

Novel Therapies for CLI Revascularization and Management

Innovative modalities on the horizon for the treatment of critical limb ischemia.

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Critical limb ischemia (CLI) represents the most advanced form of peripheral artery disease and is a chronic condition that necessitates lifelong management. Due to its rising prevalence and poor prognosis, the focus on CLI diagnosis and treatment has gained increased momentum and attention throughout the medical community. However, optimal management of this complex disease process remains controversial and inconsistent among providers. In 2015, CLI prevalence within the United States was between 2 and 3.4 million, and these numbers are conservatively projected to rise to between 2.4 and 4.7 million by 2030.¹

CLI has a grave prognosis, with 29% of cases resulting in major amputation or death within the first year and the risk of mortality increasing to 54% over 4 years.² The goals of CLI management include pain reduction and wound healing to improve overall quality of life, while preventing major amputation and prolonging survival.³ Although consensus exists that revascularization—whether endovascular or surgical—is essential to reduce the high morbidity and mortality rates,⁴ there is considerable inconsistency and debate as to the optimal initial and ongoing management of this multifaceted and multifactorial disease. Diagnostic algorithms and evidence-based treatment pathways need to be further refined to provide consistent CLI treatment guidelines,² and there is an escalating movement among multidisciplinary providers and industry to collectively meet this goal. The collaborative development and investigation of innovative devices and technology and evaluation of variable treatment pathways continue to grow, and the addition of novel CLI treatment modalities are on the horizon.

DRUG-ELUTING TREATMENT MODALITIES

Drug-Coated Balloon Technology

Historically, percutaneous transluminal angioplasty (PTA) has been the standard endovascular treatment modality for infrapopliteal arterial disease; however, contemporary studies have revealed suboptimal short-term and 1-year clinical outcomes, and loss of patency remains a therapeutic challenge.⁵ As a result, an increased focus has been given to the development of and research into drug-eluting devices in below-the-knee (BTK) vessels. The results of a 2018 meta-analysis by Katsanos et al revealed an increased risk of all-cause mortality at long-term follow-up with use of paclitaxel-coated devices in a primarily claudicant population,⁶ which resulted in a cautious and hesitant approach to drug-eluting technology. The findings of this meta-analysis were quickly challenged, and several subsequent analyses have since revealed no evidence of increased mortality with the use of paclitaxel-coated devices, including in the treatment of CLI patients.⁷⁻¹¹

Throughout the last decade, various studies have found that the use of paclitaxel-coated balloons in infrapopliteal arteries reduces restenosis and target lesion revascularization rates when compared to conventional PTA,¹²⁻¹⁴ and many argue that the benefits outweigh the theoretical risks.⁸ Despite much research of paclitaxel-coated balloons, there have been various setbacks and no paclitaxel-coated balloon has thus far received an FDA-approved indication for BTK use. Yet, the device's potential benefit for CLI treatment remains. In the environment of paclitaxel scrutiny, the Virtue sirolimus-eluting balloon (Orchestra BioMed),

MagicTouch PTA sirolimus-coated balloon (Concept Medical Inc.), and Selution SLR sirolimus-eluting balloon (MedAlliance) recently received FDA Breakthrough Device designation for treatment of BTK arterial disease.

Drug-Eluting Stent Technology

For cases in which PTA outcomes for infrapopliteal disease are suboptimal, the focus has been directed to the development of novel drug-eluting stent (DES) technology. A meta-analysis by Razavi et al revealed that DES use resulted in higher primary patency rates than atherectomy, bare-metal stents, and PTA for the treatment of infrapopliteal disease.¹⁵ One-year results of the randomized ACHILLES trial found that a sirolimus-eluting stent had lower 1-year restenosis rates and greater vessel patency when compared to PTA. The trial validated the technical feasibility of stenting in infrapopliteal anatomy with superior device, lesion, and procedure-based success rates reported in the stenting cohort.¹⁶ The single-center randomized IDEAS trial supported the value of DES treatment for long infrapopliteal lesions, with significantly lower angiographically confirmed restenosis rates at 6 months for the DES cohort versus those treated with a paclitaxel-coated balloon.¹⁷

The reported outcomes of DES technology fuel the ongoing expansion and investigation of novel DES modalities targeted toward CLI treatment. In a global, prospective, randomized, multicenter trial, the safety and effectiveness of the Saval DES BTK (Boston Scientific Corporation) are being compared to standard PTA for the treatment of infrapopliteal disease in CLI patients (NCT03551496). Historically, infrapopliteal treatment studies have focused on outcomes with short coronary DESs. The Saval DES focuses on the unique BTK anatomy and accommodates lesions of longer length.¹⁸ Although much work remains in the investigation of drug-eluting technology for treatment of CLI disease, the foundation of potential advantages has been established and the prospect of new treatment modalities is promising.

