Evidence-Based CLI Therapies in 2016

The gap between real-world CLI practice and evidence-based therapies remains wide.

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Despite the fact that the statistics highlighting the natural history of peripheral artery disease (PAD) have been commonly understood for nearly a decade, its prevalence continues to increase at an alarming pace worldwide. Large-scale studies indicate that there will be 22 million patients with PAD by 2030. PAD exerts a deleterious effect on patient morbidity and mortality, with a threefold increase in the risk of cardiovascular death compared to patients without PAD.[1-3] Advancing age, male sex, African American race/ethnicity, tobacco abuse, diabetes, dyslipidemia, hypertension, and coronary artery disease are all strongly associated with an increase in the risk of developing PAD. These patients present with a wide variety of symptoms, but only 10% to 20% have typical claudication symptoms, and almost 50% have asymptomatic PAD.[4,5] These difficulties have hindered our ability to diagnose PAD and have led to low or delayed detection rates by health care providers,[5] unfortunately leading many of these patients (< 10%) to only be discovered when they present with critical limb ischemia (CLI).[6]

NATURAL HISTORY OF CLI

The path that leads to the development of CLI is not governed by an organized progression through a series of clinical stages, as patients with PAD can be symptomatic or asymptomatic prior to reaching this terminal stage.[7] Patients with CLI have a significantly increased risk for myocardial infarction, stroke, limb loss, and death. Within the first year of clinical diagnosis, an estimated 30% of patients with CLI will undergo a major amputation, and 25% to 30% will die.[8] When revascularized, these patients require intensive care, complex procedures, surveillance, and the participation of a multidisciplinary team, utilizing resources that could be portrayed as an added strain to a health care system that is already under pressure.[9] It should be emphasized that amputations are neither the solution nor the final step for patients with CLI. Instead, the initial amputation is followed by revisions, more proximal amputations, contralateral amputations, and cardiovascular procedures, all of which add to the total economic burden.

CLI THERAPIES

The treatment of CLI in the United States has been characterized as a pathway to amputation, as 67% of Medicare patients who underwent a major amputation did not have any other exploratory or therapeutic procedures prior to losing their limb.[10] This finding was confirmed in a recent study of 20,464 Medicare patients with CLI who underwent amputations, which revealed that 71% had no revascularization and 54% did not even undergo angiography, underscoring the fact that revascularization procedures (endovascular and surgical) have largely been underutilized.[11] This could be ascribed, at least in part, to the paucity of randomized controlled trials (RCTs) comparing both strategies, which have been difficult to implement.[12] This represents a clear example of the existing gap between "real-world CLI practices" and the availability of evidence-based therapies. Over the last few years, there has been a significant increase in the amount of CLI-related data. However, these data continue to be applied mainly in the relatively few CLI centers of excellence, perpetuating the mismatch between data availability and day-to-day CLI practices.

Femoropopliteal Segment

Atherosclerotic plaque in CLI is omnipresent; however, approximately 65% of the obstructive lesions are located in the femoropopliteal space and exhibit complex features (length and degree of calcification) that qualify most of them as TASC C or D lesions. Endovascular techniques have continued to evolve

and have slowly and progressively replaced the once ubiquitous surgical bypass, which remains relevant in cases with extensive femoral artery disease, particularly if there is involvement of the common femoral artery with extension into the deep femoral artery.

The most current randomized trial comparing infrainguinal saphenous vein bypass to both above-knee and below-knee segments with percutaneous transluminal angioplasty (PTA) is the BASIL trial.[13] It found that endovascular therapy equaled the results achieved with surgery based on amputation-free survival at 6 months. Endovascular therapy was a less morbid procedure with equivalent quality of life outcomes and was significantly less expensive than surgery. There has been a widespread adoption of the endovascular-first approach since this trial, along with continuous innovations in endovascular techniques and devices.[6] It is worth mentioning that at the time the BASIL results were published, the angioplasty group did not include stents or other adjunctive procedures; therefore, the study may not be reflective of current, more effective endovascular strategies. In a meta-analysis of observational studies from 1995 to 2012, no differences were found between endovascular and open surgical revascularization regarding all-cause mortality, amputation, or amputation-free survival at 2 years.[14]

