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Epidemiology of Critical Limb Ischemia (CLI): Prevalence and Comorbidities

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GROWING PREVALENCE

In 2015, the U.S. prevalence of critical limb ischemia (CLI) was between 2.0 and 3.4 million.[1] Due to the aging population, by 2020 CLI is projected to increase to between 2.1 and 3.8 million and by 2030 to between 2.4 and 4.7 million.[1]

Notably, these projections assume a constant prevalence of diabetes. However, if diabetes continues to increase as it has over the last 20 years, the 2030 estimates are likely to be conservative. Since 1995, diabetes has doubled in the 45 to 64 age group and almost doubled in the elderly.[2-4] Currently, approximately one-third of the elderly and 17.5% of those ages 45 to 64 are diabetic.[4] By 2040, it has been predicted that more than half of the elderly and 25% of those 45 to 64 will be diabetic.[5]

MAJORITY OF CRITICAL LIMB ISCHEMIA PATIENTS HAVE DIABETES

Age and diabetes are the key risk factors for CLI.[6-8] Diabetes is an even stronger risk factor for CLI than it is for less severe lower limb arterial disease. While diabetes increases the risk of peripheral artery disease (PAD) by 2X-4X, it increases the risk of CLI by 7X-8X.[9-13] The majority of CLI patients suffer from diabetes, or an estimated 60%.[14] In contrast, only 14% of the adult population has diabetes (both diagnosed and undiagnosed).[14] The presence of comorbid diabetes has a profound impact on the severity and consequences of CLI. Diabetic patients are more likely to present with ischemic ulcers or gangrene. A higher percentage of diabetics with PAD develop critical limb ischemia and are at greater risk of progression to gangrene.[15-17]

Diabetic PAD patients are more prone to developing sudden critical ischemia due to thrombosis or a pivotal event that rapidly leads to ulcers or infection.[18] Comorbid diabetes increases both the short-term and long-term risk of major amputation (MA) in CLI.[19-26] Diabetes increases the risk of nontraumatic amputation by 28 times.[27] The rate of amputation increases with age with the highest rate occurring in diabetics ages 75 and older.[27] Diabetics have a higher risk of undergoing contralateral, as well as bilateral reamputation.[28] Diabetes has been shown to be an independent risk factor for amputation. Diabetics also undergo MA at an earlier age.[15] In addition, the risk of amputation increases with the severity of diabetes as measured by hemoglobin A1c (HbA1c).[29-31]

CHRONIC KIDNEY DISEASE (CKD): HIGHLY PREVALENT IN CLI

More than one-third of CLI patients have chronic kidney disease (CKD) (33%–44%).[32-35] The most severe form, end stage renal disease (ESRD), is present in 9% to 12%.[35,36]

CKD presence increases with severity of ischemia in CLI. In one study, 16% of Rutherford Category 4 patients had CKD with the prevalence rising to 42% of Rutherford 6 patients.[34]

Patients with CKD have an increased risk of mortality and amputation.[33,37,38] Renal insufficiency independently predicts mortality in CLI.[33] Mortality increases with declining renal function and also with increasing severity of ischemia.[38]

End stage renal disease patients have a higher risk of amputation and amputation risk increases with CLI severity. ESRD independently predicts primary amputation in CLI with an OR of 5.3X.[39] Severity of ischemia (presence of gangrene versus claudication) increases the odds of amputation by 19X.[37] In CLI patients undergoing revascularization, ESRD predicts lower survival and limb salvage rates both in-hospital, as well as at a one year and longer term.[40,41] In the hospital, dialysis patients have a significantly increased risk of either amputation or death (OR, 2.62) and major amputation (OR, 3.14).[40]

At one-year in CLI patients undergoing endovascular revascularization, dialysis independently predicts lower survival

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Intravascular Ultrasound: A Valuable, Adjunctive Tool to Identify and Guide Critical Limb Ischemia Therapy

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Every week, vascular specialists across the country are experiencing firsthand the acute influx of the epidemic called critical limb ischemia (CLI).[1,2] CLI is the most severe manifestation of peripheral arterial disease (PAD) in which the patients exhibit rest pain (Rutherford Classification IV) and ischemic ulcerations or gangrene (Rutherford Classification V/VI) due to distal hypoperfusion secondary to multi-level arterial lesions.

The introduction of angiography revolutionized the diagnosis and management of arterial disease in multiple vascular beds.[3,4,5] Nearly 60 years after its invention, angiography is still considered to be the "clinical gold standard" for defining peripheral arterial anatomy.[3,4] However, the weakness of angiography is that it is a two-dimensional image attempting to extrapolate the three-dimensional anatomical entity of the arterial blood vessel. From an anatomic perspective, a vessel is not a straight in-line pipe that carries blood flow without interruption. Its heterogenous pathology and histologic morphology mandates another mode of intravascular assessment and evaluation.

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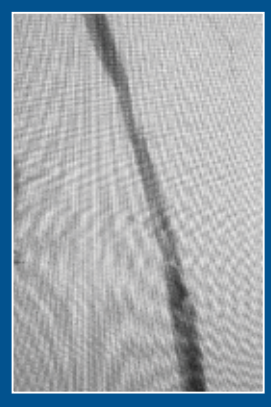

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Treatment of CLI in an Outpatient Setting: The VIC Approach to Comprehensive Care of the CLI Patient

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The office-based interventional suite is a patient-centered, alternative care model that can be the ideal outpatient experience for routine vascular care for both patients and physicians. In 2005, Centers for Medicare & Medicaid Services approved Site of Service 11 allowing physicians to perform peripheral vascular interventions in an outpatient facility. Across the United States vascular and interventional physicians took back their professional lives, patient care, and the patient experience from dysfunctional hospital systems. Office-based interventional suites were formed, interventional CPT payment structures were created, and vascular care shifted from the hospital toward the outpatient office-based environment. Successful arterial endovascular care soon followed in this outpatient setting with feasibility and safety studies proving their efficacy.[1,2] This alternative care model proved fertile ground for the development of a dedicated comprehensive care model for critical limb care and amputation prevention. In 2015, the Vascular Institute of Chattanooga (VIC) was born, "victory over amputation" our purpose and core focus. Addressing the unmet need for patients in southeast Tennessee was our goal. Chattanooga Tennessee is a thriving southern city full of good food, young entrepreneurial businesses, and large-scale gentrification and waterfront projects reshaping the region. The county hospital hosts the seventh busiest emergency room in our nation, and the fourth largest interventional stroke program. We are in the heart of the stroke belt, with a high density of aneurysm disease, peripheral artery disease (PAD), as well as, patients with critical limb ischemia (CLI). In a recent Medicare population-based cohort study on the diagnosis and outcomes of the CLI population it was found that 42% of all major leg amputations were occurring in the southern states.[3] CLI is highly prevalent in our community, and a dedicated comprehensive care model for amputation prevention became necessary.

CLI Conundrum
PAD Unrecognized
Amputation "Gold Standard"
Systemic Ineffectiveness
Critical Limb Specialist
Comprehensive CLI Program

Figure 1. Understanding and addressing these issues, as a global medical community, can optimize CLI care.

FUNDAMENTAL PROBLEMS

One of the fundamental questions that we as CLI experts need to answer is why do we fail as a global medical community to properly address CLI? We know from recent studies that major amputation is the only treatment option offered for

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Drug-Coated vs Uncoated Percutaneous Transluminal Angioplasty in Infrapopliteal Arteries: Six-Month Results of the Lutonix BTK Trial

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Abstract: Objectives. We hypothesized that a drug-coated balloon (DCB) could improve treatment efficacy while maintaining safety when compared with percutaneous transluminal angioplasty (PTA) for the treatment of atherosclerotic infrapopliteal arterial lesions. **Methods.** A total of 442 patients with angiographically significant lesions were randomized (2:1) to DCB or PTA. The primary safety and efficacy endpoints were freedom from major adverse limb events and perioperative death (MALE-POD) at 30 days, and freedom from vessel occlusion, clinically driven target-lesion revascularization (CD-TLR), and above-ankle amputation measured at 6 months. Success was achieved if safety between groups was non-inferior (margin 12%), and efficacy was statistically significant either for the overall intention-to treat (ITT) or the proximal-segment DCB groups (ie, the proximal two-thirds of the below-knee arterial pathways). **Results.** Freedom from MALE-POD for the DCB group (99.3%) was non-inferior to PTA (99.4%; non-inferiority *P*<.001). Proportional analysis of the primary efficacy endpoint was statistically significant for the proximal-segment DCB group (76%) vs PTA (62.9%; one-sided *P*<.01; Bayesian *P*-value for success of .0085) while not statistically significant for the overall ITT group (74.5% for DCB vs 63.5% for PTA; one-sided *P*=.02). Kaplan-Meier analyses demonstrated superior efficacy for DCB in both the overall ITT and proximal-segment groups at 6 months. Primary patency and CD-TLR, hypothesis-tested secondary endpoints, were also statistically better for the DCB group compared with PTA at 6 months (one-sided *P*<.025). **Conclusions.** DCB treatment for symptomatic infrapopliteal arterial lesions produced non-inferior safety at 30 days and a statistically significant difference in the primary efficacy endpoint when compared with PTA at 6 months.

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Key words: drug-coated balloon angioplasty, infrapopliteal disease, paclitaxel-coated balloon, percutaneous transluminal angioplasty, peripheral artery disease, peripheral vascular disease

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Patients with advanced peripheral artery disease (PAD) and critical limb ischemia (CLI) face an elevated risk of amputation and a mortality rate higher than most cancers.[1,2] Surgical and catheter-based revascularization are recommended to restore distal perfusion and prevent amputation in symptomatic patients.[3,4] Surgical bypass is effective when experienced surgeons use a suitable autogenous vein, and when the anatomic and patient risk factors permit this approach.[5] Patients with CLI are often poor surgical candidates because of the absence of suitable venous conduit or the presence of significant medical comorbidities.[6] Percutaneous transluminal angioplasty (PTA) is the standard endovascular treatment for hemodynamically significant infrapopliteal lesions.[7,8] Although initial technical success using PTA often exceeds 90%, restenosis necessitating repeat revascularization or amputation is common.[7,8] Percutaneous treatment with balloons or stents that deliver antiproliferative agents directly to the vessel wall may inhibit neointimal hyperplasia and lower the risk of restenosis.[9-11] To date, however, randomized trials in infrapopliteal arteries have provided mixed results.[12-14] In the Levant II study, the paclitaxel-based drug-coated balloon (DCB) used in the current trial demonstrated superior patency compared with standard, uncoated PTA in patients with femoropopliteal artery disease.[15] The purpose of the current trial was to evaluate the safety and efficacy of the same DCB in patients with infrapopliteal PAD.

METHODS

Study design and oversight. The prospective, multicenter, randomized, single-blind, concurrently controlled Lutonix below-the-knee (Lutonix BTK) study compared the use of a paclitaxel DCB to uncoated PTA in the treatment of obstructive lesions in the distal popliteal, anterior tibial, posterior tibial, and peroneal arteries. The trial protocol was approved by the institutional review board or ethics committee at each investigative site, as well as the Center for Devices and Radiologic Health (CDRH) of the Food and Drug Administration (FDA). Patients were advised of the risks and potential benefits of treatment and provided written informed consent prior to participation. Procedures were conducted in accordance with the Declaration of Helsinki, good clinical practices, and other applicable healthcare regulations in the United States, Canada, Europe, and Japan. Data were collected by on-site investigators on electronic case report forms and monitored by either clinical research associates employed by the sponsor or by contract research organizations paid by the sponsor. Data monitoring and clinical events committees provided independent oversight of patient safety. The study was sponsored by Lutonix in support of an investigational device exemption and registered on clinicaltrials.gov (NCT01870401) prior to patient enrollment.

Study population and procedures. Clinical and angiographic inclusion and exclusion criteria are listed in Supplemental Table S1 (supplemental materials available at www.invasivecardiology.com). Eligible patients initially had symptoms of CLI (Rutherford categories 4 and 5) while patients with severe claudication (Rutherford category 3) were added later in the study by protocol amendment.[16] After meeting clinical eligibility criteria, patients received an angiographic examination to confirm that the lesion could be treated with PTA and that the atherosclerotic stenosis was at least 70%. As specified by the study protocol, a patent inflow artery from the aorta to the target lesion was confirmed by angiography; treatment of inflow arteries (ie, iliac, superficial femoral, or above-knee popliteal) was allowed if successfully treated without major vascular complication. DCB treatment of inflow arteries was prohibited. Multiple lesions in up to two native infrapopliteal arterial pathways, between the tibial plateau and tibiotalar joint, could be treated; the total treated length could not exceed 320 mm, the reference vessel diameter had to be between 2 and 4 mm, and the target lesion had to be at least 20 mm from any previously deployed stent.

