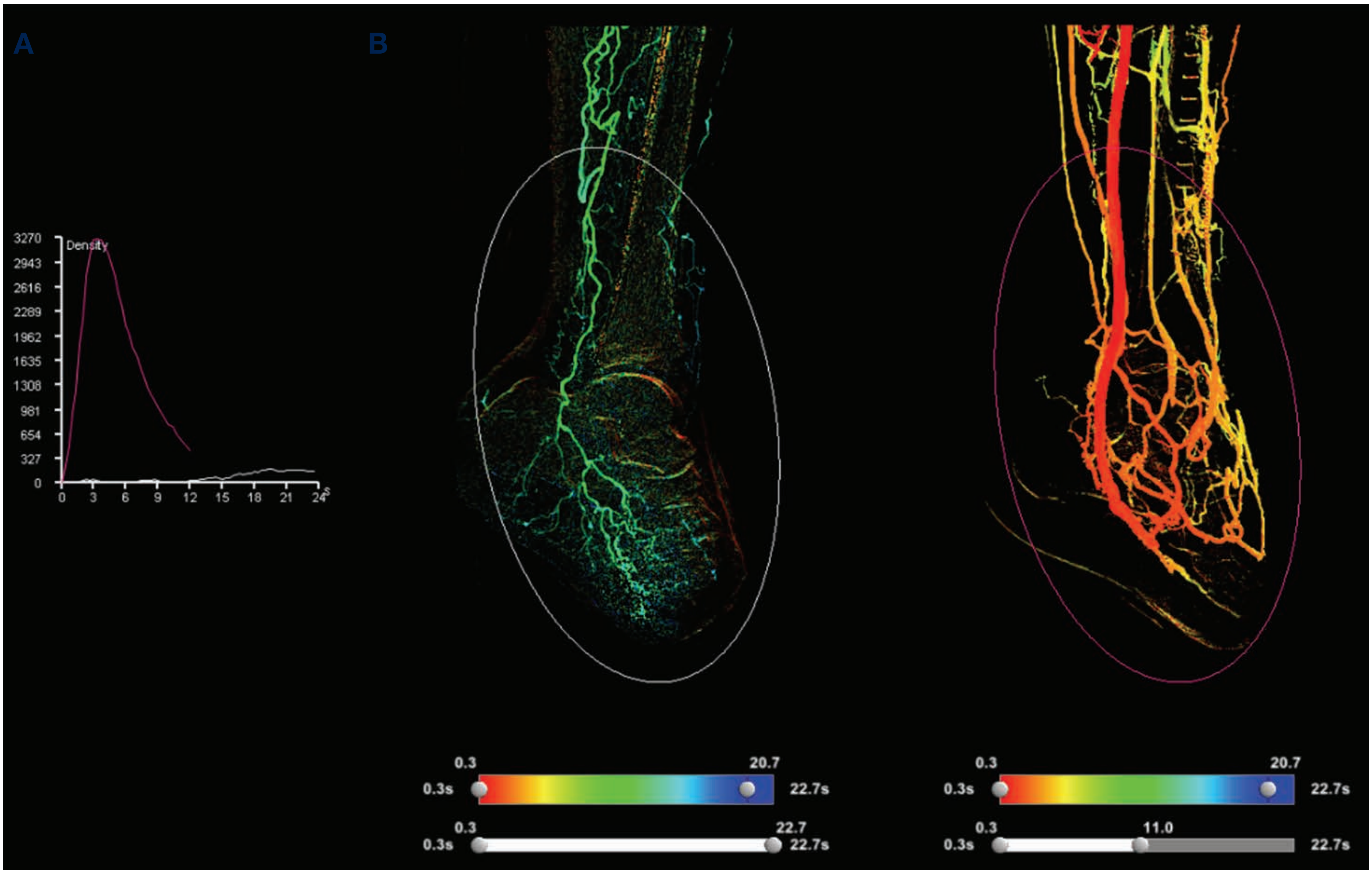

Figure 8. Perfusion scan pre and post intervention showing brisk fast flow (red) to the foot on the right as opposed to less and slower flow on the left (green).

tibial artery was patent proximally with moderate disease followed by complete occlusion in both mid and distal sections. Both anterior tibial and peroneal artery were completely occluded with scarce flow to the foot (Figures 1A and 1B). Percutaneous stick was also performed in the left posterior tibial vein in a retrograde fashion using ultrasound guidance and a pedal sheath was inserted, after which a venogram was performed (Figures 2A and 2B). A V18 wire (Boston Scientific) was inserted and brought down to the posterior tibial artery, followed by balloon angioplasty of the proximal posterior tibial artery with a 3.5 mm x 120 mm Ultraverse balloon (Bard Peripheral Vascular).