Multiple studies have compared nitinol stents (both bare and covered) with PTA in the superficial femoral artery (SFA), without evidence of advantages of using covered over bare-metal stents (BMS) for the treatment of long and complex (TASC II C/D) SFA lesions.[15] Prospective multicenter studies have shown improved patency for BMS when compared to PTA for the treatment of intermediate lesions (7 cm) in the SFA, with benefits sustained even after 3 years.[16,17] Studies looking at interwoven nitinol stents report high patency rates in the treatment of long complex lesions.[18] Adjunctive modalities such as atherectomy have also been studied as primary therapies. Orbital,[19] laser,[20] rotational/aspirational,[21] and directional[22,23] atherectomy devices have been evaluated, with promising results; however, concerns regarding the risk of distal embolization, restenosis, and perforations remain. More recently, 2-year data have emerged for the use of paclitaxel-coated, self-expanding nitinol stents (PCSES), revealing that this strategy remains superior to standard PTA,[24] and earlier this year, the 5-year data comparing PCSES and PTA were published, showing that for lesions 65 ± 40 mm in length, PCSES offer better patency rates (66.4%) and freedom from target lesion revascularization (TLR; 84.9%) than standard PTA.[25] However, the SFA presents significant challenges in achieving long-term results after endovascular intervention, secondary to the unique forces to which it is subjected.

Proximal continuity with the common femoral artery and distal continuity with the popliteal artery exposes the SFA to elongation with ambulation. Due to its superficial course and intimate interaction with the surrounding musculature, the SFA is subject to compressive and torsional forces. This can result in metal fatigue and stent fracture, which has been associated with restenosis, especially with first-generation stents. In addition, the SFA responds to stent implantation with a more potent inflammatory response than other vessels due to micromovements of the stent alongside the vessel wall, which lead to activation of the endothelium and inflammation. When stent segments overlap (often done while treating long SFA lesions), hinge points are created, potentiating the likelihood of stent fracture.

These limitations illustrate that although stent-related data for the SFA have improved, there is still a need to improve outcomes, which has led to the development of drug-coated balloons (DCBs). Results of the first large, international, prospective, multicenter RCT of DCBs versus bare PTA for the treatment of SFA disease (IN.PACT SFA) were published and demonstrated a significant advantage of DCB use when patency (82.2% vs 52.4%) and TLR (2.4% vs 20.6%) were analyzed.[26] More recently, results of the LEVANT-2 study were released, showing a superior 12-month primary patency rate of 65.2% compared to PTA (52.6%), with a safety profile that was noninferior to the standard balloon.[27] The latest study of the use of the In.Pact Admiral DCB (Medtronic) in this segment showed excellent 1-year results (83.2% primary patency) in long lesions (251.7 ± 78.9 cm) with moderate-to-severe calcification (50.4%) and 49.5% of total occlusions in a population mainly composed of claudicants (89.5%). Of note, only 10.5% of patients had CLI and, of those, only 1.6% were Rutherford class 5 and no patients were Rutherford class 6.[28] Further studies are necessary to determine the role (if any) of combination therapies.

Infrapopliteal Segment

Revascularization of infrapopliteal (IP) disease is almost exclusively utilized for patients with CLI, as it is considered that most other clinical scenarios would not justify the risk of a tibial intervention. In this respect, the Society for Cardiovascular Angiography and Interventions published the first expert consensus document on the management of IP arterial disease. Assuming that the inflow vessels are patent and the femoropopliteal segment does not exhibit a hemody-

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namically significant stenosis, single-vessel tibial disease with patency of the other tibial arteries would not be expected to result in severe limb symptoms prompting the need for revascularization (unless the severely diseased tibial is the tibioperoneal trunk, which would represent a two-vessel disease equivalent).[29]