After meeting angiographic eligibility criteria, patients underwent predilation with a standard angioplasty balloon. Multiple balloons and inflations, as well as prolonged inflations, were allowed, but specialty balloons (eg, cutting or scoring balloons) were not permitted. Following predilation, the patient was considered enrolled in the study. Patients with a post-angioplasty residual stenosis >50% were excluded from randomization, treated according to the investigator's standard of care, and followed for 30 days for safety outcomes. Patients meeting study criteria after predilation were stratified by Rutherford category and randomly assigned in a 2:1 fashion to undergo infrapopliteal angioplasty with a DCB (Lutonix; Bard Peripheral Vascular) or PTA. The Lutonix DCB was coated with a 2 μg/mm^2 dose of paclitaxel, an excipient of polysorbate and sorbitol, and supplied on a 0.014″-compatible over-the-wire catheter, while PTA was performed with any commercially available balloon chosen at the discretion of the investigator. Provisional bare-metal stent placement was allowed, if necessary, as a bailout procedure in cases of flow-limiting dissection or recoil. Patients, core laboratory evaluators, and members of the clinical events committee (CEC) were blinded to the treatment received. Investigators and their clinical teams, however, could not be blinded due to the visible differences in appearance between the DCB and standard angioplasty balloons.

An anticoagulation regimen was suggested as part of the study plan; recommended therapies varied by geographic region, however, and specifics were left to local hospital practice. Starting 3 days before the procedure, acetylsalicylic acid was recommended at a dose of 75-325 mg/day, along with a loading dose of clopidogrel (300 mg), ticagrelor (180 mg), or prasugrel (60 mg). Following the procedure, dual-antiplatelet therapy with acetylsalicylic acid (75-100 mg/day) and clopidogrel (75 mg/day), ticagrelor (180 mg/day), or prasugrel (5-10 mg/day, depending on body weight) was recommended for at least 1 month, and a dose of 75-100 mg of acetylsalicylic acid was suggested indefinitely thereafter.

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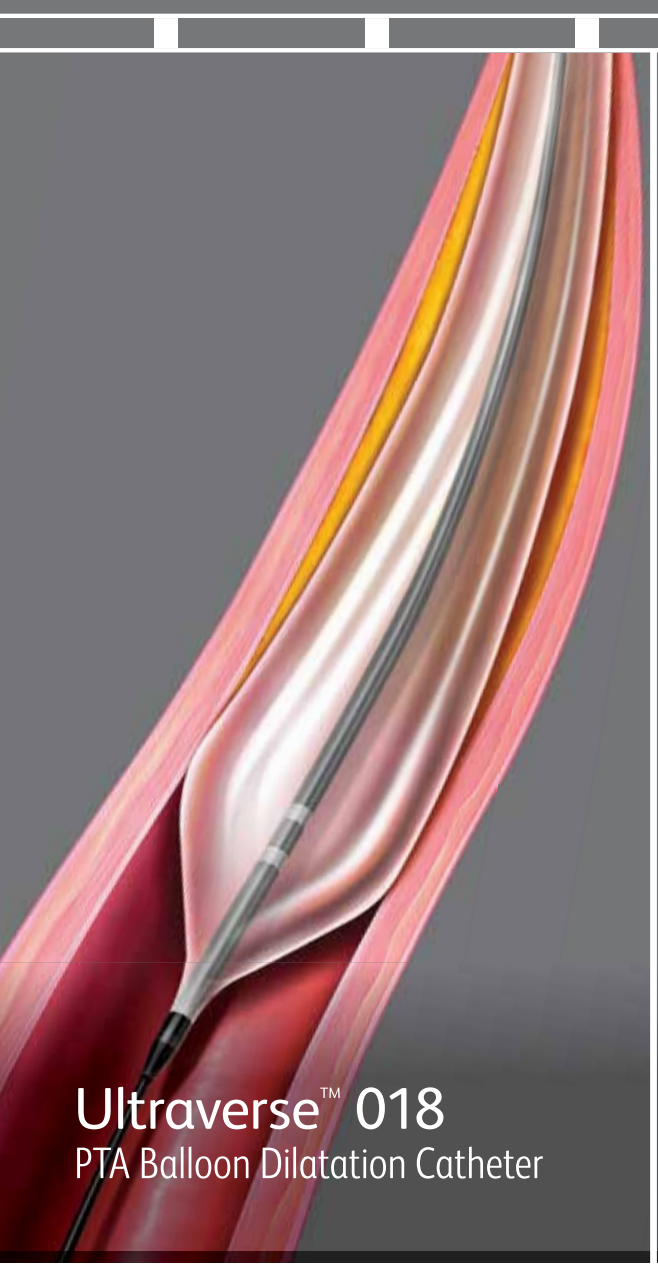

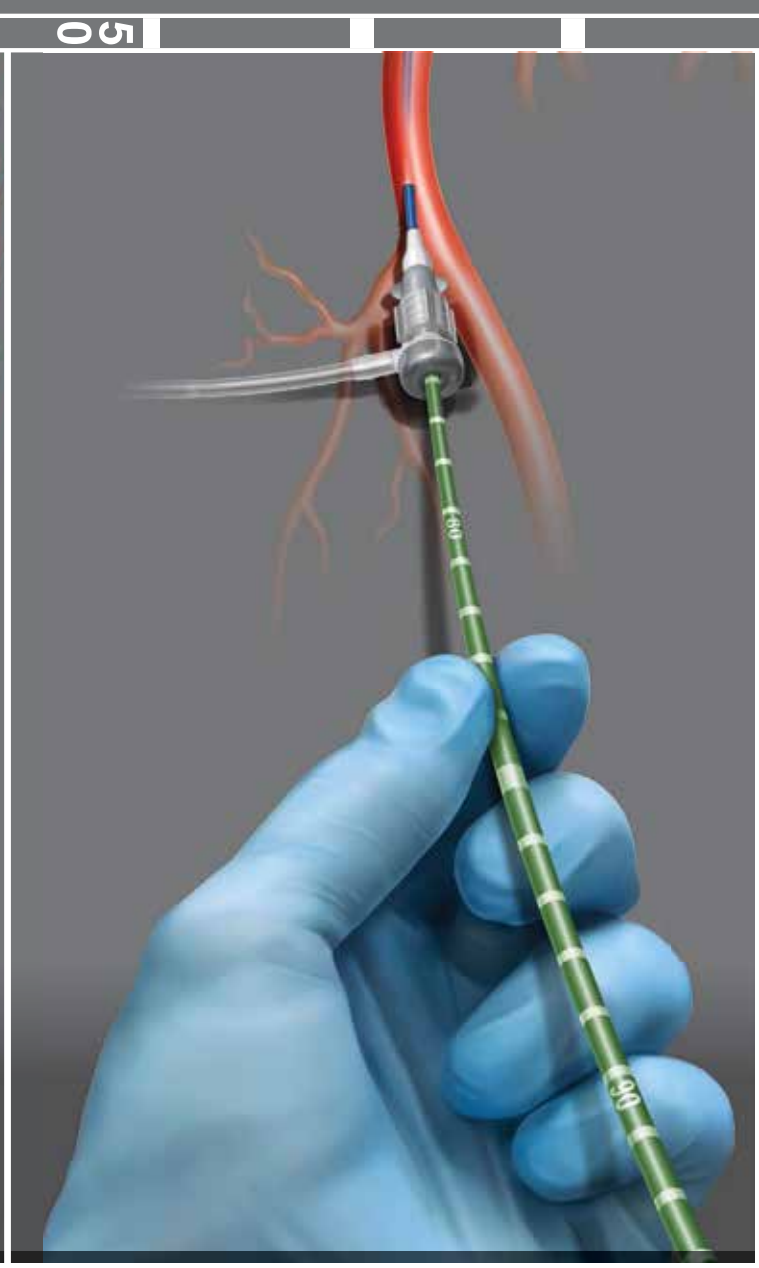

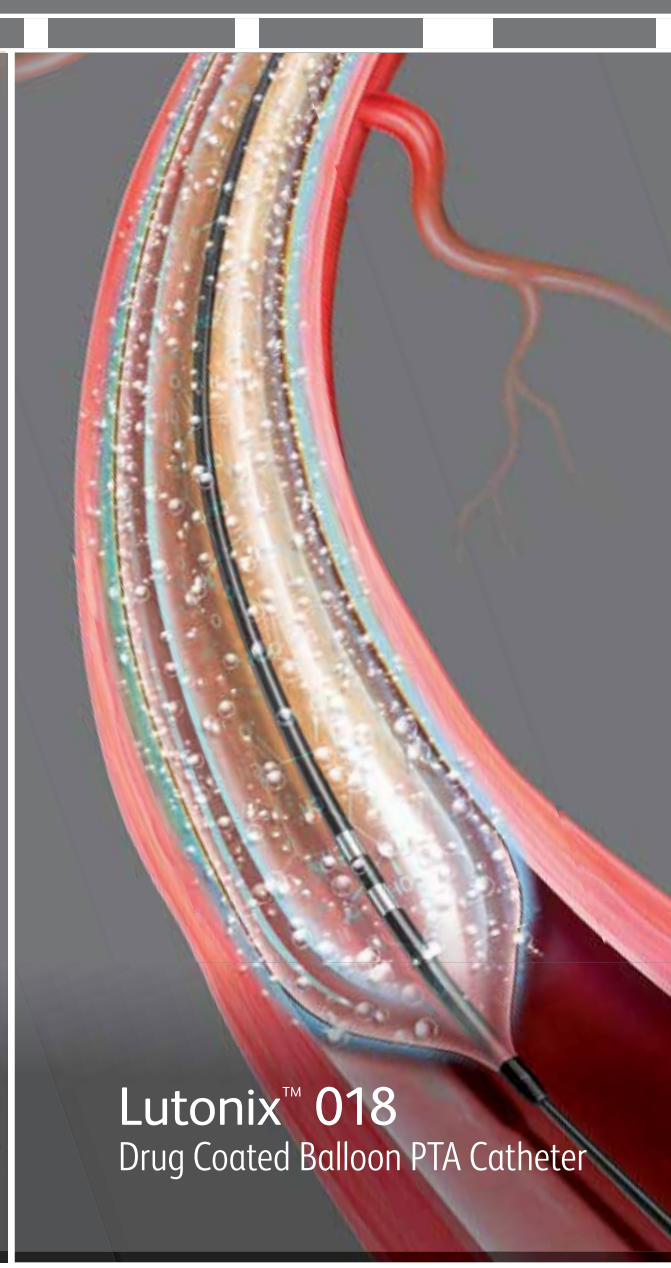

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and amputation free survival (AFS), as well as MA.[36] Two-year AFS, overall survival, and freedom from major amputation are all lower in CLI patients with ESRD compared with non-ESRD patients.[41] Examining the rapidly growing ESRD population, almost two-thirds (63%) have CLI.[42] Between 2000 and 2016 the U.S. ESRD population grew by 86% to 726,000 people.[43] Over the next 15 years, the number of ESRD patients is projected to increase by 29%-68% to between 971,000 and 1.3 million by 2030.[44]

Consequently, the increase in ESRD patients is expected to have a significant impact on the growth in numbers with CLI. Assuming 63% of ESRD patients have CLI, severe limb ischemia in the dialysis population is expected to grow from 457,000 currently to between 612,000 to 819,000 by 2030.

POLYVASCULAR DISEASE

The majority of CLI patients also have polyvascular disease. In a recent study of Medicare patients, almost half of CLI patients had comorbid coronary artery disease (CAD).[33]

Other studies in various CLI populations found that the prevalence of CAD is 48% to 85%, while that of cerebrovascular disease (CVD) is 16% to 25%, respectively.[12,20,33,45-47] Approximately 20% to 30% of CLI patients suffer from congestive heart failure (CHF).[12,45,47,48] In our recently published research on costs, we concluded that 60% of CLI patients have CAD, 20% CVD, and 20% CHF.[14]

Analysis of CLI hospital admissions found that all cardiovascular causes (including hypertension complications) accounted for over 7% of CLI admissions. CHF represented 3.5% of CLI admissions, while MI accounted for 1.84%.[32] These cardiovascular hospitalizations and revascularizations add to burden of morbidity. Cardiac disease is also one of the important causes of costly 30-day readmissions for CLI patients.[34] Major adverse cardiac events (MACE) increase with disease severity occurring more frequently in CLI patients than in those with intermittent claudication (IC).[47] MACE is defined as nonfatal MI, nonfatal ischemic stroke or cardiovascular death. At 1, 2 and 3 years after revascularization, CLI patients experienced higher MACE rates those with IC. [47]

An analysis of MACE in the Examining Use of Ticagrelor and Clopidogrel in Peripheral Artery Disease (EUCLID) trial found that CLI patients had a considerably increased risk compared to the non-CLI patients. MACE occurred in 8.85% of CLI patients compared to 4.28% of those with less severe disease. This was despite the fact that, due to the trial design, milder forms of CLI predominated with 59% suffering from rest pain.[49] More than half of deaths in CLI patients are due to cardiovascular causes.[47] Despite this, CLI patients continue to be undertreated for their cardiovascular risk factors, even in comparison to IC patients.[47,50,51]

CONCLUSION

Due to the aging population, by 2030 CLI prevalence is expected to increase by 38%.