Earlier attempts to cross the occlusion with multiple wires and catheters were unsuccessful due to the severely calcified vessel with intimal calcification and large plaque burden that consumed the majority of the posterior tibial artery. Balloon angioplasty of the posterior tibial vein was then performed using a Boston Scientific Sterling SL OTW 4.0 mm x 120 mm balloon via retrograde access (Figures 3A and 3B). The 4.0 mm balloon was exchanged for a 5.0 mm x 120 mm balloon, which was inflated in the posterior tibial vein in the proximal section closest to the patent proximal section of the posterior tibial artery.

An Outback Elite catheter (Cordis) was inserted from the arterial side from above and was brought down in position within the posterior tibial artery just across the section of the posterior tibial vein with the inflated balloon. Crossing was successful and confirmed from the artery to the vein. The balloon burst with the entry of the Outback Elite needle. A Mailman wire (Boston Scientific) was then inserted from the posterior tibial artery to the posterior tibial vein balloon via the Outback Elite needle. The balloon was then deflated and externalized from the retrograde venous access. This technique provided a solid flossing wire to help finalize the procedure (Figures 4A and 4B). An Ultraverse balloon was then inserted across the artery to the vein and transarteriovenous balloon dilatation was performed with dilatation of the entire section of the posterior tibial vein in order to interrupt any venous valves (Figures 5A and 5B). Venography was performed, followed by repeat balloon dilatation using initially an Angiosculpt 5 mm x 20 mm balloon (Spectranetics). Finally a Mustang 5.0 mm x 30 mm balloon (Boston Scientific) was used to properly dilate the distal segment of the vein with remaining venous valves. Once complete, dilatation was performed to control significant retrograde flow seen on venogram. Two 6 Fr compatible, 5.0 mm x150 mm Viabahn LP covered stents (W. L. Gore) were successfully deployed in the posterior tibial vein. The Mustang 5.0 mm x 30 mm balloon was reintroduced to dilate the stents in position. Finally, as angiography showed no excavation, a 4.0 mm x 38 mm Xience drug-eluting stent (Abbott Vascular) was deployed in the section across the posterior tibial artery to the posterior tibial vein, maintaining a direct communication (Figures 6A and 6B). The venous portion of the drug-eluting stent was postdilated with a 5.0 mm balloon.

Repeat angiography was performed showing brisk flow from the posterior tibial artery across to the distal posterior tibial vein, and down toward the foot (Figure 7A and 7B). A perfusion scan (Philips), which had been performed at the start of the procedure, was repeated at the end of the revascularization and confirmed brisk oxygenated venous flow to the foot (Figure 8). The procedure was now completed, the tibial sheath and the femoral sheaths were removed, and the patient was sent to the floor for postprocedure medical care. The patient tolerated the procedure with no immediate complications. An AV reversal was successfully performed and flow was reversed from the artery toward the vein for improved brisk flow to the foot as confirmed with the perfusion scan.

Developing expertise in advanced imaging modalities and incorporating them into CLI interventions is effective for confirmation during such procedures. Proper planning, advanced skill, and knowledge of devices, as well as knowledge of associated morbidity and mortality, are all important to successful AV reversal. While the concept of diverting flow from an artery to a vein is proven and the immediate task was achieved, the long-term benefits and outcomes still need to be studied.

Editor's note: Dr. Diaz-Sandoval, Dr. Ansari and Ms. Heaney report no disclosures. Dr. Mustapha reports consultancy to Abbott Vascular, Bard Peripheral Vascular, Boston Scientific, Cordis, Spectranetics and Terumo Medical. Dr. Saab reports consultancy to Abbott Vascular, Bard Peripheral Vascular, Spectranetics, and Terumo Medical.