Recent efforts to standardize strategies for the management of IP disease have been brought to the forefront by the creation of a supplement to the latest version of the TASC II classification, addressing for the first time the different IP clinical/anatomical scenarios and their potential combinations.[6] There is an extensive amount of literature pertaining to the surgical treatment of IP disease, primarily using the greater saphenous vein or other autologous veins as conduit material. The use of spliced grafts, allograft material, or prosthetic material such as polytetrafluoroethylene is less than ideal for this segment. One-year survival and limb salvage rates of 76% to 90% and 66% to 100%, respectively, have been reported.[30-33] Major morbidity related to surgical bypass for IP disease and CLI is clinically important. Although the BASIL trial included patients with infrainguinal rather than isolated IP disease, it offers the most relevant data in this regard. The periprocedural mortality (5.5%), myocardial infarction (7%), stroke (1.5%), and surgical wound complication (22%) rates reported in this study[13] are clearly higher than the expected rates for these outcomes with endovascular approaches.

Objective performance goals for patients with CLI have been developed from large clinical trial databases, and they define an important clinical outcome as the absence of 30-day mortality or major adverse limb events (amputation or reintervention).[34] The primary efficacy endpoint was set at 76.9% and amputation-free survival at 76.5%. This type of analysis may be helpful to provide perspective for noncomparative, nonrandomized data from clinical trials. The OLIVE registry reported data describing risk-adjusted outcomes for endovascular procedures[35] in Japanese patients with CLI. Heart failure, wound infections, and being underweight (body mass index < 18.5 kg/m^2) increased the risk for a worse outcome and decreased amputation-free survival. Since the BASIL trial, there has been a widespread temporal adoption of an endovascular-first approach for CLI. Technical success rates approaching 100% have been reported, but these likely suffer from case selection and reporting bias. In a large meta-analysis of IP PTA as the primary treatment modality, the 3-year limb salvage rate was 82.4%[36] compared to 82.3% with an open surgical approach.[31]

Currently, the BEST-CLI study is enrolling patients in an attempt to compare the best endovascular versus the best surgical approach to treat CLI. Enrollment has been slow, and most of the sites enrolling patients are centers with predominantly surgical expertise. We all hope for an equilibrated enrollment, which would truly allow us to compare which strategy is best; however, it seems intuitive that patients will be better served on an individual basis by the local expertise. We must remain tuned to these awaited results.

New Adjunctive Technologies

Several adjunctive endovascular devices, including atherectomy, cryoplasty, cutting balloons, and lasers, have shown safety and feasibility in the IP segment but have failed to show superiority when compared with PTA.[20,37-39] The data quality is compromised, as they largely represent retrospective reports or uncontrolled registries (subject to selection bias) from individual centers.

Drug-Eluting Stents

After data from the BASIL trial were released, the preferred endovascular approach was PTA, with BMS reserved for preserving patency in case of dissection as a bailout technique. As drug-eluting stent (DES) platforms became established in the coronary bed, four RCTs tested DES in IP lesions. The ACHILLES trial randomized 200 patients with IP disease to PTA or DES (Cypher Select sirolimus-eluting stent, Cordis Corporation) and found superior patency rates at 1 year for DES (75% vs 57.1% for PTA; $P = .025$).[40] There was no difference in terms of death, amputation rates, or improved clinical status. The DESTINY study randomized 140 patients with CLI and IP disease to BMS (Multi-Link Vision, Abbott Vascular) or DES (Xience V, Abbott Vascular).[41] Over 12 months of follow-up, the DES group showed superior patency (DES 85% vs BMS 54%; $P < .001$) and freedom from reinterventions (DES 91% vs BMS 66%; $P = .001$). There was no difference in clinical Rutherford class improvement, major amputations, or mortality.