The continued rapid growth in two key comorbidities, diabetes and chronic kidney disease, will increase the risk of mortality and major amputation in the CLI population. The expansion of the diabetic CLI population also has implications for disease severity. Unless glucose is adequately treated, diabetic CLI patients will initially present with more severe disease, gangrene rather than rest pain. The presence of polyvascular disease will also increase morbidity and mortality. Unless risk factor treatment improves in CLI patients, we can expect a growing number of cardiovascular events in this population, both fatal and non-fatal. ■

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Disclosure

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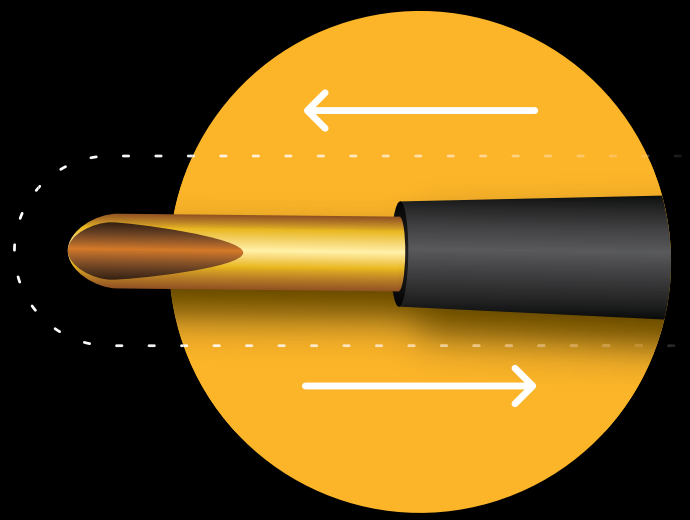

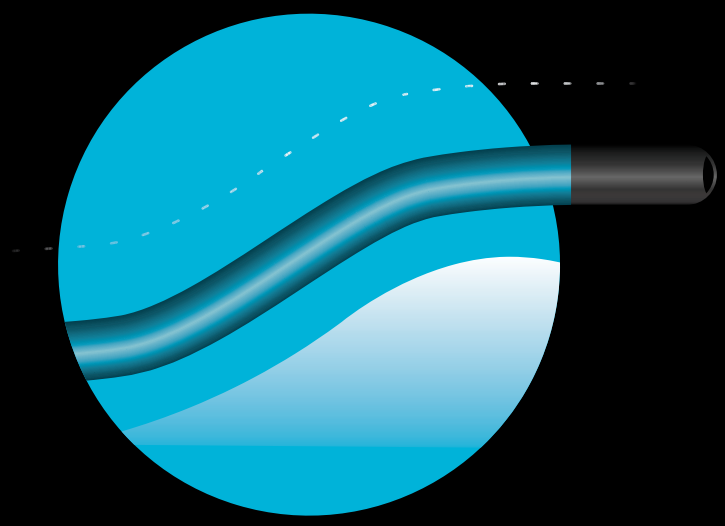

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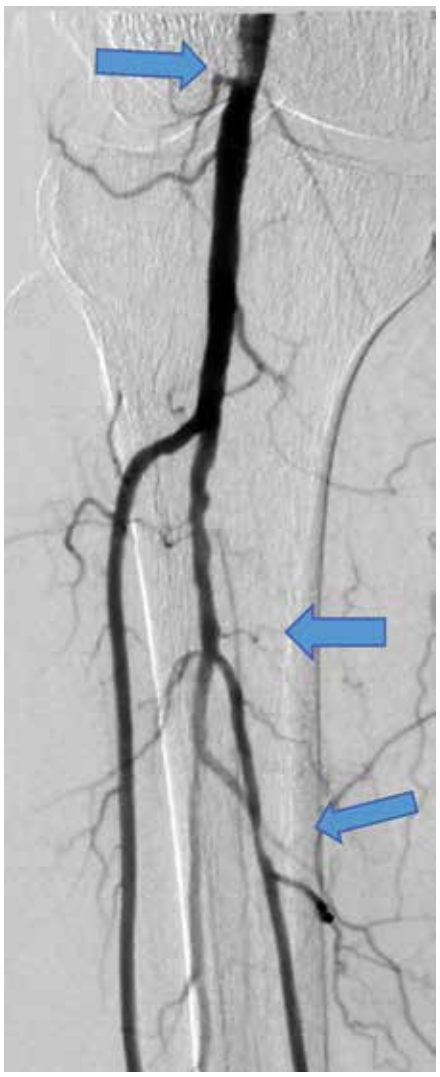

Figure 1. DSA image of three levels of atherosclerotic disease.

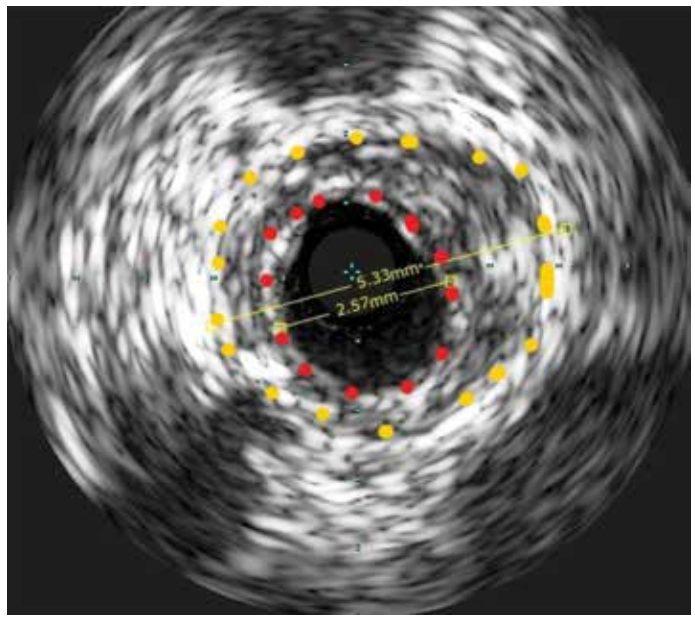

Figure 2. Right popliteal artery stenosis.

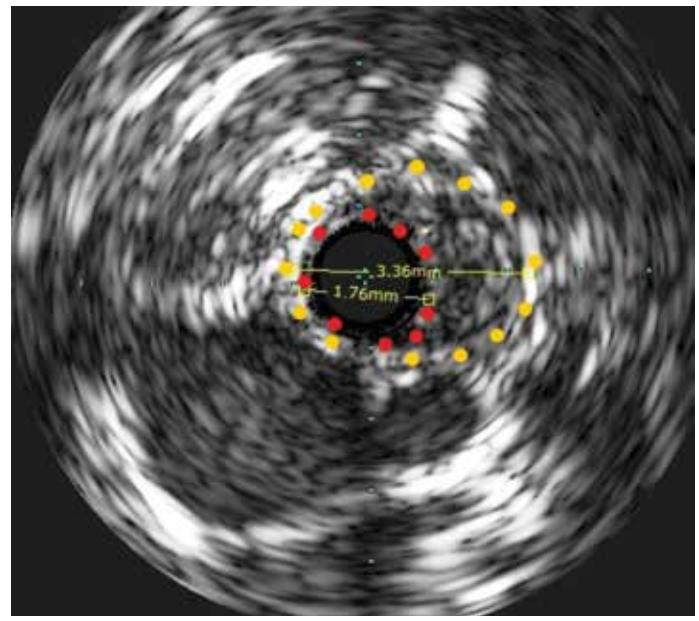

Figure 3. Severe posterior tibial stenosis.

SAAB *and* **PLIAGAS** *from cover*

Intravascular ultrasound (IVUS) gained prominence in the mid 1990s, becoming an intrinsic part of modern invasive cardiology. Its history, however, dates back to the 1980s. Due to the expansion and increased utilization of balloon angioplasty and atherectomy modalities, academic and industry-based teams directed their time and attention to the development of novel vascular imaging technologies. In 1988, Mallery et al reported the first image of plaque in vivo with a single element catheter. Through focused study and refinement in ultrasound catheter technology, Dr. Paul Yock became the key inventor of the intravascular ultrasound system.[6,7,8]

A variety of ultrasound characteristics offer advantages in the evaluation of arterial disease. The tomographic orientation allows for full circumference visualization of the vessel wall allowing for detailed characterization of lumen size and plaque morphology.[7] The high level of resolution provided by IVUS gives the operator detailed arterial wall imaging that is not available with angiography or any other surface imaging modality, and the addition of flow characteristics allow for easy assessment of dissections and stent wall apposition. It has a hydrophilic coating for increased lubricity and a long, rapid exchange lumen for improved pushability. Its versatility allows for utilization from an antegrade or pedal approach.

While digital subtraction angiography remains a crucial component of CLI diagnosis and intervention, its limitations can result in underestimation or inaccurate characterization of the burden of atherosclerotic disease.[9] The Committee on Vascular Lesions classified arterial lesions as Type I through Type V, with Type V subcategorized as largely calcified (Type Vb) and consisting mainly of fibrous connective tissue with little or no accumulated lipid or calcium (Type Vc).[10] There is no doubt that along the arterial course of the leg one will encounter different manifestations of these lesions, making it difficult to apply the same treatment algorithm. Evaluation of lesion characteristics and composition can be facilitated by IVUS.

Some of the patency issues encountered by vascular specialists are due to unrecognized or poorly recognized vessel wall disease. When interventionalists interpret and extrapolate the beginning and end of vessel wall disease with angiography alone, it may lead to inadequate treatment of the occlusive process. One comparative analysis of angiography and IVUS found that angiography derived length of plaque stenoses were 3 mm shorter than those derived from IVUS. Thus, patients may return for treatment of remnant, rather than recurrent disease.[11] Treatment of the angiographic identified portion of the lesion with disease remaining at the proximal and distal ends may result in vessel inflow or outflow complications, such as thrombosis, as well as subsequent occlusions.

Furthermore, with utilization of DSA alone, sizing determinations for endovascular devices, including balloons and stents, are made via visual interpretation of luminal measurements rather than true vessel diameters. Angiographic assessment alone can lead to under-sizing and inconsistent results and utilization of IVUS in conjunction with angiography can aid in the evaluation of complex vessel pathology. Comparatively, when IVUS was utilized to measure luminal and outer diameter of a vessel in question, the IVUS assessment of actual vessel size was repeatedly 1 to 2 mm larger than the luminal measurement.[11] It is a well-known observation that the below-the-knee vessels have a large burden of atherosclerosis. This set of patients exhibit lower procedural success rates due to increased lesion complexity (eg, plaque length, chronic total occlusions, calcific wall involvement) and IVUS imaging can assist with the interpretation of all these factors.[12] Intravascular ultrasound can evaluate the true extent of the underlying plaque burden and overall vessel size.[6]

Using the IVUS adjunctive information in real-time practice in the angiogram suite, we correlate the angiographic findings on one screen with the IVUS findings on another screen. We mark the screens and determine the overall treatment plan, including choice of balloon and stent types and lengths, based on the knowledge obtained from the combined imaging assessments. The images above reveal how utilization of angiography alone may underestimate the disease burden. The angiogram image reveals some areas of concern, which IVUS imaging confirms while delineating the extent of the disease.

The goal of every vascular specialist who treats CLI, especially below the knee, is to achieve optimal results. The understanding of the difference between angiographic luminal diameter and IVUS interpreted vessel diameter is an important aspect of CLI treatment especially when it comes to drug-coated technology where the antiproliferative drug must be delivered directly into the vessel wall.[13] One thing we can be sure of, if the balloons or stents do not make appropriate contact with the vessel wall, there is no therapy.