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Preventing Restenosis Below the Knee With Drug-Coated Balloons

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Francesco Liistro, MD

Drug-coated balloons have the potential to prevent restenosis and reocclusion in the treatment of below-the-knee vessels (BTK) in critical limb ischemia patients. The mechanism relies on the release of paclitaxel, an antiproliferative drug, into the vessel wall, which inhibits intimal proliferation related to the mechanical stress effect of balloon angioplasty. Restenosis after balloon angioplasty of BTK vessels is reported up to a rate of 70% in long occluded segments. Although the process is mainly related to intimal hyperplasia, mechanical components such as vessel elastic recoil, residual significant stenosis, and vessel dissection may also play a role particularly in early (<4 weeks) target vessel reocclusion. Thus, it is very important to obtain an optimal result before we apply drug-coated balloon (DCB) angioplasty in the target lesion. The result of balloon angioplasty in tibial vessels is assessed by angiography and Duplex scan evaluation. Angiographic assessment of plain balloon angioplasty (POBA) is used to quantify residual stenosis by QCA analysis, view vessel flow dynamics and visualize dissections. Duplex scan immediately after POBA can increase the accuracy of POBA evaluation, showing the segments where blood velocity increases (high residual stenosis) or is dumped (post stenosis). A high residual stenosis prior to DCB delivery is associated with high restenosis rates on long-term outcomes, even if the DCB provides a low late luminal loss (LLL).

A recent report by Siablis (The IDEAS Trial) compared drug-eluting stent (DES) vs DCB in the treatment of tibial vessels.[1] Immediate residual postprocedure stenosis was significantly lower in DES (9.6 ± 2.2% vs 24.8 ± 3.5% in DCB) as well as 6-month binary restenosis rate (>50%) (DES 28% vs DCB 57.9%; *P*=.0457). However, LLL was lower in DCB compared to DES, thus showing the importance of residual stenosis as a key component of restenosis. In order to improve the results of balloon angioplasty, interventionalists should use an aggressive approach to treating tibial vessel lesions with a balloon-to-vessel ratio >1, high