NOVEL TREATMENT MODALITIES

Outside of drug-eluting technology, a multitude of novel devices are being researched with a focus on CLI revascularization strategies. A recent observational study used Medicare claims data for 36,860 CLI patients to compare long-term outcomes for differing treatment modalities. Over a 4-year follow-up period, all-cause mortality was 49.3% with atherectomy, 51.4% with surgical bypass, 53.7% with stent placement, and 54.7% with PTA. Major amputation rates were 6.8%,

10.8%, 7.8%, and 8.1%, respectively. Although atherectomy was found to have statistically lower mortality and major amputation rates relative to the other modalities, high mortality and amputation rates were consistently observed throughout all cohorts. Information regarding lesion characteristics was not available for analysis within this study, but this is a primary factor in CLI treatment determination due to the complex and multifaceted disease process.¹⁹

CLI is characterized by multilevel multivessel disease, and infrapopliteal disease commonly manifests as either high-grade calcified tandem lesions or long occlusive segments with plaque of high calcium content. When moving from proximal to distal in the arterial tree, the deposition of arterial calcium increases.²⁰ The impact of lesion location, length, stenosis, and degree of calcification must be considered when determining treatment strategies and analyzing the reported findings of clinical trials. Due to the heterogeneity of the disease process, no single revascularization method will ensure success for all patients¹⁹ and the availability of myriad treatment modalities is required for successful treatment outcomes.

Stent Technology

Diverse and innovative stent technology is being developed with the focus on sustaining blood flow within the infrapopliteal vasculature. The MicroStent (Micro Medical Solutions) is designed to achieve and maintain patency of BTK vessels with the goal of reducing amputations attributed to CLI. The device is available in multiple sizes, ranging from 15 to 60 mm in length, allowing for treatment of a wider range of infrapopliteal lesions. The safety and efficacy of the MicroStent are being evaluated in the STAND trial, a randomized, multicenter, FDA investigational device exemption study (NCT03477604).

The value of bioabsorbable stent implantation within peripheral vessels has gained increased attention, yet the extrapolation from coronary to peripheral arteries remains controversial. The randomized INSIGHT trial evaluated the safety of absorbable metal stents compared with PTA for treatment of CLI infrapopliteal arterial disease. Within this trial, the 6-month angiographic patency rate for lesions treated with an absorbable metal stent was significantly lower than the rate for PTA-treated lesions (31.8% vs 58%, respectively).²¹ Conversely, 12-month outcomes of the Absorb everolimus-eluting bioresorbable vascular scaffold (Abbott) revealed primary patency rates of 96% and 84.6% at 12 and 24 months.²² The proposed benefit of absorbable therapy exists in the potential to obtain

the superior outcomes of stent implantation while reducing the risks of ongoing foreign body exposure and stent fracture. Additional research and development are essential to determine the optimal design and degradation rate to achieve ideal vessel support and prevent acute recoil, while removing long-term foreign body exposure.²³ The LIFE-BTK randomized controlled trial comparing the everolimus-eluting Esprit bioresorbable stent (Abbott) to PTA for treatment of BTK vessels is currently being developed (NCT04227899).

The novel Temporary Spur stent system (Reflow Medical, Inc.) aims to eliminate the disadvantages of residual foreign material within the artery. It consists of a retrievable stent system with radially expanding spikes designed to create pathways to deliver and promote uptake of antiproliferative drugs into the vessel wall and facilitate acute luminal gain. The first-in-human DEEPER trial evaluated the safety and efficacy of the Temporary Spur stent system in conjunction with drug-coated balloons. Analysis at 6 months revealed 88.9% patency in the per-protocol population (patients with no angiographic protocol deviations).²⁴ The results supported the initiation of the DEEPER OUS prospective, multicenter, nonrandomized trial as well as designation for the FDA's Breakthrough Devices program.

The Tack endovascular system (Intact Vascular, Inc.) is a short (6 mm), self-expanding nitinol implant designed to treat acute dissections while minimizing the amount of metal left within the artery. The device was initially evaluated for treatment of above-the-knee dissections in claudicant populations and then transitioned to BTK trials for CLI.^{25,26} The TOBA II BTK trial evaluated use of the Tack device in 233 CLI patients for the treatment of infrapopliteal dissections after PTA. Six-month study results revealed an 87.3% patency rate, with 92% freedom from clinically driven target lesion revascularization (NCT02942966).²⁷ In April 2020, FDA approval was received for the Tack endovascular system in BTK arteries.

Balloon Technology

Severe calcification of BTK arterial lesions results in resistance to the opposing force generated by balloon angioplasty inflations, increasing the likelihood of dissection and inadequate luminal gain.²⁰ The Serranator PTA serration balloon catheter (Cagent Vascular) is designed to create interrupted microserrations with the goal of improving lumen expansion while minimizing injury to the vessel wall and reducing recoil. Enrollment of the multicenter, single-arm PRELUDE BTK study has been completed (NCT03693963), and FDA 510(k) clearance was recently received for treatment of BTK vessels.