IVUS has evolved as a crucial and important tool and should be an integral part of every endovascular intervention, especially for critical limb ischemia.[14] The gaining popularity of pedal intervention as a primary approach or as part of a flossing technique displays the versatility of the IVUS system as it can be safely utilized from a pedal approach. Precision and accuracy are of the utmost clinical importance as we try to decrease target lesion revascularization rates. Accurate sizing remains important as we address escalation angioplasty algorithms that impact the internal elastic lamina and the tunica media and attain appropriate vessel diameters to improve long-term patency and decrease re-intervention rates. As CLI vascular specialists who deal with complex vascular pathology daily, we encourage the use of IVUS as part of your diagnostic and treatment algorithms. You will be amazed at how much IVUS will change your understanding of the CLI disease process and ultimate treatment plan. ■

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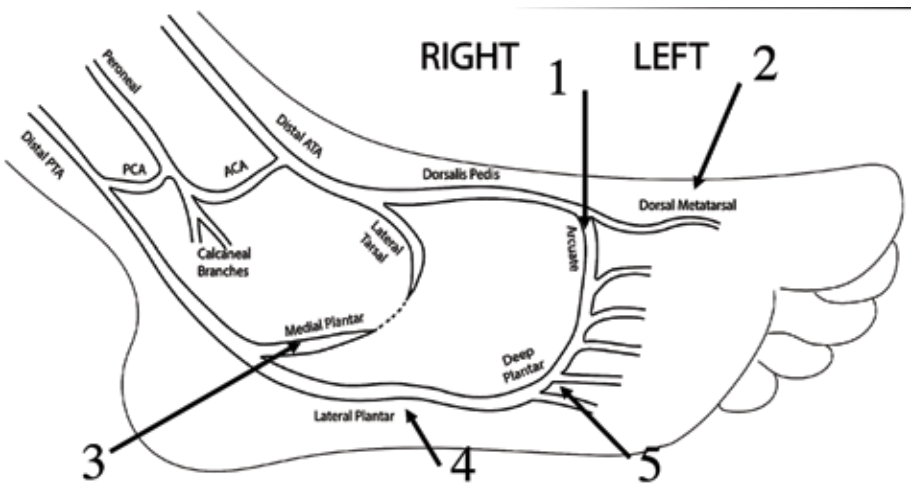

Figure 2. Pedal artery evaluation by non-invasive duplex ultrasound directly studies the angiosome supply of the foot, classifying the adequacy of perfusion.

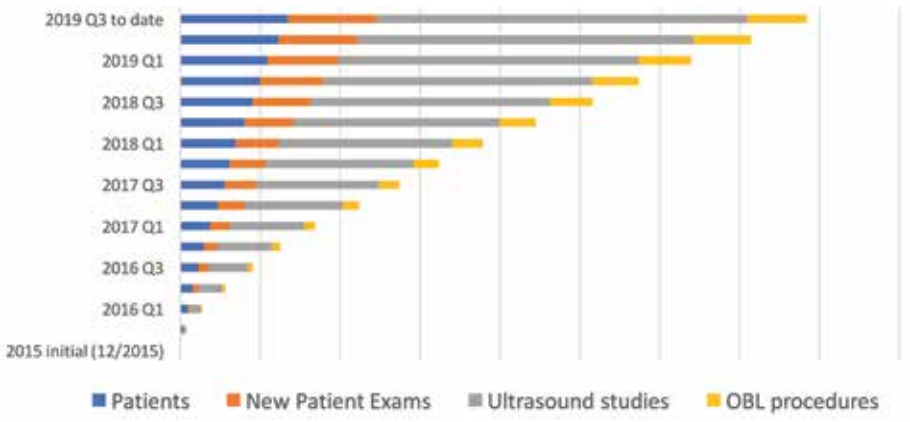

Figure 3. Cumulative distribution over time of clinical activities at VIC.

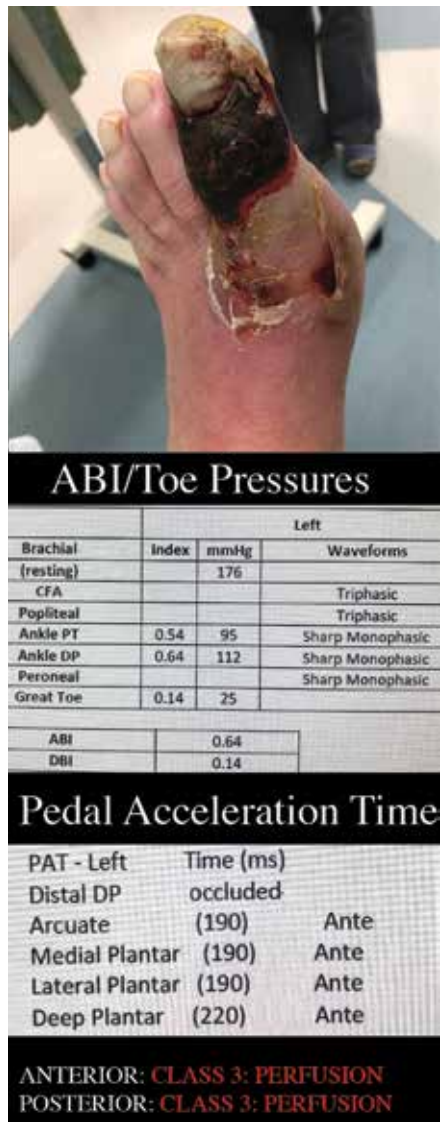

Figure 4. Pre-angiogram arterial ultrasound assessment showing PAT Class 3, moderate arterial insufficiency in the foot. PAT = plantar acceleration time.

LeSar *from page 3*

most patients with CLI. No attempt for revascularization is made in 60% to 73% of CLI patients. No angiograms are performed in 51% to 73% of CLI patients despite a 90% odds reduction for amputation with intervention.[4-8] The answer to this multifactorial conundrum, however, can be found by understanding the problems (Figure 1).

PAD often is unrecognized, undiagnosed, and untreated. In addition, PAD is ubiquitous, progressive, and slow to foster symptoms except when the disease becomes advanced. Because few symptoms are present, PAD is often not diagnosed or treated in the early stages. We rarely receive a consult with the predetermined diagnosis of PAD requesting management, rather, referral is prompted by the diagnosis of claudication, nonhealing wounds, gangrene, or severe leg pain. Therefore, when CLI manifests in this patient population, many patients will have suffered unmanaged medical risk factors for years, including the lack of proper antiplatelet, antihypertensive, ACE inhibitor, and statin therapy. In addition, poor glucose control is found in 40% of the diabetic population, with more than 50% of patients still smoking.[9,10]

From the time of the Civil War to the present, amputation of the extremity has been the "gold standard" of care for serious extremity injury: trauma, infection, and finally, gangrene. Vascular surgical reconstructions, bypass operations, and endovascular interventional care have changed this outcome. Applying the surgical principles of "do the least harm" in any cost-benefit analysis when planning surgical or interventional therapy is mandatory. Unfortunately, general surgery and orthopedic training do not foster the requisite vascular reconstructive knowledge required for limb preservation in the CLI population. Knowledge of these procedures: femoral-to-tibial bypass, popliteal-to-pedal bypass, trans-collateral reconstruction, or pedal-loop reconstruction are understood by only a relative few in selective centers. Therefore, when consults come in for "evaluation for amputation" in the community regions, the default procedures of above-the-knee or below-the-knee amputation are performed. This outcome is expected, every surgical intern is required to know the procedure and to perform a major amputation within the first year of training. This paradigm will only change when access to adequate vascular and interventional care improves, and the notion of "no amputation allowed for the diagnosis of PAD/CLI alone" becomes routine. Consults should be for "limb preservation," not "limb amputation."

Systemic ineffectiveness is the term coined to describe any institutional process, politics, resource management, supply chain limitations, or aggressive discharge planning, which limits clinical effectiveness and patient care. Not only is this process seen in hospital systems, it is endemic in many subspecialty medical and surgical practices. In regard to wait time, is it reasonable to wait 2 to 3 months for elective spine surgery if the surgeon has exceptional results? Possibly yes, if it is your back. However, is that same wait time appropriate for patients presenting with CLI? The logistics of the referral system we operate within plays a role for ultimate limb salvage. Regardless of the location, "time is tissue" remains true, whether in the brain, heart, or foot. Every system has inertia and breaking down ineffective processes is in the best interest of our CLI patients.

A critical limb specialist or team can use advanced endovascular techniques, as well as surgical therapy for limb preservation in patients with the advanced stages of PAD/CLI. Development of mastery in any one field, and especially as a CLI operator, requires dedication to the pursuit of knowledge, development of technical expertise, and an attitude of perseverance in the face of complex situations. To become a critical limb specialist, the attributes of inquisitiveness and fortitude are required, along with a desire to pursue excellence. However, experience is often taught only by failure. Many operators travel through five recognizable stages in becoming a CLI specialist. These stages include disbelief, intrigue, self-education, search for mastery, and finally Everest. It was 2009 when an "aha!" moment occurred for me and launched my CLI career while I was attending the LINC conference in Germany. An Italian doctor passed a wire from the popliteal artery, showing only a desert foot and lower leg beyond, into the subintimal space of the posterior tibial artery through the lateral plantar artery to the pedal arch followed by angioplasty and normalization of perfusion to the foot. Watching this was eye-opening for me and quite frankly unbelievable. That single event changed the course of my career in caring for vascular patients. To say that I was intrigued is an understatement. Understanding the physiology of circulation within the foot and applying the angiosome concepts, as well as learning the anatomic variability of the circulation became paramount to my further training. Self-education is now available through national and international courses and by site-specific travel to experts in the field. Mastery comes with practice and application of gained knowledge. As we climb the mountain, many will make it to base camp, but the lucky and persistent few will summit the top of Everest. This is a lofty and enigmatic goal.

Coordination of multidisciplinary care in a timely manner is necessary to achieve clinical effectiveness in a comprehensive CLI program. Employment of vascular and interventional CLI experts and systematic process validation will be needed to produce very low rates of amputation, and more importantly, to prolong amputation-free survival. Not only will the primary risk factors need to be addressed, but secondary surveillance will need to be instituted for the evaluation of recurrent ischemia, polyvascular disease, ischemic heart disease, and lung cancer in our smoking population. Whether these programs are located within a hospital system or as an independent entity is likely not as important as whether all mission parameters can be delivered in a timely manner.

MEET VIC

The first step in designing an effective solution to a problem is to clearly understand all the aspects of the problem. VIC was born in response to the issues surrounding the CLI conundrum and the unmet need of the patients and physicians in this region. Our goal was to form a center of excellence for critical limb ischemia care, a team that provides leadership, best practices, physician training, and CLI research. The vehicle to accomplish this was to establish an Amputation Prevention Center, the marriage of an office-based interventional suite, vascular nurse-practitioner clinical team, noninvasive ultrasound laboratory, and an extremity wound care program. In order to improve the paradigm of CLI care for this region, five critical components needed to be addressed: access to care, regional education, efficient diagnostics, triage-to-therapy, and activating our CLI clinical