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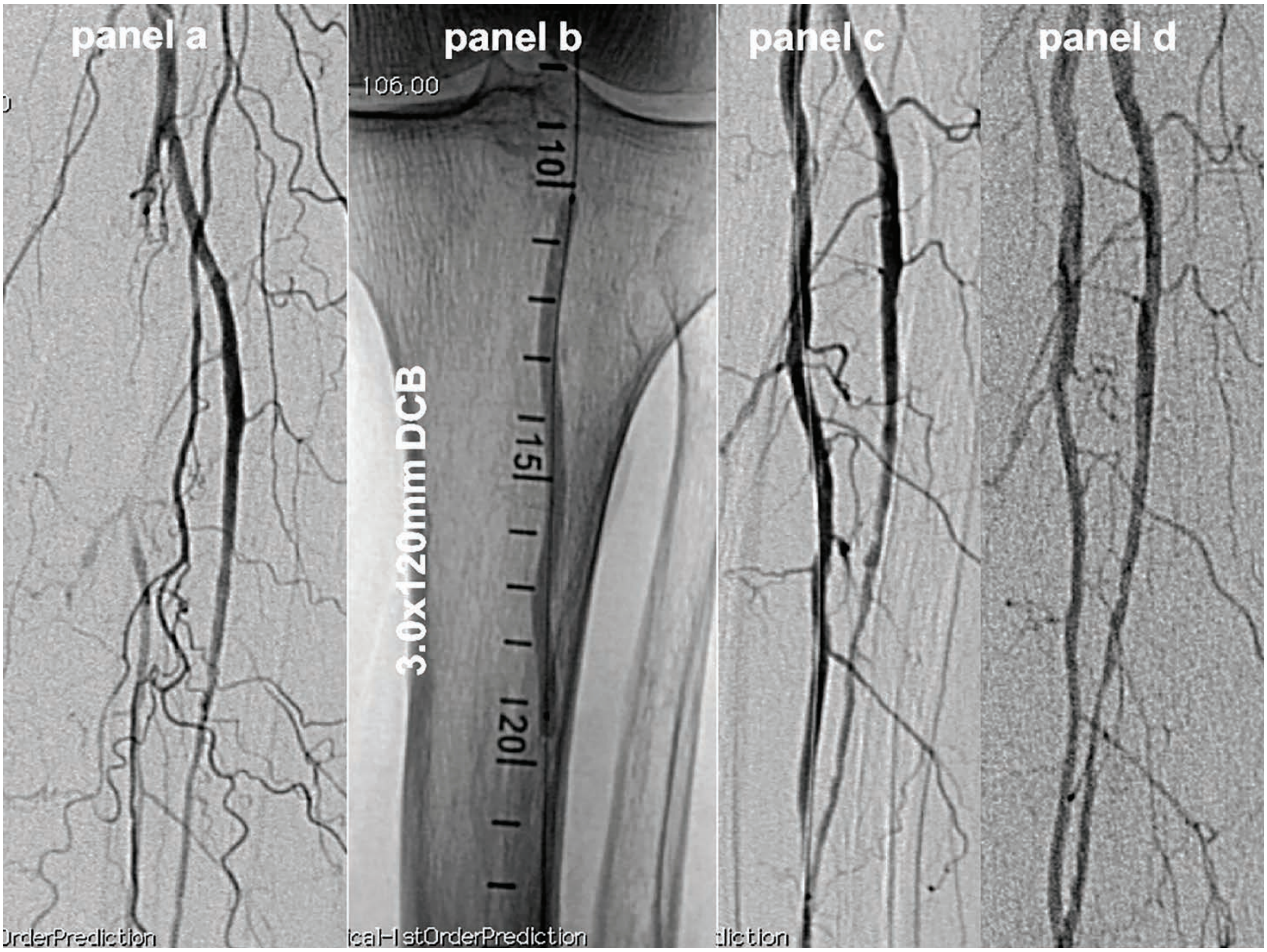

Figure 1. Tibioperoneal occlusion (A) treated with a 3.0 mm x 120 mm drug-coated balloon inflated at 16 atm for 2 minutes (B). The immediate result (C) shows an optimal result with no residual stenosis and no residual dissection.Twelve-month angiography shows the persistence of optimal residual result with no late lumen loss (D).