The YUKON-BTX trial randomized 161 patients to IP treatment with BMS or DES (Yukon sirolimus-

eluting stent, Translumina) and found superior patency at 12 months for the DES group but no difference in event-free survival.[42] The IDEAS RCT compared DCB versus DES in long (> 70 mm) IP lesions in patients with Rutherford categories 3 to 6. Restenosis was significantly lower in the DES group (28% vs 57.9%; *P* = .046). There were no differences in TLR rates.[43] However, the preponderance of the evidence for IP DES use has demonstrated a significant benefit over both BMS and PTA in terms of patency, reduced reinterventions, reduced amputations, and improved event-free survival. These results are not specific to CLI, as most trials have included severe claudicants in their populations. It is also likely that the lesions selected for randomized trials do not reflect real-world IP lesions (ie, fewer lesions, more discrete lesions, less calcified lesions, and fewer occlusions). There are only limited clinical data available on the IP applications of DCBs.

A registry of 104 patients treated with IP PTA using a DCB (In.Pact Amphirion, Medtronic) demonstrated favorable results compared to historical controls for restenosis reduction, and there were no safety issues noted.[44] The DEBATE-BTK trial randomized 132 diabetic patients with CLI and 158 IP lesions to either DCB (In.Pact Amphirion) or PTA.[45] Notably, the mean lesion length was 129 ± 83 mm, which is dramatically longer (~100 mm) than lesions treated in the IP DES randomized trials. Restenosis (DCB 27% vs PTA 74.3%; *P* < .001), target vessel occlusion (DCB 17.6% vs PTA 55.4%; *P* < .001), and 1-year major adverse events (DCB 31% vs PTA 51%; *P* = .02) all favored DCBs. However, there was no difference in amputation, limb salvage, or mortality rates. The IN.PACT DEEP trial outcomes resulted in the withdrawal of the In.Pact Amphirion DCB from the worldwide market by the sponsor. The trial enrolled 358 CLI patients with IP lesions. Twelve-month late lumen loss and clinically driven TLR for those in the DCB group were not different from the control group, and there was a nonsignificant trend toward higher amputation rates in the DCB group.[46] There are few adverse periprocedural events with endovascular therapy for the treatment of IP disease, with mortality rates in observational series approaching < 1%. Several mechanisms have been proposed to explain the lack of benefit in this study (compared to DEBATE-BTK), including the use of a balloon that was coated with a different technique and a balloon size that was an average of 0.5 mm smaller (by visual estimate) than those used by Liistro et al.[45] The difference in balloon size has the potential to cause vessel-balloon mismatch, leading to a lack of contact between the balloon and the intima and therefore compromising the drug transfer to the media.

CONCLUSION

It appears evident that PTA results have reached their zenith, and adjunctive modalities deserve to be systematically studied in order to analyze their likely superior results. Appropriate study design can potentially shine a different light on outcomes of endovascular therapies for below-the-knee disease. There is a need for large-scale, multicenter, prospective studies with inclusion criteria that encompass real-world patients with CLI along with currently available and future disruptive technologies in order to generate relevant and generalizable data that can be used as the best source of evidenced-based standards to treat this complex disease.

Although challenging, the future of CLI treatment is exciting, with increasing focus on optimal wound care and prevention; adherence to proven medical therapies; improving revascularization results with novel techniques; devices and approaches; and, most definitely, with the establishment of CLI centers of excellence with dedicated multidisciplinary teams. A gap remains between real-world CLI practice and evidence-based therapies, which is fed by the disparity between real-world patients and those enrolled in clinical trials. The education of patients, physicians, health-allied personnel, institutions, politicians, industry, and all of the stakeholders is one of the missions of the recently created CLI Global Society (www.cliglobal.com), and its accomplishment will undoubtedly continue to narrow this gap. This society was founded with the purpose of bringing CLI to the forefront. Global experts carry the baton and will be responsible for creating awareness, guidelines, protocols, and tools that adapt to the reality of each individual country, as we understand the nuances introduced by the different cultures, politics, and socioeconomic realities. ■

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