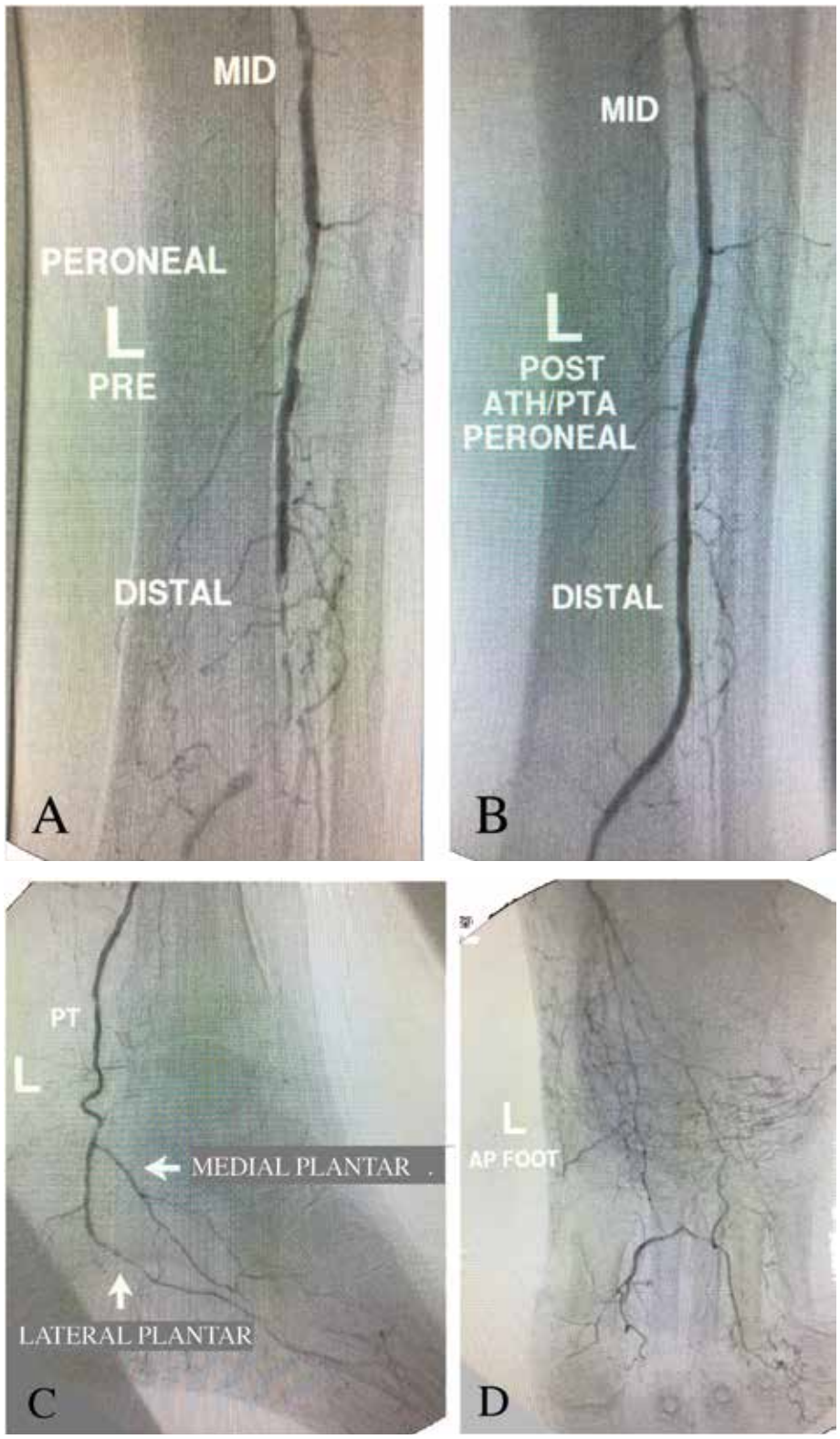

Figure 5. (A, B, C, D) Endovascular reconstruction of the peroneal artery and the dominant posterior communicating artery improving perfusion to the medial and lateral plantar arteries.

network. Over the last four years this has been an evolving work in progress.

Improved access to care starts in the front office with direct phone person-to-person communication. We have no automated phone trees. All referrals to the practice are dealt with promptly and urgent or emergent consults are seen and triaged within 48 hours. In fact, patients are encouraged to come for evaluation on the initial consult day. As a fast rule, all non-urgent consults are offered an appointment within a two-week time period. Additionally, growth within the practice by adding support or clinical staff is based on increasing referral density without extending the two-week maximum evaluation wait time.

Regional education and PAD/CLI awareness efforts were developed for direct patient education, as well as for the purpose of informing referring physicians of the capabilities of the center. The various outlets utilized were health radio and TV, news and health magazine articles, and social media (Facebook, LinkedIn, and Twitter). During September, which is PAD awareness month, we supported the White Sox Campaign and created a road race called "the Victory Run" with the tag line, "Using our legs to save theirs." Not only was this a community participation and educational event, but all proceeds went to cover costs for indigent CLI care in this region. Additionally, a simple pneumonic was developed describing leg FLOW problems; Feelings of pain, Loss of sensation, Open sores that don't heal, or Weakness when walking. This simple and easy to remember messaging accentuates

Figure 6. Post-angiogram arterial ultrasound assessment showing PAT Class 1, normal perfusion to the foot with clearance for podiatric surgery. PAT = plantar acceleration time.

the need for evaluation whenever symptoms are present. In this practice, all marketing efforts were educational events driving home the point: "Know More, No More Amputations!"

An active accredited vascular laboratory is vital for the sustainable growth of a CLI center. Accurate diagnostic studies create the baseline of preoperative perfusion, the location of the vascular obstructions, and allow access planning prior to therapy. In addition to the standard testing: ankle-brachial index, toe-brachial index, absolute toe pressures, and waveform analysis, we have employed plantar acceleration times (PAT) within the anterior and posterior circulation of the foot. There are five arterial zones in the foot that are insonated to determine the waveform characteristics that define the acceleration time, the adequacy of perfusion (Figure 2). Plantar acceleration times are divided into four subgroups: class I normal perfusion, class II mild ischemia, class III moderate ischemia, and class IV severe ischemia consistent with a CLI diagnosis.[11,12] Normalization of PAT immediately after interventional therapy suggests in my experience, adequate perfusion predictive of wound healing.

Triage-to-therapy is a team-based concept utilizing highly trained vascular nurse practitioners to maximize care. They obtain the requisite history,

Figure 7. Well-healed incision 12 weeks after endovascular repair and toe amputation with maintained normal PAT Class 1 perfusion of the foot. PAT = plantar acceleration time.

physical, and diagnostic tests, with the goal of helping each patient progress in the fastest possible manner to the next available therapeutic time slot. Consequently, the majority of patients and families are met by the physicians for the first time in the preoperative area where all data are reviewed, and questions can be answered prior to the procedure. This system is acceptable to patients and families who appreciate the expedited care plan. Additionally, in our destination medicine patients, and those traveling from a long distance, nurse practitioner evaluations, ultrasound testing, and endovascular therapy can be delivered in the same day. The hotel is directly across the street from the center allowing for early next-day post-op evaluation prior to travel home.

The CLI clinical network for an individual patient is the medical support team required to address all the primary cardiovascular risk factors that need to be corrected including smoking cessation counseling. VIC is primarily an outpatient community-based program organizing the connections required to gain access to the required medical subspecialties. CLI is a chronic disease state requiring extensive medical support not just intermittent interventional care. The goal for CLI patients should not only be amputation prevention, but amputation-free survival.

The VIC facility is a 12,000-square-foot first floor space designed to maximize

Continued on page 12

Revascularization Strategies for Critical Limb Ischemia Studied By the CLI Global Society

Jihad A. Mustapha, MD, Founding Board Member of the CLI Global Society

Patients with advanced peripheral artery disease (PAD) suffer from lifestyle limitations brought on by pain with ambulation. Despite currently available modern medicine, many patients continue with severe claudication and rest pain, which limits their activities. Recently approved medical therapy options are of significant value, but, in real-world scenarios, by the time the patients present with advanced PAD disease levels, adequate treatment will require more than medical therapy alone. Due to lack of awareness by the general healthcare community and the public, patients typically are late to seek medical attention. At the time of initial presentation, they will already require endovascular or surgical revascularization.

Inadequately treated PAD can progress to critical limb ischemia (CLI), which carries the risk of serious short- and long-term poor outcomes. We must ensure the CLI patients enter the multidisciplinary CLI team circle of care. Patients entering this circle of care have the best chance of receiving the most advanced treatment available to date. Members of a strong CLI team hold each other accountable with a single common goal in mind: to provide the PAD/CLI patient amputation-free survival with reintroduction back into the work force and back to an independent lifestyle. Imagine the impact we can make if we are able to positively impact the currently 200 million people with PAD world-wide.

The prevalence of PAD continues to rise as baby boomers enter advanced age and develop multiple comorbidities, especially diabetes mellitus, chronic kidney disease, and coronary artery disease. As patients develop additional high-risk diseases, their risk of developing CLI also increases. When our patients cross into the realm of CLI, they enter into a circle of care that, unfortunately, by the fault of no one, continues to be severely limited by a lack of evidence guiding treatment decisions for CLI.

A recently published study on behalf of the CLI Global Society titled "Propensity Score-Adjusted Comparison of Long-Term Outcomes Among Revascularization Strategies for Critical Limb Ischemia" compared four different treatments modalities for CLI hoping to answer questions for both patients and physicians. The aim of this study was to compare long-term outcomes with percutaneous transluminal angioplasty (PTA), stent placement, atherectomy, or surgical bypass in patients diagnosed with critical limb ischemia.1 To the author's knowledge, this is the first study to compare long-term outcomes of three or more revascularization strategies in this patient population.

Among the more than 36,000 Medicare beneficiary patients studied, all-cause mortality over 4 years was 49.3% with atherectomy, 51.4% with surgical bypass, 53.7% with stent placement, and 54.7% with PTA ($P<$ 0.05 for all pairwise comparisons). Major amputation rates more than 4 years were 6.8% with atherectomy, 7.8% with stent placement, 8.1% with PTA, and 10.8% with surgical bypass ($P < 0.05$ for all pairwise comparison except PTA versus stent).[1]

The tendency for atherectomy to yield statistically lower rates of mortality and major amputation relative to PTA, stent placement, or surgical bypass among patients with CLI may be a surprising finding to some. Personally, I am not surprised with the results based on my observations treating thousands of CLI patients over the past decade. Owing to the large sample size in each treatment group, the study was highly powered to detect group differences of questionable clinical importance. For example, 4-year mortality rates ranged from 49.3% with atherectomy to 54.7% with PTA, and all pairwise group comparisons were statistically different. Because of the observational nature of this study, these results should be viewed as hypothesis-generating and further well-designed, adequately powered trials are needed.[1] ■

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the efficiencies of the three primary components: clinic with 12 rooms, ultrasound lab with six rooms, and procedural space with two interventional suites, and one vein room. Currently, three full-time vascular surgeons are on staff with seven full-time nurse practitioners and nine vascular technologists in the ultrasound lab. Over the last four years, approximately 12,000 clinical encounters have occurred, 23,000 ultrasound tests were completed, and 3,700 interventional procedures were performed (Figure 3). Regarding lower extremity arterial care, 2,373 interventions were performed for PAD, and, of those, 45% were for Rutherford 4-6 critical limb ischemia with 1,060 CLI interventions, in 793 limbs, for 663 patients. At VIC, CLI care is a team-based approach focusing on rapid triage, diagnosis, and appropriate interventional therapy with a long view on aggressive risk factor modification; over the last four years, the total limb salvage rate for this center was 95.4%.

CONCLUSION

In global communities where CLI is highly prevalent a dedicated comprehensive care model for amputation prevention is necessary in order to address inappropriate amputation care in the CLI patient. The Amputation Prevention Center at VIC is a patient centered alternative care model that is the ideal outpatient experience for routine vascular and critical limb care for both patients and physicians.

CASE STUDY

An 81-year-old diabetic white male presented with progressive gangrene to the left great toe. The patient stated that the ulcer formed on the bottom of his toe two months before, which only partially healed. The anterior aspect of the toe formed a blister which rapidly turned to gangrene. His past medical history and risk factors were reviewed: Diabetes type II with well-controlled glucose (range 120–140), dyslipidemia on high-dose lipid therapy, chronic hypertension that was medically controlled, and history of smoking having quit 40 years prior. This patient was referred to our practice and seen urgently by a vascular nurse practitioner. Ultrasound testing was completed on this same initial consult day showing evidence of Class III arterial insufficiency by PAT assessment (Figure 4). The following day he underwent an endovascular procedure with antegrade superficial femoral artery catheterization and reconstruction of the peroneal artery and the posterior communicating artery with orbital atherectomy and angioplasty to reestablish flow into the foot (Figure 5 A–D). This patient was seen one week after intervention with normalization of the anterior and posterior PAT assessment, which then prompted referral for great toe amputation by podiatry (Figure 6). Twelve weeks after the procedure, the patient presented back for reevaluation showing sustained normal anterior and posterior PAT assessment, and a well healed wound (Figure 7). He was walking normally with a prosthesis within his shoe. Primary risk factor assessment was adequate with his current medical regimen. ■

"Triage-to-therapy is a team-based concept utilizing highly-trained vascular nurse practitioners to maximize care."

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Disclosures:

Speakers bureau: CSI, Philips, and Terumo.

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CLI GLOBAL SOCIETY

The Critical Limb Ischemia (CLI) Global Society's mission is to improve quality of life by preventing amputations and death due to CLI.

PROPENSITY SCORE–ADJUSTED COMPARISON OF LONG-TERM OUTCOMES AMONG REVASCULARIZATION STRATEGIES FOR CRITICAL LIMB ISCHEMIA

Circulation: Cardiovascular Interventions
September 2019

Full article and editorial at www.cliglobalsociety.org/publications

WHAT IS KNOWN:

- A diagnosis of critical limb ischemia portends a grave prognosis that is more fatal than most cancers.
- Few studies have reported long-term comparative outcomes among specific revascularization techniques for critical limb ischemia patients.