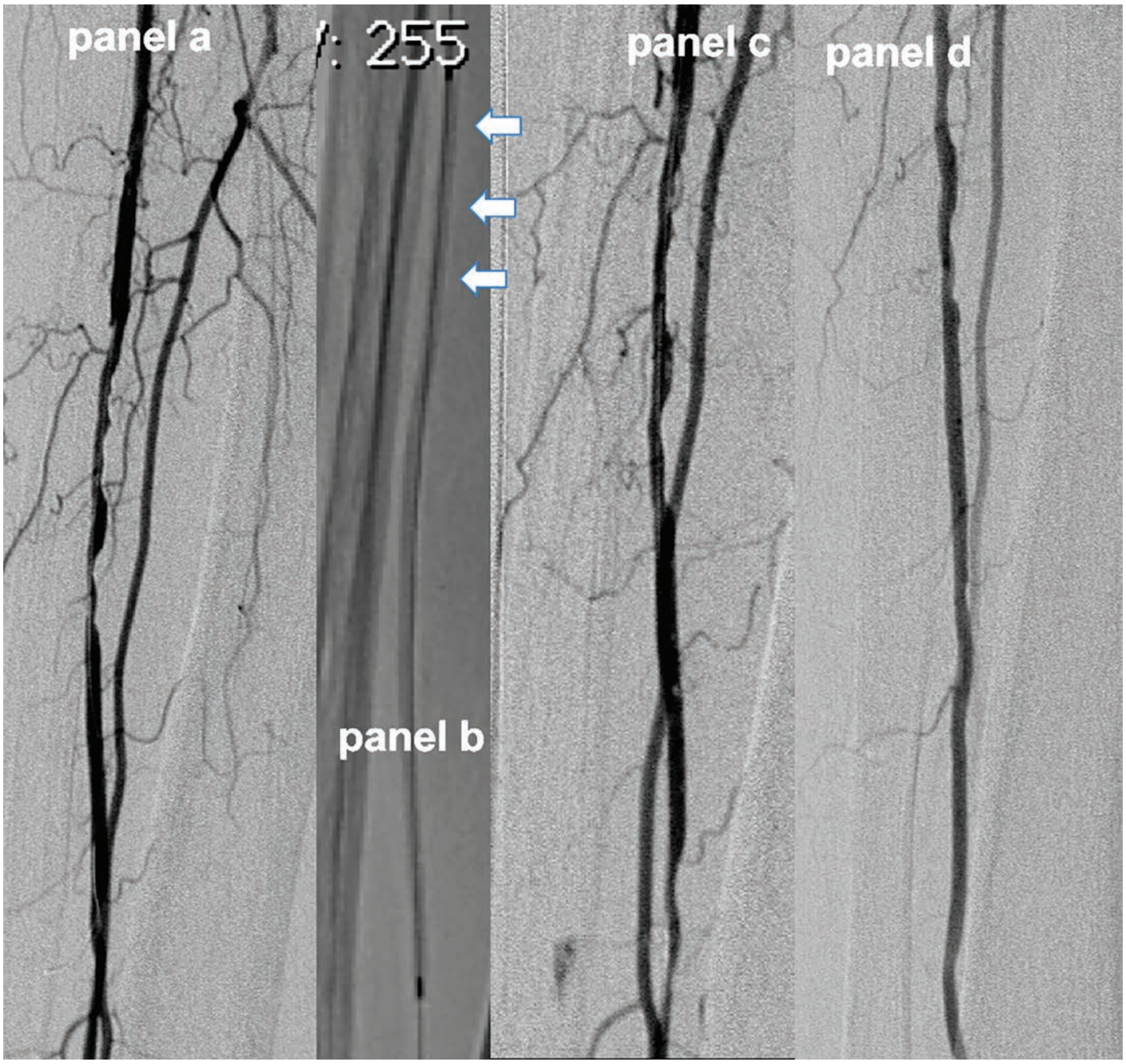

Figure 2. Peroneal disease (A) treated with a 2.5 mm x 120 mm drug-coated balloon at 12 atm for 2 minutes (B). The immediate result (C) is suboptimal, showing a significant residual stenosis, which remained similar on 12 months angiography (D).