Atherectomy Technology

Due to the diverse pathologic patterns of CLI's multilevel disease process, a need exists for therapeutic modalities that effectively treat the entire disease spectrum.²⁰ The FreedomFlow system (Cardio Flow, Inc.) is a novel orbital atherectomy system that consists of five diamond-coated abrasive spheres that provide simultaneous vessel wall contact when rotated at high speeds. The system aims to remove and modify calcified and fibrotic plaque within arterial vessels ranging from 2 to 8 mm in diameter. The abrasive spheres have the potential to create microcracks in difficult-to-remove plaque, which may enable use of lower-pressure balloon angioplasty and reduce the risks of dissection and perforation. The safety and effectiveness of the FreedomFlow system are being evaluated in the FAST II study (NCT03635190).

Endovascular Bypass Technology

Because approximately two-thirds of CLI patients present with a combination of femoropopliteal and infrapopliteal disease,²⁰ successful treatment of inflow disease must first be achieved and treatment of long femoropopliteal occlusive disease remains a challenge. Endovascular treatment outcomes for long lesions remain suboptimal; however, surgical risks in an already critically ill population cannot be ignored.^{4,28} Focused on this treatment challenge, the PQ Bypass system (PQ Bypass, Inc.) is an endovascular approach to femoropopliteal bypass that aims to provide long-term durability and minimize surgical risks. The prospective, single-arm, international DETOUR II study is in process to investigate the device's safety and effectiveness (NCT03119233).

Deep Vein Arterialization

Up to 20% of end-stage CLI patients continue to face "no-option" situations due to the complexity of their lesions, extensive comorbidities, and/or lack of adequate conduits, and major amputation is presented as the only viable option.^{29,30} The LimFlow percutaneous deep vein arterialization system (LimFlow, Inc.) emerged from the historic concept of venous arterialization and offers a promising revascularization option for this end-stage CLI population. Interim results from the PROMISE I study of 10 patients demonstrated amputation-free survival through 6 months.³⁰ Additional investigation of the novel stent graft system continues through the PROMISE I feasibility trial and larger-scale clinical investigation (NCT03124875).

MEDICAL MANAGEMENT

Although sustaining arterial blood flow with revascularization modalities remains the principal focus for CLI treatment, it is essential that increased investigation and attention are given to the ongoing medical management. Given the complex disease process of CLI and associated comorbidities, as well as its increasing incidence, it is not surprising that the economic and quality-of-life burden associated with CLI is significant. Information obtained from CLI Medicare beneficiaries in 2011 revealed an average total cost of \$93,800 over a 4-year follow-up period per CLI patient.² A diagnosis of CLI is met with the reality of managing rest pain, nonhealing ulcers, and/or gangrene, requiring dependency on caregivers, management of chronic pain, and recurrent wound care treatment.³¹

After sufficient arterial blood flow is established, comprehensive wound care treatment is essential for limb preservation. Innovative wound care treatment methods are being developed and utilized (eg, amniotic membrane grafts), and ongoing investigation is essential to advance the wound healing process. Unfortunately, despite the reality that CLI is more fatal than many deadly cancers,^{19,32} insufficient and inconsistent attention continues to be given to proper CLI diagnosis and life-long medical management. Regardless of recommendations for diagnostic imaging and diabetic, antihypertensive, and lipid-lowering medical therapy, only approximately 25% of patients undergo angiography at time of diagnosis and less than one-third receive optimal medical therapy.^{33,34} The 2016 American Heart Association/American College of Cardiology guidelines recognized critical evidence gaps to support the determination of optimal antiplatelet and statin therapy, role of dietary intervention, and appropriate exercise programs.²⁸ Although the historic investigation of statin therapy for CLI patients is limited, a meta-analysis by Kokkinidis et al including 19 studies involving 26,985 CLI patients found that patients treated with statin therapy were 25% less likely to undergo amputation and 38% less likely to have a fatal event.³⁵ This study confirmed the value and impact of optimal medical management and the essential need for increased systematic study of medication, dietary, and exercise therapy to optimize and prolong successful revascularization outcomes.

SUMMARY

As we enter a new decade, the growing collaboration among industry and the multidisciplinary medical team to develop and evaluate new technologies is encouraging and essential to combat and reduce CLI morbidity and mortality. Additional investigation and focus must

be directed to CLI diagnosis and ongoing medical management to establish comprehensive, evidence-based guidelines and treatment pathways. Establishment of realistic long-term goals of revascularization along with advancement of novel treatment modalities will lead to better defined optimal outcomes. The ongoing role of revascularization within long-term CLI management, as well as whether repeat revascularization is an expected and integrated component of the long-term treatment plan, should continue to be discussed to avoid graver outcomes of amputation and mortality. ■

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