WHAT THE STUDY ADDS:

- Among Medicare beneficiaries with critical limb ischemia who received percutaneous transluminal angioplasty, stent placement, atherectomy, or surgical bypass, minor differences in mortality (ranging from 49.3% to 54.7%) and major ampu-tation (ranging from 6.8% to 10.8%) rates were observed among treatment groups over 4 years.

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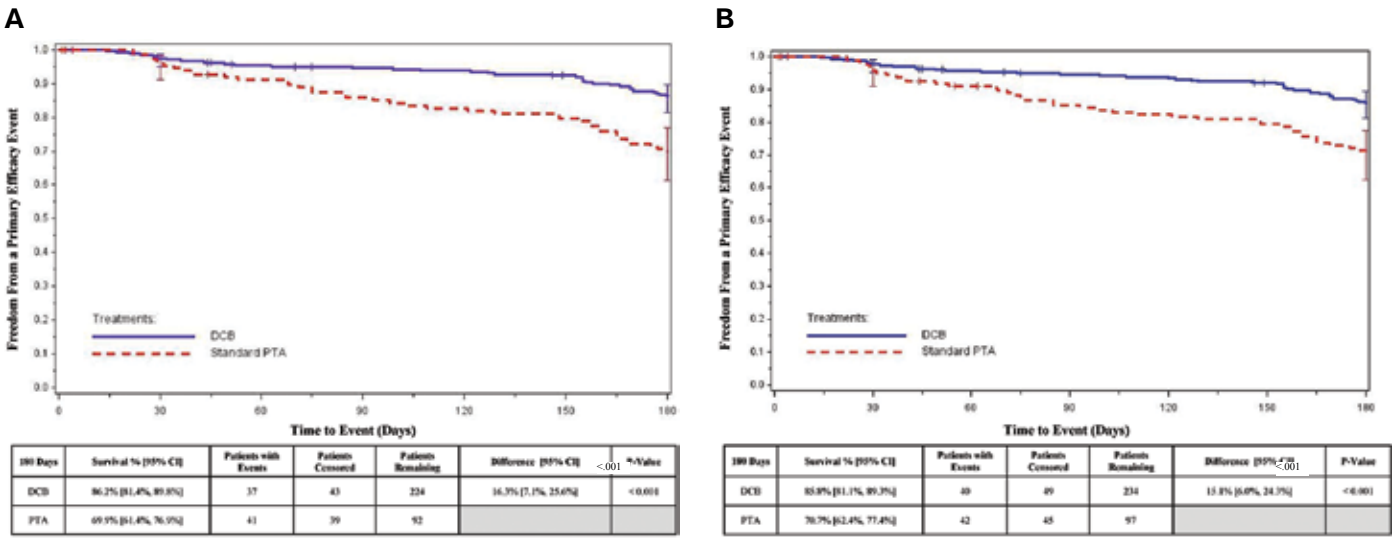

180 Days	Survival % [95% CI]	Patients with Events	Patients Censored	Patients Remaining	Difference [95% CI]	P-Value
DCB	86.2% [81.4%, 89.8%]	37	43	224	16.3% [7.1%, 25.6%]	<.001
PTA	69.9% [61.4%, 76.9%]	41	39	92		

180 Days	Survival % [95% CI]	Patients with Events	Patients Censored	Patients Remaining	Difference [95% CI]	P-Value
DCB	85.8% [81.1%, 89.3%]	49	89	234	15.1% [6.0%, 24.3%]	<.001
PTA	70.7% [62.4%, 77.4%]	42	45	97		

Figure 1. Freedom from the composite primary efficacy endpoint at 6 months. The primary efficacy endpoint was a composite of freedom from above-ankle amputation, occlusion (< 100% stenosis), and clinically driven target-lesion revascularization (CD-TLR) measured at 6 months for the proximal portion of flow pathways. (A) The Kaplan-Meier curves represent the probability of survival through 180 days for the proximal-segment population. The estimated probability of survival was 86.2% for the drug-coated balloon (DCB) group and 69.9% for the percutaneous transluminal angioplasty (PTA) group, with a mean difference of 16.3% (*P*<.001). (B) The Kaplan-Meier curves represent the probability of survival through 180 days for the overall intention-to-treat population. The estimated probability of survival was 85.8% for the DCB group and 70.7% for the PTA group, with a mean difference of 15.1% (*P*<.001).

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Angiography was required during the procedure, and at the time of any reintervention. Duplex ultrasonography (DUS) was required after completion of the procedure, at all follow-up visits, and at the time of any reintervention. In addition, clinical evaluations (consisting of physical examination, wound assessment, and adverse events), assessment of limb hemodynamics, and a health-related quality-of-life (QoL) questionnaire were completed at all follow-up visits. Treatment decisions (in particular the need for reintervention) were based on patient symptoms at follow-up. Accordingly, patients completed QoL evaluations prior to follow-up physical examinations, and investigators completed clinical evaluations and indicated if reintervention was clinically necessary prior to viewing DUS exam results. SynvaCor, the Core Laboratory at Prairie Education and Research Cooperative (Springfield, Illinois) independently analyzed angiographic images while VasCore, the Vascular Ultrasound Core Laboratory at Massachusetts General Hospital (Boston, Massachusetts) independently reviewed DUS images.

Study endpoints. The *primary safety measure* was a composite of freedom from major adverse limb events and perioperative death (MALE-POD) at 30 days adjudicated by the CEC; a major adverse limb event was defined as above-ankle amputation or major reintervention (ie, new bypass graft, interposition graft revision, or thrombectomy/thrombolysis) of the treated limb involving a BTK artery. The *primary efficacy endpoint* was a composite of primary patency and freedom from above-ankle amputation measured at 6 months. Primary patency was defined as freedom from vessel occlusion (<100% stenosis), determined by the angiographic or DUS core laboratories, as well as freedom from clinically driven target-lesion revascularization (CD-TLR, defined as reintervention due to delayed or worsening wound healing, new or recurrent wound, or worsening Rutherford class) adjudicated by the CEC.

Patients with severe PAD and CLI have poor vessel compliance because of the concentration of calcium in the arterial wall.[17-19] This lack of compliance is most prevalent in the more distal infrapopliteal arteries, increasing the risk of acute vessel recoil following PTA and leading to restenosis. Since recoil negatively impacts clinical outcomes following angioplasty, the primary efficacy endpoint in the current trial was calculated for both all arterial flow pathways in the intention-to-treat (ITT) population as well as for the proximal-segment flow pathways. The proximal segment was calculated by the angiographic core laboratory based on the total length of the BTK arterial segment measured from the tibial plateau to the ankle; the proximal two-thirds of this overall length was considered the proximal segment flow pathways.

Secondary efficacy measures included: CD-TLR; primary patency; change in patient QoL as measured by the EuroQoL Group 5-Dimension (EQ-5D) Self-Reporting Questionnaire (scores ranged from 1 to 5, with lower scores indicating a better quality of life); change in Rutherford class; Walking Impairment Questionnaire (WIQ) scores (scores ranged from 0 to 100, with lower scores indicating more difficulty in walking); and hemodynamic outcome, a measurement of the change in toe and ankle pressures of the treated limb. *Secondary safety measures* included: wound healing, an observational status of patients with wounds at baseline compared to follow-up (scored as improved, stagnant, or worse); freedom from major amputation (above-ankle); and all-cause death.

Statistical analysis. The maximum sample size of 840 treated vessels (allocated in a ratio of 2 DCB to 1 PTA) was calculated to provide 93% power to detect a 6-month primary efficacy endpoint difference of 15% between groups at a one-sided alpha of 0.025 (assumption: 55% in the DCB group and 40% in the PTA group). It was also adjusted for a 15% patient attrition rate to account for study withdrawal or missing imaging data. A Bayesian adaptive design incorporated interim analyses to determine the final sample size for the study. A minimum sample size of 300 and a maximum of 840 were set with the final estimate to be based on the predictive probability of primary-efficacy success. The adaptive design included planned interim analyses after 400, 500, 600, and 700 vessels were treated to calculate the predictive probability of trial success. Enrollment was stopped, however, for administrative reasons after 507 vessels were treated; patient accrual was low and slowing at that point, and the study sponsor felt clinical-benefit questions could be addressed with the available data.

Primary efficacy and safety analyses were performed on an ITT basis, with patients analyzed as randomized regardless of treatment received through the close of the 6-month follow-up window. The primary efficacy endpoint was analyzed per arterial flow pathway using logistic regression to account for the possibility of multivessel treatment in some patients; it was calculated for all flow pathways and for the proximal-segment flow pathways (ie, proximal two-thirds of the BTK flow pathway measured by the angiographic core laboratory). To preserve the type-I error level for the primary efficacy analysis below 0.025, the *P*-value was set at .0085 (one-sided test). Success of one or both efficacy analyses was considered success of the primary efficacy endpoint. The primary safety endpoint was analyzed per patient using a Farrington-Manning test for non-inferiority of proportions with a non-inferiority margin of 12% and a one-sided *P*-value of .025. Kaplan-Meier (K-M) estimates were included in addition to proportional analyses, where applicable, to account for missing data (eg, death, un-interpretable imaging data, or withdrawal from the study); survival estimates were presented with two-sided 95% confidence intervals (CIs) and log-rank *P*-values (one-sided *P*-value for success of .025). Success of the primary efficacy and safety endpoints triggered sequential hypothesis testing of four secondary outcomes – primary patency excluding early (ie, ≤30 days) mechanical recoil, primary patency (ie, freedom from total occlusion and CD-TLR), freedom from CD-TLR, and one secondary composite safety endpoint (ie, freedom from amputation, unhealed wound, resting pain, target-vessel occlusion, and clinically driven TVR). Descriptive statistics included frequency counts and percentages along with 95% CIs. Summary statistics, including mean, standard deviation, and 95% CIs were provided for continuous variables. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

Study population and treatment. Between June 2013 and December 2017, a total of 462 patients were enrolled at 51 investigative centers in the United States, Europe, Japan, and Canada. Supplemental Figure S1 details enrollment and distribution of patients. Of the total, ten were roll-in training cases that were treated with the DCB and followed as a separate cohort. Ten patients did not fit the criteria for randomization after initial predilation, were treated according to standard of care, and were screened for safety at 30 days (standard-practice subgroup). The remaining 442 patients were randomly assigned (2:1) to either treatment with DCB (287 patients) or standard PTA (155 patients). Of the overall ITT population, 420 patients (95%) were considered by the angiographic core laboratory to have lesions in the proximal BTK flow segment.

Baseline patient demographic and medical histories are summarized in Supplemental Table S2. Patients were well matched, with both groups exhibiting medical histories and risk factors expected of patients with PAD. Mean patient age was 73 years, most (69%) were male, and 56.1% in both groups presented with ischemic tissue loss (Rutherford category 5). The majority of patients were hypertensive (93.2% in the total population), diabetic (70.1%), had high cholesterol (77.1%), were current or former smokers (58.6%), and had undergone previous peripheral vascular interventions (53.8%). Baseline lesion characteristics are provided in Supplemental Table S3. A total

of 605 lesions were treated in 507 flow pathways (ie, one or more contiguous arterial segments that provided in-line flow to the foot following treatment) in the ITT population (380 lesions in 323 flow pathways in the DCB group; 225 lesions in 184 flow pathways in the PTA group); 476 of the arterial flow pathways were located in the proximal segment (304 in the DCB group; 172 in the PTA group). The most common lesion location was the anterior tibial artery (38.4% in the DCB group; 36% in the PTA group), followed by the tibial-peroneal trunk (23.9% vs 25.3%, respectively), the posterior tibial artery (23.7% vs 25.8%, respectively), and the peroneal artery (23.4% vs 20.9%, respectively). The mean total lesion length, measured by the angiographic core laboratory, was 111.8 ± 92.6 mm in the DCB group and 94.7 ± 85.4 mm in the PTA group. Total occlusions accounted for 36.1% of lesions in the DCB group and 33.3% of lesions in the PTA group, lesions were reported as calcified in 59.9% of the DCB group vs 54.2% of the PTA group, and TASC C and D lesions were reported in 30.8% of the DCB group vs 22.0% of the PTA group.