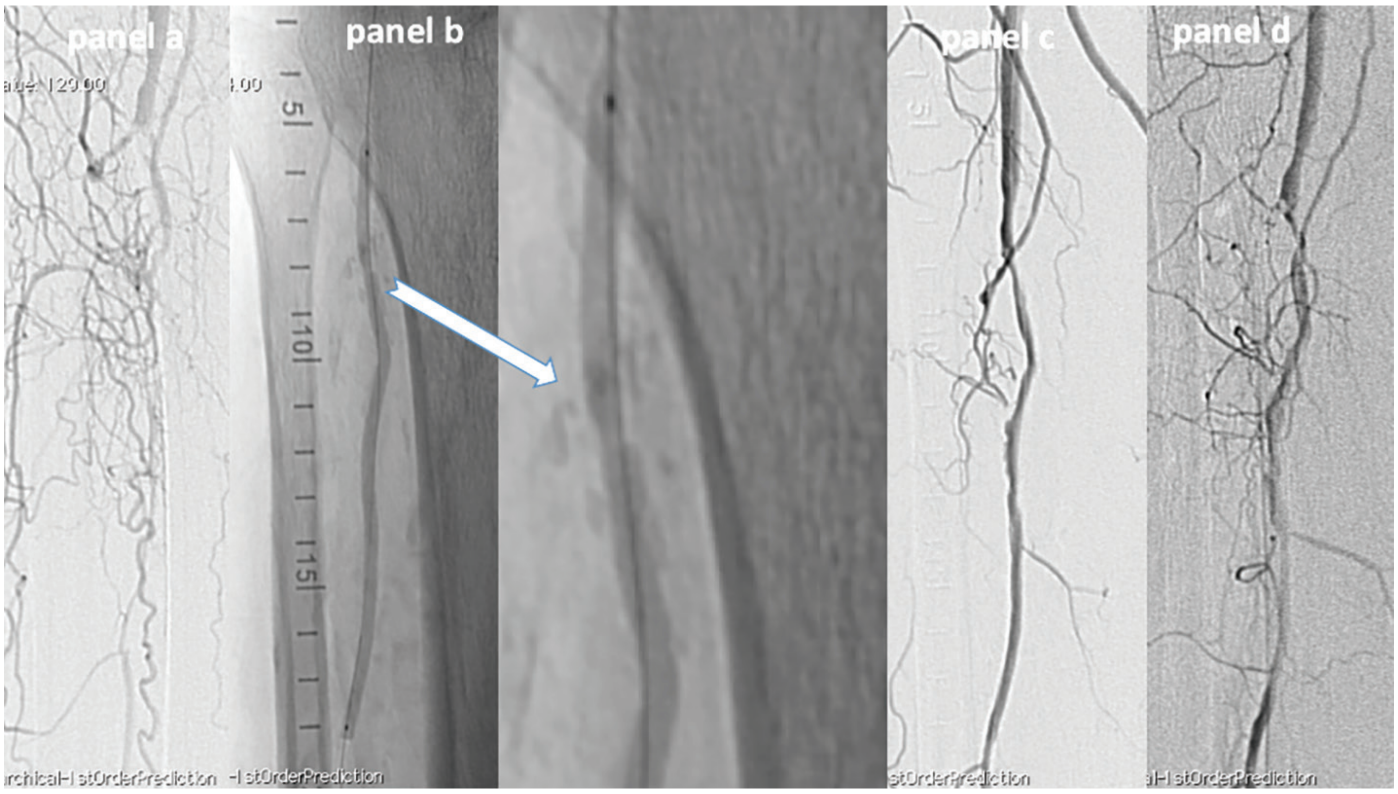

Figure 3. Tibioperoneal occlusion (A) treated with a 3 mm x 120 mm drug-coated balloon (DCB) at 12 atm (B) with a persistent waist on the proximal DCB segment. The vessel reoccluded at 12 months where there was a waist in the DCB (C, D).

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pressure inflation (16-18 atm), and long inflation time. After aggressive predilatation, angiography evaluation and exploration of the entire vessel by Duplex ultrasound are useful. In cases with documented optimal results, DCB with a balloon-vessel ratio >1 and intermediate pressure (10 atm) should be used to ensure contact between the balloon surface and vessel wall. The DCB must always be inflated for a minimum of 2 minutes. With suboptimal results after POBA, noncompliant balloon, scoring balloon, or an atherectomy device can be used to optimize the result. In cases of flow-limiting dissections that do not heal with long balloon inflation, short DES can be used to seal the proximal dissection entry. Figure 1A shows a tibioperoneal occlusion treated with a 3.0 mm x 120 mm DCB inflated at 16 atm for 2 minutes (Figure 1B). The immediate result (Figure 1C) shows an optimal result with no residual stenosis and no residual dissection. Figure 1D shows the 12-month angiography with the persistence of optimal residual result with no LLL.

Figure 2 shows a similar case of peroneal disease (Figure 2A), which was treated with a smaller DCB (2.5 mm x 120 mm) at 12 atm for 2 minutes (Figure 2B). The waist on the proximal part of the balloon, which is not fully expanded, is clearly visible. The immediate result (Figure 2C) is suboptimal, showing a significant residual stenosis, which remained similar on 12 months angiography, due to the low LLL provided by the DCB (Figure 2D).

Figure 3 shows another similar tibioperoneal occlusion (Figure 3A) treated with a 3.0 mm x 120 mm DCB at 12 atm (Figure 3B) with a persistent waist on the proximal DCB segment. The result (Figure 3C) is suboptimal and the vessel reoccludes at 12 months at the area where there was a waist in the DCB.

In conclusion, prior to DCB, vessel preparation must be performed very aggressively in order to understand immediately how the lesion is going to react. In case of persistent residual stenosis, noncompliant balloons, scoring balloons, or atherectomy devices should be used to optimize the outcome.

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