Absence of an angiographically confirmed inflow obstruction (≥50%) was required for study enrollment; therefore, treatment of inflow vessels was allowed prior to or during the index procedure. Inflow lesions were treated in 34.8% of DCB patients and 28.4% of PTA patients. The most common inflow location treated was the superficial femoral artery (71.4% of the DCB group and 72.7% of the PTA group), while the most common inflow treatment procedure was a combination of PTA and provisional stent placement, observed in 41.3% of pathways in the DCB group and 41.8% of pathways in the PTA group. No major vascular complications were reported during inflow treatment. Vascular access was achieved through the femoral artery in 99.5% of cases, with an additional ipsilateral, retrograde access obtained in 7.7% of the DCB cases and 10.3% of the PTA cases (Supplemental Table S3). A single BTK flow pathway was treated in most cases (87.8% of the DCB group and 76.8% of the PTA group), although treatment of lesions in up to two parallel flow pathways was allowed. Angiographic analysis after completion of the procedure demonstrated a final mean residual stenosis of 29.5 ± 13.8% in the DCB group and 30.0 ± 12.8% in the PTA group.

Postprocedure follow-up and endpoint analyses. Six-month data were evaluated for this analysis. Overall, 83.7% of the ITT population completed a 6-month evaluation (370/442 patients). Thirty-three patients discontinued participation in the study prior to 6 months; 22 (7.7%) in the DCB group and 11 (7.1%) in the PTA group. Fourteen patients in the DCB group and 6 patients in the PTA group died prior to their 6-month follow-up, 6 patients in the DCB group and 3 patients in the PTA group withdrew consent to participate, and 4 patients were either lost to follow-up or were removed for other reasons (2 DCB patients and 2 PTA patients). An additional 39 patients did not complete a 6-month evaluation (20 DCB patients and 19 PTA patients), are still enrolled in the study, and are potentially available for longer-term follow-up examination (Supplemental Figure S1).

Primary endpoint analyses are summarized in Supplemental Table S4. The primary safety endpoint, freedom from 30-day MALE-POD for the DCB group (99.3%) was statistically non-inferior to the PTA group (99.4%; $P<.001$ with a non-inferiority margin of 12%). Safety data were available for 440 patients and were evaluated by the CEC. The composite primary efficacy measure – freedom from vessel occlusion, CD-TLR, and above-ankle amputation – was measured per flow pathway rather than per patient, and was calculated for both the proximal-segment group and the overall ITT population; vessel occlusion was confirmed by the angiographic or DUS core laboratories, and CD-TLR was adjudicated by the CEC. At 6 months, a total of 386 flow pathways (81.1%) were available for binary, proportional analysis in the proximal-segment analysis group. The composite success rate was 76.0% (193/254; 95% CI, 70.2-81.1) for the DCB group and 62.9% (83/132; 95% CI, 54.0-71.1) for the PTA group; the mean difference of 13.1% between groups was statistically significant (one-sided $P=.0079$, compared to the Bayesian one-sided P-value for success of .0085). When evaluated for the 404 flow pathways (79.7%) in the overall ITT population where data were available for analysis at 6 months, the rate of primary efficacy success was 74.5% (199/267; 95% CI, 68.9-79.6) for the DCB group vs 63.5% (87/137; 95% CI, 54.9-71.6) for the PTA group; the mean rates were numerically different (11.0%), but not statistically significant (one-sided $P=.0179$, compared to the Bayesian one-sided P-value for success of .0085). To account for missing data in the proportional analyses, freedom from primary efficacy failure (i.e., freedom from occlusion, CD-TLR, or above-ankle amputation) was also evaluated by Kaplan-Meier analysis (Figure 1); there was a statistically significant difference in the means between groups favoring treatment with DCB for both the proximal-segment and the overall populations at 180 days ($P<.001$). Freedom from primary efficacy failure for the proximal-segment population was 86.2% for the DCB group and 69.9% for the PTA group, a mean difference of 16.3% (Figure 1A), while the mean difference between the DCB group (85.8%) and the PTA group (70.7%) for the overall ITT population was 15.1% (Figure 1B).

Based on successfully meeting the composite primary safety and efficacy endpoints, four protocol-prescribed secondary endpoints were hypothesis tested in sequence at 6 months (Supplementary Table S4). Three secondary efficacy endpoints were evaluated for the proximal segment – primary patency excluding early (≤30 days) mechanical recoil, primary patency, and freedom from CD-TLR – while one secondary safety endpoint was evaluated for the overall ITT population – freedom from amputation, unhealed wound, resting pain, target-vessel occlusion, and clinically driven TVR. The DCB group performed statistically better than the PTA group for the three secondary efficacy parameters. Primary patency at 6 months, excluding early mechanical recoil, was 77.8% for the DCB group vs 65.6% for the PTA group ($P=.01$), freedom from total occlusion and CD-TLR (ie, primary patency) at 6 months was 76.9% for the DCB group vs 64.3% for the PTA group ($P=.01$), and freedom from CD-TLR was 91.3% for the DCB group vs 81.4% for the PTA group ($P<.01$). The hypothesis-tested secondary safety endpoint was not statistically different between the two treatment groups at 6 months ($P=.41$).

Survival curves (K-M) for CD-TLR and primary patency for the overall ITT analysis population are displayed in Supplemental Figures S2 and S3. Freedom from CD-TLR was 93.8% (95% CI, 90.5-96.0) for the DCB group vs 85.6% (95% CI, 79.3-90.1) for the PTA group, a mean difference of 8.2% (95% CI, 2.1-14.8) at 180 days ($P<.01$). Primary patency, the absence of occlusion and CD-TLR, was 86.7% (95% CI, 82.1-90.2) for the DCB group vs 72.2% (95% CI, 64.0-78.9) for the PTA group – a mean difference of 14.5% (95% CI, 5.4-23.5) at 180 days ($P<.001$). Patency was analyzed by the angiographic or DUS core laboratory, and CD-TLR was adjudicated by the CEC.

Additional secondary outcomes for the overall ITT population are summarized in Supplemental Table S5. Numerical differences were observed between the DCB and PTA groups, but the differences in secondary outcomes did not reach statistical significance. The mean index score at 6 months with the EQ-5D was 0.74 ± 0.24 in the DCB group and 0.73 ± 0.28 in the PTA group, with similar improvement from baseline (0.07 ± 0.3 and 0.05 ± 0.3, respectively). The mean improvement in Rutherford categories from baseline to 6 months was -2.5 ± 2.0 categories for the DCB group vs -3.0 ± 1.8 for the PTA group; mean improvement in the WIQ total score was 2.9 ± 21.6 for the DCB group vs 3.6 ± 20.3 for the PTA group; the mean change in ankle-brachial index (ABI) was 0.16 ± 0.36 for the DCB group vs 0.17 ± 0.43 for the PTA group; and the mean change in toe-brachial index (TBI) was 0.15 ± 0.24 for the DCB group vs 0.09 ± 0.29 for the PTA group. Wound status was qualitatively evaluated by the investigative site at each follow-up visit; if a wound that was present at baseline had not healed, the site reported the status as improved, stagnant, or worse. The number of patients with wounds at baseline was similar in both treatment groups (59.0% in the DCB group vs 58.0% in the PTA group). At 6 months, wounds were reported as not healed in 30.7% of the DCB group vs 21.0% of the PTA group; of the non-healed wounds, 51.0% of the DCB group vs 35.3% of the PTA group were reported as improving. Infected wounds were reported in 25.9% of DCB patients vs 26.5% of PTA patients at baseline, while infected wounds were observed in 5.5% of the DCB group and 16.3% of the PTA group at 6 months. Gangrene was reported in 22.0% of the DCB group and 21.2% of the PTA group at baseline, while gangrenous wounds were observed in 7.4% of DCB patients and 6.3% of PTA patients at 6 months. Freedom from above-ankle amputation at 6 months was 98.9% in the DCB group vs 98.0% in the PTA group (K-M survival estimate).

There were 14 deaths (5.0%) in the DCB group and 6 deaths (4.0%) in the PTA group through 6 months. Deaths in the DCB group were due to respiratory insufficiency and failure (n = 4), metastatic bladder cancer, pancreatic cancer, heart failure and cardiac arrest (n = 8), non-treatment limb gangrene (the patient refused treatment), and unknown cause (n = 1). The causes of death in the PTA group were pneumonia, congestive obstructive pulmonary disease, respiratory failure, acute heart failure, congestive heart failure, and clostridium with uncontrolled diarrhea. All deaths through 6 months were adjudicated by the CEC, and no deaths were determined to be related to the device or procedure. Freedom from all-cause death at 180 days (K-M survival estimate) was 96.8% (95% CI, 93.9-98.3) for the DCB group and 96.0% (95% CI, 91.4-98.2) for the standard PTA group (no difference between groups at 6 months; observational one-sided $P=.70$).

DISCUSSION

We compared drug-coated to uncoated PTA for the treatment of obstructive, atherosclerotic lesions in the BTK arteries (ie, popliteal, tibial, and peroneal arteries), and found that safety, a composite of freedom from MALE-POD at 30 days, for the Lutonix DCB group was non-inferior to PTA (99.3% vs 99.4%, respectively) while efficacy, defined as freedom from above-ankle amputation, occlusion, and CD-TLR, was statistically better for the proximal segment DCB group vs the PTA group (a difference of 13.1%; one-sided $P=.0079$) at 6 months. Primary patency and CD-TLR, hypothesis-tested secondary endpoints, also demonstrated statistically significant differences in outcomes favoring the DCB group at 6 months (one-sided P-values <.025).

Patients with CLI from infrapopliteal atherosclerotic disease comprise a challenging population, most often accompanied by multilevel arterial disease

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with limb-threatening pathology and comorbidities that account for a high mortality rate.[8] Previous trials of interventional therapies to treat infra- popliteal disease have provided mixed results. Romiti et al systematically reviewed 30 studies and provided a meta-analysis of PTA for the treatment of infrapopliteal arterial disease; they concluded that the long-term durability of angioplasty alone was lower than surgical bypass, but PTA provided acceptable rates of limb salvage and overall survival that were equivalent to bypass surgery.[20] Three randomized trials (YUKON-BTK, DESTINY, and ACHILLES), evaluating over 500 patients, compared the use of coronary drug-eluting stents (sirolimus- or everolimus-eluting) to PTA or bare-metal stents.[21-23] Katsanos et al pooled the results from these studies and reported a primary patency rate of 80% for the drug-coated stents vs 58.5% for the PTA and bare-metal stent controls at 1 year.[24] Similarly, the rates of TLR, event-free survival, and wound healing were better for the drug-eluting stent group; however, the lesions treated were focal, ranging in length from 16-31 mm, and were not representative of the typical clinical patient presenting with lower-limb disease and CLI. Maximum lesion lengths in the current trial were much longer, ranging from 340-361 mm (mean total lesion length of 111.8 mm in the DCB group), with primary efficacy in the longest-lesion quartile (182-360 mm) of 65.7% for the DCB group vs 32.3% for the PTA group using logistic regression covariate analysis. An early, single-center randomized trial of 132 patients with 158 infrapopliteal arterial lesions treated with DCB (DEBATE-BTK) demonstrated that binary restenosis was 27% in patients treated with DCB vs 74% in the PTA group ($P<.001$), the rate of TLR was lower in the DCB group, and wounds healed in 86% of the patients in the DCB group vs 67% in the PTA group at 12 months.[25] A multicenter, randomized study of 358 patients randomized to DCB vs PTA found that CD-TLR was 9.2% in the DCB group vs 13.1% in the PTA group ($P=.29$), but there was a numerically higher rate of amputation at 12 months (8.8% in the DCB group vs 3.6% in the PTA group; $P=.08$).[12]

Early findings from the Lutonix BTK study are encouraging, but longer-term follow-up is needed to determine the clinical benefit of DCB use for obstructive infrapopliteal arterial lesions. The trial at 6 months met the primary safety and efficacy endpoints of non-inferior MALE-POD between groups and a statistically significant difference favoring DCB for primary efficacy in the proximal BTK segment. Over 50% of wounds were reported as improving in the DCB group vs 35% in the PTA group, and fewer infected wounds were reported in the DCB group at 6 months (5.6% vs 16.3%, respectively). Other secondary observations, however, were similar between the two groups at 6 months (eg, improvement in Rutherford scores, quality of life measures, and hemodynamic improvements). No deaths were adjudicated as related to the devices or the procedure, and the rates of all-cause death were similar between groups at 6 months (4.9% in the DCB group vs 3.9% in the PTA group). The trial protocol mandates clinical follow-up through 3 years, and that data will augment the early results presented herein.

In addition to short-term follow-up, there were other limitations to the trial. Patients, core laboratory staff, and members of the CEC were blinded to the treatment received; however, the investigators performing the study procedures were aware of the specific devices used, thereby introducing potential investigator bias. Outcomes may not be specific to just the study lesions and treatment received; patients with CLI have severe, progressive PAD with multiple comorbidities and high rates of mortality and limb loss. The two-part efficacy endpoint (ie, overall ITT population or the proximal segment group) and the Bayesian adaptive design provided a strict threshold for efficacy success (P-value of .0085). Proportional analysis of the composite efficacy endpoint for the overall ITT population did not reach this strict level of statistical significance; however, when estimated by K-M analysis, to account for patients missing from the proportional analysis (eg, those who died, had un-interpretable imaging data, or withdrew from the study), the difference between the DCB group and PTA group in the overall ITT population reached statistical significance (one-sided $P<.001$). The use of DCB or standard PTA does not cure systemic atherosclerotic disease, so changes in outcomes may be due in part to the progression of disease rather than to a difference in the devices used. Predilation was performed by standard angioplasty alone; the effects of vessel preparation using atherectomy or cutting balloons or focal-force balloons to debulk the treatment area or score the lesions are unknown.

CONCLUSION

In patients with symptomatic infrapopliteal PAD, treatment with a paclitaxel drug-coated angioplasty balloon provided non-inferior safety to uncoated PTA at 30 days and a statistically significant difference in composite efficacy favoring treatment with DCB at 6 months. Primary patency and CD-TLR, both hypothesis-tested secondary endpoints, also demonstrated statistically significant differences in outcomes favoring the DCB group at 6 months. Clinical and functional outcomes were similar between groups at this early timepoint, with more complete analysis and longer-term follow-up needed to determine whether DCB provides significant long-term clinical benefit to patients with severe, infrapopliteal arterial disease. ■

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Inaugural AMP Europe Meeting in Lugano, Switzerland

The Inaugural AMPutation Prevention (AMP) Symposium Europe convened in Lugano, Switzerland October 2-4, 2019. Course Directors Jihad A. Mustapha, MD (Grand Rapids, Michigan, USA), and Jos C. van den Berg, MD, PhD (Lugano, Switzerland) were joined by Course Co-Directors Marianne Broadman, MD, PhD (Graz, Austria), Marco Manzi, MD (Padua, Italy) and Thomas Zeller, MD (Bad Krozingen, Germany). This global meeting focused exclusively on critical limb ischemia (CLI). The latest data, diagnostics, innovation and treatment for CLI was presented over this three-day congress. Over 200 attendees attended to hear CLI-focused presentations and discussion from global thought leaders.

CLI Global Society Board Members, Dr. Mustapha, Professor Zeller, Dr. Robert Lookstein (New York, New York USA) and Dr. van den Berg kicked off the opening session. Dr. Mustapha began with a discussion on "A Historical Perspective on CLI Definition and Treatment. Why is CLI So Deadly?" He stated "As of 2019 there is no single agreed upon definition of critical limb ischemia (CLI). Initial CLI therapy was comprised of P3 or proximal tibial bypass surgery only. CLI therapy has evolved to include endovascular and hybrid procedures due to the development of advanced techniques and interventional, low profile tools. Currently, we are awaiting the new generation of treatment modalities for CLI such as bioabsorbable stents, drug-eluting balloons, intramural drug delivery, drug-eluting stents with polymers and the ability to accommodate the variable diameters of the tibial arteries. I see only good things coming for the future of CLI therapy because this disease is as bad as cancer. We should place the same attention on CLI as we do cancer therapy."

Dr. Roberto Ferrarresi (Bergamo, Italy) noted that despite CLI having a worse prognosis than many cancers, we do not offer the same intensity of care. "Cancer centers have palliative care and psychologists available. We should offer the same care for our CLI patients."

Professor Zeller spoke about the need to raise awareness of CLI. "Patients with CLI remain underserved with regard to diagnostic evaluation, medical therapy and utilization of revascularization. Because CLI is both common and deadly, more incident cases die over 5 years after a CLI diagnosis than with any type of cancer, except for lung cancer. Currently less than 10% of all CLI patients are receiving optimal medical therapy which may contribute to high morbidity and mortality." Optimal medical therapy for peripheral arterial disease (PAD) and CLI continues to be studied. Drs. Brodmann, Lookstein, Fadi A. Saab (Grand Rapids, MI, USA) and George L. Adams (Raleigh, NC, USA) provided updates on the COMPASS, CANTOS, ODYSSEY and ASPREE trials.

Dr. Adams expanded on the ASPREE trial which compared 100mg aspirin to placebo in healthy elderly subjects and led to three publications in *the New England Journal of Medicine* and shows that low dose aspirin is not beneficial in this healthy, elderly population. "The median age studied was 74 with 56% female and 11% diabetic. Primary outcomes showed non-significant differences in all cause death, dementia or physical disability in this population. Secondary outcomes showed that major hemorrhage was worse in the aspirin group with no significant difference in cardiovascular disease or all-cause mortality."

Day two of the symposium began with a popular session led by Professor Zeller titled, "How Would You Treat This? Drs. Manzi, Giacomo Clerici (Milan, Italy), Antonio Micari (Cotignola, Italy), Mauro Gargiulo (Bologna, Italy), and Lorenzo Patrone (London, England) each presented CLI cases from their respective institutions with interactive faculty and audience discussion following each case.

The ongoing paclitaxel situation following the Katsanos meta-analysis was discussed at AMP Europe. General consensus by the faculty was that the shared decision-making approach recommended by the FDA where the goal is to involve patients as much as possible during the informed consent process has been a good idea in theory. However, even the most astute patients remain confused and faculty report that the majority of their patients put the question back on the physician, as "what do you recommend?" When a participant asked Dr. Mustapha "what do proponents of paclitaxel need to do next?" he responded with "I don't see anything changing anytime soon. We need to continue to share information with patients and help them come to the best clinical decision for each individual situation."

Dr. Lookstein shared an update from the CLI Global Society who, in conjunction with Society for Cardiovascular Angiography and Intervention, Society for Vascular Medicine, Society for Vascular Surgery, Society of Interventional Radiology, submitted a proposal to the ICD-10 Coordination and Maintenance Committee at the National Center for Health Statistics. The submission proposed incorporating critical limb ischemia into ICD-10-CM. "CLI, also

Figure 1. AMP Europe Course Co-Directors, left to right: Drs. Marco Manzi, Jos van den Berg, Jihad Mustapha, Marianne Broadmann and Thomas Zeller.

Figure 2. Course Directors Drs. Jihad Mustapha and Jos van den Berg.

Figure 3. Drs. Fadi Saab and Jihad Mustapha from Advanced Cardiac and Vascular Centers for Amputation Prevention in Grand Rapids, MI, USA

"CLI does not attack healthy people. Healthy people do not have chronic ulcers. The black toe is only the tip of the iceberg."

– Vlad Alexandrescu, MD (Belgium)

Figure 4. Dr. Marco Manzi (Padua, Italy) and Jihad Mustapha (right).

Figure 5. Dr. Andrew Holden (Auckland, New Zealand).

Figure 6. AMP Europe attendees enjoyed an interactive experience during the exhibit hours.

Figure 7. Drs. Antonio Micari (Cotignola, Italy) and Jos van den Berg (Lugano, Switzerland).

Figure 8. Drs. Jos van den Berg, Marianne Brodmann (Graz, Austria) and Michael Lichtenberg (Arnsberg, Germany).

"Currently primary amputation is still the most common CLI treatment. In 2019, angiography is still only done in approximately 25% of CLI patients despite the knowledge that by doing so there is a 90% lower risk of amputation."
– Thomas Zeller, MD

known as chronic limb-threatening ischemia (CLTI), has long been defined in the clinical literature as ischemic rest pain, tissue loss (ulceration), or gangrene in the presence of peripheral artery disease (PAD) and hypoperfusion of the lower extremities. As the most advanced form of PAD, it is a challenging condition associated with significant morbidity and mortality. Patients with CLI are at high risk for amputation and, after lower extremity amputation, are at a heightened risk for amputation of the contralateral limb. CLI is not sufficiently understood or recognized as a disease state. Because of this lack of identification, we are concerned that CLI is not appropriately tracked in the clinical data. Identifying CLI accurately and completely in the data is essential to ensure appropriate reporting of outcomes, to better distinguish and account for the higher patient complexities, and to drive best practices for quality patient care." A multi-specialty workgroup within the CLI Global Society was tasked with reviewing data issues and noted that CLI is not currently referenced in ICD-10-CM. The working group proposal addressed this gap by bringing CLI into the ICD-10-CM Tabular and Index. The ICD-10 Coordination and Maintenance Committee proposed the adoption of our proposal after receiving the submission. The proposal is currently up for public comment and if approved, will be adopted for fiscal year 2021.

Professor Zeller's topic "Is it a Crime to Perform Amputation Without a Vascular Workup in 2019?" included some grim facts. In 2000-2001, 67% of US CLI patients had primary amputation as their initial treatment. More shockingly, in 2005, David Allie reported at Euro PCR that 50% of primary amputations are performed without angiography or even a simple ankle brachial index (ABI). Only 35% had an ABI performed before primary amputation and only 16% had angiography prior. "Currently primary amputation is still the most common CLI treatment. In 2019, angiography is still only done in approximately 25% of CLI patients despite the knowledge that by doing so there is a 90% lower risk of amputation. Amputation still plays a relevant role in hospitals. It is a higher revenue procedure than revascularization." He reported that a recent study by the CLI Global Society found that more than 30% of patients who underwent major amputation had presented with rest pain or ischemia ulcer and not gangrene.

Fahad Shuja, MD (Minnesota, USA) noted that gender, geography & ethnicity are predictors of limb loss and PAD-related mortality. Women and blacks remain under-represented in randomized controlled trials. Women with diabetes mellitus (DM) have a two-fold higher risk of PAD than men with DM.

Overall, the meeting emphasized that there remains a global lack of awareness of CLI diagnosis and therapies. CLI is truly a global issue. The general consensus of the faculty was the need for a multidisciplinary treatment approach to this aggressive multi-vessel, multi-level disease. There is hope for the future of CLI treatment due to upcoming clinical trials, innovation, and expanded techniques. ■

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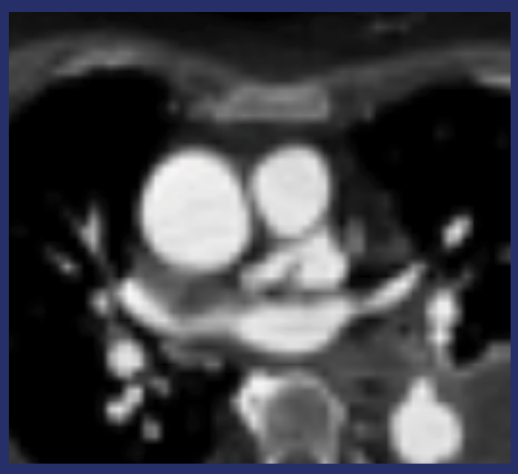

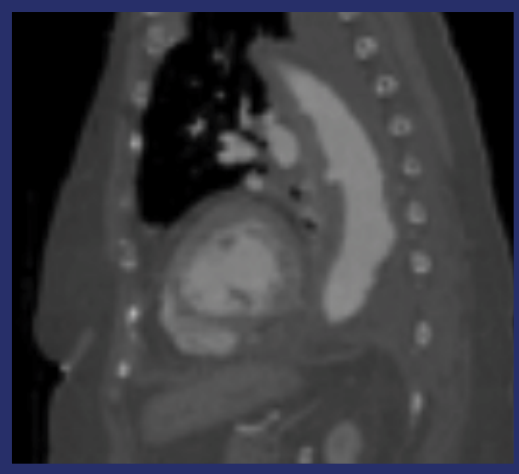

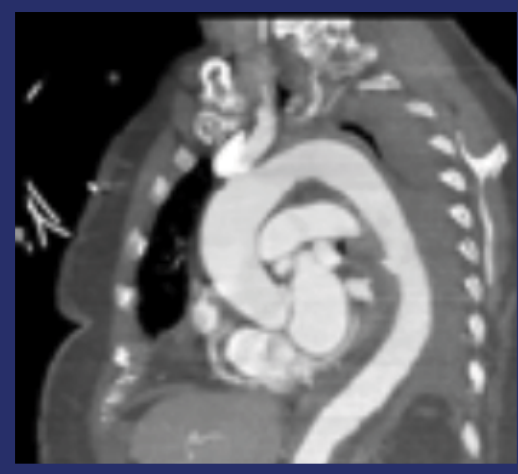

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